Hyperperfusion syndrome after carotid revascularization

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Cerebral hyperperfusion syndrome is a rare, serious complication of carotid revascularization either after carotid endarterectomy or carotid stent placement. Impaired cerebral autoregulation and post-revascularization changes in cerebral hemodynamics are the main mechanisms involved in the development of the syndrome. Hyperperfusion syndrome may be fatal once an intracranial hemorrhage occurs. This article reviews the literature, intending to make a synthesis of all new data concerning the clinical manifestations of hyperperfusion syndrome, the pathophysiologic pathways involved in its development, the prediction, and the appropriate management. Also, a review of the most recent series of hyperperfusion syndrome following carotid revascularization, both with classic open endarterectomy and carotid artery stenting has been performed. (J Vasc Surg 2009;49:1060-8.)

Carotid endarterectomy (CEA) is still regarded as the gold standard therapy for prevention of primary and secondary stroke in patients with significant carotid artery disease while carotid stenting has been emerged as a potential alternative to carotid endarterectomy under certain indications.1 Cerebral hyperperfusion syndrome (CHS) is a relatively rare but potentially devastating event that can complicate both techniques.2-7 In the worst case scenario, hyperperfusion syndrome may be fatal once an intracranial hemorrhage occurs.8-7

DEFINITION OF HYPERPERFUSION AND CEREBRAL HYPERPERFUSION SYNDROME

Since Sundt described the combination of increased arterial blood pressure with the clinical triad of ipsilateral migraine-like headache, seizure, and transient focal neurologic deficits in the absence of cerebral ischemia after a successful CEA in 1981, the term cerebral hyperperfusion syndrome (CHS) has been used to describe this clinical entity.13 Spetzler had first described the phenomenon of hyperperfusion three years earlier following surgical resection of arteriovenous malformations. He had used the “theory of normal perfusion pressure breakthrough,” emphasizing the impaired cerebral autoregulation, which remained after the fistulae resection.14

Various authors have supported the definition of the syndrome based on the combination of the clinical picture with imaging techniques. In order to confirm the clinical diagnosis, they have suggested as diagnostic imaging criteria an increase in cerebral blood flow (CBF) compared with preoperative or baseline values and/or the demonstration of hyperperfusion on perfusion magnetic resonance imaging (MRI) or computed tomography (CT) scans.5,4,15-23 The presence of symptoms is essential in the definition of the syndrome.

This last comment emphasizes a critical distinction between hyperperfusion and hyperperfusion syndrome. Hyperperfusion is defined as the increase in CBF, compared to preoperative or baseline values, expressing a hemodynamic parameter of cerebral circulation. Hyperperfusion following CEA occurs in 0.2% to 18.9% of patients.2 Some patients, after carotid revascularization, demonstrate only a modest increase in CBF, less than 100%.2 CHS is most common in patients with CBF increases of more than 100% compared with baseline values after carotid revascularization and is rare in patients with increases in perfusion less than 100% compared with baseline values.2 In series by Ogasawara, Suga, and Fukuda (Table 1), 16.7% to 28.6% of the patients with an increase of CBF >100% developed CHS.

Based on this finding, some authors have suggested that this syndrome should also be called “reperfusion syndrome” rather than hyperperfusion syndrome, to reflect the reperfusion injury effects.2-4 The key event in the expression of syndrome seems to be a combination of increased cerebral blood flow (compared with preoperative levels) with individualized disturbed cerebro-vascular autoregulation.

PATHOPHYSIOLOGY OF CHS

Two interlinked and synergistic mechanisms may lead to increased CBF. First, impaired cerebral autoregulation seems to play a significant role. The normal brain has the
able to maintain constant intracranial pressure by its autoregulatory mechanisms, when a change in blood flow occurs. The main autoregulatory mechanism is the cerebrovascular reactivity, the ability of the arterioles to constrict or dilate in response to the alterations of blood flow or to other stimuli (ie, hypocapnia). Patients with extracranial carotid stenosis often present exhausted cerebrovascular reactivity. This situation represents a status of maximal carotid stenosis often present exhausted cerebrovascular reactivity; they are associated with the grade of the ipsilateral carotid stenosis, the presence of contralateral lesion, the severity of microvascular autoregulation impairment may be dependent on the duration and intensity of cerebral hypoperfusion; they are associated with the grade of the ipsilateral carotid stenosis, the presence of contralateral carotid occlusion, and poor collateral flow. However, the syndrome has also been described in the absence of contralateral occlusion or severe stenosis, reflecting not a contradiction with the previous statement but the significant role of disturbed cerebral autoregulation that can be developed in the cerebral territory of ipsilateral carotid stenosis even in the absence of contralateral lesion. This consideration is confirmed by a recent study demonstrating that patients with moderate carotid artery stenosis may also have impaired dynamic cerebrovascular autoregulation. Increased nitric oxide levels during clamping of the ICA and increased oxygen-derived free radicals produced during the restoration of the perfusion pressure are involved in endothelium dysfunction and the deterioration of autoregulatory mechanisms after CEA. Besides, several studies have demonstrated significant elevations in malondialdehyde, diene conjugates, or lipoperoxides, products of free radical-induced lipid peroxidation, in jugular vein plasma immediately after declamping of the ICA in patients undergoing CEA.

The second significant mechanism in the pathogenesis of hyperperfusion syndrome is postoperatively elevated systemic blood pressure. Both hypertensive and hypotensive alterations of blood pressure after carotid endarterectomy have been reported in up to 66% of patients following carotid endarterectomy. Although transient hypertension and bradycardia can occasionally be observed due to stimulation of the carotid body nerves, baroreceptor reflex failure due to receptor denervation during CEA may contribute to hypertension after endarterectomy.

Especially after bilateral CEA, the baroreflex breakdown induced hypertension leads to an increase of CBF; in contrast, autoregulation mechanisms are diminished and thus lead to hyperperfusion in the previously hypoperfused tissue. Both cerebral hyperperfusion associated with cerebral edema and elevated intracranial pressure may lead to an increase of central and peripheral norepinephrine levels and

### Table I. Incidence of hyperperfusion, cerebral hyperperfusion syndrome, and intracranial hemorrhage after carotid endarterectomy in the reviewed series from 2003 to 2008

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients (n)</th>
<th>Definition of hyperperfusion/CHS</th>
<th>Patients with hyperperfusion (%)</th>
<th>Patients with CHS (%)</th>
<th>Patients with ICH (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ogasawara</td>
<td>2007</td>
<td>1596</td>
<td>Acute neurological deterioration</td>
<td>n.d.</td>
<td>30/1596 (1.9%)</td>
<td>6/1596 (0.4%)</td>
</tr>
<tr>
<td>Maltezos</td>
<td>2007</td>
<td>100</td>
<td>in the immediate</td>
<td>14/100 (14%)</td>
<td>n.r.</td>
<td></td>
</tr>
<tr>
<td>Wagner</td>
<td>2005</td>
<td>1602</td>
<td>postoperative period</td>
<td>6/1602 (0.4%)</td>
<td>3/1602 (0.2%)</td>
<td></td>
</tr>
<tr>
<td>Karapanayiotides</td>
<td>2005</td>
<td>388</td>
<td></td>
<td>5/388 (1.3%)</td>
<td>4/388 (1%)</td>
<td></td>
</tr>
<tr>
<td>Fujimoto</td>
<td>2004</td>
<td>95</td>
<td></td>
<td>12/95 (13%)</td>
<td>n.r.</td>
<td></td>
</tr>
<tr>
<td>Courts</td>
<td>2003</td>
<td>129</td>
<td></td>
<td>4/129 (3.1%)</td>
<td>1/129 (0.8%)</td>
<td></td>
</tr>
<tr>
<td>Fukuda</td>
<td>2007</td>
<td>70</td>
<td>CBF increase of 100% compared with preoperative values assessed by TCD</td>
<td>7/70 (10%)</td>
<td>2/70 (2.8%)</td>
<td>n.r.</td>
</tr>
<tr>
<td>Ogasawara</td>
<td>2005</td>
<td>67</td>
<td>CBF increase &gt;100%, compared with preoperative values measuring BFV in MCA by TCD or assessed by SPECT images</td>
<td>7/67 (10.4%)</td>
<td>2/67 (3%)</td>
<td>n.r.</td>
</tr>
<tr>
<td>Hosoda</td>
<td>2003</td>
<td>41</td>
<td>CBF increase &gt;100%, compared with preoperative values</td>
<td>4/41 (9.8%)</td>
<td>n.r.</td>
<td>0%</td>
</tr>
<tr>
<td>Yoshimoto</td>
<td>2005</td>
<td>18</td>
<td></td>
<td>7/18 (11%)</td>
<td>2/18 (11%)</td>
<td>n.d.</td>
</tr>
<tr>
<td>Suga</td>
<td>2007</td>
<td>90</td>
<td></td>
<td>12/90 (13%)</td>
<td>2/90 (2.2%)</td>
<td>n.d.</td>
</tr>
<tr>
<td>Komoribayashi</td>
<td>2006</td>
<td>89</td>
<td></td>
<td>10/89 (11%)</td>
<td>2/89 (2.2%)</td>
<td>n.d.</td>
</tr>
<tr>
<td>Ascher</td>
<td>2003</td>
<td>404</td>
<td>Increased ipsilateral headache, seizures</td>
<td>n.r.</td>
<td>9/404 (2.2%)</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

Total: 4689

<table>
<thead>
<tr>
<th>Patients with hyperperfusion (%)</th>
<th>Patients with CHS (%)</th>
<th>Patients with ICH (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>47/375 (12.5%)</td>
<td>90/4648 (1.9%)</td>
<td>14/3756 (0.37%)</td>
</tr>
</tbody>
</table>

BFV, Blood flow velocity; CEA, carotid endarterectomy; CHS, cerebral hyperperfusion syndrome; ICA, intracranial artery; ICH, intracranial hemorrhage; MCA, middle cerebral artery; n.d., not determined; n.r., not reported; PWI, perfusion-weighted magnetic resonance imaging; SPECT, single-photon emission computed tomography; TCD, transcranial Doppler.
FOLLOWING CAS AND CEA

AND INTRACRANIAL HEMORRHAGE

CEREBRAL HYPERPERFUSION SYNDROME AND CHS BETWEEN 2003 AND 2008

A multiple electronic health database search was performed including Medline, Embase, Ovid, and Cochrane Database of Systematic Reviews, on all articles published between 2003 and 2008 and referring to cerebral hyperperfusion after carotid revascularization. The full text of the studies was retrieved and was independently assessed by the authors. Thirteen studies on hyperperfusion after CEA were included with a total of 4689 patients and 9 studies on hyperperfusion after CAS with a total of 4446 patients. The incidence of CHS and ICH after CAS was 1.16% (range, 0.44% to 11.7%) and 0.74% (range, 0.36% to 4.5%), respectively. CHS and ICH were observed in 1.9% (range, 0.4% to 14%) and 0.37% (range, 0% to 1%) of reviewed patients after CEA, respectively (Tables I and II). In addition, the incidence of each clinical manifestation of CHS after CAS was estimated by analyzing the available data from the collected series (Table III).

CEREBRAL HYPERPERFUSION SYNDROME AND INTRACRANIAL HEMORRHAGE FOLLOWING CAS AND CEA

Hyperperfusion syndrome can complicate carotid revascularization, after both classic open endarterectomy and carotid artery stenting (CAS). The incidence of cerebral hyperperfusion after CAS has not been extensively investigated and only a small number of studies have been conducted to estimate it. It is unclear if the risk for CHS is comparable between CEA and CAS. Patients who are referred for CAS are usually high risk patients exhibiting many pre-procedural predisposing factors for CHS; they are discussed later in the manuscript. Additionally, endovascular treatment involves more aggressive anticoagulation protocols in combination with dual antiplatelet therapy. Some authors claim that this extensive use of anticoagulants and antiplatelet agents is associated with an increased incidence of ICH following CAS, whereas others do not assert any correlation. Ogasawara described two more differences in the development of CHS and ICH following CAS and CEA. First, postoperative ischemic cerebral lesions due to emboli are more frequent after CAS than during CEA. Following the emboli resorption and the artery recanalization, cerebral hyperperfusion can occur leading to hemorrhagic transformation in an unviable cerebral area. Additionally carotid baroreceptor stimulation during CAS via a balloon or a carotid stent induces transient, sometimes prolonged bradycardia and hypotension that can result in more intense cerebral ischemia than during clamping of the ICA in CEA. Furthermore, subsequent rebound arterial hypertension may induce delayed cerebral hyperperfusion.

CLINICAL PRESENTATION

Symptoms of CHS may occur up to several weeks after revascularization but usually within the first few days (Table III). Ogasawara suggested that the onset of CHS peaks on the sixth postoperative day in patients who undergo CEA and within 12 hours after surgery in those who undergo CAS; this could be explained considering the above mentioned differences in CHS development after CEA and CAS. Deterioration of consciousness, confusion, and headache are the most common symptoms of CHS; headache is usually moderate to severe, ipsilateral to the revascularized artery, pounding, and migrainous. The neurologic deficit of CHS, which is secondary to cerebral edema is usually transient. It includes manifestations derived from the cortex (ie, hemiparesis, hemiplegia, hemianopia, obtundation, and aphasia), and epileptic disturbances – focal motor seizures or seizures with further generalization. Ataxia and visual disorders are less common. Miscellaneous symptoms such as cognitive impairment and psychotic disorders have been also reported in patients with CHS.

The most catastrophic event that can occur secondary to hyperperfusion is intracerebral hemorrhage (ICH). Intracerebral hemorrhage, as previously reported, occurs in 0.37% (range, 0% to 1%) of patients in large series of carotid endarterectomy (CEA), and in 0.74% (range, 0.36% to 4.5%) in CAS (Tables I and II). Since intracerebral hemorrhage is associated with CHS, manifestations of increased intracerebral pressure (eg, vomiting or altered sensorium) can be present. It is important to note an ICH entity following CAS, described as hyperacute ICH; it occurs within hours. This type of ICH is less common but almost always unpreventable (since it usually occurs without prodromata) and fatal. The pathophysiologic mechanism of this early variant of ICH involves rupture of the perforating...
arteries in the basal ganglia that are acutely exposed to suddenly normalized perfusion pressure after CAS.

RISK FACTORS AND PREDICTION OF HYPERPERFUSION AND CEREBRAL HYPERPERFUSION SYNDROME

Understanding of the pathophysiology of the hyperperfusion is multifactorial, while cerebral haemodynamics and cerebral autoregulation, as previously mentioned, are individualized in each patient. CBF changes after revascularization vary, while there is no evidence directly linking the CBF modifications and the degree of stenosis. This could be explained by the different extent of collateral circulation available in each patient and by the autoregulatory mechanisms of the cerebral circulation stimulated after the detection of the hyperperfusion. These changes are hard to be explained only by the restoration of the patency of a narrowed vessel; other autoregulatory mechanisms are, probably, implied.

Although clinical studies have indicated a potential role for various risk factors, definitive prediction of subgroups of patients as those at increased risk of developing CHS after CEA or CAS, is not feasible. This point expresses not the ambiguity of the risk factors but the complexity and the

Table II. Incidence of hyperperfusion, hyperperfusion syndrome, and intracranial hemorrhage after carotid artery stenting in the reviewed series from 2003 to 2008

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients</th>
<th>Definition of hyperperfusion / CHS / ICH</th>
<th>Patients with hyperperfusion (%)</th>
<th>Patients with CHS (%)</th>
<th>Patients with ICH (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sfyroeras</td>
<td>2008</td>
<td>29</td>
<td>Neurological symptoms (hemispheric or non hemispheric) associated with hyperperfusion in brain SPECT scan and increased MFV in the ipsilateral MCA</td>
<td>n.d.</td>
<td>2/29 (6.9%)</td>
<td>0%</td>
</tr>
<tr>
<td>Ogasawara</td>
<td>2007</td>
<td>2898</td>
<td>Severe headache, seizure, deterioration of consciousness level, and/or development of focal neurological</td>
<td>n.d.</td>
<td>31/2898 (1.1%)</td>
<td>21/2898 (0.7%)</td>
</tr>
<tr>
<td>Abou</td>
<td>2007</td>
<td>836</td>
<td>Ipsilateral headache with or without nausea and vomiting, ipsilateral focal seizures, or focal neurological deficit</td>
<td>n.d.</td>
<td>8/836 (0.96%)</td>
<td>3/836 (0.36%)</td>
</tr>
<tr>
<td>Kablak-Ziembicka</td>
<td>2006</td>
<td>92</td>
<td>Headache, seizures, focal neurologic deficits</td>
<td>n.d.</td>
<td>2/92 (2.2%)</td>
<td>2/92 (2.2%)</td>
</tr>
<tr>
<td>du Mesnil de Rochemont</td>
<td>2006</td>
<td>50</td>
<td>Neurologic deficits and vasogenic oedema on MR imaging</td>
<td>n.d.</td>
<td>1/50 (2%)</td>
<td>0%</td>
</tr>
<tr>
<td>Imai</td>
<td>2005</td>
<td>17</td>
<td>Greater flow in the ipsilateral hemisphere than on the contralateral side assessed by SPECT images</td>
<td>4/17 (23.5%)</td>
<td>2/17 (11.7%)</td>
<td>2/17 (11.7%)</td>
</tr>
<tr>
<td>Kaku</td>
<td>2004</td>
<td>30</td>
<td>CBF increase of &gt;100% compared with the normal side</td>
<td>n.d.</td>
<td>3/30 (10%)</td>
<td>1/30 (3.33%)</td>
</tr>
<tr>
<td>Abou</td>
<td>2004</td>
<td>450</td>
<td>Ipsilateral headache with or without nausea, vomiting, ipsilateral focal seizures, or focal neurological deficit</td>
<td>n.d.</td>
<td>2/450 (0.44%)</td>
<td>3/450 (0.67%)</td>
</tr>
<tr>
<td>Coutts</td>
<td>2003</td>
<td>44</td>
<td>Hemispheric neurological deficit ipsilateral to the revascularized artery</td>
<td>n.d.</td>
<td>3/44 (6.8%)</td>
<td>2/44 (4.5%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>4446</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CBF, Cerebral blood flow; CHS, cerebral hyperperfusion syndrome; CT, computed tomography; ICH, intracranial hemorrhage; MCA, middle cerebral artery; MFV, mean flow velocity; MR, magnetic resonance; n.d., not determined; SPECT, single-photon emission computed tomography.
multifactorial contribution in the pathogenesis of the syndrome. Table IV describes risk factors, which have been identified to be significantly involved in hyperperfusion pathophysiological pathways and the development of CHS. Preoperative variables such as low pulsatility index, severe ipsilateral or contralateral carotid disease, bilateral carotid artery stenosis, and an incomplete circle of Willis, increase the risk of CHS. Abou and colleagues suggested that the risk of CHS development was 16% for patients with treated stenoses of >90% luminal narrowing or occlusion, contralateral stenoses of >80%, and longstanding preprocedural hypertension. Additionally, one study suggested that the interval between the procedures (in case of bilateral carotid stenosis) is a predictive factor of CHS development; incidence of CHS in patients underwent recent contralateral CEA (<3 months) was higher than in patients who underwent the second procedure in longer interval. The authors suggested that inconsistencies in baroreceptor function may be a causative factor for CHS.

Patient age, impaired cerebrovascular reactivity, measured preoperatively by assessing acetazolamide or breath holding, induced changes in cerebral blood flow, asymmetry index, and preoperative CBF reduction have also been suggested as significant predictors of hyperperfusion syndrome after CAS or CEA. Diseases that can result in microangiopathy affecting endothelium of small vessels (ie, diabetes mellitus or longstanding pre-existing hypertension) have been found to predispose to hyperfusion and CHS development.

The use of anticoagulants and antiplatelet agents is routine after CAS as well as after surgery. In the absence of sufficient data, it remains uncertain whether the use of post-procedure anticoagulation therapy may be associated with an increased risk of developing CHS and ICH.

### Table III. Clinical presentation of hyperperfusion syndrome in the reviewed series of Table I

<table>
<thead>
<tr>
<th>Type of symptom</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deterioration of consciousness, confusion</td>
<td>37.1% (23/62)</td>
</tr>
<tr>
<td>Headache</td>
<td>30.6% (19/62)</td>
</tr>
<tr>
<td>Epileptic disturbances, focal seizures</td>
<td>25.8% (16/62)</td>
</tr>
<tr>
<td>Motor disturbances (hemiparesis, hemiplegia)</td>
<td>17.7% (11/62)</td>
</tr>
<tr>
<td>Abnormal speech, aphasia</td>
<td>6.4% (4/62)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4.8% (3/62)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>4.8% (3/62)</td>
</tr>
<tr>
<td>Psychotic disorders</td>
<td>3.2% (2/62)</td>
</tr>
<tr>
<td>Visual disturbances (hemianopsia)</td>
<td>3.2% (2/62)</td>
</tr>
<tr>
<td>Ataxia</td>
<td>1.6% (1/62)</td>
</tr>
</tbody>
</table>

### Table IV. Risk factors of hyperperfusion and cerebral hyperperfusion syndrome

**Preoperative**
- Long standing increased BP with hypertensive microangiopathy
- Diabetes mellitus
- Increased age
- Recent contralateral CEA (<3 months)
- High grade ipsilateral carotid stenosis with poor collateral flow
- Contralateral carotid occlusion
- Incomplete circle of Willis
- Attenuated cerebrovascular reactivity after acetazolamide challenge

**Intraoperative**
- Intraoperative distal carotid pressure of <40 mmHg
- High doses of volatile halogenated hydrocarbon anesthetics
- Periprocedural cerebral infarction
- Intraoperative ischemia
- Refractory postoperative cerebral hyperperfusion
- Postoperative hypertension
- Administration of anticoagulants or antiplatelet agents

BP: Blood pressure; CEA, carotid endarterectomy.

INVESTIGATORY TECHNIQUES IN PREDICTION AND DIAGNOSIS OF CHS

Several techniques have been applied to investigate potential predisposing factors and identify patients at risk for CHS. Transcranial Doppler (TCD) is the most widely available method for predicting CBF changes by measuring the cerebral blood flow velocity (CBFV) in intracranial vessels. TCD has been used to assess cerebrovascular reactivity using vasodilatory agents such as acetazolamide, CO₂ inhalation, or the breath holding test. Preoperative significant reduction in velocity of the MCA in patients with exhausted cerebrovascular reactivity. Preoperative significant reduction in flow velocity compared with baseline values is indicative of hypoperfusion and is associated with postoperative hyperperfusion.

Recent studies demonstrate that TCD has considerable technical difficulties including an insufficient cranial window. Despite the technical difficulties and the level of operator’s experience, findings of TCD should be critically evaluated as measurement of intracranial vessels velocities; they may depend on anatomic variants, the grade of collateralization, and the presence of contralateral ICA occlusion or stenosis. Only 18% to 54% of people have a complete circle of Willis, while in patients considered for CEA, the severity of the contralateral ICA disease is an important determinant of the pattern of cerebral blood flow redistribution. Results in TCD studies demonstrate that blood flow redistribution, through the anterior communicating pathway and ophthalmic artery is achieved, in case of contralateral ICA stenosis, and through the posterior communicating pathway in patients with contralateral ICA occlusion.

Intraoperative distal internal carotid artery pressure (dICAP) measurement has been proposed to predict the occurrence of hyperperfusion after CEA; intraoperatorively low dICA (<40 mm Hg) has a high predictive value for postoperative hyperfusion. In addition, Asher reported a significant increase in mean internal carotid artery volume flow (MICAVF) in all patients with CHS during the symptomatic period. In that study, the values were proportional.
to the severity of the symptoms and decreased after symptoms subsided.21

Conventional CT scan is not useful preoperatively and it can also be normal in postoperatively symptomatic patients. CT findings, such as diffuse or patchy white-matter edema, mass effect, and petechial or massive ipsilateral hemorrhages ipsilateral to CEA, are considered to be correlated with CHS. Single-photon emission CT (SPECT) can detect alterations in brain perfusion and the impairment of preoperative cerebrovascular reactivity (after acetazolamide). It is a sensitive method for recognizing CHS, differentiating between ischemia and hyperperfusion and identifying patients at risk for hyperperfusion after CEA.17,57,67 A diffuse asymmetric pattern of preoperative CBF reduction seems to be characteristic in these patients. However Sfyroeras et al did not find an association between preoperative asymmetry in brain perfusion in rest and CHS.68 Ogasawara et al suggested that hyperperfusion lasting at least to the three postoperative days on SPECT predisposes to CHS development.69 Advanced imaging processes and statistical analyses can further improve the predictive value of this technique.18

Magnetic resonance techniques, such as multislice dynamic susceptibility contrast MRI or perfusion-weighted MRI (PWI), can also be used in the preoperative CBF assessment.70,71 Karapanayiotides et al reported no abnormalities on diffusion-weighted MRI, ruling out acute ischemia; in contrast, PWI revealed relative interhemispheric CBF differences in patients with CHS after CEA.74 PWI, however, is not a quantitative method and can only help in the absence of contralateral ICA steno-occlusive disease. Conventional MRI findings in patients with CHS include white-matter edema, focal infarction, and local or massive hemorrhage. These abnormalities, however, are not pathognomonic for CHS.

Alternative methods have been applied to identify risk factors for postoperative hyperfusion, but their use is not widespread and their utility for this indication is not yet clearly established. Although electroencephalogram is widely used for neurological monitoring during CEA, it is of low predictive value for CHS.27 Ocular pneumoplethysmography has also been used to predict post-CEA CHS. Nicholas et al reported that a postoperative increase of ocular blood flow greater than 204% is associated with a high risk for CHS.72 Transcranial color-coded real-time ultrasonography with echo contrast agents is another method that has been assessed for the diagnosis of hyperperfusion and prediction of CHS following CEA. A 1.5-fold postoperative increase of MCA mean flow velocity (MFV) compared with preoperative levels yielded high accuracy predictions of CHS.73 Recent studies have proposed that transcranial regional cerebral oxygen saturation estimated by near-infrared spectroscopy can indicate CBF changes detecting hyperperfusion following CEA.74,75 However, this technique has several technical limitations that should be surmounted in order to improve its sensitivity and specificity in the diagnosis of post-CEA hyperfusion.

**MANAGEMENT OF HYPERPERFUSION SYNDROME**

There are no data from randomized trials comparing the optimal perioperative management protocol for patients with CHS, due to the rarity of this complication. Intracranial hemorrhage as part of a hyperperfusion syndrome is associated with a poor prognosis. Therefore prevention is critical and is based on recognition of vulnerable patients at risk for developing CHS based upon pre-, peri-, or postoperative criteria.10,76,77 In patients with raised suspicion of CHS, prompt diagnosis and initiation of appropriate treatment is crucial (Fig).
Intensive hemodynamic monitoring, including control of systolic blood pressure and use of TCD postoperatively to assess CBF changes, is believed to play a significant role in the prevention of the syndrome.4,5 Many authors suggest that postoperative blood pressures should be maintained to normal or slight subnormal values, a point that seems obvious and reasonable based on the pathophysiology of the syndrome.4,5 However, the syndrome may also be developed in normotensive patients or in subjects with levels of systolic pressure minor of 160 mmHg, reflecting the role of impaired autoregulatory mechanisms.10,21,78,79

Consensus consists in that the extent of the symptoms may be limited by intensive blood pressure control, even if the patient’s pressure is “normal.”80 There is no definitive evidence favoring any particular antihypertensive drug and indicative levels of systolic pressure. It has been proposed that cerebral vasodilating medication with dihydralazin, nitrate or calcium channel antagonists should be avoided on the basis of intensifying the brain edema although reducing the systolic blood pressure.5 In addition, β-blocker drugs could be limited due to aggravation of a potential induced bradycardia after revascularization.

There are no available data recommending prophylactic use of anticonvulsant therapy in patients undergoing carotid revascularization.2,81 Reigel, in an old study, considered prophylaxis when periodic lateralized epileptiform discharges are present on EEG.27 However, in the presence of seizures, treatment with anticonvulsants is always indicated.

In a study by Ogasawara pretreatment with edaravone (60 mg in 100 mL physiological saline intravenously, 30 minutes immediately before internal carotid-artery clamp ing) decreased the incidence of carotid endarterectomy hyperperfusion as measured by single-photon-emission CT.82 Additionally, Kusmič suggested that cerebral oxidative stress associated with carotid endarterectomy can be attenuated by pretreatment with oral dipyridamole.83 However, further trials are warranted to support the benefit of these agents.

Cerebral edema treatment, which includes adequate sedation, hyperventilation, administration of mannitol, or hypertonic saline, may also be effective.16,56,69,74 Corticosteroids and barbiturates have also been used in CHS but their effectiveness in clinical outcome remains uncertain.16,56,69,74

Modern clinical guidelines suggest a short hospital stay while in case of CAS patients are discharged within 24 to 48 hours. Family doctors should be aware of the possible delayed CHS and tend to monitor and treat an increased and uncontrolled blood pressure.69 Once patients are discharged, they should be advised to return to the hospital if they develop a severe headache within the first weeks of surgery.

SUMMARY

Cerebral hyperperfusion syndrome is a serious complication of carotid revascularization, including carotid endarterectomy and carotid stent placement. Two interlinked and synergistic mechanisms may lead to development of syndrome; impaired cerebral autoregulation and postoperatively elevated systemic blood pressure. Although clinical studies have identified potential risk factors, definitive prediction of subgroups of patients as those at increased risk of developing CHS after CEA or CAS is not feasible. CHS, if not treated properly, can result in severe brain oedema, intracerebral hemorrhage, or death. Treatment strategies are directed towards regulation of blood pressure and limitation of rises in cerebral perfusion.

AUTHOR CONTRIBUTIONS

Conception and design: KM, SM
Analysis and interpretation: KM, SM
Data collection: SM, KM, GS
Writing the article: SM, KM
Critical revision of the article: SM, KM, GS
Final approval of the article: VA
Statistical analysis: SM, KM
Obtained funding: N/A
Overall responsibility: KM

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