

Letters to the Editor

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Osmotherapy: A Call to Arms

To the Editor:

We read with interest the report by Bereczki and colleagues,¹ who failed to find evidence supporting the use of mannitol in acute stroke after a thorough search of the available medical literature. The authors found only one “unconfounded” randomized clinical trial evaluating mannitol in stroke. Not surprisingly, mannitol holds a preeminent position in the limited clinical armamentarium of neurological critical care, despite the virtual absence of well-designed studies addressing its role in stroke. The rationale of osmotherapy in brain ischemia is mainly inferred from two circumstances: (1) brain edema is intricately involved in cellular damage during ischemia and (2) the blood-brain barrier (BBB) remains basically intact during the first few hours after the onset of ischemia. Perivascular glial edema occurs within minutes after the induction of ischemia and is followed by neuronal edema.² Due to the small pore size of cerebral endothelium, the BBB has a very low hydraulic conductivity, which limits the passage of small molecules and even restricts the permeability of water.³ A hydrostatic pressure gradient across the BBB develops early after ischemia, leading to the accumulation of interstitial fluid.⁴ In addition, an osmotic gradient develops 3 to 6 hours after ischemia.⁴ Nevertheless, experiments using Evans blue and Na-fluorescein fail to demonstrate leakage of dye into brain parenchyma, indicating that BBB remains intact during the initial phase of ischemia.⁵

The choice of an osmotic agent should not remain a matter of tradition, since some rational points can be made. The ability of solutes to cross a membrane can be expressed by the osmotic reflection coefficient (ORC). The ORC value ranges from 1 for an “ideal” osmotic agent to 0 for substances that provoke no osmotic drive.⁶ The ORC of mannitol is estimated to be close to 0.5, while that of NaCl is almost 1. However, these parameters were mostly obtained in experiments using circulatory circuits different than the brain, like kidney and muscle. It is not known whether these values can be applied to the BBB. The ideal osmotic agent should not accumulate in the edematous brain parenchyma, since it may create more edema and “rebound phenomenon.”⁶

Although no controlled trials have investigated hypertonic saline in acute stroke, numerous controlled trials have compared glycerol with placebo and found no net effect on outcome (Table). All of these trials, however, share the same essential flaws: none has demonstrated an actual change in blood osmolality, blood viscosity,

or intracranial pressure (including midline shift measurements on imaging studies).⁷ Another pertinent effect of glycerol in acute stroke, hyperglycemia, has not been systematically addressed. Finally, the number of enrolled patients has been small, compromising the statistical power of the studies.⁷

Despite its early failures, osmotherapy holds a potential that should be rigorously investigated. Future trials should employ a rational, physiological approach to therapy as opposed to arbitrary, nonphysiological regimens. They should use enough doses of agents to exert an efficient osmotic drive, guided by physiological parameters such as intracranial pressure monitoring, evidence of decreased lateral shift of the brain parenchyma on neuroimaging, and serial determinations of serum osmolality, viscosity, glucose, sodium, BUN, and creatinine.

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1. Bereczki D, Liu M, Fernandes do Prado G, Fekete I. Cochrane Report: A systematic review of mannitol therapy for acute ischemic stroke and cerebral parenchymal hemorrhage. *Stroke*. 2000;31:2719–2722.
2. Hatashita S, Hoff JT. Role of blood-brain barrier permeability in focal ischemic brain edema. In: Long DM, ed. *Brain Edema: Pathogenesis, Imaging and Therapy*. *Advances in Neurology*. New York, NY: Raven Press; 1990:327–333.
3. Bourke RS, Kimelberg HK, Nelson LR, Barron KD, Auen EL, Popp AJ. Biology of glial cells in experimental brain edema. In: Cervos-Navarro J, Ferszt R, eds. *Brain Edema*. *Advances in Neurology*. New York, NY: Raven Press; 1980:99–109.
4. Hatashita S, Hoff JT, Salamat SM. An osmotic gradient in ischemic brain edema. In: Long DM, ed. *Brain Edema: Pathogenesis, Imaging and Therapy*. *Advances in Neurology*. New York, NY: Raven Press; 1990: 85–92.
5. Reulen HJ, Tsuyumu M, Prioleau G. Further results concerning the resolution of vasogenic brain edema. In: Long DM, ed. *Brain Edema: Pathogenesis, Imaging and Therapy*. *Advances in Neurology*. New York, NY: Raven Press; 1990:375–381.
6. Paczynski RP. Osmotherapy: basic concepts and controversies. *Crit Care Clin*. 1997;13:105–129.
7. Restrepo L, Balish M. Role of glycerol in cerebrovascular disease. *Neurologist*. 2000;6:338–347.

Clinical Trials Using Glycerol for Acute Cerebrovascular Disease

Group	Type	No. of Patients	Dose/Pathway of Glycerol	Results
Meyer et al (1971)	Descriptive	36	IV/PO given within 72 h, for 4 d	Better mental status and motor strength. No clear long-term benefit.
Mathew et al (1972)	Double-blind randomized	54	IV glycerol versus placebo for 4–6 d	Significant improvement in neurological exam. No long-term data. No improvement in mortality.
Larsson et al (1976)	Randomized	27	IV glycerol versus IV dextrose, given within 6 h, for 6 d	No immediate (1–10 d) or late (3 mo) benefit. No difference in mortality.
Bayer et al (1987)	Double-blind randomized	173	IV glycerol versus placebo started within 48 h	Significant improvement in cognition, motor strength, and speech during early treatment. Significant improvement in early mortality. No differences in morbidity or mortality at 12 mo.
Yu et al (1993)	Double-blind randomized	113	IV glycerol versus placebo	No significant differences (Barthel Index and Scandinavian Stroke Scale).

Response

We thank Drs Restrepo and Silverman for drawing attention to several pathophysiological aspects of osmotherapy and to some clinical trials on glycerol in acute stroke. We fully agree with their statements that osmotherapy might have a potential in stroke therapy, that this therapeutic option should be rigorously investigated, and that the clinical application of an osmotic agent should not remain a matter of tradition. In fact, these were among our reasons for performing a systematic review of unconfounded randomized trials of mannitol therapy in acute stroke.¹

As far as glycerol is concerned, in addition to the trials Drs Restrepo and Silverman referred to in their letter, several other randomized trials have been performed. Eleven randomized trials are included in the systematic review of Righetti et al,² and this review comes to a slightly different conclusion than that of Drs Restrepo and Silverman. Righetti et al found that among patients with definite or probable ischemic stroke, glycerol was associated with a significant reduction in the odds of death during the scheduled treatment period, although this favorable outcome could not be detected at the end of the scheduled follow-up period. They recommended that because of the small number of patients, the results should be interpreted cautiously, and emphasized that the lack of evidence of benefit in long-term survival does not support the routine or selective use of glycerol treatment in patients with acute stroke.

The fact that we could not identify a sufficient amount of evidence to prove that mannitol influences short- or long-term outcome after stroke should not be considered as a proof against the effect (beneficial or harmful) of mannitol in acute stroke. It simply means that there is not enough evidence from randomized controlled trials to come to a final conclusion, and therefore more studies are needed. We agree with the recommendations of Drs Restrepo and Silverman that when designing such trials the applied optimal dose should be based on previous pathophysiological observations and neuroimaging should be a part of the study protocol. Because midline shift was not altered by mannitol in patients with cerebral edema after a large hemispheric infarction,³ measuring changes in lateral shift does not seem to be a useful method for monitoring osmotherapy. A noninvasive transcranial Doppler monitoring of osmotherapy might be promising.⁴ Although it might be useful to monitor physiological and serum parameters during osmotherapy, in clinical trials the primary outcome measures that are important for the patients and their families—such as survival, dependency, and quality of life—should be evaluated.

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1. Bereczki D, Liu M, do Prado GF, Fekete I. Cochrane report. A systematic review of mannitol therapy for acute ischemic stroke and cerebral parenchymal hemorrhage. *Stroke*. 2000;31:2719–2722.
2. Righetti E, Celani MG, Cantisani T, Sterzi R, Boysen G, Ricci S. Glycerol for acute stroke (Cochrane review). In: *The Cochrane Library*, issue 4, 2000. Oxford, UK: Update Software.

3. Manno EM, Adams RE, Derdeyn CP, Powers WJ, Diringner MN. The effects of mannitol on cerebral edema after large hemispheric cerebral infarct. *Neurology*. 1999;52:583–587.
4. Treib J, Becker SC, Grauer MT, Haass A. Transcranial Doppler monitoring of intracranial pressure therapy with mannitol, sorbitol and glycerol in patients with acute stroke. *Eur Neurol*. 1998;40:212–219.

Association of Intraoperative Transcranial Doppler Monitoring Variables With Stroke From Carotid Endarterectomy

To the Editor:

I read with great interest today the article by Ackerstaff et al¹ regarding transcranial Doppler monitoring during carotid endarterectomy (CEA). In particular, the editorial remarks by Drs Babikian and Cantelmo that “a wider use of transcranial Doppler monitoring seems reasonable because it can possibly improve the outcome CEA”² should be interpreted with caution. I believe that Ackerstaff et al have failed to demonstrate how transcranial Doppler monitoring can improve the stroke rate following CEA. I will not dispute the fact that the authors’ data support the use of transcranial Doppler monitoring as an equivalent means of practicing selective shunting compared with other modalities, namely, EEG monitoring. However, I believe the suggestion that improved outcomes might be obtained by using transcranial Doppler monitoring is potentially dangerous and subject to misinterpretation. The fact that one can detect emboli does not necessarily lead to the ability to prevent them or their consequences. The only remark that I noted to have any potential use as far as prevention of complications relates to early distal clamping of the internal carotid artery in the face of emboli detected during the dissection. This must be balanced, of course, with the potential for this leading to ischemic complications if the artery is not otherwise completely prepared for the surgeons who go on to proceed with a rapid completion of endarterectomy. Moreover, the detection of emboli during wound closure as an indicator of impending occlusion is a problem that can generally be detected by routine inspection of the artery with hand-held Doppler prior to closure. This is a technique that can readily detect intimal flaps and can lead to intraoperative revision.

I do not dispute the fact that transcranial Doppler monitoring may be a good tool for detecting patients at risk for hyperperfusion syndromes. In my experience, clinically significant episodes of hyperperfusion can often be predicted on the basis of a study of the preoperative patient’s angiogram in the context of the patient’s clinical history.

The editorial reviewers² go on to comment on the issue of making public the morbidity and mortality rates of every medical center. Again, in the United States, I find that this is an issue in which the application of such information may potentially backfire. For instance, if a young, well-trained surgeon, fresh from training, experiences a stroke on his third endarterectomy out of training, should that surgeon’s privileges for performing this procedure be suspended? I think that this is slippery slope, given the fact that we still do not know what would be an adequate N on which to evaluate a single surgeon’s operative outcomes. I would therefore strongly urge professional associations to spearhead maneuvers to continue to educate their members who perform this operation in proven means of reduction the risk of complications.

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1. Ackerstaff RGA, Moons KGM, van de Vlasakker CJW, Moll FL, Vermeulen FEE, Algra A, Spencer MP. Association of intraoperative trans-

cranial Doppler monitoring variables with stroke from carotid endarterectomy. *Stroke*. 2000;31:1817-1823.

2. Babikian VL, Cantelmo NL. Cerebrovascular monitoring during carotid endarterectomy. *Stroke*. 2000;31:1799-1801. Editorial.

Response

Recently, we have illustrated that information provided by transcranial Doppler (TCD) monitoring during carotid endarterectomy (CEA) independently predicts postoperative stroke.¹ In their editorial, Babikian and Cantelmo² welcomed our results but also commented that our study was not randomized and that the efficacy of TCD monitoring on patient outcome cannot yet be considered established. In his letter, Dr Rabb has raised the same concern. Here, we contemplate whether a randomized study is truly necessary to infer the usefulness of TCD during CEA.

In the present era of evidence-based medicine, a medical technology must have been proved to be effective (improve patient outcome) or more efficient (contain costs). This also applies to diagnostic and monitoring tests.³ Various authors have proposed that, as with therapeutic strategies, medical tests also should undergo consecutive phases of evaluation before implementation in practice.⁴⁻⁶ They more or less propose that after the technical and diagnostic performance of the test (its ability to detect presence or absence of a disorder) has been evaluated, the impact on health (ability to change patient outcome) and cost-effectiveness should be quantified. Obviously, the paradigm for a valid evaluation of therapeutic strategies on patient outcome is the randomized trial. But, even in the realm of evidence based medicine, is this a necessity for diagnostic tests?

TCD monitoring can be considered a diagnostic test to detect cerebral microemboli during CEA. As most diagnostic tests, TCD itself has no impact on patient outcome. Its information directs patient management, which may alter the prognosis of the patient. Hence, especially the therapies chosen on the basis of TCD determine the (cost-)effectiveness of TCD. Diagnostic studies have shown that TCD is capable of detecting microemboli.⁷⁻¹⁰ Therapeutic studies demonstrated that interventions administered to decrease emboli resulted in reduction of perioperative morbidity.^{8,11,12}

In general, we find that the beneficial effect of a diagnostic test on patient outcome may be considered established if (1) diagnostic studies have shown the test's ability to detect a particular disorder and (2) therapeutic studies have provided evidence on efficacy of the management of this disorder. Following this reasoning and combining the available evidence of TCD monitoring and emboli treatment, there may be enough evidence that TCD monitoring during CEA improves patient outcome.

In the case of TCD, the limiting factor may be the strength of the evidence from the therapeutic studies: none was randomized. A classic trial would pragmatically randomize patients eligible for CEA to surgery with or without TCD monitoring. A difference in postoperative outcome in favor of the TCD arm would prove the usefulness of TCD during CEA. However, such a study would require large numbers of patients, given the relatively low occurrence of stroke in these patients.^{1,2} Second, such a design may be perceived to be unethical, as many surgeons already rely on the use of TCD during CEA. Finally, it would be difficult to avoid the learning effects of the surgeon. The experience with TCD monitoring may make surgeons more careful at the moments they expect emboli when no TCD is used. This learning effect would dilute the effectiveness of TCD. Given these limitations and our reasoning that many tests, including TCD, by themselves have no effect on patient outcome and the results of diagnostic and therapeutic studies ought to be combined, another trial design may be more efficient. Assuming that the value of TCD to detect emboli is established, each patient eligible for CEA will undergo surgery with the use of TCD. Only if emboli occur, patients are randomized to 2 treatment regimens (eg,

dextran-40 or platelet glycoprotein IIB/IIIA receptor antagonist). Such a trial design still has the drawback of large patient numbers but lacks the second and third limitations discussed above.

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1. Ackerstaff RGA, Moons KGM, van de Vlasakker CJW, Moll FL, Vermeulen FEE, Algra A, Spencer MP. Association of intraoperative transcranial Doppler monitoring variables with stroke from carotid endarterectomy. *Stroke*. 2000;31:1817-1823.
2. Babikian VL, Cantelmo NL. Cerebrovascular monitoring during carotid endarterectomy. *Stroke*. 2000;31:1799-1801. Editorial.
3. Moons KGM, van Es GA, Michel BC, Büller HR, Habbema JDF, Grobbee DE. Redundancy of single diagnostic test evaluation. *Epidemiology*. 1999;134:276-281.
4. Fryback D, Thornbury J. The efficacy of diagnostic imaging. *Med Decis Making*. 1991;11:88-94.
5. Mackenzie R, Dixon AK. Measuring the effects of imaging: an evaluative framework. *Clin Radiol*. 1995;50:513-518.
6. Dalla-Palma L, Dixon AK, Durand-Zaleski I, Reiser M, Soimakallio S. An overview of cost-effective radiology. *Eur Radiol*. 1997;7:147-150.
7. Jansen C, Ramos LMP, Heesewijk van JPM, Moll FL, Gijn van J, Ackerstaff RGA. Impact of microembolism and hemodynamic changes in the brain during carotid endarterectomy. *Stroke*. 1994;25:992-997.
8. Levi CR, O'Malley HM, Fell G, Roberts AK, Hoare MC, Royle JP, Chan A, Beiles BC, Chambers BR, Bladin CF, Donnan GA. Transcranial Doppler detected cerebral microembolism following carotid endarterectomy: high microembolic signal loads predict postoperative cerebral ischaemia. *Brain*. 1997;120:621-629.
9. Spencer MP. Transcranial Doppler monitoring and the causes of stroke from carotid endarterectomy. *Stroke*. 1997;28:685-691.
10. Cantelmo NL, Babikian VL, Samaraweera RN, Gordon JK, Pochay VE, Winter MR. Cerebral microembolism and ischemic changes associated with carotid endarterectomy. *J Vasc Surgery*. 1998;27:1024-1031.
11. Lennard N, Smith J, Dumville J, Abbott R, Evans DH, London NJ, Bell PR, Naylor AR. Prevention of postoperative thrombotic stroke after carotid endarterectomy: the role of transcranial Doppler ultrasound. *J Vasc Surgery*. 1997;26:579-584.
12. Nicholls SC, Olson A, Moore A, Douville C, Smith W. TCD evaluation of antiplatelet therapy for postoperative thromboembolism in carotid endarterectomy. *Stroke*. 2000;31:323. Abstract.

Decompressive Craniectomy for Early Therapy and Secondary Prevention of Cerebral Infarction

To the Editor:

We read with great interest the recent article by Oppenheim and colleagues.¹ The authors reported a small, retrospective series of 28 patients at high risk of developing malignant middle cerebral artery (MCA) infarction and identified quantitative volume measurement of diffusion-weighted imaging (DWI) ischemic hyperintensity as a reliable tool to predict malignant MCA infarction.

Ischemic cerebral infarction associated with extensive edema and marked elevation of intracranial pressure may cause ischemia of neighboring brain tissue and thus lead to further infarc-

tion.² Decompressive craniectomy may interrupt this vicious cycle by decreasing intracranial pressure. This may increase cerebral perfusion pressure and optimize retrograde perfusion of MCA branches via leptomeningeal collaterals; functionally compromised but viable brain may thus be able to survive.³

The clinical⁴ and our experimental^{5–7} results indicate that decompressive craniectomy for space-occupying cerebral ischemia not only reduces mortality but also significantly improves outcome and reduces infarction size, especially when performed very early after vessel occlusion. MR studies revealed a better retrograde perfusion via leptomeningeal collaterals as possible mechanisms for reduced infarction volume in our early-treated animals.^{7,8}

In addition to the authors, we would like to draw particular attention to the primary goal of decompressive craniectomy: not only to be lifesaving, but also to achieve survival in an acceptable clinical condition. Our experimental results indicate that decompressive craniectomy as an early secondary prevention of cerebral infarction may limit the further evolution of cerebral ischemia. Clinically, hemicraniectomy is technically a simple procedure that can be performed with minimal ancillary support, and in contrast to thrombolytic therapy, without increased risk of intracerebral hemorrhage.⁹

However, one problem facing the clinician is to determine the length of time to continue conservative therapy before considering an invasive therapy such as craniectomy. For early and probably most effective treatment, the “malignant” character of the ischemic lesion has to be recognized during the first hours after the onset of symptoms. We agree with the authors that an early predictor of malignant hemispheric infarction would be desirable and of crucial value for the further therapeutic management of these patients. Clinical signs such as hemiparesis and coma are neither signs nor indicators of a “malignant” hemispheric stroke. Intracranial pressure monitoring is invasive and partially unreliable. Conventional imaging methods such as CT or T1- and T2-weighted MRI are insensitive in this early stage.^{10,11} The unique advantage of MRI is the possibility of obtaining multimodal information of the ischemic tissue with a single imaging modality. The combination of perfusion-weighted imaging (PWI) and DWI (“mismatch”) provides information on the “tissue at risk” as a time-independent marker, individually for each patient.¹² We therefore wonder why the authors did not perform MR perfusion measurements. Considering patient selection for craniectomy, it is of crucial value to know this extent of the tissue at risk. Using DWI alone, appropriate patient selection is difficult, concerning the primary goal of early ischemic therapy. Additionally, an absolute cutoff value of DWI ischemic hyperintensity may be not sufficient to characterize the complex and dynamic process of cerebral ischemia.

We believe that in the future, imaging techniques such as perfusion and diffusion MRI may enable determination of the clinical significance of cerebral ischemia early after onset, thereby allowing initiation of aggressive treatment forms, such as craniectomy, before life-threatening brain swelling and herniation occur. The retrospective study by Oppenheim and colleagues is one important step in this direction. However, further prospective studies are necessary to determine valid predictors and threshold values for malignant cerebral infarction.

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malignant middle cerebral artery infarction by diffusion-weighted imaging. *Stroke*. 2000;31:2175–2181.

- Hacke W, Schwab S, Horn M, Spranger M, De Georgia M, von Kummer R. The “malignant” middle cerebral artery territory infarction: clinical course and prognostic signs. *Arch Neurol*. 1996;53:309–315.
- Forsting M, Krieger D, von Kummer R, Hacke W, Sartor K. The prognostic value of collateral blood flow in acute middle cerebral artery occlusion. In: del Zoppo GJ, Mori E, Hacke W, eds. *Thrombolytic Therapy in Acute Ischemic Stroke II*. Heidelberg, Germany: Springer-Verlag; 1993:160–167.
- Schwab S, Steiner T, Aschoff A, Schwarz S, Steiner HH, Jansen O, Hacke W. Early hemicraniectomy in patients with complete middle cerebral artery infarction. *Stroke*. 1998;29:1888–1893.
- Forsting M, Reith W, Schaebitz WR, Heiland S, von Kummer R, Hacke W, Sartor K. Decompressive craniectomy for cerebral infarction: an experimental study in rats. *Stroke*. 1995;26:259–264.
- Doerfler A, Forsting M, Reith W, Staff C, Heiland S, Schaebitz WR, von Kummer R, Hacke W, Sartor K. Decompressive craniectomy in a rat model of “malignant” cerebral hemispheric stroke: experimental support for an aggressive approach. *J Neurosurg*. 1996;85:853–859.
- Engelhorn T, Doerfler A, Beaulieu C, Kastrup A, De Crespigny A, Forsting M, Moseley ME. Reperfusion decompressive craniectomy or a combination of both: an MRI-based study in rats. *Stroke*. 1999;30:1456–1463.
- Doerfler A, Engelhorn T, Heiland S, von Kummer R, Forsting M. Perfusion-MRI for monitoring of decompressive craniectomy in experimental hemispheric stroke. *Stroke*. 1999;30:275. Abstract P41.
- Hacke W, Brott T, Caplan L, Meier D, Fieschi C, von Kummer R, Donnan G, Heiss WD, Wahlgren NG, Spranger M, Boysen G, Marler JR. Thrombolysis in acute ischemic stroke: controlled trials and clinical experience. *Neurology*. 1999;53:S3–S14.
- Crain MR, Yuh WTC, Greene GM, Loes DJ, Ryals TJ, Sato Y, Hart MN. Cerebral ischemia: evaluation with contrast-enhanced MR imaging. *AJNR Am J Neuroradiol*. 1991;12:631–639.
- Yuh WTC, Crain MR, Loes DJ, Greene GM, Ryals TJ, Sato Y. MR imaging of cerebral ischemia: findings in the first 24 hours. *AJNR Am J Neuroradiol*. 1991;12:621–629.
- Schlaug G, Benfield B, Baird A, Siewert B, Lovblad K, Parker R, Edelman R, Warach S. The ischemic penumbra: operationally defined by diffusion and perfusion MRI. *Neurology*. 1999;53:1528–1537.

Response

We thank Doerfler et al for their letter concerning our article about DWI prediction of malignant MCA infarction.¹ We agree that the 145-cm³ threshold volume needs to be confirmed by a prospective study. We are now planning such a prospective study, and we will be happy to hear about any center interested in collaborating in such a study (contact: yves.samson@psl.ap-hop-paris.fr). As stated by Doerfler et al, we believe that hemicraniectomy may now be considered an established “lifesaving” procedure, but we think that further studies are still necessary to fully assess functional outcome of hemicraniectomy. Finally, Doerfler et al suggested that combining perfusion imaging with DWI would be of greater value than DWI alone in predicting the risk of malignant edema. It may well be, and we would be delighted to hear about data supporting this hypothesis. In our experience, however, it is not always possible to obtain reliable perfusion measurements in restless, acutely ill patients such as those included in our “malignant” group; even with the currently available postprocessing tools, perfusion MR still has some limitations. In addition, the DWI-perfusion mismatch is only an approximation of the ischemic penumbra and is more likely to reflect the “true penumbra” when DWI hyperintensity is small rather than large. We have concerns about the pathophysiological and clinical significance of the mismatch when the average volume of DWI hyperintensity already reaches 244 cm³, as was the case in our malignant group.

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- Oppenheim C, Samson Y, Manai R, Lalam T, Vandamme X, Crozier S, Srour A, Cornu P, Dormont D, Rancurel G, Marsault C. Prediction of

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1. Oppenheim C, Samson Y, Manai R, Lalam T, Vandamme X, Crozier S, Srour A, Cornu P, Dormont D, Rancurel G, Marsault C. Prediction of malignant middle cerebral artery infarction by diffusion-weighted imaging. *Stroke*. 2000;31:2175–2181.

Recommendations for the Management of Patients With Unruptured Intracranial Aneurysms

To the Editor:

I read with great interest a recent article concerning recommendations for the management of unruptured intracranial aneurysms, published both in *Stroke* and in *Circulation*.¹ The authors state, “Thus far, all natural history studies have been performed on patients *selected* for conservative management [*italics added*].” The reason for this seems to be that the recommendations are based almost exclusively on the results obtained from the International Study of Unruptured Intracranial Aneurysms (ISUIA). However, it is well known that the results of the ISUIA are in conflict with those of other studies.

The above-quoted statement is not true. In Helsinki, patients with unruptured aneurysms diagnosed before 1979 were not treated surgically.^{2–5} This gave us the possibility for a long-term follow-up of patients with unruptured aneurysms but without surgical selection of cases, and thus there was no bias caused by surgery. Our first cases have been reported as case reports, but the results of patient series have been repeatedly published with improved use of statistics since 1970, as the number of patients and follow-up years increased.^{2–5} The follow-up has been prospective, without loss of cases during the follow-up.

For my detailed opinions for potential sources of bias of the ISUIA, see our last follow-up study.⁵ In brief, patients of the ISUIA were collected from the time period when unruptured intracranial aneurysms were operated on, and the retrospective part of the follow-up study did not include all patients with conservative treatment who also were very likely older than those who were excluded due to surgical treatment. In addition, patients with a prior subarachnoid hemorrhage were younger than those without, and it was not analyzed statistically whether aneurysm group really was an independent risk factor for aneurysm rupture when age was taken into account.

Our patients with unruptured aneurysms and long-term follow-up (total of 2575 person-years, median 19.7 years per patient) showed that current cigarette smoking, size of unruptured aneurysm, and age, inversely, were significant predictors for subsequent aneurysm rupture.⁵ Because the prevalence of cigarette smoking is now decreasing in North America and Europe, the risk of rupture possibly also diminishes. However, this cannot explain the very low rupture rates of the ISUIA. Therefore, I am worried because operation on incidental aneurysms <10 mm in diameter is not recommended, and also because analysis of additional radiological findings of aneurysm or family history of aneurysms, or waiting for specific symptoms (ie, rupture of aneurysm), is recommended before a decision is made to operate.¹

According to our long-term follow-up,⁵ I recommend surgical or endovascular treatment for all aneurysms <10 mm in patients aged <50 (to 60) years if there are no contraindications. The indication for surgery is higher—even in older patients—if the patient is smoking, since cigarette smoking hastens the growth of preexisting aneurysms, which is associated with an increased risk of aneurysm rupture.⁶ I also recommend operating on small aneurysms in young (<50 to 60 years) patients with either polycystic kidney disease (PKD) or systemic lupus erythematosus

(SLE). Among our 142 patients, we had 2 patients with PKD; 1 of them died of aneurysm rupture. Two young women (aged 22.6 and 35.0 years at diagnosis) with SLE who were not cigarette smokers or hypertensives suffered aneurysm rupture after the aneurysms had increased 5 mm and 8 mm in diameter, respectively. One of them with an incidental aneurysm died of this aneurysm rupture 3.8 years after its diagnosis, at age 38.8 years.

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1. Bederson JB, Awad IA, Wiebers DO, Piepgras D, Haley EC Jr, Brott T, Hademenos G, Chyatte D, Rosenwasser R, Caroselli C. Recommendations for the management of patients with unruptured intracranial aneurysms: a statement for healthcare professionals from the Stroke Council of the American Heart Association. *Stroke*. 2000;31:2742–2750; *Circulation*. 2000;102:2300–2308.
2. Heiskanen O, Marttila I. Risk of rupture of second aneurysm in patients with multiple aneurysms. *J Neurosurg*. 1970;32:295–299.
3. Heiskanen O. Risk of bleeding from unruptured aneurysms in cases with multiple intracranial aneurysms. *J Neurosurg*. 1981;55:524–526.
4. Juvela S, Porras M, Heiskanen O. Natural history of unruptured intracranial aneurysms: a long-term follow-up study. *J Neurosurg*. 1993;79:174–182.
5. Juvela S, Porras M, Poussa K. Natural history of unruptured intracranial aneurysms: probability of and risk factors for aneurysm rupture. *J Neurosurg*. 2000;93:379–387.
6. Juvela S, Poussa K, Porras M. Factors affecting formation and growth of intracranial aneurysms: a long-term follow-up study. *Stroke*. In press.

Response

Dr Juvela's experience with epidemiological studies of unruptured aneurysms makes him one of the world's foremost authorities on this subject. His published work was extensively reviewed by our writing group and formed the basis for several of our Recommendations.

It should be noted that we did not suggest conservative management of patients with the smallest incidental aneurysms in patients without prior SAH. Rather, we stated that while “treatment rather than observation cannot *generally* be advocated, special consideration for treatment should be given to young patients in this group [*italics added*].” This language differs significantly from the conclusions reached by the authors of the ISUIA. It was specifically chosen because of concerns about potential selection bias in the ISUIA that could have led to underestimating the rupture rate in patients selected for conservative management. This was discussed in detail in the Recommendations.

Even if one accepts Dr Juvela's assertion that the ISUIA was wrong about natural history, an annual bleeding risk of 1% to 2% means that 50 to 100 operations must be performed to prevent 1 SAH the first year. Clearly, other factors must be considered. I am gratified that Dr Juvela has reached essentially the same conclusions we did. Namely, that for the smallest incidentally discovered aneurysms in patients without prior SAH, age is the most important factor in deciding whom to treat.

Although we have learned a great deal about unruptured aneurysms, many diverse and important questions still remain. For example, what is the influence of aneurysm morphology on bleeding risk? What factors underlie the significantly higher prevalence of intracranial aneurysms in populations such as the Japanese and those studied by Dr Juvela? Do these factors also influence apparent rupture rates? What is the effect of incomplete versus complete endovascular coiling on bleeding risk of a previously unruptured aneurysm? What is the true cognitive deficit rate after surgery? What is the demonstrable impact on quality of life of harboring a known unruptured aneurysm? Who should be screened for aneurysms, and how should conservatively treated aneurysms be followed?

My experience as a cerebrovascular surgeon and as the chair of this writing group lead me to believe that the data do not support blanket statements about any category of unruptured intracranial aneurysm. I believe treatment should be *considered* for all “young” patients regardless of aneurysm size, for all symptomatic aneurysms, and for any patients or aneurysms with other factors (ie, prior SAH from another aneurysm, family or genetic history, certain aneurysm morphologies) that predispose to rupture. Most importantly, management decisions must include experienced cerebrovascular surgeons at aneurysm centers that offer a full range of treatment options.

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Guidelines for Stroke Center Development

To the Editor:

The Brain Attack Coalition recently provided recommendations for establishment of stroke centers.¹ Compared with the 2-tier approach recommended in their article, I propose a 3-tier approach. I believe a 3-tier approach would include more hospitals for stroke care and would not necessarily eliminate smaller medical centers. Though I agree with the comparison of stroke centers with trauma centers, a large part of stroke care is not very different from cardiac care. In spite of larger time windows in cardiology, patients are not routinely taken to larger hospitals for emergency cardiac care. I am afraid that a 2-tier approach would exclude a large number of hospitals from this effort and would have a resistance similar to the one we already face in emergency stroke care. I propose the following as the basic structure of a 3-tier stroke center. These centers would be defined mostly in hospitals and medical centers already in that business. After creation of this network of centers, it is expected that for a stroke patient, EMS would prefer a designated stroke center.

Types of Stroke Centers

I. Level I Stroke Center

This designation carries minimum requirements. This type of center would provide minimum emergency or routine care to a patient with stroke. Anything more would be referred to the next-level stroke center. The basic elements of this center are as follows:

- A. An MD, neurologist, or a non-neurologist with interest in stroke care in charge of the stroke program.
- B. 24-hour emergency room (ER) facility with an on-call neurologist available for a personal consultation.
- C. 24-hour availability of CT or MRI equipment for an urgent scan within 30 minutes of a patient's arrival to ER.
- D. An active 24-hour program to deliver emergency intravenous therapies to appropriate stroke patients.
- E. An inpatient facility to admit patients with stroke. An intensive care unit may not be present, and a patient may be transferred to an appropriate stroke center if necessary.
- F. 24-hour neuroradiology coverage.
- G. The ongoing commitment of the hospital, reflected by the quality assurance measures for better stroke care.

II. Level II Stroke Center

This designation carries the larger responsibility of providing comprehensive, though not all-inclusive, clinical care to most of the patients with stroke. Patients who require

specialized services might be transferred to the next-level stroke center. Requirements are the following:

- A. Designated full-time or part-time stroke program director, who would be a neurologist with fellowship training or documented interest in cerebrovascular disease.
 - B. Stroke nurse-coordinator, who could be an RN or PA.
 - C. Compilation of a stroke team to provide 24-hour emergency stroke care.
 - D. 24-hour on-call system to alert the stroke team.
 - E. 24-hour ER facility with an on-call or in-house neurologist available for a personal consultation.
 - F. 24-hour availability of a CT and/or MRI equipment for an urgent scan within 30 minutes of a patient's arrival at the ER.
 - G. 24-hour availability of a vascular laboratory (eg, carotid ultrasound and transcranial Doppler) and cardiac imaging facility.
 - H. 24-hour cardiology coverage for a personal consultation.
 - I. Active 24-hour program to deliver emergency intravenous therapies to appropriate stroke patients.
 - J. Facility for on-site conventional cerebral angiography.
 - K. Intensive care unit that could admit patients with stroke.
 - L. 24-hour neuroradiology coverage.
 - M. 24-hour neurosurgery coverage for personal consultation.
 - N. Inpatient stroke unit operational under the direction of stroke director.
 - O. Continued quality assurance and stroke education programs (for medical staff and the community), overseen by the director of the program.
 - P. Ongoing program for primary and secondary stroke prevention.
 - Q. Stroke data bank to collect measures applicable to quality assurance and better patient care.
 - R. Stroke clinic to provide outpatient consultations for stroke care.
 - S. Close relationship with rehabilitation program(s) that specialize in stroke rehabilitation is expected.
 - T. Stroke research programs, clinical or basic, are optional.
 - U. This program might not accept pediatric patients.
- ### III. Level III Stroke Center
- This would be the ultimate level of the stroke care center, providing all basic and specialized clinical services. It would also develop programs for basic and clinical stroke research, which can include varieties of stroke fellowship programs. It would provide the leadership role for the smaller centers in the vicinity. This level would include the following:
- A. Stroke program director, who would be a neurologist with at least 5 years of clinical experience in cerebrovascular disease in addition to the fellowship training or documented interest in cerebrovascular disease.
 - B. At least 4 stroke-neurologists with varying interest in stroke care.
 - C. Stroke nurse coordinator, who could be an RN or PA.
 - D. 24-hour stroke response team.
 - E. 24-hour ER facility with an in-house neurology house staff and/or on-call neurologist for a personal consultation.
 - F. 24-hour availability of a CT and MRI equipment for an urgent study within minutes of a patient's arrival at the ER.
 - G. 24-hour availability of a vascular laboratory and cardiac imaging facility.
 - H. 24-hour in-house cardiology coverage.
 - I. Active 24-hour program to deliver emergency intravenous therapies to appropriate stroke patients.
 - J. 24-hour facility for diagnostic and/or therapeutic conventional angiography.

- K. 24-hour availability of a vascular intervention program to deliver pharmacological or mechanical therapeutic services.
- L. Inpatient stroke unit directed by a stroke-neurologist other than the program director. The director of the stroke unit would be assisted by another stroke unit nurse-coordinator.
- M. 24-hour in-house neurosurgery consultation.
- N. 24-hour in-house neuroradiology consultation.
- O. Neurological intensive care unit headed by a neurointensivist with appropriate training to handle all stroke patients.
- P. Continued quality assurance, community education, and medical education for local medical staff and other stroke centers in that area.
- Q. Ongoing program for primary and secondary stroke prevention.
- R. Stroke clinic.
- S. Close relationship with rehabilitation program(s) that specialize in stroke rehabilitation.
- T. Stroke data bank to collect data applicable for quality assurance, research, and better patient care.
- U. Active stroke research (basic and/or clinical) programs.
- V. This center would accept patients in all age groups.
- W. A stroke fellowship program is optional.

Each stroke care center is directed by a designated person, the stroke director. Operation of the programs can vary depending on the situation or medical center.

Minimum quality assurance criterion has to be provided to all stroke centers. In fact, certain peer review organizations and HCFA already have guidelines available that could be applicable to levels I and II stroke centers. Additional guidelines are probably required for level II and definitely for level III centers.

Every stroke center should have a territorial relationship with the surrounding centers. This relationship, which would be the key to transition patient care and to providing better comprehensive stroke care to all residents of a region, would include the following: (1) a definite protocol for referral to the nearest stroke center; (2) 24-hour availability of a superior stroke care center if a need arises; (3) a referral system easy and reliable enough to be completed in minutes; and (4) extension of air medical transport coverage for patients that might need be transferred to a higher-level stroke care center.

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1. Alberts MJ, Hademenos G, Latchaw RE, Jagoda A, Marler JR, Mayberg MR, Starke RD, Todd HW, Viste KM, Gargus M, Shephard T, Emr M, Shwayder P, Walker MD, for the Brain Attack Coalition. Recommendations for the establishment of primary stroke centers. *JAMA*. 2000;283:3102-3109.

Impact of Cerebral Microcirculatory Changes on Cerebral Blood Flow During Cerebral Vasospasm After Aneurysmal Subarachnoid Hemorrhage

To the Editor:

I read with interest the recent article by Ohkuma et al.¹ The authors observed microcirculatory changes in addition to the marked marked luminal narrowing of large arteries detected as severe angiographic vasospasm. Cerebral vasospasm associated with aneurysmal subarachnoid hemorrhage (SAH), which is angiographically characterized as persistent luminal narrowing of the major extraparenchymal cerebral arteries, affects cerebral

microcirculation and causes decreased cerebral blood flow and delayed ischemic neurological deficits.

These observations are strongly supported by studies on the function of the blood-brain barrier (BBB) in the acute stage of SAH.² Disturbances in microcirculation were found to be accompanied by barrier disruption of the intraparenchymal microvessels located proximal or distal to experimental cisternal SAH.³ A significant increase in the permeability of the BBB after SAH has been described in humans and in different experimental settings.⁴ It was found in nearly two fifths of patients within 5 days of SAH, and the majority of these patients developed vasospasm and ischemic complications in the late phase of SAH and had a poor prognosis.⁵

It can be speculated that the circulatory and permeability changes of intraparenchymal microvessels are possibly involved in the pathogenesis of the post-SAH cerebral dysfunction visible in humans.⁶ There is still a need for precise understanding of basic mechanisms underlying the post-SAH global brain dysfunction, and pathophysiological and experimental data may provide significant clinical implications for the management of patients with SAH and for assessing the rationale of new pharmacological approaches.⁴

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1. Ohkuma H, Manabe H, Tanaka M, Suzuki S. Impact of cerebral microcirculatory changes on cerebral blood flow during cerebral vasospasm after aneurysmal subarachnoid haemorrhage. *Stroke*. 2000;31:1621-1627.
2. Dóczi T. The pathogenetic and prognostic significance of blood-brain barrier damage at the acute stage of aneurysmal subarachnoid haemorrhage: clinical and experimental studies. *Acta Neurochir (Wien)*. 1985;77:110-132.
3. Joshita H, Kassel NF, Sasaki T. Blood-brain barrier disturbance following subarachnoid hemorrhage in rabbits. *Stroke*. 1990;21:1051-1058.
4. Germano A, d'Avella D, Imperatore C, Caruso G, Tomasello F. Time-course of blood brain barrier permeability changes after experimental subarachnoid hemorrhage. *Acta Neurochir (Wien)*. 2000;142:575-581.
5. Dóczi T, Ambrose J, O'Laoire SA. The significance of contrast enhancement in cranial computed tomography following subarachnoid hemorrhage. *J Neurosurg*. 1984;60:335-342.
6. Dóczi T, Joó F, Sonkodi S, Ádám G. Increased vulnerability of the blood-brain barrier to experimental subarachnoid hemorrhage in spontaneously hypertensive rats. *Stroke*. 1986;17:498-501.

Cerebral Infarction Throughout Both Internal Carotid Arteries Detected by Diffusion-Weighted MRI

To the Editor:

Many recent reports have shown that diffusion-weighted MRI (DWI) is a sensitive method for detecting the early changes of cerebral infarction. Bilateral internal carotid artery (ICA) occlusion infrequently has an acute onset and rarely causes cerebral infarction throughout the territories of both ICAs. We report one such case, in which cerebral infarction was detected by DWI.

An 85-year-old man who had suddenly become comatose was admitted to our hospital. He had a history of right cerebellar embolism in the posterior inferior cerebellar artery caused by chronic atrial fibrillation 2 years earlier. He was being treated with warfarin in another hospital and had remained symptom free for 2 years until this admission. Physical examination on admission revealed a deeply comatose patient (Glasgow Coma Scale score of 3) with Cheyne-Stokes respiration. His blood pressure was 210/130 mm Hg and pulse was 130 bpm with irregular rhythm. There were no neck bruits. Radial and femoral pulses were palpable in both sides. Lung and heart auscultation were normal. Neurological examination revealed roving eye move-

ments with reactive pupils of unequal size (right pupil 2.5 mm, left pupil 3.5 mm), a normal oculocephalic reflex, and decerebrate rigidity on pain stimulation. There was moderately increased tone in the extremities and no pathological reflexes. Laboratory investigations revealed normal values for electrolytes, blood cell count, renal and liver function, blood glucose and lipid levels, coagulation studies, and erythrocyte sedimentation rate. A serological test for syphilis was negative. An ECG showed atrial fibrillation and left ventricular hypertrophy. The chest x-ray showed slight cardiomegaly. Transthoracic echocardiograms showed a small thrombus in the left atrium. A duplex scan revealed no stenosis in the carotid bulbs or proximal ICAs. The patient was intubated. Three hours after onset, emergency T1- and T2-weighted MRI findings were normal except for an old cerebellar infarction in the right posterior inferior cerebellar artery and did not show transtentorial herniation. DWI showed diffuse hyperintensities involving both hemispheres in the territory of the ICAs (Figure 1), and the territory of the posterior cerebral artery and brain stem is spared. There was no flow in either ICA on MR angiography (Figure 2). Urokinase (420 000 IU) and osmotic diuretics were administered by intravenous infusion, but these were ineffective, and the patient died 26 hours after admission. His family refused permission for an autopsy.

Bilateral ICA occlusion is known to cause fatal stroke.¹ However, the clinical course of such patients is often chronic,¹ due to collateral circulation, and most strokes result from severe atherosclerosis,¹ arteritis² and similar processes. There have been few reports of acute cerebral infarction throughout both ICAs with spontaneous and simultaneous bilateral carotid artery occlusion. To our knowledge, only 2 such cases have been reported previously, excluding trauma or iatrogenic cases. Browne et al³ reported a case in which an atrial myxoma caused fatal multiple organ embolization that included both ICAs and the cerebellum, heart, kidney, and spleen. Yamaguchi et al⁴ reported a case of simultaneous bilateral carotid occlusion. Although they did not observe cerebral infarction on CT scan or MRI, angiography revealed bilateral occlusion of the ICAs. Although postmortem examination did not reveal myxoma, the bilateral ICA was occluded by fresh thrombi at the carotid bifurcation in their case, and they suspected cardiogenic embolism from the clinical course and autopsy findings. It is an undeniable possibility that the cerebral infarction in our patient was caused by dissection of the carotid arteries, either simultaneous and bilateral, or of 1 carotid artery, with the other previously occluded. However, because of the sudden onset stroke attack, history of atrial



Figure 2. MR angiography demonstrates that there is no flow in either ICA. There is flow in the bilateral posterior cerebral artery and basilar artery.

fibrillation, and the small intra-atrial thrombosis detected by the transthoracic echocardiogram, we speculate that the infarction was also caused by a cardiogenic embolism. In our case, an embolus from the heart likely occluded both ICAs simultaneously and produced cerebral infarction throughout both ICAs. Alternatively, our patient might have had asymptomatic unilateral ICA occlusion with collateral circulation through the anterior communicating arteries from the normal ICA, which was then occluded by a cardiac embolus. There is no convincing evidence, because an autopsy was not performed.

Lövsblad et al⁵ described a comatose patient whose DWI findings showed diffuse hyperintensities involving both hemispheres; transtentorial herniation with compression of the brain stem and an absence of flow in the carotid arteries was also noted, but the lesions on DWI extended to almost whole brain. They concluded that the lesions and absence of flow in the carotid arteries had resulted from brain death. However, we speculate that the lesions in our case were the result of acute ischemic change caused by sudden bilateral ICA occlusion, because the DWI lesion corresponded completely to the territory of bilateral ICA. To our knowledge, MR findings that show cerebral infarction throughout both ICAs have not been reported previously. In this case, we could not detect stroke lesions by conventional MRI (T1- and T2-weighted, FLAIR), because we performed MRI soon after the onset of the stroke. DWI is a sensitive method for detecting the early changes of cerebral infarction. This case may be the first report of a case of cerebral infarction in both ICAs detected by DWI.

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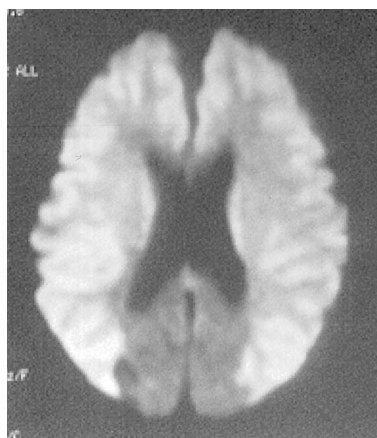


Figure 1. Diffusion-weighted MRI shows diffuse hyperintensities involving both hemispheres in the territory of the ICAs, and the territory of the posterior cerebral artery is spared (1.5 T, repetition time 4999 ms, echo time 95.9 ms, b factor 1000 s/mm²).

1. Groch SN, Hurwitz LJ, McDonnell F. Bilateral carotid artery occlusive disease: a report of four patients. *Arch Neurol.* 1960;2:130–133.
2. Howard GF, Ho SU, Kim KS, Wallach J. Bilateral carotid artery occlusion resulting from giant cell arteritis. *Ann Neurol.* 1984;15:204–207.
3. Browne WT, Wijdicks EF, Parisi JE, Viggiano RW. Fulminant brain necrosis from atrial myxoma showers. *Stroke.* 1993;24:1090–1092.
4. Yamaguchi S, Oki S, Ogasawara H, Sato H, Ito Y, Hibino S. A case of simultaneous bilateral carotid occlusion. *No Shinkei Geka.* 1997;25:247–251.
5. Lövsblad KO, Bassetti C. Diffusion-weighted magnetic resonance imaging in brain death. *Stroke.* 2000;31:539–542.