Letters to the Editor

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Systematic Comparison of the Early Outcome of Angioplasty and Endarterectomy for Symptomatic Carotid Artery Disease

To the Editor:

In a recent article by Golledge et al., the authors attempted a meta-analysis of accumulated single-center reports to compare 30-day stroke and death risk of carotid intervention and carotid endarterectomy (CEA). The authors’ conclusion that the risk of stroke is significantly higher with endovascular intervention compared to surgery was based on an incomplete collection of reports and a scientifically flawed analysis.

For any meta-analysis to provide a reliable conclusion, it should meet the minimum standards expected from a carefully conducted randomized control trial, including the use of prospective protocols, comparable definitions of key outcomes, and the inclusion of all patients from all trials in the final analysis. The analysis reported by Golledge et al. meets none of these requirements. First, the authors had the opportunity to include a more recent series of carotid stenting (an important factor with a procedure in development) but failed to do so. Further, there is no mention of the large registry of multiple “single-center experience” in carotid stenting reported by Wholey et al., which demonstrated favorable outcomes from endovascular carotid therapy. This registry has recently been updated to include over 5000 carotid stent cases, with a technical success of 98.4% and 30-day event rates (all strokes/deaths) of 5.8% in symptomatic patients with extracranial carotid artery stenoses. Importantly, the authors conveniently excluded a group of 77 symptomatic patients from the Hertzzer series that had an event rate of 19%. Similar groups are included in the endovascular series.

The analysis was based on a comparison between a prospective endovascular series and a CEA series that was largely retrospective. Complications were adjudicated by a neurologist in the majority of the endovascular series, but in most of the surgical series they were judged by the surgeon. Medical literature documents well the bias of reported post-CEA complications when the analysis is reported solely by surgeons.

The article provides no contribution to the scientific evaluation of carotid stenting, a potentially safer and less-invasive alternative to surgery. Our analysis will hinder recruitment into future prospective randomized trials that will ultimately provide the medical community with an objective conclusion about the safety and efficacy of carotid stenting.

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Response

I read the letter of Dr. Al-Mubarak and colleagues with interest. Clearly, there is a concern that surgeons fear the loss of their role in the treatment of carotid artery disease to intervention radiologists and therefore must protect their ground. In fact, the intention of our systematic analysis was to compare the present results published for carotid endarterectomy and endovascular treatment of carotid artery disease to see if we should take up this technique. Included among our authors was an experienced interventional radiologist. We wondered whether we should be learning this new technique to apply to our patients. Our analysis suggests that at the present state of the art, the use of carotid stenting should be limited to carefully controlled trials only.

In answer to the issues raised by Al-Mubarak et al.:

1. As stated repeatedly in our article (in the introduction, for example), our study was not a meta-analysis. To address the debate regarding the role of angioplasty in carotid artery disease, a systematic comparison of the reported results of angioplasty and endarterectomy has been performed. Because sufficient data are not yet available from randomized trials, the results from single-center reports from 1990 to 1999 have been used to carry out a meta-analysis.

2. With respect to the additional studies that Al-Mubarak et al. state should have been included, the inclusion criteria were clearly stated in the Methods section: “Studies were included if the following criteria were fulfilled: (1) number of strokes occurring within 30 days of carotid endarterectomy or endoluminal treatment were reported for patients with symptomatic carotid stenosis; (2) the report was a single-center study, since very few multicenter angioplasty series have been published; (3) the study was published between 1990 and 1999; and (4) only I series from any center was included unless there was clearly no overlap in cases.” The additional studies mentioned by Al-Mubarak and colleagues were excluded because they contained mainly asymptomatic patients and results for symptomatic patients were not stated separately (References 4
through 7), and 1 series from that institute was already included (References 8 and 9).

The article by Hertzer et al is included in our analysis (Reference 32), and all 750 patients with symptomatic carotid artery disease who undergo isolated carotid endarterectomy are included. We did exclude patients with asymptomatic disease and those undergoing combined coronary artery bypass, as was the case for all series. With respect to outcome assessment, while it is possible that some of the more subtle strokes may be difficult for surgeons to define, disabling strokes should be clearly evident to all. Our analysis demonstrated that disabling or fatal stroke was twice as common following endovascular treatment.

In conclusion, we believe that endovascular therapy for carotid artery disease should be widely introduced only if it is clearly as safe as the current best treatment. The increasing number of series being reported in the literature suggests that many patients are undergoing carotid stenting outside a randomized trial. At present, the evidence would not support such a practice.

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High Rate of Complete Recanalization and Dramatic Clinical Recovery During tPA Infusion When Continuously Monitored With 2-MHz Transcranial Doppler Monitoring

To the Editor: Alexanderov et al1 raise a fascinating possibility in their paper on transcranial Doppler monitoring of recanalization during systemic tPA infusion in acute ischemic stroke. They postulate that ultrasonic energy focused on intracranial thrombus might facilitate thrombolysis. It is easy to imagine an even more precise beam of energy could be directed at intracranial thrombus with the goal of clot dissolution; why not combine MR angiography with stereotactically delivered magnetic or radiation energy? Could this be a stroke treatment of the future, using technology that exists now?

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Response

I would like to thank Dr Blacker for his letter that highlights an intriguing possibility of using beams, waves, and fields of different physical nature to treat stroke. Indeed, the ideas of thrombolysis with ultrasound alone1 or combined with a lytic drug2 have been expressed long ago and since confirmed by many in several in vitro and animal experiments. Technological advances in other areas broadened applications of magnetic resonance into the interventional arena: image guided tracking of vascular guidewires3 and better focusing of an electron beam therapy in terms of dose distribution in biological tissues 4. Improvements in computer technology and development of portable high resolution diagnostic and interventional equipment can one day make these “Star-Trek” visions of future therapies a reality in the emergency rooms and physician offices.

A necessary step, however, has to cover this gap in time: demonstration of safety and efficacy. The first concern is that focusing on a clot any beam or field (that is strong enough to induce or promote clot lysis) may also damage the ischemic tissue. For instance, a prolonged 0.5°C increase in temperature of the ischemic tissue during clot-busting exposure may negate all benefits of early reperfusion. The second problem lies in selection of end points that should be realistic and relevant to the patient. The goal of new clot-disrupting therapies (besides ready availability and reasonable cost) should be to shorten the time to complete recanalization without an increased risk of hemorrhage. If achieved, this can lead to the dramatic recovery during treatment in a larger number of patients that is currently expected.

Enhancement of pharmacological treatment by various physical agents combined with noninvasive monitoring may prove the right direction for stroke therapy. We are embarking on a phase II multicenter randomized trial of intravenous tissue plasminogen activator with or without 2-MHz transcranial Doppler monitoring as the only way to confirm our pilot observations.5 Until such results become available, all of the above remain an attractive hypothesis.

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Brain MRI in Patients With Past Lupus-Associated Chorea

To the Editor: Chorea is uncommon in systemic lupus erythematosus (SLE). It usually occurs early in its course and has been strongly linked to the presence of antiphospholipid antibodies (aPL) within this setting.1 Primary antiphospholipid syndrome (PAPS) may also be complicated by chorea.1,2 Its pathophysiology remains unclear, especially with regard to possible ischemic mechanisms.3,4 MRI studies are scarce and contradictory.1 Using fluid-attenuated inversion recovery (FLAIR) and T2-weighted brain MRI sequences, we looked for possible sequelae of ischemic events affecting basal ganglia in patients with a history of SLE-related chorea.

Patients were 8 females with SLE according to 1997 revised American College of Rheumatology criteria.4 Age at onset of SLE ranged from 9 to 23 years (mean 16.6 years). In 7, chorea was the presenting manifestation of SLE, or occurred during its first year. One patient developed chorea 12 years after SLE onset. Chorea was bilateral in 5 patients. It resolved within 2 weeks to 1 year (mean 4 months). Chorea occurred after institution of estrogen-containing contraceptive pills in 1 patient and during pregnancy in 2 others. During the course of SLE, 7 patients had demonstrable aPL (lupus anticogulant in 4 and/or anticardiolipin antibodies in 6); besides chorea, aPL-related clinical events occurred in 7, including frank heart valve involve-
Patients were studied 3 to 24 years after onset of chorea, at a mean age of 31 years (range 22 to 43 years). All MRI examinations were performed on a 1.5-T MRI device (General Electric) using axial T1- and T2-weighted fast spin-echo and FLAIR images.

In 7 patients, no signal abnormality was observed at the level of the basal ganglia. Among these patients, MRI was normal in 2 and showed small areas of high signal in subcortical white matter in 5. One patient with a history of bilateral chorea had a 5-mm lesion in the right caudate nucleus.

Based on limited neuroimaging and pathological data, it has been initially suggested that SLE-related chorea might result from “common” aPL-induced thrombotic or embolic ischemic events affecting the contralateral caudate nucleus. By using very sensitive MRI methods, we observed such a persistent ischemic damage in the caudate nucleus in 1 patient only; of note is the fact that this patient had a history of bilateral chorea. On the other hand, 7 of 8 patients had no demonstrable lesions in the basal ganglia. Given that cerebral infarcts remain detectable for life, through use of MRI with T2-weighted and FLAIR sequences, a thromboembolic mechanism seems a very unlikely explanation for SLE-related chorea.

The alternative hypothesis of a non–stroke-related pathophysiology, first suggested by Asherson and Hughes, is supported by various findings, such as the frequent bilaterality of SLE-related chorea, its possible relapse occurrence associated with pregnancy or estrogen-containing contraceptive pills, the dramatic improvement observed in some patients with steroids and/or plasmapheresis, and the demonstration of reversible contralateral caudate nucleus activation by positron emission tomography scan in 2 cases of PAPS-related chorea. On the other hand, decreased circulation in the basal ganglia has been recently demonstrated by single-photon emission computed tomography in another case of PAPS, but these abnormalities resolved within 1 month with treatment, which remains consistent with the nonstroke hypothesis. Interestingly, experimental data have shown that aPL may interact directly with brain parenchyma. In addition to chorea, this original mechanism might explain some aspects of aPL-related seizures. Indeed, in Sneddon’s syndrome, defined by the association of permanent livedo reticularis with neurological ischemic events, the occurrence of seizures has been shown to be restricted mainly to the subset of patients with aPL, whereas the extent of MRI abnormalities is not related to aPL status.

Finally, our results add further evidence to consideration that SLE-related chorea does not result from ischemic strokes, at least in most affected patients. Consequently, on a practical basis, within the wide list of regimens used in patients with SLE-related chorea (which did not include steroids in 44% of published cases), we believe that prednisone should not be omitted.

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Facilitating Data Collection in Stroke Patients and the Elderly

To the Editor:

Buck and colleagues conducted a very thorough review of measures used to assess quality of life (QOL) after stroke by summarizing many important factors, including reliability, validity, responsiveness, precision, acceptability, suitability for proxy respondents, mode of administration, and use of patient-centered approaches in measure development. However, one aspect of conducting research with stroke patients or the elderly not addressed was that of methods to facilitate data collection in these groups.

The communication challenges (eg, difficulties with vision/reading, writing, hearing, speaking, comprehension) commonly experienced while researching stroke patients and the elderly are usually overcome by researchers’ progression from self-administration to interview administration, and then to proxy administration of surveys. This raises an important question: At what point should we rely on proxy respondents? Use of proxies is not a perfect solution because of the varying accuracy of the information provided. In general, proxy respondents tend to underestimate patients’ QOL ratings. There tends to be less information provided. In general, proxy respondents tend to underestimate patients’ QOL ratings. When stroke patients or elderly participants exhibit communication difficulties, researchers can make modifications to measures or to data-collection techniques to assist participants in completing the survey or interview. Although at least 2 books discuss measures to use with the elderly, neither discusses
measurement techniques.\textsuperscript{8,9} We identified a discussion article\textsuperscript{10} with several suggestions to facilitate data collection in the elderly, including the following: (1) pretesting with the elderly to identify potential problems, (2) use larger font sizes on the surveys and response cards (see below), (3) print the survey on 1 side of the page only to avoid confusion, (4) make the survey brief (<20 minutes to complete) to encourage participation, (5) obtain the information using an interview format, and (6) use response cards (rating scales enlarged and placed on cardboard) to assist participants in remembering the response items and, if necessary, to point to relevant response levels. In addition, for the hearing impaired, self-completion of surveys with a research assistant available for questions is an option. Alternatively, use of private rooms and loud voices to communicate the information to interviewees can be attempted. For situations in which the survey is more lengthy, efforts can be made to administer the interview over more than 1 session to lessen the burden for the respondent. These challenges and solutions become more complex when multiple disabilities are evident. In all situations, making concerted efforts to obtain the relevant information from the stroke patient or elderly participant lessens our need to rely on proxy respondents.

In instances such as caregiver research, in which we wish to study both the patient and the family caregiver, these issues gain in importance. Often, proxy respondents are family caregivers. Asking a family caregiver to complete both the patient and caregiver surveys may prove too burdensome, with the result that neither participates in the study. Recognizing the importance of conducting research with the elderly and with individuals who have communication difficulties (eg, stroke patients), efforts must be made to modify data-collection methods to facilitate inclusion of these individuals before relying on proxies. These modifications should be tested to ensure that reliability and validity are maintained.

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\textbf{Response}

We welcome the points raised in Ms Cameron’s letter based on our recent article.\textsuperscript{1} We are grateful for the comments by Ms Cameron on proxy response, which space did not allow us to address in detail.

She refers to a number of ways in which data collection may be enhanced in research involving people with communication problems (eg, people who have had a stroke, or with older people in general). In particular, she notes that researchers often overcome communication problems in respondents by using interviewer administration rather than self-administration of measures. If respondents are unable to communicate on this level, proxy respondents are often used. However, as Ms Cameron points out, proxies tend to underestimate patients’ QOL and should be used only if necessary. We agree with this point, to which we alluded briefly in our article.

Ms Cameron refers to several plausible methods of reducing the need for proxy respondents. These include pretesting with relevant patients to identify potential problems, making the survey brief (<20 minutes), and obtaining the information using an interview format. We have recently incorporated these criteria in developing the stroke-specific QOL measure that we refer to in our article.

In conclusion, we thoroughly agree with the points raised in Ms Cameron’s letter. Proxy respondents should be used only when there is no alternative. In stroke, it is inevitable that some studies will by necessity have to include proxy respondents in order to minimize bias. Thus, suitability for use with proxies is an important property of stroke outcome measures. Indeed, pending additional funding, we hope to compare proxy ratings with those of communicative stroke patients by using the QOL measure we have recently developed to provide some evidence about the degree of discrepancy between the ratings.

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\textbf{Adrenomedullin in Patients With Cerebral Vasospasm After Aneurysmal Subarachnoid Hemorrhage}

\textbf{To the Editor:}

Cerebral vasospasm leading to delayed brain ischemia is a major cause of death in patients who initially survive subarachnoid hemorrhage (SAH).\textsuperscript{1,2} Because of this, the prediction and treatment of vasospasm are critical in the management of SAH patients. Recent studies published in \textit{Stroke} have reported that several factors, including age $<50$ years,\textsuperscript{3} hyperglycemia,\textsuperscript{3} the duration of unconsciousness after SAH,\textsuperscript{4} and the plasma level of brain natriuretic peptide,\textsuperscript{5} could be predictors for the development of cerebral vasospasm after SAH. We suggest adrenomedullin as another possible marker of symptomatic vasospasm.

In a human pheochromocytoma, we discovered adrenomedullin, which proved to be a vasorelaxant peptide of 52 amino acids.\textsuperscript{6,7} Adrenomedullin is a ubiquitous peptide that is also found in plasma and cerebrospinal fluid (CSF).\textsuperscript{7} The adrenomedullin gene is highly expressed in vascular endothelial and vascular smooth muscle cells.\textsuperscript{2} This peptide regulates the vascular tone and growth of vascular cells as an autocrine and/or paracrine vasoactive hormone.\textsuperscript{6,7}

Several factors, such as endothelin, inflammatory cytokines, and oxygen free radicals, which seemingly play a role in
Adrenomedullin Concentrations in Plasma and CSF in Patients With and Without Vasospasm After SAH

<table>
<thead>
<tr>
<th></th>
<th>NV Group (n=5)</th>
<th>V Group (n=10)</th>
<th>P*</th>
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</thead>
<tbody>
<tr>
<td><strong>Plasma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days 1–3</td>
<td>18.32 (1.16)</td>
<td>15.01 (2.00)</td>
<td>0.656</td>
</tr>
<tr>
<td>Days 7–9</td>
<td>16.36 (1.45)</td>
<td>16.85 (1.85)</td>
<td>0.945</td>
</tr>
<tr>
<td><strong>CSF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days 1–3</td>
<td>2.55 (0.73)</td>
<td>11.02 (1.63)</td>
<td>0.011</td>
</tr>
<tr>
<td>Days 7–9</td>
<td>4.59 (1.84)</td>
<td>31.06 (7.52)†</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Values are mean (SEM) fmol/mL.

†Mann-Whitney U test; †significantly higher than days 1–3, P<0.009, Wilcoxon signed rank test.

Vasospasm, 2,8,9 stimulates the adrenomedullin production from vascular cells. 7,10 Additionally, adrenomedullin in the central nervous system (CNS) is involved in controlling brain function, 7 and its mRNA and peptide are upregulated in the ischemic cerebral cortex of rodents. 7 Therefore, if adrenomedullin plays a role in the pathological processes of cerebral vasospasm and subsequent brain ischemia in SAH patients, the CSF concentrations of adrenomedullin would be expected to change in relation to the vasospasm and brain ischemia.

We investigated plasma and ventricular CSF concentrations of adrenomedullin by radioimmunoassay in 14 aneurysmal SAH patients (3 men and 11 women, mean age 62.0 [SD 7.3] years) in the early period (1 to 3 days after SAH, before vasospasm) and late period (7 to 9 days, development and progression of vasospasm). The 14 patients, who had no preexisting neurological diseases or other chronic disorders, underwent aneurysm clipping within 48 hours after admission. At the time of surgery, each patient had a Glasgow Coma Scale score 11 exceeding 10. The plasma adrenomedullin concentration was also measured in 13 healthy control subjects (7 men and 6 women, mean age 32.2 [SD 6.6] years). Brain ischemia due to vasospasm was estimated by repeated neurological examinations and transcranial Doppler sonography and was confirmed by cerebral angiography and single-photon emission CT. We analyzed the adrenomedullin levels of plasma and CSF, comparing them to the presence of symptomatic vasospasm, with nonparametric statistical techniques.

Plasma concentrations of adrenomedullin in the healthy controls averaged 5.05 [SEM 0.21] fmol/mL. In both early and late periods, the 4 patients with no vasospasm (NV) and the 10 patients with vasospasm (V) had significantly higher plasma concentrations of adrenomedullin than the healthy controls (in the NV group, P<0.001 for both periods; V group, P=0.001 and P<0.001 for early and late periods, respectively; Mann-Whitney U test). However, the plasma adrenomedullin concentration did not differ significantly between the 2 groups of NV and V in any period. In the NV and V groups, the plasma adrenomedullin levels did not change significantly over time.

Unlike the plasma levels, the CSF adrenomedullin levels were significantly greater in the V group than in the NV group in the early and late periods (Table). Furthermore, only in the V group did the CSF concentration of adrenomedullin increase significantly in the late period compared with the early period (31.06 [SEM 7.52] and 11.02 [SEM 1.63], respectively; P=0.009). There was no statistically significant correlation between plasma and CSF adrenomedullin concentrations for the V group in the early or late periods.

The patients with symptomatic vasospasm had significantly higher CSF levels of adrenomedullin than those without vasospasm from the prevasospasm period after SAH. In addition, the CSF adrenomedullin concentration increased with time in response to brain ischemia, and the increase was unrelated to the plasma concentrations. We speculate that the production sites of CSF adrenomedullin in these patients could be ischemic neurons, 7 reactive astrocytes, 7 infiltrating inflammatory cells in the ischemic brain, 7 and/or cerebral vascular cells under oxidative stress. 7 The CNS adrenomedullin may play a modulatory role in the cerebral vasospasm and subsequent brain ischemia after SAH. We suggest that CSF adrenomedullin can be a sensitive marker for symptomatic vasospasm.

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Systematic Comparison of the Early Outcome of Angioplasty and Endarterectomy for Symptomatic Carotid Artery Disease
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