Postendarterectomy Cerebral Hyperperfusion Syndrome: The Etiological Significance of “Cerebral Reserve”

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Abstract

Postoperative cerebral hyperperfusion syndrome (CHS) in patients undergoing carotid intervention is thought to be related to the absence of cerebral reserve. Although hyperperfusion syndrome is rare, severe postoperative headache is common and is considered to be a prodromal sign. Cerebral reserve is measured by studying the response of cerebral vessels to a vasodilator such as hypercarbia. We produced hypercarbia by holding respiration for 60 seconds during carotid endarterectomy. We attempted to evaluate the relationship between intraoperatively evaluated cerebral reserve and the development of postoperative headache which was severe enough to require the patient to take an over the counter analgesic (e.g., ibuprofen, acetaminophen, aspirin). Internal carotid artery flow 1 (F1), Pco₂, and blood pressure 1 (BP1) were recorded before and after (F2, Pco₂, and BP2) 60 seconds of apnea. An increase in flow of > 20% was considered indicative of adequate cerebral reserve. Patients were evaluated before discharge and with follow-up calls at 2 to 5 days postdischarge. Fisher exact test was used to evaluate categorical predictors. Unpaired *t* test was used to compare continuous variables. Results were considered significant when *p* < 0.05. A total of 30 nonconsecutive patients were evaluated prospectively. Of the 30 patients, 4 (Group I) developed severe postoperative headache; 26 did not (Group II). Demographics were similar in both the groups. Three patients in Group I and 16 patients in Group II had > 20% increase in flow (*p* = 0.6315). Pco₂ rose in both groups and BP2 was unchanged from BP1 in both groups. Lack of cerebral reserve does not appear to be related to the development of severe postoperative headache.

Keywords

- cerebral hyperperfusion
- carotid endarterectomy
- vascular reserve
- cerebral autoregulation

Postcarotid intervention cerebral hyperperfusion syndrome (CHS) is a well-described entity. It is thought to occur in from < 1 to 7% of patients.^{1,2} Severe headache is frequently the first manifestation but can be followed by cerebral edema

and intracerebral hemorrhage (ICH).³ It usually occurs in patients who have undergone repair of high-grade flow limiting carotid stenosis. It has been postulated that the etiology of CHS markedly increased blood flow in patients

whose intracerebral circulation is maximally dilated preoperatively and is unable to autoregulate intracerebral vessels to modulate the increase in flow.^{4,5} However, this hypothesis has not been proven and there is data in the literature that does not agree with the theory.

Cerebral reserve is defined as the ability of cerebral vessels to vasodilate or constrict in response to changes in blood flow. It can be studied by measuring flow response to vasodilatation.^{6,7} Hypercarbia acts as a cerebral vasodilator and can be produced intraoperatively by hypoventilation. Patients who are unable to dilate their intracerebral vasculature should be at higher risk for the development of CHS. We have attempted to measure intraoperative internal carotid artery (ICA) flow in patients undergoing carotid endarterectomy (CE) before and after a period of apnea in an attempt to correlate changes in carotid flow with the development of CHS.

Patients and Methods

Patients undergoing CE between November 2012 and February 2013 were studied prospectively. This study was approved by the Winthrop University Hospital Institutional Review Board.

Baseline demographics were recorded as was indication for surgery (symptomatic or asymptomatic disease). Indications for surgery were based on data from the North American Symptomatic Carotid Endarterectomy Trial or the European Asymptomatic Carotid Surgery Trial, respectively, in addition to clinical judgment. The degree of ipsilateral and contralateral carotid stenosis was noted. This was determined in all patients by duplex ultrasonography and confirmed by either computed tomography angiography (CTA) or magnetic resonance angiography (MRA) in several instances where the duplex ultrasonography studies were deemed insufficient. Every patient who underwent endarterectomy based solely on duplex findings had at least two duplex studies performed by different board certified vascular technologists to confirm the original study.

Standard CE was performed in all patients. All procedures were performed under general anesthesia by the same vascular surgeon. Cerebral oximetry monitors (Somanetics, Troy, MI) and intra-arterial monitoring catheters were placed before the induction of anesthesia. The carotid artery was exposed and dissected and the vessels looped and intravenous heparin administered (100 units/kg). Transonic flow probe (Transonic Systems Inc, Ithaca, NY) was placed around the ICA. Blood pressure 1 (BP1) and cerebral oximetry values (co1) were recorded. An arterial blood gas was drawn to evaluate P_{CO_2} ($P_{CO_2}^{-1}$) and flow was measured in the ICA (F1).

The patient was then made apneic for 60 seconds during which time peripheral oxygen saturation and vital signs were continuously monitored. At the end of 60 seconds, an arterial blood gas was again evaluated for P_{CO_2} ($P_{CO_2}^{-2}$). Blood pressure 2 (BP2) and cerebral oximetry values (CO2) were recorded. Flow in the ICA was again recorded (F2). An increase in flow of $> 20\%$ was considered significant and indicative of adequate cerebral reserve.

The endarterectomy was then performed. A Javid shunt (Bard Peripheral Vascular, Inc., Tempe, AZ) was inserted in all patients from the common carotid to the internal carotid and bovine pericardial patches (Synovis Life Technologies, St. Paul, MN) were used in all patients. Postrepair duplex ultrasound was routinely employed to evaluate the repair.

BP (BP3), cerebral O_2 sat (CO_3), and ICA flow (F3) were again measured when the repair was complete. Protamine was administered and the wounds closed. A #10 Jackson-Pratt (BARD, Covington, GA) drain was used in all patients.

Patients were then transferred to the postoperative care unit. As in the OR, BP was routinely ascertained via intra-arterial monitoring. Patients were always restarted on their preoperative antihypertensive medications. If they had significant postoperative hypertension, their medication was adjusted before discharge. Patients were questioned as to the development of symptoms suggestive of hyperperfusion syndrome and/or postoperative headache unrelated to the operative field which required medication for relief.

Phone calls were placed to patients 2 to 3 days postdischarge inquiring about headache and neurologic symptoms and patients were specifically asked about these types of symptoms at their first postoperative office appointment. The primary end point was the development of headache which required the patient to take an over the counter analgesic (e.g., ibuprofen, acetaminophen, aspirin, etc.) during any of these screening sessions.

Statistical Methods

Continuous variables were presented as mean $\pm$ SD and categorical variables as proportions. Patients' demographics and other baseline characteristics were compared using Fisher exact test and two independent sample *t* test as appropriate. Mean percent changes in flow were compared between patients with headache and without headache using two independent sample *t* test of unequal variance.

Results were considered statistically significant when $p < 0.05$. All calculations were performed using SAS 9.3 (SAS Institute, Cary, NC) for windows.

Results

A total of 30 nonconsecutive patients undergoing CE at Winthrop University Hospital were evaluated. Although all patients undergoing CE were candidates for this study, the number was limited to 30 patients by the availability of the flow monitor. Patients were excluded from this study only if the flow monitor was unavailable, if the flow monitor did not fit around the patient's ICA, or if the patient declined to participate in the study.

Patient's demographics are listed in ►Table 1. Of the 30 patients, 17 patients were female, 25 had hypertension, 13 had a history of cardiac disease, and 9 patients had diabetes mellitus. A total of 24 patients underwent CE for asymptomatic disease. Six patients had symptomatic disease (one

Table 1

Variable	Group I (n = 4)	Group II (n = 26)	p value
	(Headache)	(No headache)	
Age (y), mean $\pm$ SD	76 $\pm$ 9	72 $\pm$ 19	0.5074
Stenosis operative side (%), mean $\pm$ SD	79 $\pm$ 2	77 $\pm$ 5	0.4658
Stenosis contralateral side (%), mean $\pm$ SD	50 $\pm$ 10	57 $\pm$ 15	0.3842
Female gender	3	16	0.1129
Hypertension	4	13	0.5384
Coronary disease	3	21	0.6129
Diabetes mellitus	2	11	n1.00
Smoker (current)	1	8	0.5526
HX smoking	0	6	0.1129
Right carotid	1	14	
Asymptomatic	3	21	
Symptomatic	1	5	
TIA	0	1	
CVA	1	2	
Amaurosis	0	2	

Abbreviation: CVA, cerebrovascular accident; TIA, transient ischemic attack.

transient ischemic attack, two amaurosis fugax, and three cerebrovascular accidents). Of the 30, 15 patients underwent right CE and 15 left CE.

Of the 30 patients, 4 developed significant postoperative headache (Group 1) and 26 patients had no headache (Group 2). No patient developed full-blown hyperperfusion syndrome. There were no intraoperative or perioperative strokes, and a 0% 30-day mortality rate.

In Group I, 3 patients (75%) developed greater than 20% increase in flow in response to 1 minute of apnea, as did 15 patients (61%) in Group II. The mean percentage increase in flow was 0.31 ± 0.26 in Group I and 0.22 ± 0.26 in Group II ($p = 0.525$) (**►Table 2**).

The mean percent change in flow at the completion of the procedure (F3–F1) was $0.13 \pm 0.27\%$ in Group I and $1.03 \pm 1.19\%$ in Group II. F3 could be measured in only 20 patients in Group 2 because the probe could not fit around the patched portion of the ICA. The increase in flow was more significant in the no headache group compared with the headache group ($p = 0.007$) (**►Table 2**).

Univariate analysis demonstrated no difference in demographics between patients who did and did not develop headache (**►Table 1**). In addition, age and percentage of ipsilateral and contralateral stenosis were similar between groups.

Intraoperative variables did not differ between Group 1 and Group 2. Mean BP before and after apnea were similar between groups. Although patients in Groups I and II developed an increase in P_{CO_2} after 1 minute of apnea, the patients in Group II had a higher baseline P_{CO_2} (40.2 ± 4.5 mm Hg) than the patients in Group I (35.3 ± 5.1 mm Hg) ($p = 0.055$). They also developed a greater increase in P_{CO_2} in response to 60 seconds of apnea (**►Table 3**) ($p = 0.0024$).

Discussion

CHS is a dreaded complication of patients undergoing either CE or carotid stenting. It is thought to occur in from 0.2 to 7% of patients. The typical presentation is that of a severe ipsilateral headache which may progress to seizures and focal neurologic deficits. The most severe form of postintervention

Table 2 Comparing percent change in flow between headache nonheadache groups

Variable	Headache, mean (SD), n = 4	No headache, mean (SD), n = 26	p value
Percent change (Flow2-Flow1/Flow1) (%)	0.31 (0.26)	0.22 (0.26)	0.525
Percent change (Flow3-Flow1/Flow1) (%)	0.13 (0.27)	1.03 (1.19)	0.007 ^a

Note: $p = 0.007$ suggests that percent change at flow3 from flow1 is significantly different (mean percent change for headache group is 13% vs. percent change for nonheadache group more than 100%) between patients with and without headache.

^ap value from two sample t test of unequal variance.

Table 3 Unadjusted analysis continuous variables

Variable	Headache (yes), mean (SD), <i>n</i> = 4	Headache (no), mean (SD), <i>n</i> = 26	<i>p</i> value
MBP1 (mm Hg)	87 (7)	78 (17)	0.2824
MBP2 (mm Hg)	86 (18)	80 (12)	0.429
MBP3 (mm Hg)	86 (16)	74 (9)	0.0438
Pco ₂ before holding ventilation	35.3 (5.1)	40.2 (4.5)	0.055
Pco ₂ after holding ventilation	37.7 (3.3)	47.4 (4.4)	0.0024
Stenosis operative side (%)	79 (2)	77 (5)	0.4658
Stenosis nonoperative side (%)	50 (0)	57 (15)	0.3842

hyperperfusion is the development of ICH and death.^{8–10} Symptoms can occur from the immediate postprocedure period until up to 5 to 7 days postoperatively. Although the neurologic change of CHS is most often reversible, the development of ICH is associated with a high risk of death (50–60%).

The presumed etiology for CHS is thought to be a decrease in the ability of intracranial blood vessels to autoregulate in response to an increase flow. The vessels are thought to be chronically maximally dilated to allow maximum flow distal to a high-grade stenosis. Hypertension and contralateral carotid occlusion has been associated with the development of CHS.

Various methods are used to evaluate cerebral perfusion and its relationship to hyperperfusion syndrome. These methods include transcranial Doppler (TCD), single photon emission CT (SPECT), and MRA with both diffusion- and perfusion-weighted images (PWI). Utilizing PWI, Fukuda et al¹¹ were able to predict hyperperfusion in 47% of patients who had > 100% increase in flow postrepair. Reigel et al¹² utilizing xenon-labeled technology found that in 10 patients who developed postoperative headache their post repair blood flow increased by three to four times over baseline flow. Ascher et al¹³ have used carotid duplex scanning to evaluate pre- and postoperative ICA flow. In nine patients who developed postoperative symptoms suggestive of hyperperfusion syndrome, they found no difference in postoperative flow from patients who did not develop the syndrome. However, they did determine that symptomatic patients did show an increase in flow volume at the time postoperative symptoms developed. In addition, Pennekamp et al¹⁴ have used a combination of TCD and near infrared spectroscopy (NIRS) postoperatively to identify patients at risk for developing hyperperfusion syndrome. While this dual modality yielded only 58% positive predictive value for the development of hyperperfusion syndrome, their study calculated a negative predictive value using NIRS alone of 99%.

The presence of adequate cerebral reserve has been measured by evaluating the response of cerebral blood flow to either acetazolamide or elevated Pco₂.¹⁵ Patients with normally reactive intracerebral vessels demonstrate significant flow increase in response to vasodilating stimuli. Other imaging modalities, such as TCD have been utilized in several

studies to assess the responses of cerebral blood flow to a vasodilating stimulus. Müller et al¹⁶ were able to correlate vasomotor reactivity with cerebral flow utilizing TCD. Sfyroeras et al⁵ demonstrated loss of cerebral reactivity in two of five patients who developed documented postoperative symptoms of hyperperfusion.

The lack of cerebral reserve has been shown to lead to CHS in several studies. The studies reported by Coutts et al⁴ and Sfyroeras et al⁵ have shown that lack of cerebral reactivity is associated with an increased risk of CHS. Kaku et al¹⁷ documented that an increase in flow of < 20% in response to acetazolamide was associated with the development of CHS.

In an earlier study, we attempted to demonstrate whether lack of cerebral reserve predicted the development of severe postoperative headache.¹⁸ We used headache as a prodromal symptom of hyperperfusion syndrome. We were unable to confirm our hypothesis. One of the reasons for this may have been that in that study apnea was maintained for only 30 seconds and blood gas analysis for determination of Pco₂ was not performed.

It has been shown that 60 seconds of apnea is well tolerated. Stock et al¹⁹ studied the effects of breath holding on the rate of rise of Pco₂ in awake patients. The mean period of breath holding was 39 seconds with no physiologic sequelae. They demonstrated that there was a 7 mm Hg rise of Pco₂ in the first 10 seconds, followed by a 2 mm Hg rise of over the ensuing 10 seconds.

The same group performed a study to evaluate the rate of rise of Pco₂ in apneic, intubated patients.²⁰ They maintained apnea from 120 to 300 seconds. Patients' heart rates or BP did not change by more than 7% and no patient experienced cardiac arrhythmias. No patient suffered any adverse effects. They reported a 12 mm Hg rise in Pco₂ over the first minute followed by a 3 to 4 mm Hg rise per minute after the first minute.

Of the four patients, three patients who developed postoperative headache in this study demonstrated an increase in flow in response to hypercarbia demonstrating preserved cerebral reserve. About 61% patients who did not develop headache also demonstrated increase flow. There was no statistical difference between groups (*p* = 0.1129).

F3 increased compared with F1 in three patients in Group I and decreased in one patient. The percentage change was 36,

400, 36, and (–) 21%. In Group II, F3 increased > 20% compared with F1 in 13 patients, between 0 and 20% in 4 patients, and decreased in 4 patients. F3 was unable to be measured in six patients in Group II because the probe would not fit around the patched ICA (*p* value, ns).

This study was unable to demonstrate that postoperative headache was related to lack of cerebral reserve. There was no difference in response to hypercarbia in either Group I or Group II. In addition, there was no difference in postrepair flow in either Group I or Group II.

There are several possible issues with this report. First, the cause of postoperative headache is probably multifactorial so headache may not necessarily reflect hyperperfusion in our patients. Second, the number of patients is small so there is a possibility of statistical error. Third, the increase in P_{CO_2} in Group I was less than in Group II. However, as three of four Group I patients demonstrated a significant increase in flow we believe that cerebral vasodilatation was obtained.

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