Haemodynamic stroke: clinical features, prognosis, and management

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Haemodynamic stroke is a type of ischaemic stroke that is caused by hypoperfusion rather than by embolism or local vasculopathy. It can be caused by systemic diseases such as heart failure or hypotension, but also by severe obstruction of the carotid or vertebral arteries. Patients with haemodynamic stroke or transient ischaemic attack might show specific clinical features that distinguish them from patients with embolism or local small-vessel disease. Ancillary investigations of cerebral perfusion can show whether blood flow to the brain is compromised and provide important prognostic information. Management of patients who have hypoperfusion as the major cause of ischaemic stroke or as a contributing factor is hampered by the lack of clinical trials. Treatment aimed at increasing cerebral blood flow might be considered in selected patients on the basis of information from case series. Further research is needed to define criteria for the diagnosis of haemodynamic stroke and to investigate treatment options in controlled studies.

Introduction

The term haemodynamic stroke has traditionally been used for ischaemic stroke caused by hypoperfusion and not by emboli or by local vasculopathy as in lipohyalinosis. Hypoperfusion can result from a drop in blood pressure—either regional, caused by severe obstruction of an artery, or systemic (eg, heart failure or systemic hypotension). Occlusion of arteries by emboli (eg, from the heart or atherosclerotic plaques in the internal carotid artery [ICA]), or secondary to lipohyalinosis as in lacunar stroke, also results in hypoperfusion distal to the blocked vessel and subsequently leads to a brain infarct. The feature that distinguishes haemodynamic transient ischaemic attack (TIA) and stroke from other stroke subtypes is that blood flow towards part of the brain is too low and results in ischaemia in an area of the brain or retina that is at a distance from the blocked vessel. When cerebral blood flow (CBF) is chronically marginal and no longer sufficient to meet the oxygen requirement of the brain tissue, the amount of oxygen that is extracted from the blood (oxygen extraction fraction) can increase, a condition known as “misery perfusion”.

Up to the mid-1980s, hypoperfusion was thought to be a major cause of ischaemic stroke, but in subsequent decades, thromboembolism became the main culprit in stroke aetiology. In recent years, the debate on hypoperfusion as a cause of stroke has intensified, although two issues that are crucial to the settling of this debate remain. First, there is no gold standard for the diagnosis of haemodynamic stroke. Second, in many patients, low perfusion pressure and embolism might interact to cause ischaemic stroke because both the location of the hazardous lodging of emboli in the brain-supplying arteries and their clearance might depend on the flow state of the brain. In recent years, important information has become available on clinical symptoms that might point to haemodynamic compromise and that affect prognosis, as well as on diagnostic tools to obtain information on the flow state of the brain. Recognition of hypoperfusion as a causal factor in ischaemic stroke, separately or as a contributing factor in embolic stroke, could have important consequences for the care and management of patients, and should facilitate research directed at improving the flow state of the brain to improve outcome in patients with haemodynamic stroke. Here, we review haemodynamic stroke with respect to pathophysiology, clinical manifestations, diagnostic investigations, prognosis, and management.

Pathophysiology

Several factors might contribute to the haemodynamic cause of stroke, either alone or in combination. Both structural changes in the cerebropetal arteries and systemic abnormalities associated with arterial pressure or with blood volume might play a part.

Carotid artery obstruction

In hospital-based series, about 9% of patients with a TIA or ischaemic stroke have complete occlusion of the ICA. In 146 patients with symptomatic ICA occlusion, ICA (85%) had only transient symptoms or a partial anterior circulation infarct. In the first days after the ICA occlusion occurs, propagation of the thrombus might be observed. Thromboembolism might be the main cause of an actual obstruction of the ICA and associated ischaemic stroke, but emboli from the heart or atherosclerotic lesions in proximal arteries can no longer reach the brain via the ICA when this artery is occluded. Nevertheless, some have suggested that emboli might arise from the distal or proximal stump of the occluded ICA even as long as 2 years after the ICA was found to be occluded. Plaques in the common or external carotid artery (ECA), or in the contralateral ICA, might be alternative sources of emboli that travel via collateral pathways to the hemisphere distal to the ICA occlusion. By contrast, others have favoured low perfusion pressure as the most common cause of cerebral ischaemia in patients with ICA occlusion. This haemodynamic hypothesis is supported by clinical observations that symptoms can occur in circumstances in which blood pressure is temporarily low, such as after rising from a sitting or supine posture or after the introduction of...
antihypertensive drugs.24,25 Evidence is accumulating to suggest that patients with ICA occlusion with a TIA or minor disabling ischaemic stroke associated with compromised CBF have a higher risk of future stroke than if they have a normal haemodynamic brain state.26,27

Hypoperfusion might also contribute to signs or symptoms in patients with severe ICA stenosis. The efficacy of carotid endarterectomy to prevent recurrent stroke in these patients might be largely dependent on removal of the embolic source,28,29 but re-establishing normal flow through the vessel might also contribute. In patients with symptomatic severe stenosis who were randomly assigned to receive medical treatment in the European Carotid Surgery Trial or North American Symptomatic Carotid Endarterectomy Trial and who had a contralateral severe ICA stenosis or occlusion, low blood pressure at baseline was associated with an increased risk of stroke over time.20

A rare cause of haemodynamic stroke associated with progressive stenosis of the intracranial ICA and its proximal branches is moyamoya disease, which is reviewed elsewhere.21,22

Vertebral artery obstruction

By contrast with haemodynamic stroke related to the anterior circulation, information on haemodynamic stroke from stenosis or occlusion of the vertebral arteries is scarce. In a large registry of 407 patients with posterior circulation stroke, haemodynamic compromise was thought the most likely cause in 132 (32%) patients, but clear criteria for this diagnosis were not given.23

One study showed an impaired response of the basilar artery to a vasodilatory stimulus in patients with vertebrobasilar ischaemia, which was interpreted as exhausted autoregulation.24 Others studied patients with severe bilateral vertebral artery disease and found impaired autoregulation and an increased dependency on systemic blood pressure for the flow through the posterior cerebral artery after tilting.25 Whether a low flow state of the brain supplied by the posterior circulation is a predictor of recurrent stroke in patients with vertebral artery stenosis or occlusion has not yet been studied.

Low blood pressure

Another cause of haemodynamic stroke is a drop in blood pressure during hypovolaemia or during anaesthesia. A haemodynamic TIA or ischaemic stroke might also be induced by changes to upright posture, or by treatment with antihypertensive medication.25 In 98 patients who underwent diffusion-weighted MRI after cardiac surgery, 47 (48%) had bilateral ischaemic lesions in the borderzone areas, and this was particularly likely in those who had a decrease in mean arterial pressure of at least 10 mm Hg during surgery.26 Symptoms of orthostatic hypotension have been shown to be an independent predictor of ischaemic stroke.27 The prevalence of ischaemic stroke is increased in patients with heart failure, particularly in patients with low systolic blood pressure.28 In these patients, hypoperfusion and embolism might interact because poor contraction of the heart might also result in thromboembolism, and at autopsy, cholesterol crystal emboli have been found in the arterial borderzones in patients who died after cardiac surgery.29,30 A recent cohort study of observational data showed that not only mean arterial blood pressure but also visit-to-visit variability in blood pressure and maximum systolic blood pressure are

Panel 1: Factors to be considered when treating patients with haemodynamic transient ischaemic attacks or ischaemic stroke associated with internal carotid artery occlusion

When taking the history, specifically check for the following:

- Limb shaking
- Precipitating circumstances of symptoms:
  - rising from a supine position
  - exercise
  - transition from a cold to a warm environment
  - having just consumed a meal
  - coughing
  - administration of antihypertensive drugs, or intensifying their dosage, or administration of other drugs that might lower blood pressure (eg, sildenafi)
  - bleeding
  - anaemia
- Episodes of loss of consciousness
- Monocular loss of vision after looking into bright light (retinal claudication)
- Gradual deterioration of vision of one eye, with or without pain around the eye
- Signs of cognitive impairment

Diagnostic studies

- Check for orthostatic hypotension
- On brain imaging, look for borderzone infarcts, particularly the internal borderzone type
- If occlusion of the ICA is found in the acute phase of stroke, confirm permanent occlusion several days later, because an initially occluded ICA might turn out to be a severe stenosis amenable to endarterectomy several days later
- Consider contrast angiography to assess collateral blood flow pathways and investigate presence of stenosis in arteries important for collateral blood supply
- Consider assessment of blood flow to identify patients at relatively high risk of recurrent ischaemic stroke
- Ophthalmological examination is valuable to check for venous stasis retinopathy and chronic ocular ischaemic syndrome, particularly in patients in whom the external carotid artery–ophthalmic artery collateral pathway contributes to the collateral blood supply of the hemisphere ipsilateral to the ICA occlusion

Prognostic factors

Features associated with a relatively low risk of recurrent ischaemic stroke:

- Retinal symptoms only, no symptoms of ischaemia of the brain
- No recurrence of symptoms after documentation of the carotid artery occlusion

Features associated with a relatively high risk of recurrent ischaemic stroke:

- Precipitating circumstances (rising, exercise, etc) of symptoms indicative of a haemodynamic cause of stroke
- Presence of leptomeningeal collateral blood supply from the posterior cerebral artery territory to the supply territory of the occluded ICA
- Compromised blood flow in the supply territory of the occluded ICA, most convincingly shown by an increased oxygen extraction fraction measured with PET

ICA=internal carotid artery
important predictors for recurrent vascular events.\textsuperscript{11} Patients with carotid or vertebral artery occlusion might be particularly vulnerable to a drop in blood pressure.\textsuperscript{14}

Anaemia
Anaemia can precipitate TIA and ischaemic stroke, especially in patients with severe carotid artery disease.\textsuperscript{12,13} In addition to the increased thrombogenesis elicited by anaemia, hypoxia caused by reduced haemoglobin concentration is likely to be hazardous to those parts of the brain in which cerebral perfusion is already compromised, such as the borderzone regions.\textsuperscript{15}

Clinical manifestations
In many patients with a TIA or ischaemic stroke, signs or symptoms do not allow distinction between haemodynamic failure and thromboembolism, but in some patients specific symptoms or precipitating factors are present that suggest a haemodynamic origin (panel 1).

Precipitating circumstances
Orthostatic hypotension,\textsuperscript{16} exercise,\textsuperscript{14} transition from a cold to a warm environment,\textsuperscript{12,13} consuming a meal,\textsuperscript{27–16} and coughing\textsuperscript{40} can lower the blood flow to the brain and precipitate TIA or stroke. In these circumstances, the decrease in CBF is probably caused by diversion of blood to other parts of the body. After coughing, cerebral arterial vasoconstriction induced by hypocapnia contributes in addition to the decreased venous return and a decrease in cardiac output caused by Valsalva’s manoeuvre.\textsuperscript{39}

In patients with ICA occlusion, Hankey and Gubbay\textsuperscript{15} reported that administration of antihypertensive drugs can provoke recurrent TIAs and ischaemic stroke, which is consistent with our own experience (unpublished). We have treated patients with ICA occlusion who had had recurrent TIAs after use of sildenafil. This phenomenon has also been described in the absence of stenosis of extracranial or intracranial vessels,\textsuperscript{41} and is thought to result from the hypotensive effect of sildenafil.\textsuperscript{42}

Limb shaking
About 10% of patients with symptomatic ICA occlusion complain of spells of involuntary, coarse movements of an arm or leg, which can occur separately or simultaneously. This limb shaking usually lasts for less than 5 min, is often accompanied by paresis of the involved limb, and might be precipitated by rising or exercise.\textsuperscript{43–45} Limb-shaking TIAs can resemble partial epileptic seizures, but electroencephalograms during attacks have not shown epileptiform activity.\textsuperscript{44,46} In patients with ICA occlusion, limb-shaking TIAs are associated with a poor haemodynamic state of the brain and with a relatively high risk of recurrent ischaemic stroke.\textsuperscript{45,47}

Transient loss of consciousness without focal symptoms
In general, loss of consciousness without focal symptoms is not considered a sign of TIA or ischaemic stroke, but exceptionally it can be the only manifestation of compromised CBF in patients with severe stenosis or occlusion of multiple cerebropetal arteries.\textsuperscript{40,48,49} ICA occlusion should be suspected in patients with cough syncope without lung disease,\textsuperscript{40} and has also been reported after consuming a meal.\textsuperscript{49} Case reports have documented cessation of symptoms after operative revascularisation.\textsuperscript{44,45}

Retinal claudication
Patients with ICA occlusion might complain of transient monocular blindness after exposure to bright light. This retinal claudication is thought to result from increased metabolic demand in the retina that cannot be met because of already marginal perfusion.\textsuperscript{12,13} Retinal claudication is a rare finding,\textsuperscript{6} but is highly suggestive of carotid artery occlusive disease.

Chronic ocular ischaemic syndrome
Carotid artery occlusion can cause progressive loss of vision of one eye that is sometimes accompanied by pain around the eye. This chronic ocular ischaemic syndrome
(COIS) is the result of long-term hypoperfusion of the retina. As a result, neovascularisation of the retina, the optic disc, or the iris (rubeosis iridis; figure 1) can develop. Cotton wool spots (oedema of the optic disc or the macula) can also be found. These signs and symptoms can develop into a uveitis-like syndrome with neovascular glaucoma and blindness. In particular, rubeosis iridis has been associated with a loss of vision.\(^5\) The early, often asymptomatic stage of COIS is called venous stasis retinopathy (VSR) and is characterised by dilatation, irregular calibre, and tortuosity of retinal veins, midperipheral microaneurysms, and small dot and blot intraretinal haemorrhages or nerve-fibre-layer splinter haemorrhages (figure 1).\(^5\) VSR is present in around a third of patients with a TIA or minor disabling ischaemic stroke associated with ICA occlusion; progression to clinically manifest COIS is rare.\(^5\)

**Cognitive impairment**

Chronic hypoperfusion of the brain has been recognised as a cause of cognitive impairment since 1951.\(^5\) Reversibility of cognitive impairment after extracranial–intracranial bypass surgery has been reported in a 55-year-old patient with bilateral ICA and unilateral vertebral artery occlusion, severely reduced CBF, and impaired vascular reactivity.\(^5\) In a study of 39 patients with TIA associated with ICA occlusion, we found that about half of the patients had cognitive deficits.\(^5\) Impairment was global rather than limited to certain cognitive domains, and was relatively mild. These cognitive deficits were also found in patients who had presented with eye symptoms only and in patients with a cerebral TIA in whom no structural lesion was found on brain MRI.\(^5\)

**Diagnostic investigations**

Although there is no gold standard for the diagnosis of haemodynamic stroke, diagnostic tests could provide information on whether haemodynamic compromise is likely to play a part and on the risk of recurrent ischaemic stroke. Diagnostic studies to be considered in patients with a haemodynamic TIA or mildly disabling ischaemic stroke associated with ICA occlusion are summarised in panel 1.

**Pattern of infarcts**

Classically, infarcts in the borderzones between the vascular territories of the major cerebral arteries have been associated with a haemodynamic cause. In particular, internal borderzone infarcts (infarcts between the deep and superficial arterial system of the middle cerebral artery [MCA], or between the supply territories of the anterior cerebral artery and MCA, located in the white matter along or above the lateral ventricle in a so-called “rosary-like” pattern; figure 2) have been attributed to haemodynamic failure\(^6\) and severe carotid artery occlusive disease.\(^6\)

In individual patients, diagnosis of a borderzone infarct according to the location of the lesion on brain imaging is hampered by the large variability in the supply territories of the major cerebral arteries.\(^6\) A recent selective arterial spin-labelling MRI study showed that this variability is largely dependent on anatomical variation in the circle of Willis.\(^6\) Of 11 patients with proven haemodynamic failure and recurrent stroke, only three had borderzone infarcts, whereas six had territorial infarcts (the type of infarct was undetermined in one patient, and another had a retinal infarct).\(^6\) This suggests that haemodynamic compromise and emboli might act together to cause infarction, even when the infarct appears to be caused by an embolus on CT or MRI.

**Collateral blood flow**

In patients with a TIA or minor disabling ischaemic stroke of suspected haemodynamic origin, study of collateral pathways can contribute to treatment decisions (see below). In patients with ICA occlusion, the relative contribution of the contralateral ICA, the ipsilateral ECA, and the vertebral arteries to the collateral blood supply should be assessed (figure 3). If the collateral blood supply is highly dependent on the ipsilateral ECA, particular attention should be paid to the development of VSR and COIS.\(^5\) A poor haemodynamic state of the brain has been associated

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**Figure 2: Rosary-like pattern of infarcts**

Left-hemisphere internal borderzone infarct between the deep and superficial arterial system of the middle cerebral artery in the white matter above the lateral ventricle in a rosary-like pattern on fluid-attenuated inversion recovery MRI in a 57-year-old woman with left common and internal carotid artery occlusion, who had frequent (>10) recurrent transient ischaemic attacks of the left hemisphere (dysphasia, right sensory symptoms, and mild weakness of the right arm) and recurrent transient monocular blindness of the left eye.
with the presence of collateral blood supply via the ECA and ophthalmic artery, or leptomeningeal pial branches from the posterior cerebral artery extending as far as the vascular territory of the MCA or anterior cerebral artery, although other studies did not show an association between collateral blood flow pattern and misery perfusion. In a prospective follow-up study of 117 patients with symptomatic ICA occlusion, the presence of leptomeningeal collateral blood supply from pial branches of the posterior cerebral artery on digital subtraction angiography independently predicted recurrent TIA or stroke (hazard ratio 4.1, 95% CI 1.3–13.1).

Contrast angiography might add valuable information in patients with ICA occlusion whose symptoms persist after documentation of the ICA occlusion. The less invasive procedures of CT angiography and magnetic resonance angiography can be used to determine the contribution of the anterior and posterior communicating arteries, but not the contribution of the ophthalmic artery and leptomeningeal collaterals. Stenosis in the contralateral ICA and ipsilateral ECA can be overestimated by duplex sonography and by magnetic resonance angiography in the presence of ICA occlusion.

A promising new, non-invasive technique to assess the relative contribution of collateral blood flow pathways is selective arterial spin-labelling MRI, which has been successfully applied to determine the importance of the ophthalmic artery collateral pathway in patients with ICA occlusion.

Haemodynamic measurements

Evidence of compromised CBF can be obtained with various techniques, including transcranial doppler, stable xenon or 133Xe CT, N-isopropyl-123I-iodoamphetamine single-photon emission computed tomography, PET, and more recently, CT and MRI perfusion techniques. Most of these are based on assessment of the autoregulatory response to a vasodilatory stimulus such as breath holding, inhalation of carbogen, or intravenous administration of acetazolamide. Haemodynamic compromise stage 1 is defined as failure of CBF or CBF velocity to increase in response to a stimulus, because vasodilatation has already reached its maximum. If cerebral perfusion decreases further, normal cerebral oxygen metabolism is maintained by increasing the amount of oxygen that is extracted from the blood (haemodynamic compromise stage 2), a phenomenon that can be measured only with PET. Direct comparisons of various techniques have shown that different modalities do not always identify the same patients at risk of recurrent stroke, and therefore methods are not interchangeable.

Haemodynamic compromise has been associated with a high risk of recurrent stroke, the evidence being strongest for stage 2. The risk of recurrent stroke for patients with symptomatic ICA occlusion and an increased oxygen extraction fraction is about six to seven times higher than for patients in whom the oxygen extraction fraction is within the normal range.

Figure 3: Collateral pathways in a patient with haemodynamic transient ischaemic attacks and chronic ocular ischaemic syndrome associated with occlusion of the right internal carotid artery

Angiogram of a 73-year-old man who presented with repeated episodes of transient monocular blindness and retinal claudication of his right eye for 1 year. He also had recent symptoms of chronic ocular ischaemic syndrome on the right side, and one episode of left-sided facial weakness with dysarthria consistent with a right-hemispheric transient ischaemic attack. His angiogram showed occlusion of the right internal carotid artery (green arrow), severe stenosis of the right ECA (black arrow, A), and only limited filling of ACA branches on the right (arrows) via the anterior communicating artery without collateral blood supply to the right MCA territory (B). Selective catheterisation of the right central carotid artery showed collateral blood supply via the stenosed ECA and ophthalmic artery pathway to the right MCA (arrow) and to a lesser extent the ACA territory (C, anterior-posterior view; D, lateral view). Selective catheterisation of the left vertebral artery shows extensive collateral blood supply via leptomeningeal pial branches from the posterior cerebral artery towards the vascular territory of the MCA and ACA (arrows) without collateral blood supply via the posterior communicating artery (E, anterior-posterior view; F, lateral view). ECA=external carotid artery. ACA=anterior cerebral artery. MCA=middle cerebral artery.
**Ophthalmological examination**
Measurement of visual acuity, intraocular pressure, slit-lamp examination, and fundoscopy with emphasis on the early retinal signs indicative of VSR should be considered in all patients with symptomatic ICA occlusion, particularly if the ECA–ophthalmic artery collateral pathway contributes to the collateral blood supply of the hemisphere at risk. Distinction between VSR and diabetic retinopathy might be difficult, but asymmetry of retinal abnormalities and mid-peripheral haemorrhages along and outside rather than within the vascular arcades is a sign of severe carotid artery occlusive disease. In patients with COIS, progression to blindness might be prevented by early treatment with panretinal laser therapy, and if necessary with revascularisation procedures.

**Prognosis**
Prognosis in patients with haemodynamic stroke might vary according to clinical characteristics and results of diagnostic tests (panel 1).

**Carotid artery occlusion**
In patients with a TIA or mildly disabling ischaemic stroke associated with ICA occlusion, the risk of recurrent ischaemic stroke is 5–6% per year; about two-thirds of strokes occur ipsilateral to the previously symptomatic ICA occlusion. If haemodynamic compromise can be shown, this risk is approximately two times higher, and is probably highest in the first 1–2 years after the ischaemic event. The risk of recurrent ischaemic stroke is lower in patients with only symptoms of the eye and not of the brain. In a prospective follow-up study of patients with symptomatic ICA occlusion, we found that only one of the 24 patients who presented with eye symptoms alone had an ischaemic stroke during an average period of 10 years. The risk of recurrent infarction is relatively high in patients who have clinical features suggestive of haemodynamic compromise such as limb shaking or symptoms after rising or exercise, and in patients in whom TIAAs continue after the occlusion of the ICA was shown.

**Vertebral artery occlusive disease**
Little is known about the prognosis of patients with cerebral ischaemia of presumed haemodynamic origin in association with vertebral artery stenosis or occlusion. A systematic review showed that the risk of subsequent stroke in patients with a vertebrobasilar TIA or mildly disabling ischaemic stroke was similar to that after carotid artery territory events. This comparison did not include information on the presence of stenosis or occlusion in either the carotid or vertebral artery. However, more recently, the results of a study of 50 patients with a vertebrobasilar TIA or mildly disabling ischaemic stroke suggested that low flow in the basilar artery and posterior cerebral arteries determined by quantitative flow measurements with magnetic resonance angiography is predictive of recurrent ischaemic stroke.

**Management**
To date, no randomised controlled trials (RCTs) of treatment options for patients with signs or symptoms of presumed haemodynamic origin are available to guide treatment. As with patients with TIA or ischaemic stroke in general, antithrombotic agents should be administered and hyperlipidaemia and diabetes mellitus should be rigorously controlled. Cessation of smoking should be actively pursued. Only the management of blood pressure might be different (panel 2).

**Non-surgical treatment**

**Blood pressure control**
Because clinical manifestations of cerebral ischaemia can be precipitated by the lowering of blood pressure in patients with occlusive arterial disease, treatment of hypertension in patients with a TIA or ischaemic stroke of presumed haemodynamic origin should be done with caution, particularly in the acute phase. Sometimes hypertension should not be treated, and it might even be necessary to increase the blood pressure. In our experience and that of others, tapering of antihypertensive drugs can result in cessation of recurrent TIAs in patients with ICA occlusion and haemodynamic TIAs. In individual cases, we have sometimes had to accept systolic blood pressures as high as 200 mm Hg, at least temporarily.
In the chronic phase, we advise control of blood pressure in the same way as for patients with TIA and stroke in general. Because patients with haemodynamic TIA and ischaemic stroke might be particularly vulnerable to changes in blood pressure, calcium-channel blockers might be preferred over other classes of antihypertensive drugs to avoid fluctuations in blood pressure.31

**Bed rest**

In patients with recent and multiple ischaemic events precipitated by rising, we suggest bed rest for a few days. If the symptoms have not recurred in the meantime, we then generally advise the patient to gradually resume sitting positions, standing, and walking over several days. This approach has never been tested in an RCT.

**Revascularisation surgery**

**Extracranial–intracranial bypass**

Superficial temporal artery (STA)–MCA bypass does not prevent recurrent ischaemic stroke in patients with TIAs or minor stroke associated with ICA occlusion or MCA stenosis, or occlusion in general.86,87 A new bypass trial, the Carotid Occlusion Surgery Study, began in 2002 and addresses the question of whether the STA–MCA bypass can prevent recurrent ischaemic stroke, at least in a subgroup of patients with recently symptomatic ICA occlusion and documented misery perfusion, as determined by an increased oxygen extraction fraction on PET.88 On June 24, 2010, the trial was stopped early by the US National Institutes of Health; results have not yet been published. The results of a Japanese trial have provided evidence for a beneficial effect of the STA–MCA bypass in 196 patients with ICA or MCA occlusive disease and haemodynamic cerebral ischaemia according to quantitative CBF.89 The second interim analysis showed that five surgically treated patients had a recurrent stroke versus 14 patients who were treated medically (p=0.046).90 The final results have not been published in the English literature. The complication rate for fatal or major stroke after STA–MCA bypass surgery in the Extracranial–Intercranial Bypass Study was 3–1% or 4–5%, excluding or including strokes that occurred while waiting for surgery, respectively.91 Some observational series showed that this proportion is probably higher in patients who are neurologically unstable (12%).91 or who have recurrent symptoms and a compromised CBF (14%).90

The Excimer laser-assisted non-occlusive anastomosis (ELANA) extracranial–intracranial bypass is a laser-assisted bypass procedure that enables the construction of an anastomosis with the distal ICA or proximal MCA or anterior cerebral artery, without the need to temporarily clamp the recipient vessel.92,93 This technique results in a bypass with a higher flow than can be achieved with the conventional STA–MCA technique,94 and in theory might better protect against future ischaemic stroke. An RCT to determine the efficacy of the ELANA bypass in prevention of stroke has not yet been done.

According to current clinical standards, STA–MCA or ELANA bypass operations to prevent ischaemic stroke in occlusive arterial disease should ideally be performed only in the context of a clinical trial. Nevertheless, while we await the results of the Carotid Occlusion Surgery Study, we occasionally consider STA–MCA or ELANA bypass surgery in patients with extracranial ICA occlusion and continuing ischaemic events in whom the arguments for a haemodynamic cause are compelling and in whom there are no other treatment options.95 These patients are informed that the benefit of the operation has not yet been proven.

In patients with COIS, the efficacy of bypass surgery in addition to medical therapy and panretinal photo-coagulation to prevent progression to blindness is uncertain. Disappointing and good results have been reported.96–99 In patients with cognitive deficits associated with ICA occlusion, there is too little evidence to recommend surgery to construct an extracranial–intracranial bypass.

In the absence of an appropriate donor vessel for extracranial–intracranial bypass, as might be the case in patients with common carotid artery occlusion, a contralateral donor vessel can be used with tunnelling of the bypass over the skull (so-called “bonnet bypass”).100–102 An intracranial–intracranial bypass is also possible with the ELANA technique.103 Information about the efficacy and risk of complications of these procedures is limited to case reports. The same applies to extracranial–intracranial bypass surgery for posterior circulation stroke.103 Its efficacy in stroke prevention has not been studied in an RCT, and the risk of complications is higher than for anterior circulation bypasses.104

**Other revascularisation procedures**

Treatment of stenosis in blood vessels that are important for the collateral blood supply to the hemisphere on the side of the ICA occlusion has not been studied in a large clinical trial, and precise estimates of the risks of these procedures in patients with symptomatic ICA occlusion are not available. However, endarterectomy of a contralateral ICA stenosis or ipsilateral ECA stenosis can be considered in patients with symptomatic ICA occlusion in whom these blood vessels are important for collateral blood supply. Similarly, treatment of stenosis in the brachiocephalic, subclavian, or vertebral arteries can be considered if the stenosis compromises the collateral blood supply. We showed a sustained benefit, at least in terms of blood flow to both hemispheres, after endarterectomy for contralateral ICA stenosis in patients with symptomatic ICA occlusion.105 In patients with COIS associated with ICA occlusion, endarterectomy of a stenotic ECA might be considered because the eye might be dependent on the ECA. Safety and feasibility of angioplasty for vertebral artery stenosis is currently being studied in the Vertebral Artery Stenting Trial.106
Conclusions

Prospective cohort studies have shown that when low blood flow in the brain plays a major part in causing TIAs or strokes, patients might have specific clinical features, and ancillary investigations can indicate compromised CBF. The same studies have provided evidence that these clinical features and ancillary investigations can be used to identify patients who are at high risk of recurrent ischaemic stroke. A low threshold for ancillary investigations aimed at assessment of the CBF should be used for patients in whom haemodynamic compromise is considered. Nevertheless, this diagnosis remains difficult because a gold standard for the diagnosis of haemodynamic stroke has not been established. Moreover, in many patients, embolism and hypoperfusion might act together. Despite these drawbacks, recognition of hypoperfusion as a contributing mechanism in TIAs and ischaemic stroke might guide treatment.

To date, treatment of patients with haemodynamic stroke or TIA cannot be based on evidence from RCTs. Observational non-randomised studies support therapies aimed at increasing CBF, including bed rest in the acute stage, increasing blood pressure, and revascularisation procedures such as endarterectomy or stenting of collateral pathways, or construction of an extracranial–intracranial bypass. Because none of these treatments has yet been proven effective in an RCT, risks and benefits should be carefully assessed on an individual basis until further evidence becomes available.

Future research should be directed at defining the best methods to determine the relative contribution of haemodynamic compromise to the risk of stroke, and diagnostic criteria should be established. Subsequently, treatment aimed at improving the haemodynamic state of the brain needs to be tested in RCTs in patients who are at high risk of ischaemic stroke. For posterior circulation stroke in particular, more information is needed on the natural history in patients in whom haemodynamic compromise seems to play a part.

Contributors

Both authors were responsible for the concept of the Review. CJMK selected the papers to be included and prepared the first draft. Both authors were involved in the writing and editing of the final draft of the manuscript.


