Cerebral hyperperfusion syndrome following carotid endarterectomy

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Introduction
Extracranial internal carotid artery stenosis accounts for 15–20% of ischaemic strokes and carotid endarterectomy (CEA) is the most frequently performed surgical intervention in stroke prevention. The risk of stroke and death associated with the operation has been estimated at about 5.6% (95% CI 4.4–6.9). Neurological complications following CEA are usually ischaemic in nature, due to embolization or occlusion of the carotid artery. However, in a small subset of patients, cerebral hyperperfusion or reperfusion causes post-operative neurological dysfunction, characterized by ipsilateral headache, focal seizure activity, focal neurological deficit and ipsilateral intracerebral haemorrhage or oedema. Although rare, it can lead to significant morbidity and mortality if not correctly recognized and treated.

Haemodynamic changes following CEA
The haemodynamic changes following CEA are complex and vary between patients. The main reason to perform CEA is removal of the source of emboli originating from carotid plaques. However, following successful endarterectomy there is increased blood flow in the ipsilateral carotid artery in almost all patients, related to the degree of pre-operative stenosis and hypoperfusion. In patients without pre-operative hypoperfusion, flow velocities generally peak on the first post-operative day and return to pre-operative values after 4–5 days. However, in patients with pre-operative hypoperfusion, flow velocities may remain high for many weeks.

Hyperperfusion definition
Although cerebral blood flow (CBF) and perfusion increase in almost all patients following CEA, hyperperfusion is usually defined as a >100% increase in CBF compared to the pre-operative baseline. Hyperperfusion following CEA occurs in some 9–14% of patients, but only a minority develop symptoms as a result.

Cerebral hyperperfusion syndrome
Cerebral hyperperfusion syndrome (CHS) is a clinical triad of ipsilateral headache, seizure and focal neurological symptoms occurring in the absence of cerebral ischaemia. It is accompanied by post-operative hypertension in almost all patients. The earliest description of CHS is a case report from 1964, describing intracranial haemorrhage following CEA.

CHS can develop at any time from immediately after surgery to up to a month later, but most patients develop symptoms within the first few days (mean 5 days). Headache is common after CEA, occurring in around 62% of patients, but in most patients with well-controlled blood pressure, it is mild to moderate in severity. In CHS, headaches are typically severe, ipsilateral, pounding and
migrainous in type, although in some patients they may be mild, intermittent, or even absent.\textsuperscript{15} The neurological deficit is usually cortical (e.g. hemiplegia, neglect, hemianopia, aphasia). Seizures may be focal or generalized.\textsuperscript{3,15} Features of increased intracranial tension such as vomiting and altered sensorium are common.\textsuperscript{17–19} Imaging shows either intracerebral oedema or haemorrhage.

The incidence of CHS post CEA is around 0.75–3%, and the incidence of intracranial haemorrhage (ICH) is around 0.3–1.2%.\textsuperscript{3,11,18,20–23} These rather wide ranges are partly due to the absence of uniform diagnostic criteria.

### Is hyperperfusion always present in symptomatic patients?

Hyperperfusion is seen in most cases of CHS, but symptoms can also occur in patients with only moderate increases in CBF (30–50% above baseline) following CEA. Intraoperative Xenon studies and perfusion-weighted magnetic resonance imaging have demonstrated only an increase of 20–44% in CBF in many patients with ICH.\textsuperscript{11,18,24,25} However, the risk of developing CHS is 10 times higher in patients with hyperperfusion than in those without. In one study, ICH developed in 3.3% of patients with hyperperfusion vs. only 0.24% of those without.\textsuperscript{11}

### Other procedures associated with CHS

In addition to CEA, hyperperfusion syndrome has also been reported following a number of revascularization procedures involving the cerebrovascular circulation, including carotid and vertebral artery stents, carotid and vertebral angioplasties, extra-cranial intracranial bypass, clipping of internal carotid artery aneurysm and subclavian angioplasty.\textsuperscript{26–28}

### Pathophysiology

Many interlinked factors are thought to play a role in the pathophysiology of cerebral hyperperfusion syndrome, including impaired cerebral autoregulation, hypertension, ischaemia-reperfusion injury, oxygen-derived free radicals, baroreceptor dysfunction and intraoperative ischaemia. The known risk factors so far are summarized in Table 1.

#### Table 1 Risk factors for CHS

<table>
<thead>
<tr>
<th>Risk Factor</th>
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<tbody>
<tr>
<td>Hypertension</td>
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<tr>
<td>High grade stenosis with poor collateral flow</td>
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<tr>
<td>Decreased CVR</td>
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<tr>
<td>Increased peak flow velocity</td>
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<tr>
<td>Contralateral carotid occlusion</td>
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<tr>
<td>Recent contralateral CEA (&lt;3 months)</td>
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<td>Intraoperative distal carotid pressure of &lt;40 mmHg</td>
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<td>Intraoperative ischaemia</td>
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#### Impaired cerebral autoregulation

Cerebral autoregulation protects the brain against changes in systemic blood pressure. Without it, a trivial fall in blood pressure could lead to ischaemia; a sudden rise in blood pressure could lead to cerebral oedema or haemorrhage. The autoregulatory response following a change in systemic blood pressure is rapid, and is initiated and completed within 15–30 s.\textsuperscript{29} In patients with high-grade stenosis and impaired flow, CBF is maintained at remarkably normal levels, at the expense of maximal arteriolar vasodilatation.

Chronic cerebral hypoperfusion due to critical stenosis leads to production of vasodilatory substances such as carbon dioxide and nitric oxide, causing endothelial dysfunction. Animal models have shown an increase in structurally defective and weaker capillaries in a chronically hypoperfused brain.\textsuperscript{30} The degree of microvascular dysautoregulation is proportional to the duration and severity of ischaemia, in turn determined by the severity of ipsilateral stenosis and poor collateral flow. Thus in the presence of chronic ischaemia, small cerebral arterioles remain maximally dilated, maintaining normal cerebral blood flow. Defective autoregulation can be identified pre-operatively by reduced, absent or even reversed cerebrovascular reactivity to carbon dioxide.\textsuperscript{31–34}

In the absence of cerebral autoregulation, CBF is directly dependent on the systemic blood pressure. Correction of critical stenosis causes rapid and large changes in CBF leading to vascular disruption and ICH, aggravated by peri-operative and post-operative hypertension. Extremely large increases in CBF following CEA occur only in patients with severely impaired autoregulation.\textsuperscript{33} In patients with hyperperfusion, maximal blood flow usually occurs 3–4 days after surgery and falls to a steady state by day 7.\textsuperscript{7,18,31} However autoregulation can take up to 6 weeks to stabilize.\textsuperscript{14,35}

A ‘normal perfusion pressure breakthrough’ hypothesis based on cerebral dysautoregulation has been suggested as a mechanism of CHS.\textsuperscript{30,34} Structurally weaker capillaries are more vulnerable.
to breakthrough by distension during reperfusion, and this could account for the vasogenic oedema seen in patients without severe hypertension or hyperperfusion.\textsuperscript{24}

**Hypertension**

Hypertension plays an important role in the development of CHS. Hypertension has not been proven to initiate haemorrhage, but is present in almost all symptomatic patients post-operatively.\textsuperscript{16,17,19,25,26} It clearly increases CBF and velocity during impaired autoregulation, leading to hyperperfusion. Pre-operative hypertension is the single most important determinant of development of post-operative hypertension.

Unstable blood pressure occurs in 74\% of patients during the first 24 h after CEA.\textsuperscript{36} Post-operative hypertension (defined as systolic blood pressure >200 mmHg or diastolic blood pressure >100 mmHg) is seen in some 19–35\% of patients following CEA.\textsuperscript{37,38}

**Baroreceptor dysfunction**

Baroreceptor dysfunction due to receptor denervation has been reported, especially after successive bilateral carotid endarterectomies leading to CHS.\textsuperscript{39} Baroreceptor dysfunction can cause a progressive increase blood pressure post-operatively that is refractory to treatment. Its variability for up to 12 weeks after CEA has been described as baroreflex failure syndrome.\textsuperscript{40} In one study, 6.6\% of 76 patients with bilateral CEA developed CHS, compared to 1.1\% of 379 patients with unilateral CEA. The authors suggested that contralateral CEA performed within 3 months was predictive of CHS.\textsuperscript{41}

**Intra-operative ischaemia**

Peri-operative cerebral ischaemia, indicated by decreased transcranial oxygen saturation, elevated S-100B neuronal protein and absent central somatosensory evoked potential, is an independent predictor of post-operative hyperperfusion and neurological deficit.\textsuperscript{42,43}

**Ischaemia-reperfusion injury**

Cellular damage following reperfusion in a previously viable ischaemic tissue is defined as ischaemia-reperfusion injury. It is characterized by oxidant production, complement activation and increased microvascular permeability, resulting in an impaired blood brain barrier, which could lead to intracerebral oedema and ICH following reperfusion. Oxygen-derived free radicals produced during CEA might be a mediator of this effect, and administration of a free-radical scavenger may help to prevent hyperperfusion.\textsuperscript{44}

**Pre-operative prediction of CHS**

**Transcranial doppler**

Transcranial doppler (TCD) measures cerebral blood flow velocity in the middle cerebral artery (MCA), and can provide useful information on pre-operative hyperperfusion, emboli and post-operative hyperperfusion. In two studies, TCD criteria of a low peri-operative distal carotid artery pressure (<40 mmHg) and an increase in peak blood flow velocity or pulsatility index of >100\% after declamping of the carotid artery were predictive of post-operative hyperperfusion.\textsuperscript{20,45} Since the risk of ICH is 10 times higher in patients with hyperperfusion, TCD can be used to select patients for aggressive management.

**Cerebral vasoreactivity (CVR)**

Cerebrovascular reactivity (CVR) to carbon dioxide or acetazolamide has been proposed as a test for cerebral haemodynamic reserve. In normal people, administration of acetazolamide (a carbonic anhydrase inhibitor that causes a local increase in carbon dioxide) induces a rapid increase in CBF, ranging from 20–80\%.\textsuperscript{46,47} This is usually measured using single-photon emission computed tomography (SPECT), magnetic resonance or TCD. In patients with chronic cerebral ischaemia, the cerebral blood vessels are already maximally dilated and do not show a marked change in CBF (decreased CVR). Patients with low pre-operative CVR are at risk of developing cerebral hyperperfusion, leading to CHS.\textsuperscript{33,48}

**Prevention**

**Blood pressure**

The most important factor in preventing this syndrome is early identification of hyperperfusion and control of blood pressure.\textsuperscript{49} Many centres use TCD peri-operatively and in the immediate post-operative period to identify patients with increased CBF. If hyperperfusion is demonstrated, blood pressure should be aggressively controlled, ideally in a high-dependency unit setting. Further reduction in blood pressure should be considered even in normotensive patients with hyperperfusion, as some may develop delayed hypertension.\textsuperscript{15} Exactly what blood pressure to aim for, however, is unclear.
Blood pressure should preferably be reduced using drugs such as labetolol and clonidine that do not increase CBF, rather than angiotensin-converting-enzyme inhibitors, calcium-channel blockers or vasodilators like nitroprusside and glycerol trinitrate. However, beyond this criterion, there is no evidence favouring any particular drug. Even with such drugs, blood pressure control can be extremely difficult, and hyperperfusion can still occur even with normal blood pressure.\textsuperscript{15,45,49}

**When to operate**

When to do CEA following a stroke is controversial.\textsuperscript{50} A few studies have suggested that CT scan evidence of stroke carries an increased risk of CHS, and surgery should be delayed for up to three months, but many of these studies are retrospective and limited by small numbers.\textsuperscript{51–53} Data from the large endarterectomy trials suggests that the benefit of CEA is greatest in the first 2 weeks following an ischaemic event. The current recommendation is that CEA should be done within 2 weeks of the patient’s last symptoms.\textsuperscript{1,54} Contralateral CEA performed within the last 3 months has been identified as a risk factor, and this should be taken into account when planning surgery.\textsuperscript{41}

**Free-radical scavengers**

Oxygen-derived free radicals produced during ischaemia have been implicated in ischaemia-reperfusion injury. In cerebral tissue, these radicals could lead to endothelial dysfunction and a break in blood brain barrier, leading to post-ischaemic hyperperfusion, oedema and haemorrhage. In one small case series with historical controls, edaravone, a free-radical scavenger that inhibits lipid peroxidation and vascular endothelial injury decreased the incidence of hyperperfusion following CEA, mainly in patients with decreased CVR.\textsuperscript{44} This is encouraging, but clearly further trials are needed.

**Prognosis**

The prognosis of CHS depends on timely recognition of hyperperfusion and adequate treatment of hypertension before cerebral oedema or ICH develops. The prognosis following ICH is very poor, with mortality of 36–63% and significant morbidity (80%) in the survivors.\textsuperscript{11,12,25,26,55} The prognosis of CHS in patients without ICH is more difficult to estimate, because symptom severity varies widely, but the outlook is clearly better, with very low mortality. Recent studies suggest lesser incidence of ICH and better prognosis when patients are identified and treated early.\textsuperscript{45,49}

**Hyperperfusion or reperfusion syndrome?**

Hyperperfusion is common in symptomatic patients, but it is not invariably present. With complex pathophysiology, and some patients showing only a modest increase in CBF (20–44% above baseline), some authors suggest that this syndrome should be called ‘reperfusion syndrome’ rather than hyperperfusion syndrome.\textsuperscript{24} Reperfusion symptoms are increasingly recognized in many other organs following revascularization procedures. For example, reperfusion arrhythmia is well-recognized following thrombolysis or surgical revascularization; gastrointestinal injury following reperfusion, leading to decreased intestinal barrier function has been reported;\textsuperscript{56} and marked polyuria (up to 5 l/day) has been reported during reperfusion following renal angioplasty in patients with renovascular disease.\textsuperscript{57}

In the light of this increasing recognition of reperfusion injuries, we agree that this syndrome might be better named ‘cerebral reperfusion syndrome’.

**Summary**

Cerebral hyperperfusion or reperfusion syndrome is a rare, but a serious complication following CEA. Unifying diagnostic criteria recently suggested include: headache, neurological deficit, and seizure due to ipsilateral haemorrhage after cerebral revascularization, with evidence of hyperperfusion measured by TCD, MRI or SPECT.\textsuperscript{58} TCD should be made available in all centres to identify patients with hyperperfusion who may benefit from aggressive post-operative blood pressure control. This should ideally be provided in a high-dependency unit.

**References**

Cerebral hyperperfusion syndrome 243


