

# Bilateral reperfusion injury after carotid endarterectomy with contralateral carotid occlusion

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## Abstract

Cerebral hyperperfusion syndrome represents a clinical spectrum characterized by severe unilateral headache, acute changes in mental status, vomiting, seizures, focal neurologic deficits, and, in its most severe form, intracranial hemorrhage. With the exception of one early case report, reperfusion injury to the brain following carotid endarterectomy has been reported only ipsilateral to the side of surgery. We report the unique case of a patient with symptomatic severe right internal carotid artery stenosis and contralateral carotid occlusion who underwent carotid endarterectomy complicated by cerebral hyperperfusion syndrome and associated bilateral intracranial hemorrhage.

## Keywords

Reperfusion injury, carotid endarterectomy, contralateral carotid occlusion, hyperperfusion syndrome, high risk

## Introduction

Cerebral hyperperfusion syndrome (CHS) represents a clinical spectrum characterized by severe unilateral headache, acute changes in mental status, vomiting, seizures, focal neurologic deficits, and, in its most severe form, intracranial hemorrhage (ICH). The incidence of CHS after carotid endarterectomy (CEA) is estimated to be less than 2%, with intracranial hemorrhagic complications occurring in 0.4% of patients.<sup>1,2</sup> A myriad of factors are believed to play a role in the development of CHS, including ischemia-reperfusion injury, baroreceptor dysfunction, oxygen-derived free radicals, and intraoperative ischemia. Of particular importance, increasing evidence has linked CHS to the >100% over baseline increase in regional blood flow following carotid revascularization, a rapid physiologic change likely exceeding the autoregulatory capacity of maximally dilated cerebral arterioles that become chronically adapted to lower post-stenosis arterial pressures.<sup>3</sup> Increased hydrostatic pressure, especially when exacerbated by perioperative hypertension, predisposes to vascular disruption, edema formation, and ICH.

With the exception of one early case report,<sup>4</sup> reperfusion injury to the brain following CEA has been reported only ipsilateral to the side of surgery. We report the unique case of a patient with

symptomatic severe right internal carotid artery (ICA) stenosis and contralateral carotid occlusion (CCO) who underwent CEA complicated by CHS and associated bilateral ICH.

## Case report

A 66-year-old male with a history of squamous cell cancer of the tongue who had previously undergone primary resection with right-sided modified radial neck dissection and neck radiation therapy was transferred to our facility with visual disturbances and left upper extremity paraparesis. Magnetic resonance angiography (MRA) of the brain demonstrated bilateral anterior circulation embolic infarctions, as well as critical carotid stenosis of the right ICA and complete occlusion of the left ICA (Figure 1a). During preoperative evaluation, the patient was noted to have multiple paroxysmal neurologic events that were intermittently associated with transient bradycardia and hypotension.

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Therapeutic intravenous anticoagulation was initiated due to concern for crescendo transient ischemic attacks (TIA) and potential for recurrent stroke. Given the high-risk nature of his presentation, the patient was informed of all risks and benefits associated any surgical intervention.

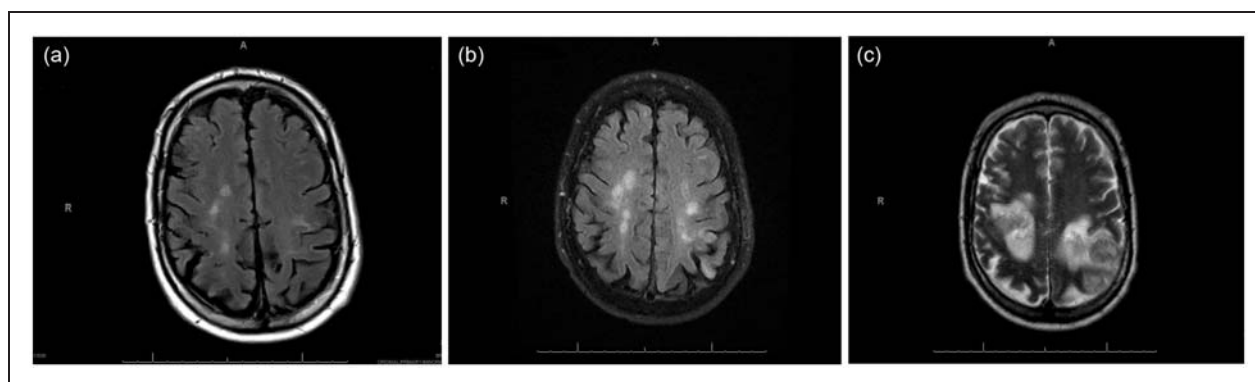
Seventeen days following initial onset of stroke, the patient underwent right CEA using continuous electroencephalographic (EEG) monitoring. The operation was carried out from a slight lateral approach using one of two previous curvilinear incisions overlying the anterior border of presumed remnant sternocleidomastoid. To facilitate exposure of the common carotid artery, the sternocleidomastoid was detached from its midline sternoclavicular insertion site and retracted in a lateral direction. Multiple episodes of bradycardia occurred during dissection of the ICA which responded promptly to the administration of 1% xylocaine directly into the carotid bulb and perivascular tissue. There was no evidence of any slowing on EEG monitoring following clamping of the right ICA. A Sundt shunt was immediately available but not used. Endarterectomy and patch angioplasty of the right ICA were then performed using previously harvested right greater saphenous vein. Intraoperative duplex revealed excellent flow signals throughout the right common, internal, and external carotid arteries. Neuromonitoring remained unchanged during the entire duration of the operation. Intravenous anticoagulation, which the patient had been maintained on preoperatively, was discontinued. The patient awoke from general anesthesia neurologically intact.

In the first 6 h postoperatively, the patient exhibited severe hypertension (mean arterial blood pressure, 100–120 mm Hg) and developed right upper extremity paraplegia. Arterial hypertension was initially refractory to boluses of metoprolol but was ultimately aggressively controlled following initiation of a

nicardipine infusion (goal mean arterial pressure of 70–90 mm Hg). Brain MRA on postoperative day one revealed new and increased regions of small hemorrhagic infarcts in the left occipitoparietal lobe, right head of the caudate, and bilateral superior parietal lobes (Figure 1b). While paraplegia of the right upper extremity persisted over the ensuing two days, the patient was coherent and able to participate with physical therapy. On the morning of postoperative day three, the patient became minimally responsive and was noted to have quadriplegia and a left gaze preference. Repeat MRA demonstrated multiple evolving bilateral infarctions with new widespread hemorrhagic transformation (Figure 1c). The patient was immediately intubated for airway protection and transferred to the neurosurgical intensive care unit. Given the poor prognosis associated with bilateral motor cortical involvement, the family elected to withdraw care. The patient expired on postoperative day five.

## Discussion

The patient in our report possessed multiple important risk factors for the development of CHS, including recent stroke, non-elective CEA, hypertension, and high-grade ipsilateral stenosis with CCO. Several pathologic studies and clinical series have demonstrated that restoration of full cerebral blood flow into an area of recent ischemia or frankly necrotic cerebral tissue can lead to fatal ICH.<sup>5–7</sup> Similarly, Maas et al.<sup>8</sup> identified patients undergoing CEA urgently after a symptomatic event to be at increased risk for the development of CHS in their prospective analysis of 841 patients undergoing CEA. Furthermore, critical ( $\geq 90\%$ ) ipsilateral carotid stenosis in the setting of compromised collateral cerebral blood flow has been shown to contribute to the development of CHS.<sup>9–11</sup> Ouriel et al.<sup>12</sup> examined outcomes



**Figure 1.** Magnetic resonance angiography of the brain 17 days preoperatively (a), postoperative day 1 (b), and postoperative day 3 (c) demonstrating the evolution of multiple bilateral embolic infarctions and associated hemorrhagic transformation.

in 1471 patients undergoing CEA over a six-year period and found that the 0.75% ( $n=11$ ) of patients who experienced postoperative ICH had both a higher degree of ipsilateral and contralateral carotid stenosis, as well as a higher rate of CCO. Additional flow-related risk factors for CHS include an incomplete circle of Willis, intracerebral steal, and diminished cerebrovascular reactivity or reserve as detected on brain imaging after administration of acetazolamide.<sup>13,14</sup> In a review encompassing over 24,000 patients undergoing open or endovascular carotid revascularization, postoperative hypertension was also found to be a major risk factor for CHS and ICH.<sup>13</sup> This finding was corroborated in a separate review article which noted the mean postoperative systolic blood pressure of patients who went on to develop CHS was 164 mm Hg, with the cumulative incidence of cases increasing considerably above systolic pressures of 150 mm Hg.<sup>15</sup> Long-standing, poorly-controlled preoperative hypertension is also common finding among patients who develop CHS and may represent an element of baseline endothelial dysfunction secondary to hypertensive microangiopathy.<sup>3,16,17</sup>

CHS occurred early in the postoperative period in our patient, with focal neurologic deficits and early signs of evolving ICH evident on imaging within 24 h of CEA. Ninety-two percent of all cases involving CHS occur within the first week following carotid revascularization.<sup>15</sup> The peak incidence of intracranial hypertension following CEA has been observed to be between the third and fifth postoperative days (range 2–17 days), although cases occurring immediately after surgery have been well documented.<sup>5,12,16</sup> The rapid neurologic decline and subsequent death in our patient is consistent with the poor outcomes generally seen in these patients, including a 37–80% mortality rate and 20–37% risk of poor functional recovery in those who survive.<sup>18</sup>

The complexity of the present case highlights several important issues, including the nature and timing of carotid revascularization after a symptomatic event, impact of CCO in patients undergoing CEA, and perioperative management of CHS. First, we underwent significant debate regarding the optimal method of carotid revascularization in our patient. The final operative strategy was based on our judgment that the risk of neurologic and cardiovascular morbidity associated with carotid angioplasty and stenting (CAS) exceeded that from conventional CEA due to the critical degree of carotid stenosis (string sign on preoperative imaging), preoperative hemodynamic lability, and appearance of vulnerable atheromatous plaque on imaging. While technically more demanding, CEA in patients with prior neck surgery and radiation can be performed with a comparable risk of perioperative stroke and

death relative to other patients undergoing carotid intervention.<sup>19</sup> Autogenous vein was used in our patch angioplasty in order to address issues related to the potential for delayed wound healing.

There is increasing evidence that CEA can be performed safely within a shorter period of time following ischemic cerebrovascular events. Indeed, current research shows that deferral of carotid revascularization is associated with up to a 10% risk of recurrent ischemia events in the first seven days.<sup>20,21</sup> Annambhotla et al.<sup>22</sup> analyzed their series of 312 patients who underwent CEA following stroke or TIA and found no difference in the 30-day and long-term adverse outcomes relative to timing of intervention, including a perioperative stroke rate of 0% in early (<4 weeks) and 1.6% in late (>4 weeks) CEA. Pooled data from the North American Symptomatic Carotid Endarterectomy Trial and the European Carotid Surgery Trial similarly showed that the 30-day perioperative risk of stroke or death was unrelated to the time since the last symptomatic event and was not increased in patients operated <2 weeks after non-disabling stroke; this perioperative stroke or death risk in patients with non-disabling stroke and incomplete recovery at randomization was 10.4% at <2 weeks, 4.4% at 2–4 weeks, 8.0% at 4–12 weeks, and 7.2% at >12 weeks.<sup>20</sup> Based on these data, early intervention within two weeks of symptom onset is considered the standard of care for the majority of patients with symptomatic carotid artery disease.

The influence of CCO and the utility of shunting on the outcome of carotid revascularization are debated. While several series have failed to demonstrate any meaningful impact of CCO on the occurrence of neurologic events following CEA,<sup>23–25</sup> separate subgroup analyses of randomized controlled trials in both symptomatic and asymptomatic patients have identified CCO as an independent risk factor for adverse CEA outcomes.<sup>26–28</sup> Such reports have cited a risk of perioperative neurologic complications of up to 14% in these patients. A recent systematic review concluded that patients undergoing CEA in the presence of an occluded contralateral carotid artery had an increased perioperative and early postoperative risk of stroke (3.3% vs. 1.9%; odds ratio (OR), 1.65; 95% confidence interval (CI), 1.30–2.09;  $p < 0.001$ ), TIA (2.2% vs. 1.4%; OR, 1.57; 95% CI, 1.11–2.21;  $p = 0.01$ ), and death (1.1% vs. 0.5%; OR, 1.76; 95% CI, 1.19–2.59;  $p = 0.004$ ).<sup>29</sup> While the same study found that the increased risk of stroke in patients with CCO persisted even after comparing homogenous groups of patients by symptomatic status, the clinical significance of these results may still be limited given that none of these factors reached an OR of 2.0. In another recent review, Faggioli et al.<sup>30</sup> observed a 3.6% rate of

combined cerebral events and death in patients with CCO undergoing CEA compared to 8.2% in those undergoing CAS. The authors concluded that CCO should be considered a risk factor in CEA, but not in CAS. Other studies have not supported the superiority of CAS over CEA in the presence of CCO.<sup>31</sup>

In regards to the utility of intravascular shunting in CEA cases involving CCO, comparable rates of stroke and death have been demonstrated even in spite of a higher rate of shunting.<sup>32–34</sup> Schneider et al.<sup>32</sup> reviewed their experience of 564 primary CEAs (57 cases with CCO, 507 cases with patent contralateral carotid arteries). Despite patients with CCO having increased rates of EEG changes associated with carotid clamping (39% vs. 16%,  $p < 0.001$ ) and a correspondingly higher use of intravascular shunting (55% vs. 13%,  $p < 0.001$ ), no difference in early ipsilateral stroke (0% vs. 1%,  $p = 1.0$ ), early ipsilateral TIA (0% vs. 1.6%,  $p = 1.0$ ), or perioperative death (2% vs. 0.2%,  $p = 0.19$ ) was observed. More recently, Goodney et al.<sup>35</sup> noted a higher risk of 30-day stroke or death during CEA among surgeons who selectively placed shunts and lower for surgeons who routinely placed shunts (5.6% vs. 1.5%,  $p = 0.05$ ) in the setting of CCO. The role of prophylactic shunting in the setting of CCO as a means of minimizing potential for ischemia-reperfusion injury appears justified. However, we caution surgeons to consider their own practice pattern in shunt use preoperatively when faced with a patient who may likely require shunt placement.

Early detection of CHS and aggressive blood pressure control is essential until cerebrovascular autoregulation is restored. Blood flow is pressure-dependent in patients who develop CHS and blood pressure should be titrated to a goal systolic pressure of less than 120–140 mm Hg.<sup>3</sup> The duration of time required for autoregulation to be restored varies among patients, prompting many practitioners to either treat empirically for six months or use transcranial doppler signals to guide treatment duration. Intracranial hypertension resulting from progressive cerebral edema may be treated with the use of sedatives, osmotic agents, hyperventilation, and paralysis.<sup>36</sup>

Patients with symptomatic severe carotid artery disease with CCO pose a significant challenge. Optimal timing of carotid revascularization in these patients may not be clear, although data currently supports early intervention. Treatment of these high-risk patients should be individualized based on the extent of cerebral infarction and clinical improvement in neurologic status. Strict perioperative blood pressure control is of paramount importance in the prevention and management CHS. A higher rate of untoward events in this subset of patients should likely be anticipated even despite all precautionary measures.

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## Conflict of interest

None declared.

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