Intracranial Hemorrhage and Hyperperfusion Syndrome Following Carotid Artery Stenting
Risk Factors, Prevention, and Treatment

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OBJECTIVES
The study defined the incidence of cerebral hyperperfusion syndrome and intracranial hemorrhage (ICH) and the risk factors for their development following carotid artery stenting (CAS).

BACKGROUND
Hyperperfusion syndrome and ICH can complicate carotid revascularization, be it endarterectomy or CAS. Although extensive effort has been devoted to reducing the incidence of ischemic stroke complicating CAS, little is known about the incidence, etiology, and prevention strategies for hyperperfusion and ICH following CAS.

METHODS
We retrospectively reviewed the prospective database of 450 consecutive patients who were treated with CAS in our department to identify patients who developed hyperperfusion syndrome and/or ICH.

RESULTS
The mean age of the patients was 72.7 ± 10.9 years, and the mean diameter narrowing was 84 ± 12.8%. Five (1.1% [95% confidence interval 0.4% to 2.6%]) patients developed hyperperfusion. Three (0.67%) of the five developed ICH. Two of these patients died (0.44%). Symptoms developed within a median of 10 h (range, 6 h to 4 days) following stenting. All five patients had correction of a severe internal carotid stenosis (mean 95.6 ± 3.7%) with a concurrent contralateral stenosis >80% or contralateral occlusion and peri-procedural hypertension. These same risk factors are involved in cerebral hyperperfusion following carotid endarterectomy. The use of platelet glycoprotein IIb/IIIa receptor blockers did not appear to increase the risk ICH.

CONCLUSIONS
The hyperperfusion syndrome occurs infrequently following CAS, and ICH occurs in 0.67% of patients. Patients with severe bilateral carotid stenoses may be predisposed to ICH, particularly if there is concurrent arterial hypertension. Patients with these factors may require more intensive hemodynamic monitoring after CAS, including prolongation of hospitalization in some cases. (J Am Coll Cardiol 2004;43:1596–601) © 2004 by the American College of Cardiology Foundation.

Carotid artery stenting (CAS) is emerging as a potential alternative to carotid endarterectomy (CEA) (1,2). Postsurgical hyperperfusion syndrome (HPS) and intracranial hemorrhage (ICH) have been well described following CEA and are associated with significant morbidity and mortality (3–11). Little is known about the incidence of HPS and ICH following CAS (12–17). It is also not known if the risks of HPS and ICH are comparable between CEA and CAS, especially as anticoagulants and potent antiplatelet regimens are used during CAS. Improvements in endovascular techniques and the development of emboli-prevention devices have markedly reduced the incidence of ischemic stroke following CAS; as a result, HPS and ICH may become major causes of morbidity and mortality following endovascular carotid artery revascularization (1,2).

To study the incidence and clinical and laboratory predictors of HPS and ICH we reviewed a prospective database at our institution to identify patients who developed ICH following CAS.

METHODS
We retrospectively reviewed a prospectively collected database of all patients who underwent CAS in our department to find patients who had HPS or ICH. The database included demographic information, clinical history, symptomatic status of the internal carotid artery (ICA), angiographic findings, procedural details, adjunctive antithrombotic/anticoagulant agents used, and peri-procedural events. Perioperative and follow-up data on neurological events including any transient ischemic attack, stroke, seizure, or change in neurological status were also collected. Following hospital discharge, patients paged the interventional fellow on-call if they developed any symptoms; all such events were captured into the database.

Hyperperfusion syndrome was defined by the occurrence, either singly or in combination, of ipsilateral (to the treated artery) temporal, frontal or retro-orbital throbbing headache with or without nausea, vomiting, ipsilateral focal seizures, or focal neurological deficit without radiographic evidence.
of infarction. Intracranial hemorrhage was defined by computed tomography evidence of punctate or confluent hyperdensities consistent with blood within the parenchyma of the cerebral hemispheres or within the subarachnoid space.

A neurologist evaluated all patients before and after the procedure to determine whether any patients showed neurological signs or symptoms. The technique of CAS has been described elsewhere (18) but evolved over the three years of this study. The major change was the introduction of mechanical emboli-prevention devices, which led to cessation of the use of platelet glycoprotein IIb/IIIa receptor blockers (GPIIb/IIIa). The doses and agents used for GPIIb/IIIa blockade varied, but when they were utilized the goal was 75% platelet inhibition as measured by a bedside test of platelet aggregation. Patients were pretreated with aspirin 325 mg/d and clopidogrel 75 mg/d for at least one week. In cases of urgent intervention, a clopidogrel 300-mg load was given. All patients were treated with heparin intraoperatively with a bolus of 50 U/kg with additional doses as necessary to achieve an activated clotting time (ACT) of 250 to 325 s. Procedural success was defined as a post-stent luminal narrowing of <30% using the North American Symptomatic Carotid Endarterectomy (NASCET) method (19). All patients underwent CAS as part of institutional review board-approved protocols.

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Without Hyperperfusion</th>
<th>With Hyperperfusion</th>
</tr>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>72.7 ± 10.9</td>
<td>72.7 ± 4.5</td>
</tr>
<tr>
<td>Age range (yrs)</td>
<td>36–90</td>
<td>67–79</td>
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<tr>
<td>Atherosclerosis risk factors, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>255 (78.9)</td>
<td>3 (60)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>339 (76.2)</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Cigarettes</td>
<td>225 (69.7)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>197 (61.6)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>176 (54.5)</td>
<td>3 (60)</td>
</tr>
<tr>
<td>High-risk criteria, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous carotid endarterectomy</td>
<td>179 (55.4)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Pre-open heart surgery</td>
<td>96 (29.7)</td>
<td>0</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>67 (20.7)</td>
<td>0</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>55 (17)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Neck radiation therapy</td>
<td>43 (13.3)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>16 (5)</td>
<td>0</td>
</tr>
</tbody>
</table>

RESULTS

Data from 450 consecutive patients were analyzed. The baseline characteristics are presented in Table 1. The indication for CAS was at least one high-risk criterion for CEA, most frequently previous CEA or active coronary artery disease. Isolated hyperperfusion occurred in two (0.44%) patients and ICH occurred in three (0.67%) patients, for a combined incidence of 1.1% (95% confidence interval 0.4% to 2.6%). All five patients had hypertension. The other baseline characteristics were similar between the HPS and non-HPS patients.

Table 2 details the lesional and technical characteristics. Of the 445 patients without HPS, 228 (51.2%) received a GPIIb/IIIa and 216 (48.5%) were treated with an emboli-
Three patients with ICH had received a GPIIb/IIIa, whereas one was treated with an emboli-prevention device. Two patients with isolated HPS did not receive a GPIIb/IIIa but were treated with an emboli-prevention filter. Two-thirds of the patients in both groups had symptomatic carotid stenoses. The treated stenosis was significantly more severe in the five patients with HPS (mean stenosis 95.6 ± 3.7%) than in those without HPS (mean stenosis 83.8 ± 11.3%), p = 0.001. All five patients with HPS had ≥80% contralateral ICA stenosis (n = 3) or a contralateral ICA occlusion (n = 2). Of those without HPS, only 84/445 (18.9%) had similar contralateral disease. All five of the patients with HPS had a treated stenosis of >90% luminal narrowing, a contralateral stenosis of ≥80% or occlusion, and hypertension. Of the patients without HPS only 26 of 445 (5.8%) had these three characteristics. The results of the Boolean analysis of the null hypothesis yielded a sample correlation between the Boolean statistic and the presence of hyperperfusion of 0.40161. Thus, the hypothesis that our Boolean “and” statistic (i.e., the presence of all three criteria) and hyperperfusion are uncorrelated must be rejected, and this suggests that hyperperfusion is associated with the presence of all three criteria. The risk of HPS if a patient had all three characteristics was 16% (5/31).

**Review of cases.** Intracranial hemorrhage occurred without antecedent symptoms immediately after the intervention in one patient (Fig. 1). In the other four cases, severe, ipsilateral, retro-orbital throbbing headache developed between six h and four days postoperatively (median 10 h). Two of the patients developed postoperative hypertension (systolic blood pressure [SBP] >180), both of whom subsequently developed ICH. In the three patients who developed a headache while hospitalized, intravenous treatments were immediately initiated to maintain the minimum SBP that resulted in resolution of symptoms, which was <120 mm Hg in all three cases. Clopidogrel and aspirin were withheld until the symptoms resolved. This occurred within 12 to 36 h in all three cases. Upon symptom resolution, antiplatelet agents were restarted. Patients and their families were instructed to strictly adhere to their antihypertensive regimen and to monitor blood pressures at least twice daily, with instructions to call the interventional fellow on-call for any recurrence of symptoms or blood pressure values >140/90 mm Hg. Both patients who developed ICH after discharge did not take their antihypertensive medicines. One patient presented with a seizure and confusion on the fifth postoperative day, and the other presented with recurrent severe headache, nausea, and vomiting followed by rapidly progressive hemiparesis and coma on postoperative day three (Figs. 2 and 3). Two of the three patients with ICH died; the third survived with a moderate disability.

**DISCUSSION**

This current series is the largest study to date focusing on hyperperfusion and ICH following CAS. We found an incidence of HPS of 1.1%, and the incidence of ICH was 0.67%. Intracranial hemorrhage following CAS was associated with a high mortality and morbidity rate. The five patients from our institution who developed HPS had several characteristics in common: all had a ≥90%-treated ICA stenosis and all had severe stenoses (≥80%) involving the contralateral carotid artery. All five patients were hypertensive at baseline, and two of them developed significant
postprocedural hypertension preceding the onset of ICH. Although one patient developed ICH immediately postprocedure, the others developed typical hyperperfusion syndrome features within days of the intervention. Progression to neurological dysfunction and ICH occurred in two of the four patients.

Although there are no published, systematic analyses of HPS in CAS patients, three groups have published their experience with ICH following cervicocranial interventions. The first two reports consisted of heterogeneous patient populations (13,15). The series by Schoser et al. (13) consisted of 86 patients who were treated with ICA angioplasty alone, and the series of Meyers et al. (15) reported on their stenting results in 140 patients, only 66 of whom had carotid interventions. In these two series the incidence of ICH was 1.4% and 2.3%, respectively. Meyers et al. (15) did report on isolated hyperperfusion in their patients, and they found the incidence to be 5%. The third report described 90 patients undergoing CAS without emboli-prevention devices (16). The stenting protocol included a 100 U/kg heparin bolus with a 1,000 to 2,000 U/h infusion. The incidence of ICH was 3.8%, with a mean ICA stenosis of

Figure 2. Preoperative angiograms (A and B) from Patient 2 show a 99% stenosis of the left internal carotid artery (ICA) (arrow in A) distal to a common carotid artery stenosis (arrowhead in A). The right ICA is occluded at its origin (arrow in B). Four days following stenting, a computerized tomography scan (C) shows a left frontal lobe, confluent hematoma.

Figure 3. Angiograms from Patient 3 show a near occlusive lesion of the right internal carotid artery (ICA) (arrow in A) and an 80% stenosis of the left ICA (arrow in B). Three days following right carotid stenting, a computerized tomography of the brain (C) reveals a large right-hemisphere hematoma, with midline shift and intraventricular hemorrhage.
95% in those with ICH. The investigators concluded that, compared with CEA, CAS is associated with a higher rate of ICH. The results of these three series likely do not reflect the true incidence of hyperperfusion and ICH following CAS. The reasons for this are multiple: 1) The first two series included patients who had interventions of vessels other than the carotid artery, including intracranial arteries. 2) The heparin doses used in the series described by Meyers et al. and Morrish et al. were very high, and heparin was continued for 12 h postoperatively in the Meyers et al. series. The investigators did not report on the intraoperative ACTs, which were likely much higher than those in our patients who received a 50% lower dose of heparin. 3) Lastly, because recent ischemia is a known risk factor for ICH, the lack of emboli-prevention devices in all three series may have increased the risk of ICH.

Reports of ICH following CEA first appeared in the 1960s, but the term “hyperperfusion hemorrhage” was initially coined by Sund et al. (4) in 1981 (21,22). They measured increases in cerebral blood flow in patients who developed the clinical syndrome after CEA. Hyperperfusion is now a well-recognized complication of CEA (3,5,7,10,11,23). The incidence of ICH associated with HPS following CEA is 0.3% to 1.2% (3–5,7,11,23). The rates of occurrence in our series are in keeping with these figures, suggesting that there is not an increased risk of ICH following CAS compared with CEA. The exact incidence of HPS without ICH following CEA is not known but is estimated at 0.75% to 3% (24,25). Meyers et al. (15) studied the incidence of HPS prospectively in endo-vascularly treated patients and found an incidence of 5%, but in their series only 66 of 140 patients had had carotid interventions, so their results may be inaccurate. Initially, we did not record data prospectively on the occurrence of unilateral headache, nausea, and vomiting, and therefore our results likely underestimate the occurrence of HPS without ICH. It seems likely that the true incidence of HPS without ICH is closer to 2% to 5% rather than the 1.1% we found. This highlights a limitation of our study, which despite being based on prospective collection of information for the database, was a retrospective review. Our estimate, however, of the incidence of symptomatic ICH is accurate. This is because the clinical manifestations of ICH are obvious and often catastrophic and because all peri- and postoperative neurological deficits and events were collected into the database.

The most widely held view is that HPS occurs as a result of impaired autoregulation of cerebral blood flow (CBF) (4,7). The chronic low-flow state induced by severe carotid disease results in a compensatory dilation of cerebral vessels distal to the stenosis as part of the normal autoregulatory response to maintain adequate CBF. As a result of chronic dilation, the vessels lose their ability to autoregulate vascular resistance in response to changes in blood pressure. This results in increased CBF after recanalization; thus the term “hyperperfusion.” This model of HPS is supported by findings of noninvasive testing such as transcranial Doppler ultrasound (TCD), by histopa-thology on postmortem examinations, and by experimental studies in animal models (9,10,24,26).

The typical clinical finding of HPS following CEA is an ipsilateral throbbing headache in a facial, temporal, or retro-orbital distribution, which may be the only manifestation of the syndrome (9,11,23). Other common symptoms include nausea, vomiting, focal deficits, and seizures (focal or generalized) (5,6,11). Postprocedural hypertension is a critical, though not essential, finding associated with HPS (5,6,11). Four of our patients had this typical clinical pattern, which suggests that they did indeed have the HPS despite the fact that we did not measure CBF. In our series, ICH developed on the third and fifth postoperative days, respectively. This is in keeping with a peak incidence between the third and fifth postoperative days (range 2 to 17 days) observed following CEA (11). There have been cases observed immediately after surgery, as occurred in one of our patients (5,6,11). Following CEA, ICH carries a 37% to 80% mortality rate and a 20% to 37% risk of poor recovery in survivors (3,23). The outcomes in our series are in keeping with the grim prognosis associated with ICH.

Risk factors for developing HPS following CEA have been identified (5,6,8,9,11,20). The essential risk factor is the presence of a critical ICA stenosis ≥90% (9,11,24,27). Other important risk factors following CEA include severe contralateral ICA disease, poor collateral flow, hypertension, and recent stroke or ischemia (5,6,8,9,11,20,24). In our series, all patients with HPS had these same risk factors, which is in keeping with the hypothesis that the mechanisms of hyperperfusion are similar between CEA and CAS. Although CAS and CEA are markedly different procedures, the resultant changes in cerebral vascular physiology are similar. In addition to the above clinical/anatomical predictors, TCD may be able to predict which patients are at increased risk of HPS and ICH by measuring mean flow velocities in the ipsilateral middle cerebral artery (MCA) (24).

Safety concerns have been raised about the effects of anticoagulants and antiplatelet agents and the risk of ICH following CEA, but no causal link has been found (11,25). Similarly, although anticoagulants and antiplatelet agents are used more frequently following CAS than following CEA, there did not appear to be an increased risk of ICH following their use in our study. Nonetheless, we avoided excessive anticoagulation intraprocedurally, and we did not continue anticoagulants postoperatively. These two factors alone might explain the lower incidence of ICH in our series compared with those previously discussed (15,16).

The progression of HPS to ICH is associated with an extremely poor prognosis. Prevention is critical. The most important component of perioperative management is vigilant monitoring and control of systemic blood pressure (3,6,10,11,24,25,28). It has been suggested that even blood pressures in the “normal” range may be deleterious in patients at high risk for HPS (3,11,28). For blood pressure control after CAS, beta-blockers have several advantages over other antihypertensive agents (e.g., hydralazine), which
may further increase cerebral blood flow, leading to a counterproductive effect, or nitrates, which may cause headache (25). Careful monitoring of blood pressures should continue for at least two weeks following the procedure. This can be accomplished using either home nursing visits or over-the-counter automated blood pressure monitors. Although we did not systematically measure changes in CBF with lowering of blood pressure in our patients, the patients did respond clinically to lower pressures (24,28).

Additional efforts to reduce the risk of ICH may include limiting the duration of balloon inflation and employing emboli–prevention devices. These measures help minimize procedural brain ischemia, which potentiates the risk of HPS and ICH (4,24,26). If patients develop clinical symptoms suggestive of HPS or if patients have a documented elevation in MCA velocities to twice their baseline value we typically withhold antplatelet agents until symptoms have resolved and the blood pressure is optimally controlled. Although there are no outcome data to support this approach following CAS, we believe that the risks of this approach are far outweighed by the potential consequences of ICH. In our two patients who presented with HPS but without ICH we were able to control arterial pressures within hours, so a single missed dose of aspirin and Plavix was not significant in terms of precipitating acute stent thrombosis.

Conclusions. Hyperperfusion syndrome is a potentially devastating complication of percutaneous carotid revascularization and has become increasingly more important as the rates of ischemic complications have declined. High-risk patients include those with a severe ICA stenosis, severe contralateral ICA stenosis or occlusion, poor intracerebral collaterals, elevated MCA velocities following the procedure, and perioperative hypertension. Careful screening to identify high-risk patients, vigilant postoperative monitoring for signs of HPS, and aggressive management of postoperative blood pressure are important steps in both preventing and minimizing the impact of this potentially devastating complication.

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REFERENCES