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HOW TO IDENTIFY RISK FOR CEREBRAL HYPERPERFUSION SYNDROME AFTER CAROTID REVASCULARIZATION PROCEDURES

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ABSTRACT:

Cerebral hyperperfusion syndrome (CHS) is a rare, but potentially severe complication after carotid revascularization procedures and could be a result of absence or severe impairment of cerebral autoregulatory mechanisms. It is classically described as an acute neurologic deficit occurring after a carotid procedure, associated with severe hypertension and preceded by a severe headache. Also, CHS represents a variety of neurological symptoms, ranging from severe ipsilateral headache to seizures and focal neurologic deficit and even death. Although well described, the exact pathophysiology behind it is still unknown, due to its rarity. Researchers have been trying to establish risk factors that contribute to development of symptoms. This has been proven as a difficult task, given the rarity and multiple confounding factors in patient groups that underwent these procedures. The purpose of this review is to summarize the readily available data and to focus on pathophysiology, with an emphasis on identifying the patients at risk preoperatively, how to prevent the development of CHS and treatment of this condition.

Key words: Cerebral hyperperfusion syndrome, Reperfusion, Intracerebral hemorrhage, Internal carotid artery endarterectomy, Internal carotid artery stenting.

SAŽETAK:

Sindrom cerebralne hiperperfuzije je retka ali potencijalno ozbiljna komplikacija moždanih revaskularizacionih procedura. Može biti posledica nedostatka ili oštećenja cerebralnih autoregulatornih mehanizama. Obično se opisuje kao akutni neurološki događaj nakon revaskularizacionih procedura, praćen izraženom hipertenzijom i snažnom glavoboljom. Takođe sindrom cerebralne hiperperfuzije predstavlja niz neuroloških simptoma – od već pomenute snažne ipsilateralne glavobolje, do fokalnih neuroloških deficita pa čak i smrti. Iako dobro opisan, tačni patofiziološki mehanizmi koji dovode do razvijanja ovog sindroma su i dalje nepoznati. Istraživači pokušavaju da odgonetnu koji faktori rizika doprinose razvijanju simptoma, što se pokazalo kao veoma težak zadatak, zbog toga što se retko javlja, kao i zbog mnogobrojnih pridruženih faktora koji postoje u pacijenata kod kojih se ovakve procedure rade. Svrha ovog pregleda je da se sumiraju postojeći podaci, sa posebnim osvrtom na patofiziologiju i preoperativnu identifikaciju rizičnih pacijenata, kao i sprečavanje odnosno lečenje ovog sindroma.
1. INTRODUCTION

Atherosclerotic lesions of the extracranial part of carotid arteries are one of the most common causes of stroke\(^1\). Carotid endarterectomy (CEA) and carotid stenting (CAS) are therapeutic options in the prevention of primary and secondary stroke in the patients with significant stenosis of internal carotid arteries (ICA)\(^2\). Although both of these procedures are considered to be relatively safe, there are certain neurological and non-neurological complications. One of more serious is cerebral hyperperfusion syndrome (CHS). Albeit rare, CHS is a potentially devastating event that can even be fatal if intracranial hemorrhage (ICH) occur\(^3\)-\(^7\). In this review, we will summarize available data on this phenomenon and focus on its pathophysiology, prevention, diagnostics and management.

2. DEFINITION OF HYPERPERFUSION AND CEREBRAL HYPERPERFUSION SYNDROME

First and foremost we must differentiate between the concept of hyperperfusion and CHS. In general, hyperperfusion occurs when cerebral blood flow (CBF) in the revascularized territory increases by 100% or more with respect to the baseline values\(^8\). However, not every patient with hyperperfusion develops CHS. The term CHS was used to describe the clinical entity consisting of symptoms triad: ipsilateral migraine-like headache, seizure, and transient focal neurologic deficits in the absence of cerebral ischemia in combination with high post-procedural blood pressure (BP). This was first described by Sundt in 1981\(^9\).

3. PATHOPHYSIOLOGY

Although this phenomenon is well described in the literature, not much is known about pathophysiological mechanisms which lead to CHS. As mentioned before, not all patients with increased CBF develop CHS. In series conducted by Ogasawara et al., 16.7% - 28.6% of the patients with an increase in CBF 100% developed CHS\(^10\). Also, in some cases with slightly elevated CBF, CHS can be developed\(^11,12\). That leads to the conclusion that other factors play a role in the occurrence of CHS.

All authors agree that two interlinked and synergized mechanisms lead to increased CBF; first, impaired cerebral autoregulation and second increased postprocedural BP\(^13,18\).

The main autoregulatory mechanism is the cerebrovascular reactivity (CVR), the ability of the arterioles to constrict or dilate in response to the alterations of blood flow or
to other stimuli (i.e., hypocapnia)\textsuperscript{13}. In order to compensate the reduced blood flow to the brain in patients with severe ICA stenosis arteriolae remain in the state of maximal dilation to maintain sufficient cerebral blood supply.

The severity of CVR impairment is likely due to several different factors – degree of ipsilateral and contralateral ICA stenosis, an incomplete circle of Willis and insufficient collateral flow\textsuperscript{3, 14,15}. However, the syndrome has been described even in patients without contralateral lesions, thereby giving even more significance to disturbed autoregulation mechanisms that can develop in the region of ipsilateral stenosis even without severe contralateral ICA lesion. After CEA, 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\textsuperscript{16}. 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\textsuperscript{17}.

Increased BP after CEA is largely attributed to baroreceptor reflex failure after denervation during the procedure. This is especially expressed 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 in central and peripheral norepinephrine levels and a subsequent further elevation of the systemic blood pressure.

Increased CBF, which can not be controlled by autoregulatory mechanisms, leads to transudation of fluid into the pericapillary astrocytes and interstitium. This results in vasogenic white matter edema, especially in the vertebrobasilar circulation territory of the posterior parietal and occipital regions. New studies on rodent models are trying to shed more light on mechanisms of occurrence of CHS\textsuperscript{49}.

4. CLINICAL PRESENTATION, RISK FACTORS AND DIAGNOSTICS

CHS can develop at any time; immediately after the procedure to up to a month later, but most patients develop symptoms within the first few days (mean 5 days)\textsuperscript{7,22,23}.
Although most commonly appears after CAS and CEA, CHS has been described and after subclavian artery stenting and after endovascular reconstruction of carotid artery in high-flow carotid-jugular fistula. The reported incidence rate of CHS and ICH after CEA is 1.9% and 0.37% and 1.16% and 0.74% after CAS. Most common symptoms include: headaches, fluctuation of consciousness, confusion and focal neurologic deficit. Headaches are usually moderate to severe, ipsilateral to the revascularised artery, pounding and migrenous. Focal neurologic deficit is a result of cerebral edema and usually is transient. It includes cortex derived symptoms – hemiplegia, hemiparesis, hemianopsia, dysphasia, seizures and less commonly ataxia and visual disorders. Seizures can sometimes present even as status epilepticus.

By far the most devastating complication of CHS is ICH. It is a very rare complication, as previously stated, but it is often fatal (36-63%), and up to 80% of surviving patients are left with significant morbidity. Since ICH is associated with CHS, symptoms of increased intracranial pressure can be present (nausea, vomiting, or altered sensorium). There is a form of hyperacute ICH that occurs within hours after CAS, and it is almost always unpreventable since it occurs without prodromal signs. It could be a result of rupture of perforating arteries in basal ganglia which are exposed with suddenly normalized perfusion pressure after CAS.

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>INCIDENCE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deterioration of consciousness, confusion</td>
<td>37.1</td>
</tr>
<tr>
<td>Headache</td>
<td>30.6</td>
</tr>
<tr>
<td>Epileptic disturbances, focal seizures</td>
<td>25.8</td>
</tr>
<tr>
<td>Motor disturbances (hemiparesis, hemiplegia)</td>
<td>17.7</td>
</tr>
<tr>
<td>Abnormal speech, aphasia</td>
<td>6.4</td>
</tr>
<tr>
<td>Nausea</td>
<td>4.8</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>4.8</td>
</tr>
<tr>
<td>Psychotic disorders</td>
<td>3.2</td>
</tr>
<tr>
<td>Visual disturbances (hemianopsia)</td>
<td>3.2</td>
</tr>
<tr>
<td>Ataxia</td>
<td>1.6</td>
</tr>
</tbody>
</table>
The occurrence of CHS is multifactorial, while cerebral perfusion and autoregulation are individualized in each patient. CBF changes in each patient is variable, and there is no proof that degree of stenosis is directly linked with CBF variations\textsuperscript{30}. This could be explained by the presence of collateral circulation, and the degree of cerebral autoregulation impairment in each patient. Various studies indicated a potential role for risk factors, definitive prediction of subgroups of patients with an 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 multifactorial contribution in the pathogenesis of the syndrome. Risk factors that have been described to have a significant involvement in developing CHS are shown in table II.

**PREOPERATIVE**

- Long standing hypertension with cerebral microangiopathy
- Diabetes mellitus
- Older age
- Recent contralateral CEA
- High-grade ipsilateral stenosis
- Contralateral occlusion/high grade stenosis
- Incomplete circle of Willis
- Attenuated cerebrovascular reactivity after acetazolamide challenge

**PERIOPERATIVE**

- Intraoperative distal carotid pressure of <40 mmHg
- High doses of volatile halogenated hydrocarbon anesthetics
- Periprocedural cerebral infarction
- Intraoperative ischemia
- Refractory postoperative cerebral hyperperfusion

**POSTOPERATIVE**

- Postoperative hypertension
Administration of anticoagulants or antiplatelet agents

Table 2. – risk factors for developing CHS

Some risk factors are identified as more significant than others to increase the risk of CHS; low pulsatility index, severe ipsilateral or contralateral carotid disease, bilateral carotid artery stenosis, and incomplete circle of Willis\textsuperscript{14,31,32}. Additionally, one study suggests that interval between two procedures should be no less than 3 months\textsuperscript{3}. That study reports 6.6% of patients developing CHS after bilateral CEA within less than 3 months. The authors suggested that inconsistencies in baroreceptor function may be a causative factor for CHS.

The use of anticoagulants and antiplatelet agents is routine after CEA and CAS. 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\textsuperscript{26,27}.

Several techniques have been suggested to identify patients at risk for developing CHS. Most widely available method is transcranial color Doppler (TCD). It is used to determine CBF changes via monitoring cerebral blood flow velocities (CBFV) changes in intracranial vessels. TCD is used to assess cerebrovascular reactivity using vasodilator agents such as acetazolamide, CO2 inhalation, or the breath holding test\textsuperscript{33-35}. Blood flow is severely restricted when there is a critical ICA stenosis present and, after it is removed, the blood flow increases dramatically. In patients with badly impaired cerebral autoregulation this dramatically increases mean flow velocity in middle cerebral artery (MCA)\textsuperscript{33-35}. Preoperative drop in CBFV is indicative of hypoperfusion and can lead to postoperative hyperperfusion and thus the CHS.

However, TCD has several limitations. First is an insufficient cranial window and second experience of the operator\textsuperscript{23,36}. Despite those drawbacks, TCD findings should always be evaluated carefully. Results in TCD studies demonstrate that blood flow redistribution, through the anterior communicating pathway and the ophthalmic artery is achieved, in case of contralateral ICA stenosis, and through the posterior communicating pathway in patients with contralateral ICA occlusion. Asher reported a significant increase
in mean internal carotid artery volume flow (MICAVF) in all patients with CHS during the symptomatic period. After the symptoms receded, the flow volume returned to normal³.

Standard computerized tomography (CT) has limited value preoperatively and can be completely normal postoperatively. It can still be useful as a quick tool to remove suspicion of ICH. Also, brain edema that can be seen early can be indicative of CHS (fig. 1). A recent study showed pretreatment CT perfusion imaging (CTP) with acetazolamide challenge could identify patients at risk for CHS after CAS. CTP maps were assessed for absolute and relative cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT). Although the CTP parameter that most accurately identified patients at risk for HPS was the absolute value of post-acetazolamide MTT, resting MTT was sufficiently accurate⁴. Single photon emission CT (SPECT) can detect alterations in preoperative cerebral perfusion (after administering acetazolamide). It is also very useful in differentiating between cerebral ischemia and hyperperfusion, and identifying patients at risk of CEA. However, some studies didn’t find any correlation between preoperative asymmetry in brain perfusion in rest and CHS⁴¹. Ogasawara et al suggested that hyperperfusion lasting at least to the three postoperative days on SPECT predisposes to CHS development⁴².

Fig. 1 Brain CT showing a)- brain swelling as a result of CHS  
b)- Older date ischemic lesion after a stroke
Magnetic resonance imaging (MRI) techniques also proved useful in diagnosis of CHS. Especially power-weighted MRI that can reveal intrahemispheric differences in CBF in patients after CEA\textsuperscript{11}. However as it is not quantitative method PWI MRI can only be used in absence of contralateral steno-occlusive ICA 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 of diagnosing CHS have been proposed such as intraoperative EEG and ocular pneumoplethysmography. However, these methods are yet to prove their worth.

5. MANAGEMENT OF HYPERPERFUSION SYNDROME

Most important stage in the prevention of CHS is aggressive BP management postoperatively. This needs to be performed in order to prevent the most dangerous complication of CHS, the ICH. Further reduction of BP even in normotensive patients should be considered, if hyperperfusion is detected, as they can develop hypertension later. Drugs like labetalol and clonidine should be used. Vasodilating drugs with hydralazine, nitrate and Ca\textsuperscript{+} channel blockers should be avoided, as they can add to already existing brain swelling\textsuperscript{22,45,46,50}. Beyond this criteria, there is no evidence favoring any other specific drug. Also, beta blockers should be limited\textsuperscript{46,50}.

Cerebral edema treatment includes adequate sedation, hyperventilation, manitol administration and hypertonic saline solution\textsuperscript{10, 42,44}. Corticosteroids have been tried with, but their effectiveness remains uncertain\textsuperscript{10,42,44}.

Oxygen-derived free radicals produced during ischemia have been implicated in ischemia-reperfusion injury. In cerebral tissue, these radicals could lead to endothelial dysfunction and a break in blood brain barrier, leading to post-ischemic hyperperfusion, edema and hemorrhage. 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{47}.
6. CONCLUSION:

CHS is rare but potentially deadly complication of brain revascularization procedures. Two key, interlinked and synergistic mechanisms play part in its occurrence – impaired cerebral autoregulation and elevated BP after procedure. It is important to understand the complexity and multiple factors that contribute to symptom appearance. Although different studies developed risk factors, the determination of subgroups of patients in danger of developing CHS after CAS or CEA is still not feasible. If not treated promptly and properly CHS can lead to fatal ICH. Treatment strategies are developed towards regulating BP, reducing brain swelling, and most importantly limiting the extreme bloodflow rising in potentially at risk patient.

REFERENCES:


Fig 1. – Brain CT showing a) brain swelling as a result of CHS
b) Older date ischemic lesion after a stroke
CT- computerized tomography
CHS – Cerebral hyperperfusion syndrome

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