Diagnosing Hyperperfusion Syndrome: CT Perfusion or Transcranial Doppler?

David Orion MD1,2, Yarden Yavne1, Shlomi Peretz MD1 and Gili Givaty MD1

Departments of 1Neurology and 2Radiology, Division of Interventional Neurology, Sheba Medical Center, Tel Hashomer, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

1Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

KEY WORDS: cerebral hyperperfusion syndrome (CHS), computed tomography (CT) perfusion, transcranial Doppler (TCD), carotid stenosis, carotid endarterectomy

Cerebral hyperperfusion syndrome (CHS) is an uncommon complication of carotid stenosis revascularization procedures. The incidence of CHS varies in the literature, occurring in 0.2–18.9% of patients who undergo carotid endarterectomy and 1.1–25% of patients undergoing carotid angioplasty and stent placement [1]. The current definition for cerebral hyperperfusion syndrome is a sudden increase in cerebral blood flow [1,2]. It is hypothesized that hyperperfusion develops as the result of prior damage to the cerebrovascular mechanism of autoregulation [3]. CHS classically presents a few days after the procedure, with a range of acute neurological symptoms such as headache, severe hypertension, focal seizure activity and focal neurological deficits, and can result in ipsilateral intracerebral edema or hemorrhage [4]. Risk factors for developing CHS include severe (over 90%) ipsilateral stenosis, impaired collateral blood flow as a result of progressive occlusive disease in extracranial cerebral vessels, incomplete circle of Willis, and perioperative and postoperative hypertension [3,5].

CHS is a neurological crisis with a 40% chance of intracranial hemorrhage and death if not diagnosed and treated promptly [2]. Treatment today mainly consists of symptom management, including strict blood pressure control, anticonvulsants and careful monitoring with electroencephalography. Since prevention is possible by applying rigorous blood pressure control, there is a clear need for an accurate method that will correctly identify patients at risk for developing this syndrome prior to the appearance of symptoms, as well as rapidly diagnose the syndrome once the symptoms have begun.

There are a number of indications that transcranial Doppler (TCD) may be used for assessing even subclinical postoperative hyperperfusion. TCD, which measures the changes in the mean blood velocity (Vmean) in the major cerebral vessels, can assist in hyperperfusion monitoring and subsequent treatment adjustment [1,2].

CT perfusion (CTP) is known as a quick and accessible tool for the evaluation of brain perfusion and is used most often for the assessment of acute stroke. To obtain the perfusion data a bolus of iodinated contrast material is injected followed by dynamic sequential scanning of the brain. Post-processing software is used to analyze the raw data and calculate quantitative parameters, such as cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT) and time to peak (TTP), in different regions. Lastly, the two hemispheres are compared to detect areas with a perfusion disparity. As a perfusion imaging modality, CTP has proven to be effective for rapid diagnosis and appraisal of the scope of CHS. It has been proposed that performing CTP before the vascularization procedure may help predict patients at high risk for developing CHS [4]. In this report, we present a 74 year old patient who developed severe CHS as a result of carotid endarterectomy and discuss the abilities of CTP as a diagnostic tool, as compared to TCD.

PATIENT DESCRIPTION

A 74 year old woman was admitted to our emergency department with a left femoral neck fracture due to a fall. Her past medical history included diabetes mellitus, hypertension and hyperlipidemia. A brain CT ruled out hemorrhage but demonstrated slight ischemic changes. At questioning, the patient reported an intermittent weakness in her left arm during the preceding month. Ultrasound Doppler of the carotid arteries demonstrated critical stenosis of the right internal carotid artery, and brain magnetic resonance imaging (MRI) revealed a number of diffusion weighted imaging (DWI)-positive lesions in the right corona radiata, indicating minor acute stroke. A successful endarterectomy of the right internal carotid artery was performed a week after her initial admission and no subsequent neurological dysfunction was observed. Three days later, closed reduction surgery with internal fixation was performed on her left femoral artery following treatment with clopidogrel and aspirin.

Three days after the femoral fracture surgery and 6 days after the carotid endarterectomy, the patient awoke complaining of weakness in her left arm, which quickly developed into repeated focal seizures of her left arm and left hemianopsia. A treatment regimen of 5 mg diazepam and
2 g levetiracetam was administered and a brain CT, including CT angiography (CTA) and CTP, were performed immediately. Hyperperfusion of the right hemisphere was prominent in the CTP and CTA, appearing mainly in the occipital region with a slight emphasis in the frontal region as well. On the CTA a large right posterior communicating artery and a hypoplastic segment of the right P1 segment emerging from the basilar artery were observed, explaining the intensity of the hyperperfusion in the occipital region. In the CTP, the CBF and CBV parameters were significantly elevated and MTT and TTP were significantly decreased in the right hemisphere in comparison with the left. A perfusion MRI performed 2 days later showed similar findings. An EEG demonstrated a focal epileptic area in the right hemisphere.

Transcranial Doppler the following day revealed that the Vmean (cm/sec) of the right cerebral vessels was in the normal range and similar to the Vmean (cm/sec) of the left cerebral vessels, thus failing to diagnose the presence of hyperperfusion in the right hemisphere (right MCA 50, ACA 42, PCA 42; left MCA 57, ACA 51, PCA 29). An additional TCD the next day revealed a slight increase in the Vmean (cm/sec) of the right cerebral vessels yet still within normal range (right MCA 90, ACA 62; left MCA 70, ACA 47).

Various anticonvulsants were prescribed, including phenytoin, levetiracetam and topiramate, which led to a gradual improvement on EEG in the following weeks. Three weeks later a follow-up CT revealed a slight asymptomatic hemorrhage in the right frontal region which resolved after aspirin was temporarily stopped. The patient continued to improve and was discharged to rehabilitation a month later without any major neurological deficits.

**COMMENT**

Cerebral hyperperfusion syndrome is a rare, yet potentially fatal complication of carotid revascularization procedures that can result in neurological impairment and even death if not diagnosed quickly [2,3]. Although the pathophysiology is not completely understood, it is currently held that hyperperfusion results from the impairment of the autoregulation mechanism in the cerebral arterioles, which causes them to react to the increased blood flow with vasodilatation and increased permeability. The degree and duration of the hyperperfusion prior to the revascularization are closely associated with the endothelial dysfunction of the arterioles, thus clarifying the connection between preexisting severe carotid stenosis and a higher risk of CHS. Moreover, it has been shown that a low cerebral vascular reserve negatively impacts the region’s ability to respond appropriately to the sudden increase in blood flow [5]. In addition, it was suggested that the free radicals released during reperfusion may also contribute to the development of post-ischemic hyperperfusion and edema [1]. Since hypertension further damages the arterioles, the current treatment regimen relies on rigorous blood pressure control in an effort to restore autoregulation and anticonvulsants for symptom management.

Although several risk factors for CHS are known, the demand for a method that can accurately predict patients at risk for developing CHS so they might be pre-treated and closely monitored remains valid. Prior screening with MR angiography (MRA) and acetazolamide-challenged single-photon emission CT (SPECT) have both been suggested as ways to detect patients at risk for CHS development due to low vascular reserve. MRA is used for evaluation of potential escape routes for the increased blood flow while SPECT detects patients with poor escape routes that do not respond to the acetazolamide challenge. The main drawback of these methods is that both MRI and SPECT are not widely available tools in most hospitals [5]. A significant difference in MTT, TTP and CBV between the hemispheres as demonstrated on CTP, a quick and more accessible imaging modality, was also associated with increased risk for CHS, thus enabling its use as a screening technique [4].

Both TCD and CTP have proven to be rapid and simple techniques for CHS diagnosis once indicative symptoms have appeared. TCD monitors the Vmean of the cerebral blood vessels which increases during hyperperfusion, while CTP quantifies and compares perfusion between the two hemispheres [2,4]. Although TCD is considered a sensitive tool for CHS evaluation, it is an operator-dependent technique that requires a constant vessel diameter and laminar blood flow in order to accurately reflect the blood volume flow [2], constraints that do not apply to CTP. CTP also has the additional advantage of differentiating between CHS and other carotid intervention complications, such as thromboembolic and hemorrhagic stroke [4]. It should be noted that MR perfusion can be used to assess brain perfusion similarly to CTP; however, it is not a relevant tool for rapid diagnosis in most hospitals.

In our case, the patient presented with clear risk factors that potentially contributed to the development of CHS after carotid revascularization – severe symp-
tomatic stenosis, dyslipidemia, and hypertension. Hyperperfusion was demonstrated quickly and clearly on CTP as opposed to TCD, and the rapid diagnosis allowed the proper treatment to be administered in a timely manner. This case report demonstrates the usefulness of CT perfusion for rapid diagnosis of CHS following carotid revascularization and urges the inclusion of perfusion modalities such as CTP or MR perfusion in the clinical workup of patients with symptoms indicative of CHS.

Correspondence
Dr. D. Orion
Dept. of Neurology, Sheba Medical Center, Tel Hashomer 52621, Israel
email: david.onlion@sheba.health.gov.il

References

Capsule

Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence

Noury et al. re-analyzed SmithKline Beecham’s Study 329 (published by Keller and colleagues in 2001), the primary objective of which was to compare the efficacy and safety of paroxetine and imipramine with placebo in the treatment of adolescents with unipolar major depression. The re-analysis under the restoring invisible and abandoned trials (RIAT) initiative was performed to determine whether access to and re-analysis of a full dataset from a randomized controlled trial would have clinically relevant implications for evidence-based medicine. The study, a double-blind randomized placebo-controlled trial, was conducted in 12 North American academic psychiatry centers from 20 April 1994 to 15 February 1998. The participants were 275 adolescents with major depression of at least 8 weeks duration. Exclusion criteria included a range of comorbid psychiatric and medical disorders and suicidality. Participants were randomized to 8 weeks double-blind treatment with paroxetine (20–40 mg), imipramine (200–300 mg), or placebo. The efficacy of paroxetine and imipramine was not statistically or clinically significantly different from placebo for any pre-specified primary or secondary efficacy outcome. HAM-D scores decreased by 10.7 (least squares mean) (95% confidence interval 9.1–12.3), 9.0 (7.4–10.5) and 9.1 (7.5–10.7) points, respectively, for the paroxetine, imipramine and placebo groups ($P = 0.20$). There were clinically significant increases in harms, including suicidal ideation and behavior and other serious adverse events in the paroxetine group and cardiovascular problems in the imipramine group. The authors concluded that neither paroxetine nor high dose imipramine showed efficacy for major depression in adolescents, and there was an increase in harms with both drugs. Access to primary data from trials has important implications for both clinical practice and research, including that published conclusions about efficacy and safety should not be read as authoritative. The re-analysis of Study 329 illustrates the necessity to make primary trial data and protocols available to increase the rigor of the evidence base.

Biol 2015; 351: h4320
Eitan Israeli

Capsule

A close up view of retrovirus spreading

Viral infections typically begin with a small number of viral particles gaining access to the host at a specific tissue site. But how do viruses that cause systemic infections, such as HIV, spread more widely? Sewald et al. visualized how the retroviruses murine leukemia virus (MLV) and HIV spread within lymph nodes in mice. Specific macrophages that line the lymph-draining sinuses in lymph nodes first captured the virus using the carbohydrate-binding protein CD169. These macrophages subsequently transferred virus to the B1 subclass of B lymphocytes, which migrated further into the lymph node, disseminating the virus more widely.

Science 2015; 350: 563
Eitan Israeli

“It’s good to have money and the things that money can buy, but it’s good, too, to check up once in a while and make sure that you haven't lost the things that money can't buy”

George H. Lorimer (1867–1937), American journalist and author