Collateral blood vessels in acute ischaemic stroke: a potential therapeutic target

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Ischaemic stroke results from acute arterial occlusion leading to focal hypoperfusion. Thrombolysis is the only proven treatment. Advanced neuroimaging techniques allow a detailed assessment of the cerebral circulation in patients with acute stroke, and provide information about the status of collateral vessels and collateral blood flow, which could attenuate the effects of arterial occlusion. Imaging of the brain and vessels has shown that collateral flow can sustain brain tissue for hours after the occlusion of major arteries to the brain, and the augmentation or maintenance of collateral flow is therefore a potential therapeutic target. Several interventions that might augment collateral blood flow are being investigated.

Lancet Neurol 2011; 10: 909–21

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Introduction

Stroke continues to impose an overwhelming burden on global health, imparting devastating disability, but few therapeutic advances have been made despite decades of research. It is the second most common cause of death, with most of the 16 million cases occuring in developing countries.[1,2] Ischaemia, or restricted blood flow, is the main cause of stroke, typically due to occlusion of a cerebral artery as a result of progressive atherosclerosis or an embolus from the heart or neck vessels.[1–3] In some patients, the blockage or occlusion can develop within small intracranial vessels, often because of uncontrolled hypertension or diabetes.[4,5] Irrespective of cause or mechanism of ischaemia, collateral flow—ie, perfusion via alternative, indirect pathways—might offset potential injury to the brain.[6–8]

Digital subtraction angiography 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. Evidence is emerging that this information could help to improve long-term prognosis. Additionally, patients with good collaterals might respond better to reperfusion therapy[9] and have a lower risk of haemorrhagic complications from such treatments than do other patients.[10]

The pathophysiology of the evolving stroke has been well studied in animals and people.[11,12] Ischaemic thresholds have been established in in-vivo models; generally, these thresholds parallel cellular damage in other tissues of the body, but with a few important differences.[13] Normal cerebral blood flow (CBF) is between 50 and 60 mL/100 g/min and is tightly controlled by cerebral autoregulation.[13] The pace of cellular death in the brain after an arterial occlusion is closely linked to the severity of decrease in blood flow within the local environment. When blood flow is less than 10 mL/100 g/min, damage is rapid and most cells die within minutes of the insult.[13–15] When CBF is between 10 and 20 mL/100g/min, neurons cease to function but remain structurally intact and are potentially revivable if normal blood flow is restored.[15] Therefore, neuronal damage is not uniform when an intracranial artery is occluded, especially in the first few hours after the insult. Depending on the extent of collateral perfusion, infarction might not be complete for hours or even days.[16]

Modern neuroimaging techniques, particularly multimodal CT and MRI (including non-invasive angiography and perfusion imaging), allow identification of cerebral injury in the first few hours after arterial occlusion. Detailed imaging studies have shown that progression to complete infarction, especially after occlusion of the middle cerebral artery (MCA), is highly variable.[9,17] In some cases, infarction is complete in less than an hour, but other patients might show evidence of viable tissue for days, if not indefinitely.[18] In patients whose tissue survives for a long period despite proximal arterial occlusion, retrograde filling of pial arteries (a surrogate indicator of leptomeningeal collateral vessels) is often evident in imaging studies and might have an important protective role.[9]

Enhancement of blood flow through collateral vessels might be therapeutically useful in the treatment of acute stroke. The notion of CBF augmentation by volume expansion and induced hypertension has been tested in several small trials dating from the 1970s.[19,20] Newer methods of CBF augmentation in acute ischaemic stroke have also been assessed.[21]

In this Review, we summarise the anatomy and physiology of the collateral circulation, and its potential as a therapeutic target in ischaemic stroke. We focus on the importance of emerging CT and MRI technologies that can be used to identify collateral blood vessels in the very early stages of ischaemic stroke. We present evidence that good collateral circulation can prevent or delay permanent neural damage, and assess how the presence of collateral blood vessels helps to improve patient outcomes with thrombolysis. Finally, we present information about therapies that have been used to enhance collateral blood flow in patients with acute ischaemic stroke.

Anatomy of the collateral circulation

Three principal anatomical features underlie collateral perfusion to the brain (figure 1). The first consists of

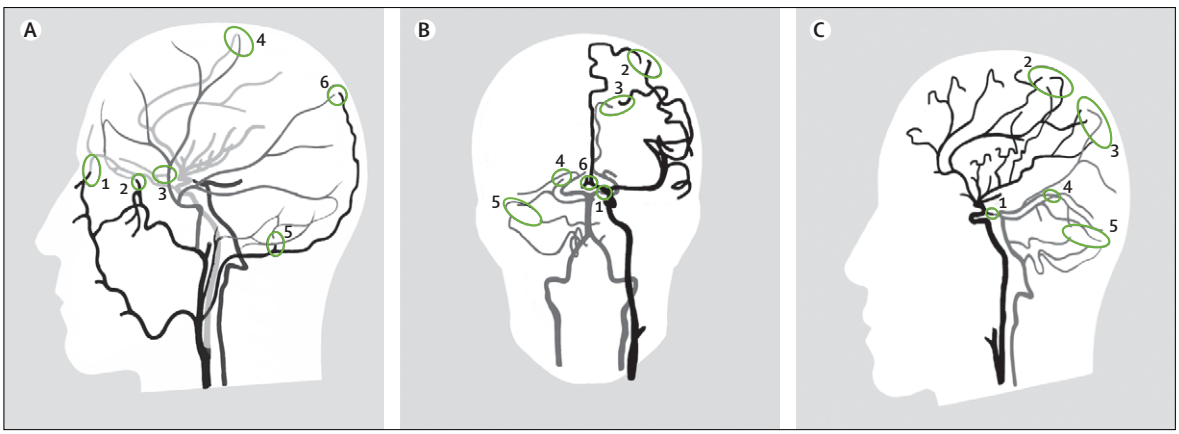

Figure 1: **Cerebral arterial circulation**
(A) Extracranial arterial collateral circulation. Shown are anastomoses from the facial (1), maxillary (2), and middle meningeal (3) arteries to the ophthalmic artery, and dural arteriolar anastomoses from the middle meningeal artery (4) and occipital artery through the mastoid foramen (5) and parietal foramen (6). Intracranial arterial collateral circulation in frontal (B) and lateral (C) views. Shown are the posterior communicating artery (1); leptomeningeal anastomoses between anterior and middle cerebral arteries (2) and between posterior and middle cerebral arteries (3); the tectal plexus between posterior cerebral and superior cerebellar arteries (4); anastomoses of distal cerebellar arteries (5); and the anterior communicating artery (6). Reproduced from Liebeskind,[7] by permission of Wolters Kluwer Health.

large-artery communications between the extracranial and intracranial circulations. The external carotid artery gives rise to many branches in the neck that are a potential source of collateral flow, especially in the event of chronic stenosis or occlusion of the internal carotid artery. Important collateral circuits include flow through the ophthalmic (retrograde) and superficial temporal arteries to the intracranial vessels, normally supplied by the internal carotid artery.[22] In the posterior circulation, many anastomoses exist between the vertebral arteries and muscular branches at the cervical level. The anterior and posterior spinal arteries also communicate with branches of the proximal intracranial arteries supplying the medulla and pons.[8]

Second, the blood supply to the brain is unique because four major arteries coalesce to form an equalising distributor, the circle of Willis, which can redistribute blood flow in the event of a sudden occlusion of a parent vessel. The anatomy of the circle of Willis varies between patients and is an important determinant of how well blood flow diversion can occur in the presence of an arterial occlusion. Roughly 50% of individuals have a normal or complete configuration of the circle of Willis.[23] Common variations are, in order of frequency, atretic or string-like anterior or posterior communicating arteries, triplication or duplication of vessels, and a fetal origin of one or both posterior communicating arteries.[23,24] The presence of any of these abnormalities, particularly atretic communicating vessels, can seriously compromise ability to compensate for sudden occlusions.[8]

Third, leptomeningeal anastomoses potentially provide arterial blood to the cortical surface.[22,25–28] In these vessels, blood can flow in both directions as a function of the haemodynamic and metabolic needs of the two territories that they connect. The leptomeningeal anastomoses linking distal sections of the major cerebral arteries are small arteriolar connections (~50–400 μm) that allow retrograde perfusion of adjacent territories.[23,28] They are important routes for collateral flow, especially in times of acute vascular occlusion. Such connections display variable configurations, including end-to-end and end-to-side anastomoses.[23,29] These arteriolar anastomoses join the MCA with both the anterior cerebral artery and posterior cerebral artery. Anastomoses from the anterior cerebral artery potentially supply the superior or anterior divisions of the MCA, with most collateral flow of posterior or inferior divisions of the MCA arising from the posterior cerebral artery.

In 1954, the seminal work of Vander Eecken[23] on 20 cadavers delineated the main characteristics of leptomeningeal anastomoses, and showed substantial variability in size, number, and location of these collaterals. Such great variability probably affects the results of anatomical studies and accounts for much of the controversy in correlative investigations of collateral function and age. Anastomoses also converge over the cerebellar convexities, where the distal branches of the posterior inferior cerebellar arteries, anterior inferior cerebellar arteries, and superior cerebellar arteries meet. The posterior meningeal artery might also provide collateral flow when posterior inferior cerebellar arteries are occluded.[30] Because of the symmetrical anatomy of posterior fossa structures, such anastomoses might allow collateral flow between cerebellar hemispheres and from proximal to distal aspects of the basilar distribution.

Two anatomical features unique to the cerebral circulation play a part in CBF regulation and might have a role in flow redistribution during ischaemic stroke.[31] In intracranial vessels, intimal cushions, which consist of smooth muscle cells, are located within the tunica intima and are especially prominent at arterial bifurcations.[31]

One of the putative functions of intimal cushions is the regulation of blood flow in cortical vessels. The extensive autonomic innervation in these regions might also be related to CBF regulation and the response to regional ischaemia.[32] The other anatomical structures that might be related to collateral flow are valve-like protrusions, formed from intimal folds,[33] which become more prominent with age.[34] Their physiological role is unknown, but they are more prominent in hypertensive animals, which suggests a role in cerebral autoregulation.[34]

Physiology of collateral blood flow regulation

Normally, CBF is regulated by the metabolic demands of the brain itself, which vary regionally and with activity. Although the precise mechanisms underlying cerebral autoregulation are not fully understood, the process seems to be mediated at several levels, including neurons, neuropil, and cerebral blood vessels.[35]

Blood flow is also regulated by intrinsic and extrinsic innervations of the blood vessels.[36,37] The intrinsic nerves originate mainly in the brainstem and are distributed predominantly on the parenchymal vessels, whereas the extrinsic nerves supply the vessels on the surface of the brain.[38] Stimulation of the sympathetic nerves, especially in the region of the locus coeruleus and parabrachial nucleus, causes a reduction in CBF and brain water permeability.[39,40] Stimulation of several other structures throughout the brainstem and cerebellum (dorsal medullary reticular formation, rostral ventrolateral medulla, dorsal raphe nuclei, and fastigial nucleus of the cerebellum) can result in vasodilation of cortical vessels.[37] Most work into intrinsic-innervation stimulation and its effects on blood flow has been done in animals and has not been replicated in human beings.[37] Because of the invasive techniques involved, use of such effects would be impractical in patients with acute stroke.

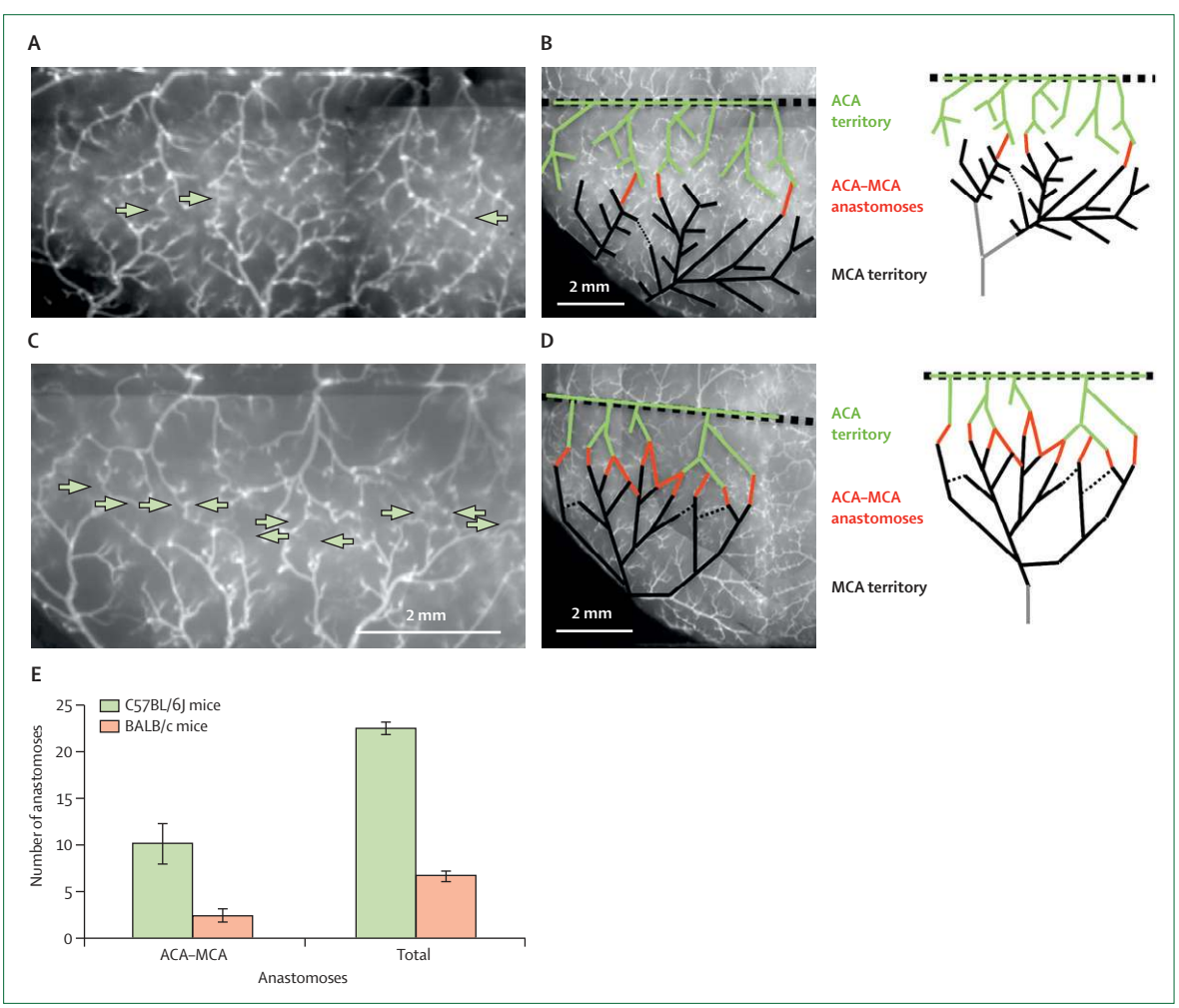

Figure 2: **Cortical pial collaterals between ACA and MCA vessels in C57BL/6J mice with robust collaterals versus BALB/c mice with fewer collaterals**
(A, C) The pial anastomoses are identified by arrows. (B, D) A colour vessel-tracing technique was used to quantify the pial collateral connection in mice with robust collaterals (C57BL/6J mice; D) and those with fewer pial collaterals (BALB/c mice; B). (E) Number of connections in the two stains. ACA=anterior cerebral artery. MCA=middle cerebral artery. Adapted from DeFazio and colleagues,[48] by permission of Springer.

Panel 1: Conditions that might adversely affect collateral status

- Congenital lack of collateral anatomy (ie, incomplete circle of Willis)
- Dehydration
- Hyperthermia
- Hyperglycaemia
- Increased blood viscosity
- Systemic infections
- Pulmonary compromise
- Cardiac failure
- Electrolyte and renal dysfunction
- Drugs that inhibit physiological augmentation of blood pressure (ie, high-dose antihypertensives)*
- Widespread cerebral atherosclerosis

*Some vasodilatory antihypertensives, particularly nitric oxide donors, might enable collateral flow.[50]

	Modality	Grading system	Comments
Kucinski et al[25]	Cerebral angiography	1 (good): ≥3 MCA branches (retrograde filling) 2 (poor): <3 MCA branches	Small series; scoring system not validated
Higashida et al[59]	Cerebral angiography	0: no collateral vessels filled 1: slow collateral filling to periphery 2: rapid collateral filling to periphery 3: collaterals with slow but complete flow in ischaemic bed 4: rapid and complete flow in entire ischaemic territory	Scoring system not validated
Miteff et al[9]	CT angiography	1 (good): entire MCA distal to occlusion reconstituted with contrast 2 (moderate): some branches of MCA reconstituted in Sylvian fissure 3 (poor): distal superficial branches reconstituted	Large thrombolysis series; excellent outcome in patients with good collaterals
Maas et al[60]	CT angiography	1: absent 2: less than contralateral side 3: equal to contralateral side 4: greater than contralateral side 5: exuberant	Large series from two centres; scoring system not validated
Tan et al[61]	CT angiography	0: absent 1: <50% collateral MCA filling 2: >51–99% 3: 100%	Small series; clot volume also calculated; scoring system not validated
Lee et al[62]	MRI, magnetic resonance angiography	Distal hyperintense vessels on FLAIR MRI 1: absent 2: subtle 3: prominent	Small series; all patients had proximal MCA occlusion; prominent hyperintense vessels predicted good outcome; scoring system not validated
Silvestrini et al[63]	Transcranial doppler	Collateral supply inferred by direction of flow in ophthalmic artery, anterior cerebral artery, and posterior cerebral artery Good: ≥2 vessels insonated Poor: ≤1 vessel insonated	Carotid dissection case series; good collateral flow associated with good prognosis; no validation study

MCA=middle cerebral artery. FLAIR=fluid-attenuated inversion recovery.

Table: **Collateral vessel grading systems by study**

Clinical trials are underway to assess the potential therapeutic value of stimulating the extrinsic parasympathetic innervations. The parasympathetic nerves arise from the superior salivatory nucleus and pass along cranial nerve VII to the sphenopalatine and otic ganglia.[41] Innervation of the carotid and intracerebral arteries is extensive, and several neurotransmitters (such as acetylcholine, vasoactive intestinal polypeptide, peptide histidine isoleucine, and nitrous oxide) are involved in vasodilation.[42,43] Stimulation of the sphenopalatine ganglion in rats, cats, and human beings results in an almost immediate vasodilatory response in the ipsilateral cerebral vessels.[44] This neurogenic response lasts as long as the stimulus is applied. The effect can be quite profound, with an increase in blood flow of more than 40% in the ipsilateral cortex.[44] Stimulation of the trigeminovascular system can also cause vasodilation of the ipsilateral cerebral vessels.[45] Stimulation of the sympathetic cervical nerves results in vasoconstriction.[37] However, few clinical data are available on the effects of manipulation of these extrinsic systems.

Studies in rodents have shown that there is much variation in collateral vessel density and diameter, and in their capacity to enlarge during ischaemia. In mice, genetic factors (especially *Vegfa* or *Clic4* expression) and environmental factors (eg, tissue oxygenation) might regulate collateral circulation.[46] Studies of permanent MCA occlusion in mice have shown that infarction size is significantly smaller in inbred mice with extensive collateral vessels than in those with fewer collaterals.[47] Number, length, and diameter of collateral vessels were inversely related to the volume of cerebral infarction.[47] In another study[48] of an MCA model, C57BL/6J mice, with good pial circulation, had significantly smaller cortical strokes than did BALB/c mice, with poor pial circulation (figure 2). The effect of growth factors on pial collateral circulation has not been investigated. Nevertheless, a study[49] of hind-limb ischaemia in mice showed that vascular endothelial growth factor plays an important part in collateral development.

Acute ischaemia and collateral perfusion

Systemic changes during acute stroke that compromise collateral recruitment

Collateral flow could restrict the extent of infarction in ischaemic stroke. However, the effectiveness of collateral flow varies greatly between patients. Several systemic factors might adversely affect recruitment of collateral vessels, resulting in extensive infarction (panel 1).

In thrombotic and embolic stroke, intravascular pressure distal to the occlusion falls immediately. Concurrently, pressure within the pial vessels is relatively well preserved, resulting in a gradient that can promote flow through anastomoses.[28] Animal studies[51,52] suggest that systemic blood pressure can affect the magnitude of this gradient and the ability to stimulate collateral recruitment. Induced hypotension in these animals results in neurological deficits, which can be reversed if systolic blood pressure is high.[51]

In a study of patients with acute ischaemic stroke,[53] a history of systolic hypertension at time of admission was associated with poor collateral circulation, and previous use of statins was linked to better collateral circulation. The investigators speculated that chronic hypertension might downregulate cerebral autoregulation, leading to poor collateral vessel development, whereas the use of statins could enhance new vessel development mediated by an increase in endothelial progenitor cell growth.[54] The functional compensatory capacity of collaterals might also diminish with age.[28] Atherosclerosis, especially intracranial disease, also results in vessel stiffening and could inhibit blood flow.[28]

Another factor that could have an important effect on the robustness of collaterals is the pace of occlusion. Gradual chronic occlusion—eg, progressive atherosclerotic internal carotid artery stenosis at the bulb, or neovascularisation that occurs in moyamoya syndrome[55]—allows compensatory collateral flow changes more often than does abrupt arterial occlusion. Severe intracranial arterial stenosis was also shown to be an important determinant of pial collateral circulation in the Warfarin Aspirin Symptomatic Intracranial Disease (WASID) trial.[56] Patients with mild-to-moderate intracranial stenosis did not have the same degree of pial collaterals.[57]

Imaging of collateral vessels

Although no ideal or specific imaging modality is available for demonstration and accurate measurement of the collateral circulation,[58] several techniques can provide insight into collateral flow in patients with ischaemic stroke (table). However, these methods measure the general status of collaterals and not actual anatomical connections. Furthermore, no techniques used to study cerebral collaterals have been systematically studied or validated.

Conventional digital subtraction angiography (figure 3) is referred to as the gold standard against which all other methods are compared.[7,64,65] It allows assessment of all three major collateral routes: extracranial–intracranial anastomoses, and Willisian and leptomeningeal collaterals. Reported studies have relied on rather rudimentary methods to assess collateral flow status. Kucinski and co-workers[25] deemed retrograde filling of three or more branches of the MCA up to the M2 segment to be evidence of good collaterals, whereas anything less was rated as poor (table). Higashida and colleagues[59] used a five-point scale to study collaterals that was based on a score endorsed by the American Society of Interventional and Therapeutic Neuroradiology and the Society of Interventional Radiology to study collateral status (table).

A few studies[9,53,60] have used CT angiography to score collateral status (figure 4, 5). In these investigations, the vasculature in the ischaemic hemisphere was compared with that on the unaffected side. The non-invasive nature of CT angiography and its rapid availability for patients with acute stroke makes it ideal for study of collateral status. Miteff and colleagues[9] used three categories for collateral status (table). Good collaterals were noted in 51 of 92 (55%) patients with proximal arterial occlusions,[9] moderate collaterals in 24 (26%), and poor in 17 (18%). The National Institutes of Health Stroke Scale (NIHSS) score was significantly lower in patients with good collaterals than in patients in the other two groups (NIHSS 16 *vs* 18, p=0·012). Robust collaterals as evident on CT angiography were associated

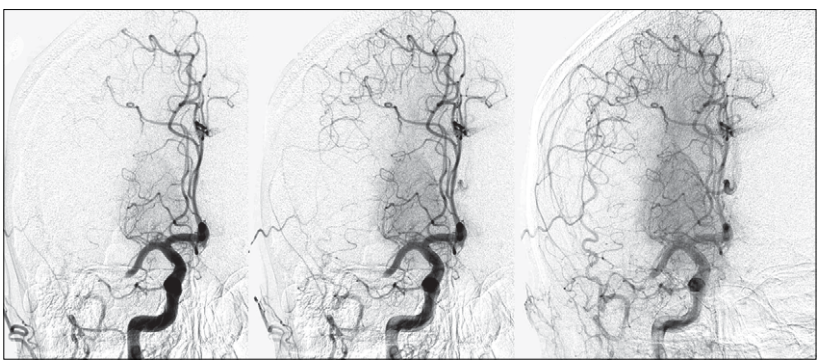

Figure 3: **Collateral flow viewed with cerebral digital subtraction angiography**
Acute right middle cerebral artery occlusion in a 63-year-old man with sudden onset of left hemiparesis, showing (from left to right) the temporal sequence of leptomeningeal collateral flow filling the ischaemic territory from the right anterior middle cerebral artery.

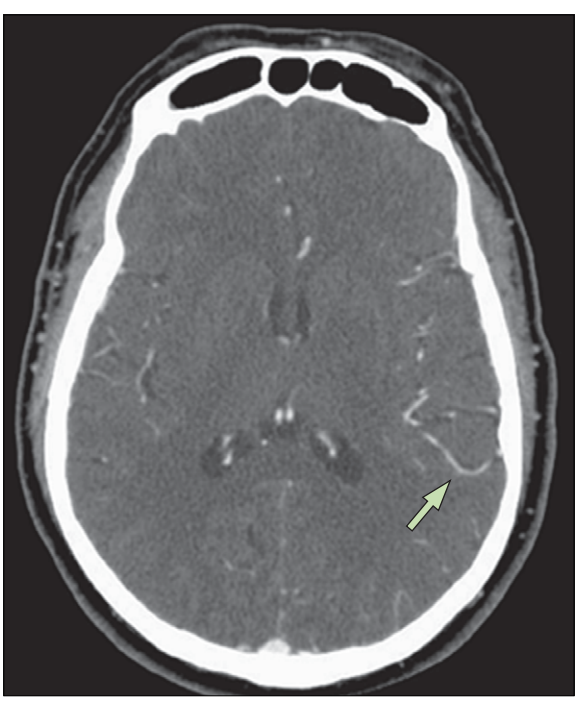

Figure 4: **Non-invasive imaging of collaterals viewed with CT angiography**
CT angiography source image showing robust collaterals filling the left middle cerebral artery territory from the ipsilateral posterior cerebral artery (arrow) in a 75-year-old woman with aphasia and right hemiparesis due to acute ischaemic stroke.

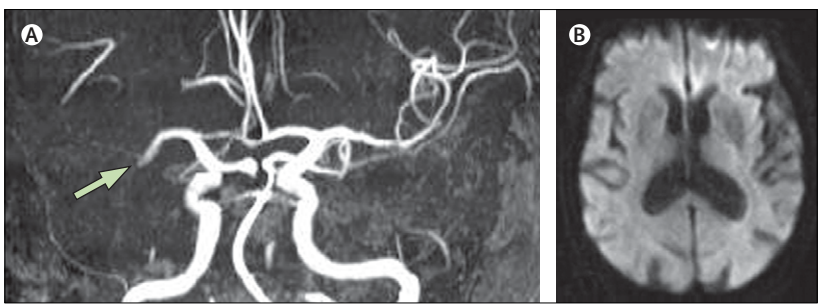

Figure 5: **Right middle cerebral artery occlusion with leveraged collateral flow**
Acute occlusion of the right middle cerebral artery (arrow) with collateral circulation in a 53-year-old man with left hemiparesis (A; viewed with CT angiography) averting any diffusion-weighted imaging evidence of ischaemic injury (B).

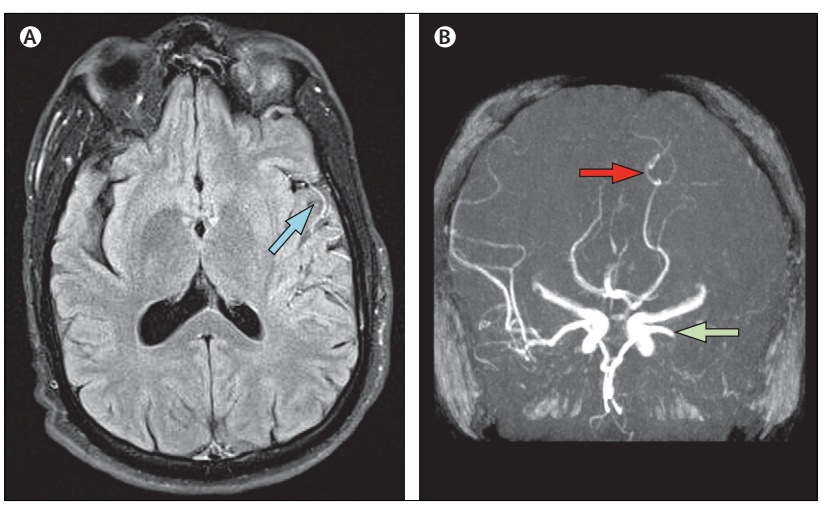

Figure 6: **Collaterals on MRI and magnetic resonance angiography**
(A) Fluid-attenuated inversion recovery (FLAIR) vascular hyperintensity in the distal left middle cerebral artery territory (blue arrow) resulting from slow collateral filling of an occluded left middle cerebral artery in a 48-year-old woman with aphasia due to acute ischaemic stroke. (B) Asymmetry and apparent elongation of the posterior cerebral artery (red arrow) ipsilateral to an acute occlusion of the left middle cerebral artery (green arrow) in a 73-year-old man with right hemiparesis and aphasia.

with smaller stroke size and better prognosis in patients with MCA occlusions.[9]

Maas and co-workers[60] graded collateral flow viewed with CT angiography using a five-point scale (table). The study[60] included 134 patients with acute stroke and MCA occlusion, and a comparison group of 235 patients with no occlusions. Investigators assessed the effects of collaterals on prehospital clinical fluctuations, size of the ischaemic stroke, and clinical worsening in the days after admission to hospital. Poor collaterals were evident in 38% of patients within 1 h of symptom onset and this value decreased to 12% of patients imaged 12–24 h after onset. There were no fluctuations in prehospital symptoms in patients with poor collaterals. However, in-hospital worsening of symptoms was four times more likely in patients with poor collaterals than in those with normal or exuberant collaterals.[60]

Magnetic resonance angiography has been used to grade collateral status and its relation to outcome.[62] Hyperintense proximal intracranial vessels on MRI obtained with fluid-attenuated inversion recovery (FLAIR) in patients with acute stroke are indicative of intraluminal thrombus.[62] However, distal hyperintense vessels have a serpentine appearance, and might be an indicator of slow retrograde collateral flow (figure 6), although this theory is open to debate. Of 52 patients assessed within 3 h of the onset of stroke with proximal intracerebral arterial occlusion (including M1: 22 patients; M2: 16 patients; and M3: 11 patients) prominent distal hyperintense vessels were evident in 46% of patients, and subtle distal hyperintense vessels in a further 27% of patients.[62] Patients with distal hyperintense vessels had smaller initial lesions, smaller 24-h and subacute lesions, larger diffusion–perfusion mismatch, and smaller final lesions viewed with diffusion-weighted imaging than did patients with no distal hyperintense vessels. Although the exact mechanisms underlying the smaller ischaemic lesions and the milder clinical defects at presentation are unknown, enhanced collateral blood flow could have contributed to the superior tissue status of these patients.[62]

Transcranial doppler (TCD) was used to investigate collateral blood vessels in a study[63] of 66 patients with cervical arterial dissection. Flow velocity was systematically measured within the ophthalmic, anterior, and posterior communicating arteries. Good collateral status was reported if two or all three vessels were recruited within 24 h of stroke onset (ie, flow diversion occurred) (figure 7). The researchers used TCD to judge collateral status within 24 h of a stroke secondary to carotid dissection (table), and showed how this non-invasive technique could help to establish the long-term prognosis in such patients.[63] 40 of 66 patients had good collaterals, and less than 5% of these patients had a score on the modified Rankin scale of more than 1 at 90 days, compared with 77% of patients with poor collaterals. Patients with good collaterals were younger, were more likely to be men, and had a lower NIHSS at time of admission than those with poor collaterals.

Collateral vessel assessment is inconsistent and often indirect in clinical practice. Although digital subtraction angiography provides excellent temporal and spatial resolution of collateral vessels, this invasive approach is not routinely used, especially in the acute setting. CT angiography shows the anatomical configuration of collateral vessels and is becoming more routine, but the low temporal resolution can result in overestimation of collateral flow. Conversely, the high sensitivity of magnetic resonance angiography might restrict its ability to detect leptomeningeal collaterals. TCD provides little information about collateral flow and only at the circle of Willis.

Effectiveness of collateral perfusion

The effectiveness of collateral vessel flow can be assessed only with measurements of tissue perfusion, which reflect the status of both the microcirculation and

macrocirculation. CT and MRI perfusion techniques provide insight into the collateral flow in patients with cerebrovascular disease. Physiologically effective collateral perfusion is evident when CBF and cerebral blood volume are maintained within the territory of the occluded artery. Additionally, time-domain perfusion parameters, such as time to peak, mean transit time, and T_{max} (time to peak of the impulse residue calculated with deconvolution algorithms), reflect the delay associated with perfusion via longer collateral routes. Delays in time to peak indicate regional collateral supply with high sensitivity. A common clinical scenario is carotid occlusion, when time to peak in the affected hemisphere is delayed, but CBF is maintained by collateral supply via the circle of Willis. Similarly, time to peak can be protracted in areas that are collaterally perfused via leptomeningeal vessels after MCA occlusion.

Delays in T_{max} and mean transit time are generally more limited in distribution than are those seen on time-to-peak maps, because of the correction for contrast bolus delays introduced by proximal stenoses or occlusions, but they still reflect collateral flow to the affected region. Although T_{max} theoretically shows only time taken to travel to the tissue bed and mean transit time is a measure of flow through the parenchyma, both are affected by microcirculatory and macrocirculatory changes in acute stroke.[66,67] Both of these parameters will therefore be altered in areas where collateral flow is present.

The most promising clinical application of perfusion imaging in acute stroke is in the identification of penumbral tissue to select patients for thrombolysis on the basis of pathophysiology.[68–73] The ischaemic penumbra is the tissue in which blood flow is decreased sufficiently to result in impairment of neuronal function, but is still adequate to temporarily maintain cellular integrity. It can therefore be thought of as a region of tissue with effective collateral perfusion. By contrast, areas in which irreversible injury has occurred—ie, the ischaemic core—will have little or no collateral perfusion. The definition of absolute thresholds for effective versus ineffective collateral perfusion is problematic, because they vary between patients, can be altered by treatment, and are time dependent.[74]

Even when perfusion-based penumbral imaging is not done, in some cases the presence of effective collateral flow can be inferred—eg, when parenchymal imaging studies show little infarction despite the presence of a severe clinical deficit on neurological examination.[75] This clinical–radiological mismatch probably occurs because blood flow diversion through good collaterals maintains tissue viability, although CBF is insufficient to conserve neuronal function. This discrepancy has been best studied with multimodal MRI of the brain. In a study by Dávalos and colleagues[75] of 166 patients with cortical cerebral infarction imaged within 12 h of symptom onset, such mismatch (defined as a clinical deficit of >8 on the NIHSS and a lesion viewed with diffusion-weighted imaging of <25 mL) was evident in 52% of patients. The frequency of mismatch was time dependent. Mismatch was evident in 74% of patients who presented to hospital within 3 h of symptom onset and decreased to 48% 3–6 h after onset and to 46% 6–12 h after onset, possibly because of collateral flow failure. In an investigation from Japan[76] that used mismatch criteria similar to those of Dávalos and co-workers,[75] clinical–diffusion mismatch was present in 35 of 87 patients assessed prospectively. Neurological deterioration was earlier in patients with mismatch than in those with no mismatch. However, as yet there is no evidence that mismatch results from flow through collaterals or that the progression of symptoms indicates collateral failure.

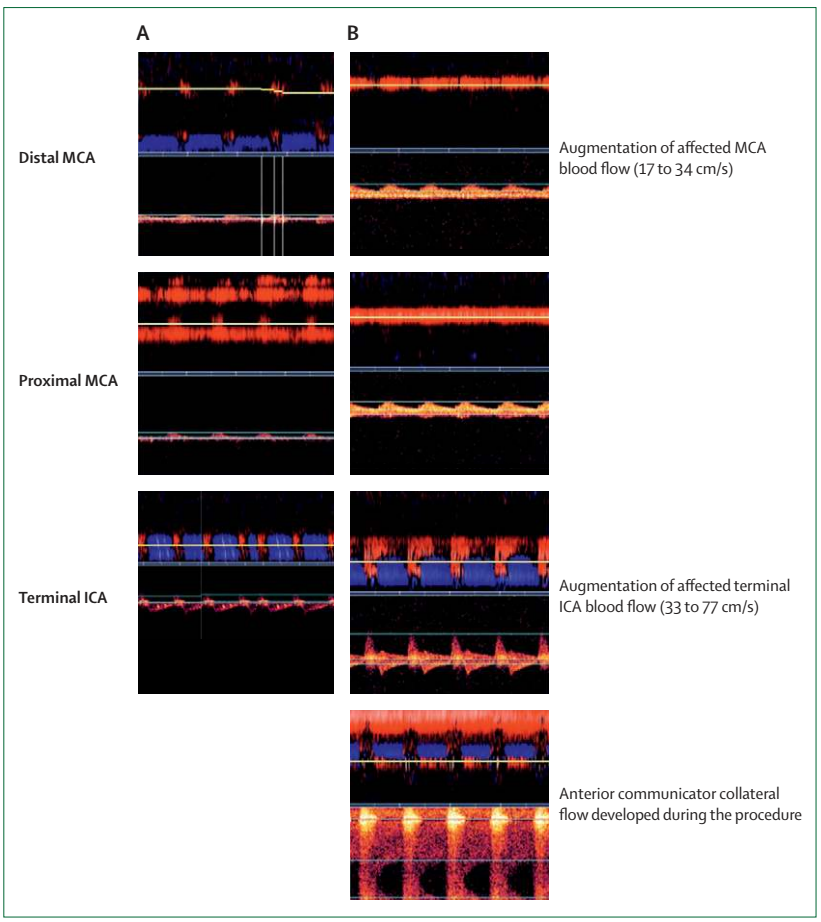

***Figure 7*: Blood flow assessed with transcranial doppler**
Increased MFV in the cranial blood vessels before (A) and after insertion of an aortic occlusion device (B) in a 63-year-old man with acute ischaemic stroke. MFV increased from 17 cm/s to 34 cm/s in the distal MCA, and from 33 cm/s to 77 cm/s in the terminal ICA. Additionally, anterior communicator flow was detected only after insertion of the aortic device. MFV=mean flow velocities. MCA=middle cerebral artery. ICA=internal carotid artery.

Clinical effect of collaterals in acute ischaemic stroke

The effect of collateral supply on tissue fate is best assessed in the context of occlusion site and reperfusion,

which can be accomplished only with serial multimodal imaging studies. In a series of 92 patients with proximal intracranial vessel occlusion assessed within 6 h of symptom onset, 55 patients had penumbral patterns visible on baseline CT perfusion scans.[9] The response to thrombolytic therapy was strongly related to the presence or absence of collateral vessels. A favourable response was described as a modified Rankin score of 0–2 at follow-up day 90. The primary objective of this study was to determine the positive predictive value of perfusion estimates on the outcome of acute ischaemic stroke. All patients with good collaterals and reperfusion (n=17) had a favourable response. Seven of 19 (37%) patients with good collaterals but no reperfusion had a positive response to treatment. Conversely, when imaging did not show collaterals in patients for whom reperfusion was established with thrombolysis (n=9), a favourable outcome was noted in only three (33%) patients. Finally, an absence of collaterals and persisting hypoperfusion (n=10) was associated with a poor outcome in all cases.[9]

The most recent study[53] of the relation of collateral circulation to prognosis prospectively assessed 196 patients with acute stroke and occlusions in large proximal intracranial vessels (distal carotid, and M1 and M2 branches of the MCA). A simple three-point scale was used to document collateral circulation viewed with CT angiography, collapsing the five-point scale used by Maas and co-workers.[60] Patients were assigned to groups with the following grades: less collateral circulation than on the contralateral side (score 1 and 2), equal to the contralateral side (score 3), and greater than on the contralateral side (scores 4 and 5). The Alberta Stroke Program Early CT (ASPECT) score was used to grade the infarction. Patients had follow-up assessments for 6 months after the acute event.[53] Of 196 patients, 60 received thrombolytic therapy. 45 patients (23%) were graded as having less collateral flow, 96 (49%) as equal, and 55 (28%) as greater when compared with the contralateral, unaffected side. The presence of leptomeningeal collaterals on CT angiography was associated with later infarction changes on admission non-contrast CT, shown by higher ASPECT scores.[52] Statistically fewer early deaths occurred in patients with equal (13%) or greater (13%) scores than in those graded as having less collateral circulation (33%; p=0·01). Similarly, patients with equal or greater scores had lower 6-month mortality than did those with lower collateral scores. In a multivariate analysis, younger age, lower baseline NIHSS score, the use of alteplase, and pattern of leptomeningeal collaterals (equal to or greater than the contralateral, unaffected side) were associated with a significantly better clinical outcome.[53]

Studies using multimodal MRI to image the early diffusion–perfusion deficits in acute stroke have shown similar results. In a study of interventional treatment used in 44 patients with acute stroke,[64] conventional angiography showed good collaterals in 17 (39%) patients, intermediate collaterals in 20 (45%), and poor collaterals in seven (16%). Infarction growth was assessed on repeat MRI studies 3–5 days after symptom onset. The degree of pretreatment collateral circulation was best correlated with infarction growth. In patients with good collaterals, the infarction grew slowly or not at all. The degree of collateral circulation had a positive effect on recanalisation therapy. None of the patients with poor collateral circulation had complete recanalisation. Compete recanalisation was evident in 25% of patients with intermediate collateral circulation and in 41% of patients with good collateral circulation. Successful recanalisation in the presence of poor collaterals often caused infarction growth. With multiple regression analysis, pretreatment collateral circulation was independently correlated with infarction growth.[64] A later study from the same researchers[10] showed that the presence of good collaterals significantly lowered risk of haemorrhage in patients requiring interventional therapy.

In a study of 111 patients (84 men) with occlusions of the intracranial vessels of the distal carotid, and M1 and M2 segments of the MCA,[25] cerebral angiography was used to assess collateral status. Most patients were treated with intra-arterial thrombolysis, and the Barthel index was used at 90 days to establish outcome. Collaterals were most frequently seen with M1 MCA occlusion, and were less frequent with distal carotid or distal M2 MCA occlusions. In patients with distal carotid occlusions, the presence of good collaterals was associated with a significantly improved outcome compared with no collateral supply (40% *vs* 8%, p<0·01). Similarly, in M1 and M2 MCA occlusions, the presence of collaterals was linked to better outcomes. Age, sex, CT evidence of early signs of infarction, presence of collateralisation, and treatment with thrombolysis and successful recanalisation were assessed for prognosis. The only significant parameter that was predictive of good outcome on logistic regression analysis was the presence of good collaterals.

Augmentation of cerebral blood flow in acute stroke

Supportive medical care for patients with acute stroke, including adequate hydration and the avoidance of wide fluctuations in blood pressure, can help to maintain collateral flow capabilities. Optimisation of systemic factors (panel 1) could help to minimise the risk of collateral failure, particularly in patients with proximal arterial occlusions. Several interventions aimed at increasing CBF via collateral vessel recruitment or stabilisation might be therapeutically useful in acute ischaemic stroke (panel 2). The rationale and evidence for these investigational therapies is summarised below. Before describing some of the therapeutic modalities that have been used to increase blood flow to the brain, it

Panel 2: Experimental techniques aimed at increasing cerebral blood flow

- Volume expansion with or without increased blood pressure
- Stimulation of the sphenopalatine ganglion
- Partial aortic occlusion
- External pressure cuffs
  - Lower-body positive-pressure application
  - Counterpulsation

is worth emphasising that large, randomised trials in appropriate patients with acute stroke have not been done. Plasma expanders,[20] vasodilators,[77] and induced hypertension[78] have all been assessed in small studies with varying results. So far, none has tested the effects of such interventions on the collateral blood vessels and collateral flow.

Volume expansion, vasodilators, and induced hypertension

Investigations with volume expanders and haemodilution date back to the 1960s. Early studies were not controlled and were underpowered, and patients were enrolled many hours to days after onset of symptoms. Dextran 40[79] and hydroxyethyl starch[80] were used as plasma expanders. No improvement in neurological outcome or reduction in mortality was recorded, although there was a non-significant reduction of deep venous thrombosis and pulmonary embolism. On the basis of the available evidence, the American Heart Association's 2007 guidelines[81] conclude that volume expansion or haemodilution is not recommended in patients with acute stroke.[79]

Drugs that cause cerebral arterial vasodilation could potentially increase blood flow to ischaemic tissue through collateral channels. In addition to being potent cerebral arterial vasodilators, methylxanthine derivatives (pentoxifylline, propentofylline, and pentifylline) inhibit platelet aggregation and the release of oxygen free radicals.[82] Small trials in which treatment was offered for 3–7 days have not shown any consistent benefit in neurological outcome.[77,83] Again, all trials were underpowered, and none specifically assessed the effect of the drugs on blood flow through collateral channels. The American Heart Association's 2007 guidelines advise against the use of vasodilators in acute ischaemic stroke.[81]

A rise in systemic blood pressure could improve blood flow to the brain, possibly through increased collateral flow. Although use of antihypertensives soon after ischaemic stroke might antagonise collateral flow, this idea has never been conclusively proven. Furthermore, the cerebral vasodilatory effects of some antihypertensives, particularly nitric oxide donors, might actually promote collateral flow.[50]

Studies in small numbers of patients have shown that an increase in blood pressure might reduce the penumbra as measured with SPECT imaging. In a retrospective assessment of a series of 30 patients, Rordorf and colleagues[84] reported that a third of patients with phenylephrine-induced hypertension showed neurological improvement. Treatment with phenylephrine was initiated within 12 h of symptom onset and continued for between 24 h and 6 days.[84] Wityk and Restrepo[78] studied patients treated within 12 h of symptom onset and used diffusion–perfusion MRI to guide therapy. Patients who benefited from therapy responded within an hour and showed a slow increase in diffusion deficits.[78] Again, studies were either non-randomised[84] or very small,[85] and the collateral status was not assessed. 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.[81]

Sphenopalatine ganglion stimulation

Stimulation of the sphenopalatine ganglion activates the parasympathetic innervation of the intracranial blood vessels, which causes vasodilation and increased ipsilateral hemispheric blood flow.[86] The sphenopalatine ganglion is accessible from the oral cavity and is amenable to electrical stimulation.[44] Experiments in animal focal ischaemia models have shown that stimulation of this ganglion increases blood flow and reduces infarction volume.[87,88] Treatment effects have been shown by functional behavioural tests, MRI measures of infarction volume, and histological studies.[87,88]

The feasibility and usefulness of sphenopalatine ganglion stimulation in patients with ischaemic stroke is being investigated. An open-label pilot study[89] indicated that the treatment seems to be well tolerated in patients with acute stroke. A multicentre randomised controlled trial of sham versus actual sphenopalatine ganglion stimulation will begin shortly (ClinicalTrials.gov number NCT00826059).

Partial aortic occlusion

Augmentation of blood flow to the brain by the restriction of abdominal aortic blood flow was initially tested in animals in the late 1980s. Temporary occlusion of the abdominal aorta in rodents with embolic stroke reduces infarction volume when used alone and in combination with alteplase.[90] The microvasculature of the brain was also assessed with double-staining techniques that showed 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 (suprarenal and infrarenal) has been developed for use in patients with acute stroke (NeuroFlo, CoAxia, USA; figure 8). The device is safe in patients treated up to 24 h after symptom onset.[16] The NeuroFlo catheter has also been tested in patients

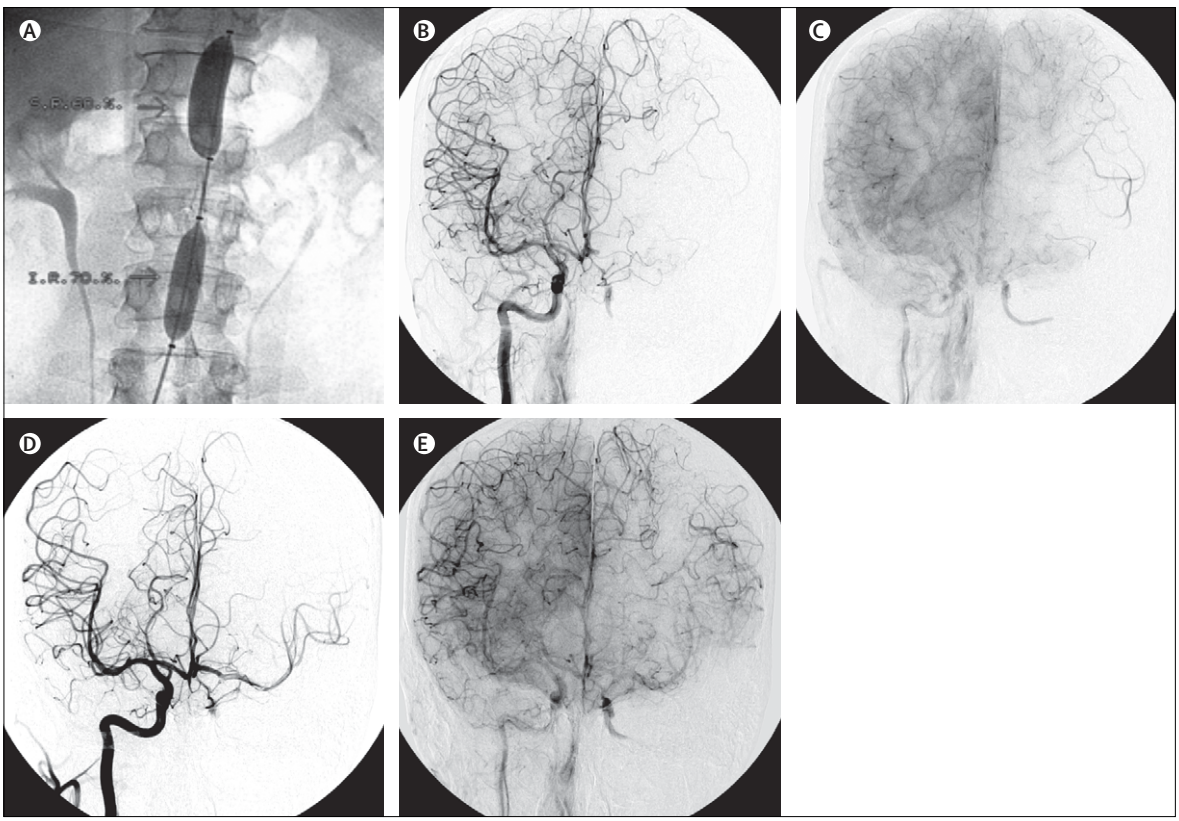

Figure 8: **NeuroFlo catheter**
(A) NeuroFlo balloon catheter inflated in the aorta (suprarenal and infrarenal locations) of a 50-year-old patient with acute ischaemic cortical left hemisphere stroke secondary to occlusion of the left internal carotid artery. (B,C) Angiogram through a right carotid injection before insertion of the balloon catheter. No blood flow is evident in the vessels on the left side. (D, E) Collateral diversion of blood to the left middle cerebral artery from the right side, probably secondary to the opening of collateral channels as the aortic balloons were inflated.

initially treated with intravenous alteplase, and it does not seem to be associated with an increased risk of haemorrhagic transformation.[91] However, the SENTIS trial,[21] which included 515 patients enrolled within 14 h of symptom onset, did not show a clinical benefit of the device compared with standard medical therapy.[21] Better outcomes were reported in patients with moderate deficits at onset (as measured on the NIHSS) who were treated early, and in those older than 70 years.[21] This study probably did not have the power to show a clear clinical benefit, which is likely to be small in unselected patients treated well after symptom onset. It remains possible that this approach is effective in patients with persisting penumbral tissue before treatment onset. Future trials of this and other interventional therapies will benefit from careful patient selection.

External compression devices

Experiments in dogs have shown that CBF can be increased with intra-aortic counterpulsation.[92] Blood flow can also be diverted from the capacitance vessels in the lower limbs with external compression. Although this less invasive intervention might increase CBF, its effects on collateral flow have not been established. Antigravity suits[93] and external counterpulsation[94] have been assessed in a few patients with acute or subacute stroke. These simple interventions seem to be safe, but there are no data to lend support to their use outside clinical trial settings.

Conclusions

In acute stroke, the severity of ischaemia determines how fast brain tissue might sustain irreversible damage. Pial collaterals, if well developed, might allow protracted tissue survival in the event of a proximal

Search strategy and selection criteria

We searched Medline for all reports related to acute ischaemic stroke in which imaging techniques were used to measure collateral flow. We used "stroke", "ischemia", "collaterals", "circle of Willis", and "brain imaging" as search terms. We included reports from Jan 1, 1980, to July 31, 2011. Only papers published in English and German were considered. Additionally, we carefully examined the reference section of relevant reports to ensure that we had not missed any important previous references pertinent to this Review.

occlusion of a large intracranial blood vessel. Imaging of collateral blood flow is challenging, but multimodal CT and MRI techniques (perfusion combined with vessel imaging) seem to be the most promising methods for the routine assessment and quantification of this important phenomenon. Research has shown that the presence of good collaterals leads to better clinical outcomes with intravenous and intra-arterial reperfusion therapy. Important advances in the imaging of collateral blood vessels and collateral blood flow will need to be followed by a rigorous assessment of the therapeutic value of techniques aimed at improving or maintaining collateral flow in patients with acute ischaemic stroke. Large, randomised controlled trials in appropriate patients have not been done, but this is an area of active research.

Contributors

AS conceived the idea, reviewed published studies, and prepared the first draft and subsequent revisions of the Review. KB and MS helped with the first draft and the review of published studies. AAM contributed to the search of published work and prepared the figures. DSL contributed to the initial concept, preparation of the first draft and subsequent revisions, and provided figure 1.

Conflicts of interest

AS discloses that the University of Alberta Hospital has received funding from CoAxia. AS was the principal investigator of the SENTIS study that was sponsored by CoAxia, is a member of the steering and expert committees of CoAxia, and is a consultant for Lundbeck, Bayer, CATOResearch, Photothera, and Merck. DSL is a consultant to Concentric Medical and CoAxia. KB, AAM, and MS declare that they have no conflicts of interest.

Acknowledgments

We thank Kath McKenzie for secretarial help; Khurshid Khan, Tom Jeerakathil, and Richard Camicioli (all Department of Medicine, University of Alberta, Canada) for insightful discussions; Richard Anthony DeFazio (Miller School of Medicine, University of Miami, USA) for providing original figures; and Harish Shownkeen (Neurosciences Institute, Central DuPage Hospital, Winfield, IL, USA) for providing the images for figure 7.

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