

# Letters to the Editor

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## Surgery for Intracerebral Hemorrhage

To the Editor:

We were pleased to see the report of the randomized feasibility study of early surgical treatment for supratentorial intracerebral hemorrhage by Zuccarello et al.<sup>1</sup>

This study provides yet more evidence of the need for a large randomized trial of surgery for spontaneous intracerebral hemorrhage, as has been shown previously.<sup>2–8</sup> We wish to inform your readers of the progress of such a trial. The STICH (Surgical Trial in Intracerebral Haemorrhage) has been funded by the Medical Research Council (UK) but is open to centers from any country, and we would invite interested centers to contact us.

STICH is a multicenter, pragmatic, randomized trial aiming to recruit 1000 patients. The trial is managed by a team at Newcastle University (UK). To date, we have 68 centers from the United Kingdom, Germany, Sweden, Spain, Hungary, Poland, Czech Republic, Italy, Belgium, Greece, Ukraine, Russia, South Africa, Hong Kong and the United States. Randomization is performed by telephoning the Randomisation Service at Oxford University (UK) after identifying a patient, gaining consent, and completing a randomization form. An additional form is completed 2 weeks later (or at death or discharge if earlier) to record patient status at this point and details of any surgery or adverse events. Follow-up at 6 months is obtained by the team in Newcastle, who send a questionnaire to each patient for completion.

So far we have recruited 273 patients to the study, and complete 6-month follow-up data has been achieved for 130 patients. The trial is being carried out following the MRC Guidelines for Good Clinical Practice in Clinical Trials, and the data will be analyzed by treatment group after the recruitment of the final patient. Our study will permit us to investigate whether time to surgery has an effect on outcome. Time to randomization is up to 72 hours after ictus, although 30% of patients are randomized within 12 hours. Patients randomized to early surgery receive the treating surgeon's preferred method of surgery, as soon as possible within 24 hours, and best medical care. Patients randomized to initial conservative treatment receive best medical care, including early transfer from the neurosurgery department if appropriate. Late surgery may be performed if the patient's condition changes and surgery becomes appropriate. Patients can be included in the study only if the neurosurgeon is uncertain about the need for surgery.

To achieve our target sample of 1000 as soon as possible, we would welcome participation of additional centers. Anyone who wishes to join the study should email us at [stich@ncl.ac.uk](mailto:stich@ncl.ac.uk).

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## Response

We would like to strongly echo the call of Gregson and colleagues for participation in randomized treatment trials of intracerebral hemorrhage. We applaud their ongoing STICH trial and hope recruitment goals are met quickly. Multiple attempts to obtain pilot funding for a multicenter, ultra-early clinical trial in the United States have not been successful to date.

It is our belief that a randomized surgical trial of intracerebral hemorrhage should include 2 critical components: (1) ultra-early removal of blood from the brain parenchyma and (2) standardization of techniques that minimize brain injury and maximize clot removal, such as stereotactic approaches to deep-seated hemorrhages. Timely removal of the blood clot for us would preferably be within the first 3 or 4 hours after onset, hopefully within 6 to 8 hours, and at the latest within 12 hours of onset. Such an approach requires a strong commitment to improving the logistics of rapid medical and surgical treatment of patients with intracerebral hemorrhage. Solutions to these logistical problems should first be addressed in the context of a multicenter pilot study. Such a pilot study would also help standardize the medical and surgical approaches to these patients. After completion of such a pilot trial, the benefits and risks of surgical removal of intracerebral hemorrhage should be examined in a large randomized trial.

As we search for the first proven treatment for intracerebral hemorrhage, we should observe the lessons learned in randomized trials of acute ischemic stroke. The growing number of failed neuroprotective trials and the lack of clear success using thrombolytics beyond 3 hours illustrate that it is not only the therapy that is critical but also the time at which it is delivered. We strongly urge the STICH investigators to minimize the time from onset to treatment in their trial. Otherwise, they may replicate previously negative, smaller, randomized surgical trials that also used a longer time window to treatment.

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## A Case of Cerebral Hemorrhage Early After Carotid Stenting

*To the Editor:*

We read with interest the recent case report by McCabe et al,<sup>1</sup> in which they describe a patient with fatal cerebral reperfusion hemorrhage after internal carotid artery (ICA) stenting. In their interesting discussion, the authors argue that this disastrous complication most likely occurred because cerebral perfusion pressure overwhelmed the vasoconstrictive capacity of the arteriolar circulation. Because a brain CT scan performed before carotid stenting disclosed diffuse patchy leukoaraiosis in the deep white matter, the authors suggest that leukoaraiosis could be a risk factor for reperfusion hemorrhage after carotid stenting. We provide an additional case report of reperfusion injury after carotid stenting that supports the main conclusion of McCabe and colleagues and provides some further understanding of this dreadful complication.

On November, 10, 1999, a 43-year-old right handed man was admitted to our stroke unit, 2 days after a sudden onset of left-sided facial and brachial paresis. His past medical record was relevant for a history of hypertension since the age of 20, with no other atherosclerotic risk factors or past cerebrovascular events. On admission, his blood pressure was 150/80 mm Hg and his neurological exam was normal. A brain CT scan showed a 3.5-cm ischemic infarction in the right centrum ovale consistent with acute embolism. An old ischemic lacunar infarction 10 mm in size was also observed in the genu of the right internal capsule. Periventricular or brain stem leukoaraiosis and brain stem lacunar infarctions were absent. A Doppler ultrasound of the cervical vessels suggested >90% stenosis of the right ICA and normal findings on both vertebral arteries and left ICA. The following day a selective injection on the right common carotid artery disclosed 95% stenosis of the ICA, with very slow and faint intracranial filling. A deep ulceration of the stenotic segment was also noted. A selective injection on the left common carotid artery showed marked cross-flow through the circle of Willis, a fetal origin of the posterior communicating artery and patent intracranial vessels bilaterally. The vertebrobasilar circulation lacked abnormal findings, including atherosclerotic changes. During the following week the patient remained asymptomatic, his blood pressure remained within normal values, and 1000-IU/h unfractionated heparin IV was started. One week after the onset of symptoms, a right carotid stenting was planned via a percutaneous approach under local anesthesia. In the early morning of the procedure, the patient was given aspirin (300 mg) and clopidogrel (225 mg). Our antithrombotic protocol includes, during the month after the procedure, the combination of aspirin 300 mg daily and clopidogrel 75 mg daily. An intravenous heparin bolus (5000 IU) was given and heparin was then

maintained at 1000 IU/h. In agreement with Guterman and colleagues,<sup>2</sup> urokinase (200 000 IU) was infused through a microcatheter proximal to the ulcerated lesion before introduction of the balloon. The stenosis was crossed with a Hannibal 0.014" J angioplasty wire and 0.7 mg atropine IV was given. The stenosis was predilated with a Bijou balloon (3.5 × 20 mm) and stented with a Carotid Wallstent Monorail (8 × 29 mm long). The stent was further dilated using a 5 × 20-mm RxViaTrac 14 balloon. Hemodynamic and neurological functions were constantly monitored during the procedure by an anesthesiologist. The blood pressure varied between 180/80 mm Hg and 135/75 mm Hg during the procedure. After carotid stenting an angiogram showed the complete recanalization of the right ICA without local complications. An aortic arch injection disclosed a much faster and pronounced filling of the right carotid circulation. A stroke neurologist confirmed the normal neurological state of the patient at the end of the procedure. The patient was transferred to the neurointensive care unit for observation. Over the next 6 hours, the patient was treated with 1000 IU/h unfractionated heparin IV. His blood pressure was recorded every 15 minutes, with values ranging between 100/60 mm Hg and 125/60 mm Hg. He was free of headache and his neurological exam remained completely normal. Suddenly, the patient became confused, and several minutes later he lost consciousness, disclosing no seizure activity. His blood pressure increased to 180/75 mm Hg but returned to normal in the ensuing 5 minutes without hypotensive therapy. He was immediately transferred to the CT scan room, where a large left thalamic hemorrhage was detected that extended into the ventricles and the midbrain. No radiological signs of hemispherical edema were detected. An urgent full blood count was normal, the activated partial thromboplastin time was 66 seconds (equivalent to 0.3 to 0.5 U/L heparin levels), and fibrinogen was 3.7 g/L (normal 1.5 to 4.5 g/L). Seven days later the patient died in the neurointensive care unit. Autopsy was not authorized.

In agreement with McCabe and colleagues, we believe that our patient also illustrates how hyperperfusion hemorrhage can result after carotid stenting in patients with radiological signs of small-vessel disease. The angiogram performed after carotid stenting showed prominent flow increments through previously hypoperfused vessels, which possibly overwhelmed the compensatory capacity of the microcirculation to maintain an adequate control of the cerebral perfusion pressure. The extent to which abrupt flow increments, mechanical stimulation of carotid baroreceptors, or the extent and severity of preceding small-vessel disease played a role in this syndrome is difficult to establish. More careful monitoring of cerebral hemodynamics, through use of methods such as perfusion and diffusion MRI or transcranial Doppler, direct measurements of the perfusion pressure, and pathological examination in fatal cases, would be necessary to address these effects. This information could also help in understanding why reperfusion injury after carotid stenting seems to occur at shorter time intervals after the procedure compared with the longer delay (several days) that has been described after carotid endarterectomy. Moreover, larger number of patients with the syndrome would be needed to confirm or refute this clinical presentation.

In the 37 previous carotid stenting procedures performed at our institution, we used the same antithrombotic regime and blood pressure management without hemorrhagic complications. Low-dose urokinase was given in this case because of the ulcerated nature of the stenosis. In agreement with McCabe et al, we excluded the occurrence of bleeding in relation to excessive antithrombotic or fibrinolytic therapy. However, we do not believe that a more aggressive antihypertensive management would have reduced the likelihood of bleeding, as the patient did not disclose postprocedural hypertension. Recently, it was shown

that transient hemodynamic changes are extremely frequent during and after carotid stenting.<sup>3</sup> However, these changes rarely result in clinical symptoms. On the basis of this small database, it can be argued that small-vessel disease, either as periventricular white matter disease or manifested by lacunar infarction, contributed to the development of hyperperfusion hemorrhage. The effect of chronic hypertension in our patient<sup>4</sup> and the effect of aging and tobacco in the patient of McCabe et al<sup>5</sup> could have been the most likely predisposing factors. Nevertheless, it remains to be explained why hyperperfusion hemorrhage is not reported more frequently after carotid stenting, because a high prevalence of small-vessel disease can be anticipated in the stented population. Perhaps a retrospective analysis of previous series, such as the one included in CAVATAS, could help to clarify this issue.

Lacking effective treatment for hyperperfusion, hemorrhage prevention is crucial. Although speculative, gradient-echo T2-weighted MR imaging could prove efficacious to detect candidates at greater risk of hyperperfusion complications by providing radiological evidence of previous asymptomatic bleeds. The extent of periventricular white matter could also be quantified on MRI. On theoretical grounds but pending further information, a less-aggressive dilatation of stenotic vessels in the presence of concurrent lacunar infarctions or periventricular lucencies could be made hemodynamically safer by allowing a more progressive adaptation of the microcirculation to the new cerebral blood flow state. Meanwhile, we are left with the grief of seeing how preventive therapies turned unexpectedly into devastating complications.

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## Response

We read with interest the additional case of intracerebral hemorrhage reported by Chamorro et al supporting the suggestion that this is an important complication of carotid stenting. Both our patients shared a number of clinical features, including very severe symptomatic pretreatment stenosis, aspirin therapy, transient hypertension during the procedure, small-vessel disease, and a stable neurological course for 6 to 7 hours after carotid stenting before sudden clinical deterioration. However, their patient was also treated with a high dose of clopidogrel (225 mg), intra-arterial urokinase, and therapeutic heparinization, which may have contributed to the intracranial hemorrhage in their

patient. It is also interesting to note that the hemorrhage was in the contralateral thalamus and midbrain in their patient, in contrast to the ipsilateral location in our patient.

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## Fatal Cerebral Hemorrhage After Carotid Stenting

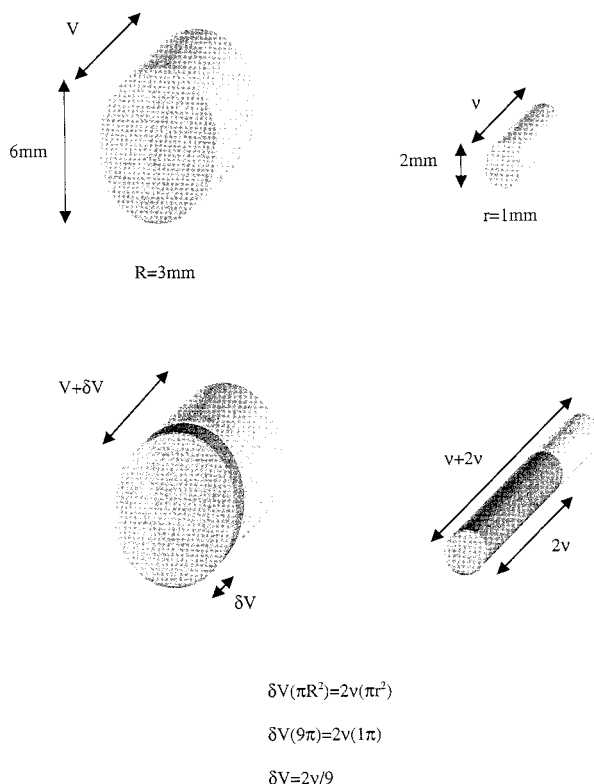
*To the Editor:*

Percutaneous transluminal angioplasty (PTA) and stenting are increasingly used as an alternative to carotid endarterectomy (CEA) for patients with carotid stenosis. Cerebral hyperperfusion syndrome following CEA has been widely reported in the surgical literature. It is timely that interventionists increase their awareness of such a syndrome, as it can also happen after PTA. In the case reported by McCabe et al.,<sup>1</sup> however, there was really no objective documentation of hyperperfusion. Moreover, the case was not heralded by or associated with any of the typical symptoms of hyperperfusion syndrome, such as unilateral headache or seizures.<sup>2</sup>

The Doppler findings of increased peak systolic and end-diastolic velocity over the stented internal carotid artery (ICA) are even more puzzling. The authors postulated that hyperperfusion may manifest as increased flow velocity in the ICA. Instead of increased blood flow, we suspect that the turbulence is caused by a sharp bend of the right ICA immediately above the stent (see Figure 3 of McCabe et al), significant residual stenosis, or spasm. It would help if the authors could state the Doppler findings of the left and right ICA before the stenting procedure. Even if the flow volume to the middle cerebral artery (MCA) is increased, it is hard to translate this into elevated flow velocity in the ICA, which is a large-caliber vessel at least 6 mm in diameter (3 to 4 times larger than the MCA in diameter and 9 to 16 times greater in cross-sectional area). In patients with the hyperperfusion syndrome, flow velocity in the MCA is increased by 2 to 3 times compared with that during baseline transcranial Doppler studies.<sup>3,4</sup> Even if the MCA flow is increased 3 times, the flow in the ICA is only increased by a factor of 2/9 (Figure). No studies on hyperperfusion syndrome, post-CEA seizures, or post-CEA intracranial hemorrhage had documented elevated flow velocity in the ICA.

In McCabe's case, the patient was taking aspirin 300 mg daily and dipyridamole 200 mg twice daily. In addition, he was given 5000 U heparin injection during the procedure, followed by 1000 U/h as an infusion for 7 hours. In the context of a major CVA only 5 months previously and potentially further silent embolic events from the carotid lesion, it is possible that the intracranial hemorrhage was a spontaneous episode as a result of the aggressive anticoagulation and antiplatelet therapy. In addition, the normal activated partial thromboplastin time (APTT) at the time of neurological deterioration was unusual despite continuous IV heparin. We would like to know the activated clotting time or APTT results between stenting procedure and the acute deterioration to see whether there was any period of over-anticoagulation or the anticoagulation was inadequate throughout the procedure.





Schematic diagram representing a 3-fold increase in flow velocity in the MCA and the corresponding increase in flow velocity in the ICA. The MCA is assumed to be 2 mm in diameter, and the ICA is assumed to be 6 mm in diameter.  $V$  indicates flow in the ICA per second at baseline;  $\delta V$ , increase in flow in the ICA per second;  $v$ , flow in the MCA per second at baseline;  $2v$ , increase in flow in the MCA per second;  $R$ , radius of the ICA; and  $r$ , radius of the MCA.

All in all, we think it was an interesting case report, but the title may more appropriately reflect the case if the word "reperfusion" is deleted.

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### Response

We thank Drs Ho and Cheung for their interest in our case report. We disagree about the lack of objective evidence for hyperperfusion, since we documented an increase in velocity of flow on color Doppler ultrasound in the treated internal carotid

artery, without significant stenosis or spasm. The fact that the intracerebral hemorrhage in our case was not heralded by or associated with any of the typical symptoms of the hyperperfusion syndrome emphasizes the importance of considering the diagnosis even if these features are not present. Ho and Cheung have suggested that the increased peak systolic and end-diastolic velocities in the ICA were caused by a sharp bend, stenosis, or spasm of the ICA immediately above the stent. These alternative explanations for the increased velocities were excluded by additional angiographic views of the left ICA taken at the time of the procedure, which were not published in the case report.<sup>1</sup> We regret that we cannot provide Ho and Cheung with the Doppler findings before treatment; this was not performed because the patient was referred to our center with the results of a digital subtraction angiogram. The calculations by Ho and Cheung of the relationship between flow in the ICA and the MCA are very interesting, but they assume that the diameter of the MCA remains unchanged, which is probably not correct. More importantly, they have assumed that all of the ICA flow is distributed to the ipsilateral MCA only. In fact, flow will be distributed between the MCA and the other branches of the circle of Willis, particularly if there is an abnormal increase in ipsilateral cerebral perfusion pressure. Using their own model, we have calculated that a doubling of the velocity of flow in the ICA, as recorded in our patient, distributed evenly between the MCA, anterior cerebral artery, and the anterior communicating artery would result in approximately a 3-fold increase in velocity in the MCA. This is entirely consistent with the figures recorded by transcranial Doppler in patients with the hyperperfusion syndrome.<sup>2</sup> We agree that antiplatelet and anticoagulant therapies could have contributed to the cerebral hemorrhage in our patient, but we discussed in our article the reasons that we favored hyperperfusion as the primary cause. The patient was not treated with an aggressive anticoagulant regimen, as suggested by Ho and Cheung, and the activated clotting time was not measured. In conclusion, we do not agree that "reperfusion" should be deleted from our title. However, further studies of carotid and transcranial Doppler ultrasound after carotid stenting are clearly warranted to improve our understanding of the mechanism of hyperperfusion injury in these patients.

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1. McCabe DJH, Brown MM, Clifton A. Fatal cerebral reperfusion hemorrhage after carotid stenting. *Stroke*. 1999;30:2483–2486.
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### Antithrombin Therapy for Intracerebral Hemorrhage

To the Editor:

We read the article by Xi et al<sup>1</sup> and the Editorial Comment by Dr J. Paul Muizelaar with great interest. In the article the authors stress that blood clot formation is required for the rapid development of persistent edema in the white and gray matter surrounding intracerebral bleeding. Thrombin itself was found to contribute to prolonged edema in gray matter. Muizelaar cautioned that the experimental findings may not be applicable to clinical practice, making

the points that the hematoma is difficult to remove in the early phase after intracerebral hemorrhage (ICH) and that tissue plasminogen activator (tPA) may worsen hemorrhage.

We propose consideration of antithrombin therapy with use of a selective thrombin inhibitor such as argatroban to avoid such problems. Argatroban differs from tPA in that it has no effect on the fibrinolytic system, so it does not promote bleeding. We suggest that intravenous administration of argatroban is an alternative to surgical clot removal. Argatroban should help to protect the brain from adverse effects of thrombin in ICH, including edema and other forms of damage.

In the article the authors emphasize that in addition to blood coagulation, thrombin is responsible for edema formation. Thrombin can also contribute to death of neurons and glia.<sup>2</sup>

Xi et al used heparin to block the activity of thrombin, although direct thrombin inhibitors, which are already in clinical use, would theoretically be better than heparin for this purpose. Limitations of heparin include high interindividual variability of anticoagulant response and a nonlinear dose-response curve, as well as inability to inactivate clot-bound thrombin, a requirement for endogenous cofactors, and vulnerability to inactivation by platelet factor 4 and heparinase.<sup>3</sup>

We now are conducting a pilot trial of antithrombin therapy in patients with ICH using intravenous infusion of argatroban. Among possible adverse effects of antithrombin therapy, hemorrhage is probably the most severe. We therefore begin the infusion 24 hours after symptom onset, because most rebleeding occurs within 6 hours after initial ICH and rebleeding is rare after 24 hours.

To date, we have tested antithrombin therapy in 4 patients with ICH. Written informed consent was obtained from the patient or family prior to enrollment in the study. No adverse effects have occurred in these cases. In these few cases, perihematoma edema was less and functional recovery seemed to be better than with conventional therapy in similar cases.

We recommend that randomized, controlled studies be performed to assess the effectiveness of selective antithrombin therapy in ICH.

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## Response

We thank Drs Hamada and Matsuoka for their interest in our report.<sup>1</sup> We agree that heparin has the limitations outlined in their letter and that there are better thrombin inhibitors. Our use of heparin in the referenced study was only as a “proof of concept,” particularly in the large animal (porcine) intracerebral hemorrhage model. Our goal was to determine whether activation of the coagulation cascade was a necessary event for early perihematomal edema development. Indeed, in the absence of clot formation essentially no edema development occurred in either white or gray matter surrounding the hematoma.

The authors describe an ongoing pilot clinical trial of the antithrombin agent argatroban for treating intracerebral hemorrhage. The rationale for this therapy has a basis not only in the referenced

report<sup>1</sup> but also previous findings<sup>2</sup> from the University of Michigan group which demonstrated that specific thrombin antagonism reduces brain edema after intracerebral hemorrhage. Furthermore, the proposed time of 24 hours for initiating treatment could prove effective, since the peak in thrombin-induced edema occurs at 24 to 48 hours.<sup>3</sup> In addition, blood-brain-barrier breakdown, which is delayed but develops by 24 hours,<sup>4–6</sup> could result in high brain thrombin levels due to high (1 to 5  $\mu$ M) plasma prothrombin concentrations. However, many of the deleterious effects of thrombin related to clot formation would have already occurred by this time point. Thus, although concerns about rebleeding with argatroban are warranted, the proper timing for administering such a drug is currently unknown.

The authors indicate that preliminary findings in 4 intracerebral hemorrhage patients suggest a reduction in perihematomal edema and no adverse events. However, we propose that animal studies demonstrating the proper timing, efficacy, and safety of argatroban be completed before embarking on a randomized, controlled clinical study. In the meantime, however, we look forward to reading the authors' full report of this pilot trial of a potentially interesting drug for treating intracerebral hemorrhage-induced edema.

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## Cerebral Dynamics of Autoregulation and Hypoperfusion

*To the Editor:*

The article by Zaharchuk et al<sup>1</sup> raises a series of questions.

First, the authors are careful to delineate many problems concerning interpretation of data gathered with the BOLD technique and the variations they employ. These limitations might help explain some of the difference between the microvascular versus the global cerebral blood volume changes they

observe during hypoperfusion. However, the authors never call our attention to a much more glaring problem: In their Figure 3, there is no decrease in either total cerebral blood volume (CBV) or microvascular volume over the whole autoregulatory “plateau.” This is impossible. There must be an increase in resistance—a decrease in diameter—somewhere to account for the good autoregulation over the plateau. Until we have a reasonable explanation for their finding, it seems premature to trust their techniques and accept their conclusion that “CBV changes during hemorrhagic hypotension are far less than . . . [those] . . . reported by some previous studies.”

Second, the authors talk about cessation of autoregulation as the pressure falls below the so-called lower limit of autoregulation. This way of expressing matters is the one usually used, but it is highly misleading. Beyond each end of the “plateau” the vessels continue to autoregulate—ie, to relax as pressure falls and to constrict as pressure rises. Thus, the resistance continues to go up at pressure above the high end of the “plateau” and to fall at pressure below the low end. However, these autoregulatory changes in tone are no longer sufficiently larger to compensate for the changes in pressure, and the flow changes more markedly for each change in pressure than it did for changes in pressure over the “plateau.” Autoregulatory responses are not absent, and the flow-pressure relationship is not truly passive until some much lower (or higher) pressure is reached. This is NOT seen in the authors’ Figure 2, in which the relationship between flow and pressure appears to be totally passive as soon as we fall off the low end of the “plateau.” Perhaps this, too, is a function of the problems in measuring CBF with the imaging techniques they use. Perhaps, also, the authors were not aware of the conundrum presented by the data in Figure 2 because they expected (erroneously) that flow would be “passive” as soon as the “plateau” was left.

Finally, the authors’ Figure 2 does show something that is in agreement with the results reflected in the work of Kontos, myself, and others cited in their Reference 14. The “plateau” is not flat (the reason I place the term in quotes or say so-called). Rather, it has a gentle slope. It is interesting that in spite of the problems I point out, their data still show this. In any case, it is correct that the famous “plateau” plotted by Lassen (see critique in the Handbook of Physiology, chapter by Heistad and Kontos on cerebral circulation) from a summary of heterogeneous papers in the literature, is not a plateau at all and animals that fail to show an absolutely flat flow over the range of maximally effective autoregulation are behaving normally.

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1. Zaharchuk G, Mandeville JB, Bogdanov AA Jr, Weissleder R, Rosen BR, Marota JJ, Iadecola C, Kim SG. Cerebrovascular dynamics of autoregulation and hypoperfusion: an MRI study of CBF and changes in total and microvascular cerebral blood volume during hemorrhagic hypotension. *Stroke*. 1999;30:2197–204.

## Response

Dr Rosenblum’s letter highlights some of the more surprising findings of our recent article reporting total and microvascular CBV changes during cerebrovascular autoregulation and hypoperfusion in the rat.<sup>1</sup> Our findings do challenge the conventional wisdom that CBV must increase dramatically to maintain CBF in the face of declining mean arterial blood pressure (MABP).<sup>2</sup> However, it is important to remember that our study was the first to use an imaging-based technique capable of sampling both the brain’s cortical surface and its deeper parenchyma. The cortical surface has a higher fraction of large vessels, so it is not entirely

surprising that CBV in the parenchymal responds differently. As most of the brain lies below the cortical surface, understanding such parenchymal changes may yield important insight into how the brain as a whole reacts to MABP alterations.

Dr Rosenblum’s first point concerns our finding of no significant increase in either total or microvascular CBV on the autoregulation plateau. Far from not calling attention to this fact, we had hoped to emphasize this most interesting finding. As Dr Rosenblum points out, it seems logical that vasodilation with concomitant CBV increase must occur to decrease cerebrovascular resistance as MABP falls within the autoregulatory range. We agree that such changes occur. However, we attribute the change in resistance (and diameter) to a very small subset of vessels, the cerebral arterioles, thought to comprise less than 5% of overall cerebral blood volume. The feasibility of such an interpretation is supported by our cerebrovascular model (more detail may be found in Reference 3), as well as previous evidence in other organ systems that CBF is regulated by changes in arteriolar diameter.<sup>4</sup> Because even large diameter changes in these relatively few vessels lead to only small overall increases in total CBV, it is possible to control CBF with minimal total CBV increases; as we have pointed out, such a system is particularly well-suited for the brain, where large changes in CBV are problematic due to the fixed overall volume of the bony cranium. Lastly, we reiterate that we cannot rule out CBV increases during autoregulation by as much as 20% due to uncertainties about the systemic concentration of the contrast agent during the course of the experiment. However, the conclusion remains that CBV does not increase dramatically (by >100%) as reported by previous methods that have sampled small amounts of tissue near the cortical surface.

Dr Rosenblum’s second point questions whether the CBF changes observed when MABP is below 50 mm Hg are consistent with previous reports and suggests that arterial spin label MRI methods may be at fault. He points out that previous studies demonstrate that the process of autoregulation is not “all-or-none”; ie, that the corners of the autoregulation curve are not sharp. He contends that we have documented “passive” CBF changes below a MABP of 50 mm Hg. We regret any confusion that may have been caused by placing a line based on a least-squares fit of CBF between 50 and 140 mm Hg onto our Figure 2 or by calculating the linear fits to our data within and below the autoregulation range in the Results section. It was never our intention to imply that autoregulation is lacking during mild hypotension; this line was placed arbitrarily only to support our selection of a range of MABP for comparison. Taking into account the error bars of the data in Figure 2, we do not believe that it is possible to argue that the CBF curve we show is inconsistent with a rounded lower limit of autoregulation. Also, the observation that CBV increases occur during mild hypoperfusion further suggests that autoregulatory processes continue to be active but are insufficient to curtail decreases in CBF.

Dr Rosenberg’s last comment points out that the autoregulation “plateau” should have a slight slope, as shown by his data.<sup>5</sup> Our data are in agreement with this. Rather than suggesting that the CBF measurement method is inaccurate, we believe that this finding argues that it is sufficiently sensitive and accurate to replicate this subtle physiological effect, which is likely secondary to anesthesia.<sup>6</sup> Unlike the CBV findings, the CBF results support previous observations during autoregulation. Because of this, we feel that the argument that the CBF measurement method is flawed cannot be based on the data presented in our article.

Last, we take issue with the contention that errors in the measurement techniques may be sufficient to “explain some of the difference between the microvascular versus the global cerebral blood volume changes” during hypoperfusion. As we have mentioned in the paper, there is a long history addressing the accuracy and robustness of susceptibility contrast MRI



methods to measure CBV changes. Because of this, we believe that differences between total and microvascular CBV are entirely physiological and may have important implications during stroke. The ability to measure changes in microvascular CBV with spin echo susceptibility contrast MRI opens a new and fascinating window into events occurring at the capillary level during ischemia, by avoiding the potentially confounding effects of large vessel diameter changes.

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## Delayed Ischemic Hyperintensity of T1-Weighted MRI

To the Editor:

Fujioka et al<sup>1</sup> reported 4 cases of transient internal carotid artery–middle cerebral artery occlusion; serial MRI revealed hyperintensity on T1-weighted (T1W) imaging in the caudoputamen in all patients and in the cerebral cortex in 2 patients. In the companion article,<sup>2</sup> Fujioka et al reproduced the MRI finding in rats by 15-minute middle cerebral artery occlusion but not by 60-minute occlusion. Histological examination revealed that this specific ischemic change on MRI corresponded to selective neuronal death and gliosis with preservation of the macroscopic structure of the brain.

I have previously reported<sup>3</sup> 10 cases with similar MRI finding; these patients presented not only with sudden hemispheric stroke followed by rapid improvement but also with hemichorea-hemiballism. A biopsy from the hyperintense putamen in one of my patients revealed a fragment of gliotic brain tissue with abundant gemistocytes. It is interesting that in both my studies and those of Fujioka et al similar conclusions were obtained.

First, the MRI finding corresponded with an incomplete infarction. This was demonstrated not only by the relative preservation of the macroscopic structure of the brain in both studies but also by the presence of patchy lesions intermixing with relatively normal brain tissue in the biopsy specimen of my patient.

Second, Fujioka's study confirmed my hypothesis that the MRI finding was related more to vascular compromise than to petechial hemorrhage or hyperglycemia, as had been proposed in patients with hemichorea-hemiballism.

Third, while Fujioka et al demonstrated the delayed appearance of the ischemic hyperintensity of the T1W MRI, the onset of hemichorea-hemiballism in some of my patients was also delayed. Both findings suggested a progressive course existing in an incomplete infarction.

Some additional findings in my study are worth mentioning.

First, <sup>1</sup>H MR spectroscopy on the biopsy specimen of my patient demonstrated an increase in lactic acid and a decrease in creatine and *N*-acetylaspartate, which suggests the presence of anaerobic glycolysis, energy depletion, and neuronal dysfunction. These findings were consistent with the presence of an ischemic injury.

Second, my study demonstrated that after years of follow-up in 2 patients, T2-weighted MRI revealed slit-shaped cystic lesions in lateral part of the putamina, consistent with the presence of watershed infarction.

Third, some of my patients presented with hemichorea-hemiballism from the onset and without preceding attacks of hemispheric stroke, which suggests that incomplete infarction alone was sufficient to produce the MRI signal change, with or without hemiparesis.

Fourth, in one of my patients the hyperintense lesion extended down to midbrain level, a location presumably remote from the site of vascular compromise. This finding suggested that the MRI signal was related to changes along the striatonigral fibers and not limited to the striatum.

Although some biochemical changes affecting the magnetic field might be responsible for the MRI signal change, in my article,<sup>3</sup> I proposed that the hyperintensity on T1W MRI could be due to the presence of abundant gemistocytes locating along the axons and persisting for years. Shortening of T1 relaxation time could result from the protein hydration layer inside the cytoplasm of swollen gemistocytes, as in a case with gemistocytic astrocytoma.<sup>4</sup> Gemistocytes are swollen reactive astrocytes that usually appear during acute injury; after that, they gradually shrink in size. However, gemistocytes are also found in some chronic diseases, which suggests the presence of a long-lasting pathological reaction.

It would be interesting to know whether the reactive astrocytes found in the rat striatum by Fujioka et al belong to the type of gemistocyte, and if the appearance and disappearance of this specific type of reactive astrocytosis correlate with the appearance and disappearance of the ischemic hyperintensity of the T1W MRI.

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## Response

We appreciate Dr Shan's comments regarding our recent articles.<sup>1,2</sup> As correctly pointed out, the "delayed ischemic hyperintensity (DIH) on T1W MRI" histologically corresponds

to the incomplete infarct of selective neuronal death and reactive astrocyte proliferation after mild ischemia.<sup>2</sup>

However, we suggest that this shortening of T1 relaxation time results at least partly from induced manganese superoxide dismutase (Mn-SOD) in mitochondria of the reactive astrocyte and may represent long-lasting oxidative stress in the incomplete infarct after mild ischemia.

Hyperintense basal ganglia on T1W MRI has been reported to occur in patients with or after various pathological conditions, including chronic hepatic encephalopathy,<sup>3</sup> long-term total parenteral nutrition,<sup>4</sup> hyperglycemia,<sup>5</sup> post-cardiac arrest encephalopathy,<sup>6,7</sup> hypoglycemic coma,<sup>8</sup> and mild focal ischemia.<sup>1,9</sup> This interesting change can lead to choreaballism.<sup>5,10</sup> The exact mechanism of the T1 hyperintensity in these cases remains controversial. Possible causative factors of this T1 hyperintensity involve the followings<sup>1,2,8</sup>: (1) factors immobilizing water molecules (ie, macromolecular hydration effect or surface relaxation mechanism eg, protein and calcification), (2) lipid, (3) flow-related enhancement,<sup>11</sup> and (4) paramagnetic substance (eg, methemoglobin in hemorrhagic tissue, free radicals, molecular oxygen, melanin, and metals such as iron, manganese, copper).

Therefore, the T1 hyperintensity in brain ischemia tends to be simplistically considered a hemorrhagic transformation. Indeed, we also reported that MRI revealed symmetrical changes suggestive of minor hemorrhages, which CT scans could not detect, in the basal ganglia, thalami, and/or substantia nigra in the patients after cardiac arrest.<sup>6,7</sup> The lesions appeared hyperintense on both T1W and T2W MRI in the late stage after heart arrest, and then could be considered to be petechial hemorrhages.

However, in patients after hypoglycemia or brief focal brain ischemia (both of which lead to relatively mild energy failure in the brain compared with cardiac arrest), MRI showed persistent hyperintensity/hypointensity on T1W/T2W MRI, respectively, in the basal ganglia, cerebral cortex, hippocampus, and/or substantia nigra from a week after each insult.<sup>1,8</sup> In the patients after brief hemispheric ischemia,<sup>1</sup> ischemic change of T1 hyperintensity subsided with time. These changes on repeated MRI and CT scans seemed to clearly differ from edema, infarct, hemorrhage and calcification. The T1 hyperintensity seemed to be caused by an unknown common mechanism that was related to neuronal death.

We tried to reproduce the ischemic change of hyperintensity on T1W and hypointensity on T2W MRI in the rat.<sup>2</sup> This MRI change appeared in the rat striatum at day 7 but not day 3 after 15 minutes' middle cerebral artery occlusion (MCAO). This DIH histologically corresponded to selective neuronal death and glial proliferation without infarct or hemorrhage.

Certainly, there may be a possibility that astrocyte proliferation per se or ultrastructural changes in astrocyte cytoplasm (eg, proliferation of mitochondria, rough endoplasmic reticulum, and vacuoles) shortened the T1 and T2 relaxation times via surface relaxation mechanism.<sup>10,12</sup> However, glial reactions appear from the early stage after ischemia.<sup>13,14</sup> In our previous study,<sup>2</sup> abundant GFAP-positive astrocytes existed in the rat striatum 3 days after 15-minute MCAO. These astrocytes had common features of "reactive astrocyte" characterized by hypertrophy with enlarged and extended processes and increases in intermediate filaments.<sup>13</sup> At this time (3 days after ischemia), MRI did not demonstrate T1 hyperintensity in the striatum. Therefore, we think that other factors, such as paramagnetic effect, are strongly related to the DIH rather than surface effect caused by those subtle structural changes of brain tissue.

Since then, we have investigated the chronological changes in the rat striatum from 4 hours to 4 months after 15-min MCAO with regard to MRI, histology, and immunoreactivity to Mn-SOD. (The details, reported at the 25th International Stroke Conference, February 10–12, 2000, in New Orleans, appear in abstract form in the January 2000 issue of *Stroke*.<sup>15</sup>) Based on the

results, we think that the delayed ischemic hyperintensity on T1W MRI results at least partly from Mn-SOD induction in mitochondria of the reactive astrocytes. This induction of Mn-SOD seems to reflect a long-lasting oxidative stress after mild ischemia.

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## Extracranial Cervical Artery Dissection

To the Editor:

Cervical artery dissection is an important cause of stroke in young patients. While the recent literature has focused on the pathophysiology,<sup>1</sup> little attention has been given to acute treatment. Based on stroke patterns, recent work has opined that heparin is a "logical" treatment for carotid territory dissection,<sup>2</sup> although this has been challenged.<sup>3</sup> To investigate the treatment preferences of stroke experts in extracranial cervical artery dissection, we developed a single-page questionnaire. Members of the Canadian Stroke Consortium (CSC),<sup>4</sup> a group consisting of neurologists with a subspecialty interest in stroke, were asked to fill out the questionnaire at their annual general meeting in 1999. In addition, the questionnaire was mailed out once to members who did not attend the meeting.

The CSC had 96 members at the time of this meeting, of whom 43 were present at the meeting. Of 49 survey responses received, 1 was excluded because of incomplete information, leaving 48 completed surveys (50% response rate) for this analysis. All of the respondents were neurologists, and the average number of years in practice was  $13.4 \pm 1.1$  (SEM). Physicians working at academic facilities (30) composed 61% of the total; those at community facilities, 37% (18 physicians); and not stated, 2% (1 physician). The average number of acute strokes seen per year per center was  $357 \pm 30$ . The mean estimated number of dissections per center per year was  $11 \pm 1$ . The centers were characterized by the availability of neuroimaging technology. All centers had duplex ultrasonography. Acute CT was available in 98%, conventional selective cerebral angiography in 90%, CT angiography in 75%, and MRI and MR angiography (MRA) in 71% of centers.

The preferred initial diagnostic modality for suspected carotid dissection was fairly evenly divided among angiography (31.3%), MRA (31.3%), and duplex (37.5%). For suspected vertebral dissection, angiography was favored (56.3%) over duplex (35.4%), MRA (6.3%), and CTA (2.1%). Although 92% of respondents believed that the gold standard test for any cervical artery dissection was conventional selective cerebral angiography, only 56% believed that all patients should undergo the gold standard test for diagnosis.

The preferred treatment for extracranial dissection was immediate anticoagulation. The favored underlying pathophysiology was distal embolism from clot in the dissected artery (Table). Logistic regression analysis identified no variable (years in practice, province of practice, community versus teaching hospital, number of stroke cases admitted per year, availability of imaging technology, or favored underlying mechanism) that was predictive of treatment choice. Once the diagnosis was made, the mean time on treatment was  $5.2 \pm 0.5$  months. Patients were seen in follow-up after discharge in a mean of  $2.3 \pm 0.2$  months. Two thirds (67%) felt that patients should be re-imaged at follow-up, and the preferred modality was MRA (58%). Few (6%) would re-image with conventional selective arterial angiography.

Although there is little direct evidence supporting anticoagulation in extracranial cervical artery dissection, this lack of evidence has not dissuaded the majority of Canadian stroke neurologists from empirically anticoagulating their patients. This is consistent with recent literature which claims that the etiology of stroke after dissection is arteroembolic in more than 90% of cases.<sup>3</sup> It remains possible that anticoagulation is not helpful; this is particularly relevant in light of increasing evidence that heparin is not generally useful in acute stroke treatment.<sup>5,6</sup> The Stroke Group at the Cochrane Collaboration is working on a review of anticoagulation in extracranial internal carotid artery dissection that may provide more information.

## Survey Responses From 48 Canadian Stroke Neurologists

	Responses, n (%)
Preferred treatment	
Parenteral anticoagulation	39 (81.3)
Antiplatelet therapy	3 (6.3)
Conservative management	3 (6.3)
Oral anticoagulation	1 (2.1)
Angioplasty and/or stenting	0 (0)
Not stated	2 (4.2)
Most likely mechanism	
Distal embolism from clot in dissected artery	24 (50.0)
Occlusion of dissected artery	5 (10.4)
Both	19 (39.6)

A randomized trial of anticoagulation versus antiplatelet therapy in stroke secondary to acute cervical artery dissection, with definitive outcomes such as recurrent stroke or death, may be impractical due to the necessary size of such a trial.<sup>7</sup> However, it remains an important question. Surrogate outcomes that would change practice—such as neurological disability, artery patency rate after 3 to 6 months of anticoagulation, transcranial Doppler analysis of high-intensity transient signals, cerebral blood flow measurement, and quality of life—need to be considered. Because stroke patients with dissection are most often young and likely to be intensively investigated, a multicenter collaboration using the outcomes described should be possible.

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