Letters to the Editor

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Immune Activation to Underlie Moderate Hyperhomocysteinemia in Stroke and Dementia?

To the Editor:

With interest we read the article by McIlroy et al,1 in which moderate hyperhomocysteinemia was described in patients with vascular dementia, stroke, and Alzheimer’s disease (AD) in comparison with control groups. The authors suggest that mild hyperhomocysteinemia may significantly increase the risk for vascular dementia, AD, or stroke. Korczyn2 argues against this conclusion, suggesting other causes like endothelial dysfunction in consequence of oxidative stress to be important as contributing factors for dementia. Likewise, hyperhomocysteinemia could be a consequence of stroke and dementia rather than its cause.

In earlier studies in patients with AD, deficiency of B-vitamins folate and vitamin B12 was associated with elevated plasma homocysteine concentrations.3–5 Thus, diminished availability of essential cofactors in the homocysteine-methionine-metabolism appears to be responsible for elevated homocysteine concentrations. Usually insufficient dietary intake is considered as the cause for the deficiency of these vitamins,3–5 and folate deficiency can cause several neurologic and psychiatric symptoms, especially in the elderly.6

There seems to exist a link between oxidative stress involved in the pathogenesis of dementia and stroke and the depletion of B-vitamins. Since activation of immunocompetent cells like T-lymphocytes and macrophages is associated with overwhelming production of oxidizing compounds, immune activation is a major cause of oxidative stress.7 Oxidative stress in scope with chronic immune activation could therefore lead to the depletion of antioxidants including oxidation-sensitive vitamins like folate and vitamin B12. Methyl-tetrahydrofolate and cobalamine are important cofactors in the biochemical conversion of homocysteine and both are readily oxidized.8,9 Chronic immune activation has been discussed to be crucially involved in the pathogenesis of AD,9 and, eg, elevated concentrations of immune activation markers like neopterin, itself being a pro-oxidant by increasing T-lymphocytes and macrophages is associated with overwhelming production of oxidizing compounds, immune activation is a major cause of oxidative stress.8 Oxidative stress in scope with chronic immune activation could therefore lead to the depletion of antioxidants including oxidation-sensitive vitamins like folate and vitamin B12. Methyl-tetrahydrofolate and cobalamine are important cofactors in the biochemical conversion of homocysteine and both are readily oxidized.8,9 Chronic immune activation has been discussed to be crucially involved in the pathogenesis of AD,9 and, eg, elevated concentrations of immune activation markers like neopterin, itself being a pro-oxidant by increasing the oxidative potential of reactive oxygen species, have been found in dementia and AD,10 but also in stroke.11

Oxidative stress resulting from immune activation indeed could represent the cause for moderate hyperhomocysteinemia. This relationship is well in line with the observation by McIlroy et al1 and the alternative interpretation by Korczyn,2 and it would also fit to the observation that not only supplementation with antioxidant vitamins but also treatment with anti-inflammatory drugs has some capacity to lower homocysteine levels and also reduce the risk for dementia.12,13 In addition to supplementation with B-vitamins, also antioxidant and anti-inflammatory strategies could therefore compensate for enhanced B-vitamin consumption in consequence of immune activation and effectively prevent the progression of cognitive impairment.

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Response

We thank Schroecksnadel et al for their interest in our article and feel that their letter raises a few interesting points. Although it appears to be true that diminished availability of essential co-factors in the metabolism of methionine homocysteine pathway are responsible for elevated homocysteine concentrations, insufficient dietary intake is not the cause as this was allowed for in our study.1 However, unlike the conclusions reached by Schroecksnadel et al, we do not believe that immune activation represents the cause of raised homocysteine levels.

It has recently been reported that homocysteine actively inhibits the activation of endothelium by the pro-inflammatory cytokine tumor necrosis factor (TNF).2 Activation of endothelial cells is a prerequisite for the recruitment of leukocytes to sites of evolving inflammation.3 Pro-inflammatory cytokines such as TNF and interleukin-1 rapidly induce activation of nuclear factor κB (NF κB) and binding to its target DNA resulting in up-regulation of NF κB-dependent genes, such as E-selectin, vascular cell adhesion molecule-1 or chemokines including macrophage chemoattractant protein-1 and IL-8.4,5 Thus since raised homocysteine levels inhibit immune activation, the statement that oxidative stress resulting from immune activation may represent the cause of moderate hyperhomocysteinemia may require modification. In addition, in a recent report Mezzano et al6 considered patients with chronic renal failure and observed that systemic inflammation which is closely associated with augmented oxidative stress is a major cardiovascular risk factor.
and that the total plasma homocysteine is completely unrelated to these events.

The exact nature of the influence of raised homocysteine in risk for stroke and dementia remains controversial. Further studies are needed to clarify links between inflammatory mechanisms, aminothiol pathways and endothelial function and as we advocated in our original article the only way to determine the nature of the risk or otherwise conferred by homocysteine is to initiate a large placebo controlled study into the effects of folate and B vitamin supplementation on rates of stroke and dementia.

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Carotid Angioplasty and Stenting in High-Risk Patients With Severe Symptomatic Carotid Stenosis

To the Editor:

In a recent article, Fox et al.1 claim to have demonstrated the beneficial effect of a carotid angioplasty and stenting (CAS) procedure performed in a consecutive series of “poor surgical candidates” with severe symptomatic carotid stenosis by comparison with the outcome observed in medically-treated patients in the North American Symptomatic Carotid Endarterectomy Trial (NASCET).2 In our opinion, the conclusions drawn by the authors are misleading for the following reasons.

First, the authors present a data analysis on a case series, for which the reader is simply informed of the fate of a relatively small sample of patients (n=42) (level V evidence).3 This type of retrospective study can hardly be used to dispute the results of a prospective, randomized trial, such as the NASCET,2 designed to test a specific hypothesis (level I evidence): this defies logic.

Second, the authors acknowledge that most, if not all, of the patients in their series would have been excluded from NASCET for specific reasons - namely, medical risk factors (9.5%), angiographic risk factors (47.6%), restenosis after carotid endarterectomy (CEA) (40.4%), and stenosis after neck irradiation (9.5%)—and that “it would have been reasonable to assume that these patients would have had a similar natural history risk of stroke if left untreated as the NASCET medical treated patients”. This assumption is a biased conjecture since the NASCET medically-treated patients form a carefully-selected group that met the same inclusion criteria as the surgically-treated patients. Indeed, the relatively strict inclusion/exclusion criteria in the most influential surgical trials4,4 rejected many patients who represent an important share of the general patient population with cerebrovascular disease. None of these trials designed their criteria as risk classification standards for carotid disease treatment, however; they were simply for the purpose of ensuring a good-quality data set to answer the questions their study had posed.

A recent consensus statement emphasized that CAS should be restricted to limited subgroups of patients, whereas the “gold standard” CEA is still preferable for the management of most patients with occlusive carotid disease.5 Even more recently, a multidisciplinary panel concluded that certain subgroups of patients, namely high-risk symptomatic patients or those unfit for surgery, should currently be considered for CAS.6 Lacking a specific definition of “high-risk” and “unfit for surgery”, there is a general tendency to identify high-risk patients as those who do not meet the inclusion criteria for multicenter randomized studies,4,4 or who have significant medical co-morbidities, or specific anatomical features associated with a worse outcome.7 Since the term “high-risk” does not imply that CEA is “absolutely contra-indicated” in such patients, we, like other investigators,8,9 have recently focused on this population subset, comparing the perioperative outcome of CEA between patients who were high-risk and those who were not (E. Ballotta, MD, et al, unpublished data, 2002). Over a 54-month period, 392 consecutive CEsAs were performed in 363 patients: all CEsAs involved carotid endarterectomy with the patient under deep general anesthesia and cerebral protection involving continuous electroencephalographic monitoring for selective shunting. A high-risk patient subset (n =126, 34.7%) was defined by the presence of a severe medical co-morbidity (ie, cardiac dysfunction, pulmonary dysfunction, renal insufficiency) and/or particular anatomical features (ie, contralateral carotid occlusion, ipsilateral carotid restenosis after CEA and “high-risk associated risk factors”). Of the 126 CEsAs, 96 (76.2%) were performed for symptomatic severe carotid lesions (stenosis greater than 70%, computed by the NASCET method). Endpoints of the study were perioperative stroke, cardiac complication or death. Overall, there were three ischemic strokes (0.7%) and four cardiac complications (1%). None of the patients died. The stroke rate in the high-risk group was comparable with that of the non-high-risk group (0.8% versus 0.7%). The only adverse neurological event, albeit minor, that developed in the high-risk group was probably related to hemodynamic reasons since the stroke was ipsilateral to the hemisphere of the occluded contralateral ICA: the endarterectomized vessel was found patent, with no technical defects, at postoperative angiography. Similarly, non-high-risk patients (n =260) met the same inclusion criteria as the surgically-treated patients. Of the 260 CEsAs, 231 (88.8%) were performed for symptomatic carotid lesions (stenosis greater than 70%, computed by the NASCET method). The perioperative end point rate was 1.1% (n =2.7% for stroke, cardiac complication or death. Overall, there were two ischemic strokes (0.7%) and one cardiac complication (0.3%). None of the patients died. The stroke rate in the high-risk group was comparable with that of the non-high-risk group (0.8% versus 0.7%). The only adverse neurological event, albeit minor, that developed in the high-risk group was probably related to hemodynamic reasons since the stroke was ipsilateral to the hemisphere of the occluded contralateral ICA: the endarterectomized vessel was found patent, with no technical defects, at postoperative angiography.
group - much higher than those of the large CEA trials\(^2,4\) on which treatment recommendations are based. In conclusion, the defining a patient as a “poor candidate for surgery” should not be considered per se a valid reason for preferring CAS to CEA, especially when the peri-procedural stroke rate is questionable.

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**Response**

Ballotta et al. have made serious errors in their reading of our article. We did not suggest or imply that angioplasty and stenting should be preferred over endarterectomy. Rather, we concluded that angioplasty and stenting was probably better than medical treatment for a very selected group of symptomatic patients that were poor surgical candidates.

We treated 42 patients with severe stenosis of a carotid artery and recent ischemic cerebral symptoms with angioplasty and stenting. All our patients were referred for endovascular treatment after evaluation by experienced surgeons. Many had lesions that were not surgically accessible. Most also had multiple medical co-morbidities. Our overall complication rate was higher than in some reported retrospective series but in the range reported in several reported prospective series in similar patients, as we discussed in our article. The complication rate we reported includes early as well as recent data, is improving over time with operators’ experience, and is expected to improve further as protection devices are incorporated into practice. The purpose of this study was not to compare complication rates of angioplasty and stenting with endarterectomy, but rather to examine long-term stroke risk after angioplasty and stenting and to compare it to data available from historical controls. The most important observation was that no patient in this study had a stroke during follow-up.

We consider carotid endarterectomy to be the standard of care for patients with symptomatic carotid artery stenosis greater than 70%. The data from the North American Symptomatic Carotid Endarterectomy Trial (NASCET) are compelling: carotid endarterectomy provides a substantial reduction in the risk of stroke at 2 years when compared with medical treatment (aspirin). Subsequent analyses have confirmed the durability of this procedure. Our data were not used to dispute the results of NASCET in any manner.

As stated above, as well as repeatedly in our article, the question that we sought to answer was whether angioplasty and stenting was better than medical treatment alone. In our opinion, the best natural history data available was the medical treatment arm of NASCET. These patients were similar to our cohort in baseline characteristics and stroke risk factors. They shared the key inclusion criteria of a high-grade stenosis and recent symptoms. The 2-year risk of stroke in this group was 29%, much higher than the 9% we observed in our cohort study. We explicitly recognized that this analysis provides a poor level of evidence. Consequently we referred to our data as preliminary and tempered our conclusions.

We stand by our conclusion and reiterate it here for the benefit of Ballotta et al: in the absence of data from randomized clinical trials, our preliminary data suggest that angioplasty and stenting are better than medical treatment for symptomatic patients with severe carotid stenosis who are poor candidates for surgery.

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**CTA Source Images in Acute Stroke**

**To the Editor:**

In their abstract, Schramm et al, describe lesions seen on CT angiography source images (CTA-SI) as “demarcation of irreversible infarct.”\(^1\) We believe this description is inaccurate and have several comments regarding the utility and future study of CTA-SI.

First, CTA-SI gives direct information about flow of contrast into the tissues and not about the viability of tissue. The inference that hypointense tissue is “irreversible infarct” may be time dependent. Irreversible damage may have occurred in most cases with clear hypointensity on CTA-SI at late time points after stroke onset, but this may not necessarily be true in the very early phase of infarct evolution. In Table 1, the authors report six cases in which the size of the area of CTA-SI hypointensity is bigger than the abnormal area of hyperintensity seen on the MR diffusion weighted image which was obtained following the CT. It has yet to be proven that volumes delineated on CTA-SI imply irreversibly damaged tissue in all cases and the relationship with time from stroke onset has not been clarified.

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Second, in the displayed examples, the areas delineated by the CTA-SI are distinctly obvious on the baseline non-contrast CT. Scales for assessing the baseline non-contrast CT, such as ASPECTS are available to supply the same information. ASPECTS has excellent reliability and prognostic capability. Where the lesion is clearly seen on the baseline CT, there appears to be no advantage to CTA-SI. Indeed, because time is so critical, even ten minutes delay to complete the CT angiogram may be disadvantageous by delaying the application of thrombolysis. Because of the learning curve in appreciating the signs of ischemia on the non-contrast CT scan, some observers may still benefit from a CTA-SI scan.

Our experience with CTA-SI is promising. CTA-SI shows great potential where the baseline non-contrast CT scan looks normal (ASPECTS score of 10), a situation that tends to occur at early time points after stroke onset. If such a patient has an occlusion on CTA and no “black hole” regions of low flow of contrast (CTA-SI) into the tissue, they would seem ideal candidates for reperfusion strategies. But if no occlusion is present on CTA or a large “black hole” is revealed such reperfusion strategies might provide no added benefit. This stratification of patients by CTA-SI is a clear testable hypothesis for a clinical trial.

Clinicians on the front lines of hyperacute stroke treatment must balance the added expense of time required to perform CTA/CTA-SI with the new information this imaging provides. Clearly not all acute stroke patients need such imaging and delays in therapy are to be discouraged. The patient with a disabling stroke, a hyperdense artery sign and a favorable non-contrast CT scan appearance within 3 hours of symptom onset needs no further imaging to make a treatment decision. Acute neurovascular imaging is an evolving area with improving methods and much debate. What is definitely clear is that CT remains an important tool for hyperacute stroke that will not easily be displaced by other modalities such as MRI.

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Response

We would like to thank Dr Hill et al for their interest and their comments. Obviously, this group is very experienced in the use of CTA-SI and their potential in the early hours of acute stroke. We agree that CTA-SI provide information about the flow of contrast medium into the brain tissue and not directly about the viability of tissue. As a surrogate parameter and by their correlation with DWI, however, they are a reliable predictor for the infarct core.

Hill et al consider the time delay caused by CT angiography, which can be disadvantageous in the first hours of acute stroke. No time should thus be spent for unnecessary neurovascular imaging that could dangerous delay treatment. We certainly agree that not every patient with acute stroke needs additional CTA imaging, eg, patients with a large and well demarcated MCA infarction. Also, the ASPECTS score may be helpful. While the HMCA and proximal MCA, renders limited information regarding distal M1 or M2 occlusions.

We believe that the additional few minutes needed for CT angiography are well compensated by the benefit of the additional information. We also believe that the vascular information obtained from the CTA-SI justifies the additional examination time with a reasonable cost-value ratio. While the experts may not need CTA-SI (and this is clearly a matter of debate), less experienced observers benefit from a CTA-SI analysis; in most instances the expert is not available 24 hours a day.

Hill et al emphasize that CT as an important tool in stroke imaging will not easily be displaced by MRI. We want to point out, though, that several recent studies have consistently shown that especially within the first 6 hours of acute stroke DWI is superior to non-contrast CT. The combination of CT, CTA and CTA-SI is superior to non-contrast CT alone, however DWI should be considered as the present gold standard for the imaging assessment in acute stroke.

In keeping with the scientific progress, the optimum diagnostic tools should be applied to improve patient management. Thus, we suggest that regarding the narrow time window either stroke CT (non-contrast CT, CTA, CTA-SI) or stroke MRI (DWI, PWI, MRA, T2, T2*), depending on availability, should be used for imaging in hyperacute stroke. An efficient stroke team can perform this diagnostic workup without a dangerous loss of time.

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AICA Infarction and Hearing Loss: Is it Peripheral or Central?

To the Editor:

I very much appreciated the article by Lee et al1 on the important hearing loss in anterior inferior cerebellar artery (AICA) stroke as they address the neglected issue of hearing loss in neurologic disease. They confirm the notion that peripheral and central disorders of the VIIIth nerve are likely to be confounded.2 Despite the unusual work-up, there are several pitfalls in the terminology, and pathophysiology to be addressed.

The term auditory brain stem response (ABR) is strongly misleading and I advocate the use of auditory evoked potential (AEP). The former would imply a generation of the entire response in the brain stem. The latter describes the modality and the evoked response type. It has become increasingly clear that the wave I of the AEP is generated outside the brain stem, and probably represents the change of conductivity when the VIIIth nerve leaves the temporal bone. The same might apply to wave II, where the nerve enters the brain stem.3 So the interpeak latencies might reflect different pathophysiologicals. The I-III interval may thus reflect a sensorineural lesion (delayed or abolished wave I/II) as well as a central lesion (wave III, probably generated at the level of the superior olivary complex).4,5 Interestingly, the AEP shown for the central-type shows complete loss of all waves, following standard criteria suggestive of peripheral loss.6 The lesions shown for the two cases do not differ significantly in my opinion, but demonstrate as well a spotty lesion pattern in the lateral pons as well as around the fourth ventricle, thus closely neighboring the auditory nuclei as well as their cranial projections.2 One has to keep in mind that the pure tone audiogram (PTA) can be pathological in peripheral as well as in central conditions, as well as the stapedius reflex might be unilaterally abolished in brain stem lesions, and the same can be true for speech discrimination tests.6 Unfortunately, the more challenging tests as gap detection or localization paradigms have not been applied, but could, together with the results of PTA and AEP give clues to the lesion localization. It might be of interest to perform MRI of the cochlea in the acute phase to see whether cochlear ischemia shows up or not. Furthermore, a thorough testing for additional central auditory disorders in the interval could separate peripheral and central hearing loss. The idea of testing the otoacoustic emissions might help, but anatomically, this depends on the integrity of the descending fibers from the auditory cortex to the superior olivary complex as well as Rasmussen’s bundle (olivocochlear tract). Thus, it remains open whether an AICA stroke constitutes a central or a peripheral hearing deficit.

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Response

We appreciate the interest of Dr. Ulbricht in our article1 on the importance of hearing loss in anterior inferior cerebellar artery (AICA) stroke. We agree that the abbreviation AEP is probably better than ABR, but like many other areas of medicine, once an abbreviation such as ABR is well established, it is very difficult to change the usage. The two cases shown in our article do have similar brain stem lesions, but the audiometric testing suggests a different localization for the hearing loss in each case. Case 1 had a moderate hearing loss with good speech discrimination and normal auditory evoked response—typical findings for a co- clear site. Case 2 had a mild hearing loss with severe impairment of speech discrimination and absent auditory evoked response—typical findings for a lesion involving the 8th nerve or more central structures. We suspect that in the majority of our cases, both peripheral and central auditory structures were involved. That the inner ear can be infarcted in cases of AICA stroke is well documented in the literature.2,3 The inner ear is particularly vulnerable to ischemia since it has a complete absence of collateral circulation unlike the other structures supplied by AICA. We agree that it might be of interest to perform an MRI of the cochlea in the acute phase of AICA stroke, but one would need special equipment to improve the resolution of the inner ear images. Possibly a special coil for the ear along with high dose contrast would allow visualization of an ischemic cochlea.

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Banning Anticoagulation in Stroke or Consequence of Poor Study Design

To the Editor:

We read with great interest the review from H.P. Adams1 who critically re-evaluates individual aspects of well-known and often-discussed studies on anticoagulation in acute stroke. These studies do not exhibit a net benefit of anticoagulant use with regard to the criteria safety, mortality, morbidity, prevention of stroke recurrence and late outcome. The author emphasized the differences among the individual studies with regard to sample sizes, time-to-start of therapy (extending up to 48 hours after stroke onset), protocols for dosages and controls of anticoagulants used and the route of administration leading to a distinct
criticism of major meta-analysis published. In addition, prominent shortcomings such as the missing baseline brain imaging studies in the dominating IST and CAST trials and the lack of any efforts to differentiate among stroke subtypes with gross under representation of embolic mechanisms are mentioned. However, despite these shortcomings, H.P. Adams concludes that he sees no indication for anticoagulation in acute stroke and suggests the future role of anticoagulants will be very limited.

In our view this conclusion is premature and not accepted by many “stroke experts” in institutions where advanced diagnostic techniques and neuro-monitoring are available. So far the albeit limited data available from these trials reveals statistically significant advantages of anticoagulation in the prevention of deep venous thrombosis, pulmonary embolism, as well as of early recurrent stroke. It is likely that a supposed increase in risk of bleeding complications is biased by restrictions of IST and CAST which do not reflect standards of acute stroke management in major European and North American hospitals. These standards include high-quality brain and vascular imaging (CCT, MRI, ECD, TCD), cardiac diagnostics (ECG-monitoring, TTE and TEE) and monitoring of blood pressure, metabolic and relevant coagulation blood parameters performed within days after stroke onset by trained neuroradiologists, cardiologists, angiologists, and stroke unit teams. Such techniques have been shown to be able to reduce symptomatic hemorrhagic transformation and bleeding complications in patients treated with rtPA in acute stroke trials even if the time window was extended beyond 3 hours. They may similarly improve the benefit/risk ratio for early anticoagulation in acute stroke.

Thus we share the careful considerations of the author toward the shortcomings and results of the existing studies on anticoagulation although we disagree with his conclusion: adapting to the risk of downhill skiing with modern technology combined with training resulted in both breathtaking records and a substantial reduction in the “complication” rate of this discipline. Similarly potential risks of anticoagulation should be minimized by appropriate selection and monitoring of patients treated with definitely more sophisticated protocols than are needed for standard aspirin recommendation. Recent therapy concepts both in the United States and Canada as well as our country surveyed in 33 dedicated stroke centers, mostly university hospitals, reflect a pathophysiologically driven, widespread careful use of anticoagulation in selected patients and the use of heparinoids for the prevention of deep vein thrombosis in most immobilized patients. In all patients individual therapy decisions are dynamically adapted by a quick stroke workup based on stroke etiology, size of the infarction, history of anticoagulation disorders, and actual bleeding risks from patient premorbidity, etc, which were not all considered in IST and CAST.

In our view the author’s conclusion to the many legitimate points of criticisms could better have resulted in formulation of timely study concepts stratifying risk and benefit of anticoagulant use in acute stroke by employing criteria such as time window, imaging criteria, and stroke etiology.

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Response

I thank the Editor for asking me to respond to the letter by Grips et al who apparently disagree with my interpretation of and conclusions about the data from recent clinical trials of anticoagulation for treatment of patients with acute ischemic stroke. An exchange of ideas about anticoagulation in the treatment of stroke is welcomed. Unfortunately, the letter contains incorrect information. Grips et al are incorrect in their statement that I see no indication for anticoagulation for treatment of patients with recent stroke. In my review, I stated that “anticoagulants do have a role in management of some patients with recent stroke as a measure to prevent deep vein thrombosis and, presumably, pulmonary embolism.” However, the focus on my review was the issue whether emergent administration of anticoagulants improves neurological outcomes, halts neurological worsening, or prevents early recurrent stroke. When these standards are used, definitive data that these medications are effective do not exist.

As reflected by the article by Al-Sadat et al, physicians continue to prescribe anticoagulants. This is not surprising because physicians often are slow to change their practices. However, Grips et al should not construe this survey’s data as proof for the utility of emergent anticoagulation. In the era of evidence-based medicine, physicians should evaluate the strength of information supporting the use of any medication—even those time-honored medications such as heparin. Recent clinical trials do not provide any definitive data that emergent anticoagulation is useful in improving outcomes of patients with acute ischemic stroke. These data are much more compelling than personal beliefs and nothing in the letter of Grips et al refutes this information.

Al-Sadat et al concluded that further research is needed on how the results of negative clinical trials affect physician behavior. The best way to influence physicians is to provide the necessary and correct data to them in an educational format. That was the mission of my article. In addition, the development of guidelines by professional groups can help change physicians’ opinions. I note that the opinions in the recent guidelines authored by a panel of experts appointed by the American Stroke Association and the American Academy of Neurology are similar to those contained in my independent review.

Because the current data do not support the use of emergency anticoagulation, the burden now is on the advocates of this therapy to provide convincing information from well-designed clinical trials. I encourage Grips et al to conduct such a prospective trial that includes the high level of technology that they recommend. The trial would need to include a number of steps to ensure the validity of the data from the ancillary diagnostic studies that they propose using. In addition, the trial also should meet the modern requirements of clinical research including randomization, blinding, careful ancillary management, and an adequate sample size to avoid false-positive and false-positive results. I would welcome new data showing the usefulness of anticoagulation in treatment of patients with stroke. I am very willing to change my view about emergency anticoagulation given credible data.

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C-Reactive Protein and Blood Pressure in the Acute Phase After an Ischemic Stroke

To the Editor:

Elevated blood pressure levels have been associated with an increased risk of stroke and of cardiovascular disease.1 It is now well established that vascular inflammation is an independent risk factor for the development of atherosclerosis.2 Furthermore, low grade of inflammation, assessed by C-reactive protein (CRP), significantly predict the risk of future ischemic stroke.3 Thus, the mechanism underlying the relationship between elevated blood pressure and an increased risk of stroke may be inflammation. Engström et al demonstrated in a recent Stroke article that increased levels of inflammation-sensitive plasma proteins are associated with elevated blood pressure and these proteins are associated with an increased risk of stroke in patient with high blood pressure. From this point of view, we have the possibility, using the data from the Villa Pini Stroke Data Bank5,6 to extend their observations regarding the relationship between CRP and blood pressure levels in acute ischemic stroke. Previous data demonstrated that ischemic stroke triggers an acute phase response resulting in a rise of circulating CRP levels.5,6 However, the amount of the inflammatory response to ischemic stroke is variable: about 25% of patients with first-ever ischemic stroke have normal level of CRP after stroke implying that ischemic stroke itself does not induce a full-blown acute phase response.5,6 CRP elevation can result from a variable intensity of the individual acute phase response to cerebral ischemia but it is not known if blood pressure levels in the acute phase after stroke can influence levels of inflammation markers. To verify this hypothesis we analyzed the relationship between systolic diastolic blood pressure and CRP levels within 24 hours after stroke onset in 507 ischemic stroke patients included in the recruitment period between March 1998 to March 2000.

At the entry, mean systolic blood pressure was 160±16 mm Hg and mean diastolic blood pressure was 94±13 mm Hg. Of course, patients with a history of arterial hypertension had a significantly higher both mean systolic (164±29 versus 148±24 mm Hg; P<0.0001, Student’s t test) and diastolic blood pressure (96±8 versus 86±19 mm Hg; P<0.0001) than patients without. Blood pressure decreased on average by 11 mm Hg in systolic and 14 mm Hg in diastolic during in-hospital stay.

Log-normalized concentration of CRP within 24 hours after stroke was significantly correlated with both systolic (r=0.47; P<0.0001) and diastolic (r=0.50; P<0.0001) blood pressure at the entry, but modestly. Patients without a history of arterial hypertension had significantly higher levels of CRP at the entry than patients with a documented history (2.0 [1.0 to 3.4] versus 1.0 [0.5 to 2.75] mg/dL; P<0.0001, Mann-Whitney U test). However, significantly higher median levels of CRP were found in patients with higher levels of both systolic or diastolic blood pressure irrespective of the history of arterial hypertension.

The association between blood pressure and the odds of having an elevated CRP level (≥1.5 mg/dL) was assessed by logistic regression analysis. In a model that adjusted for systolic blood pressure, history of arterial hypertension, diabetes mellitus, coronary heart disease, demographic factors, cholesterol, measures of obesity, smoking, alcohol abuse, stroke severity, neuro-radiological findings, and antihypertensive medication use, a 10 mm Hg increase in systolic blood pressure was associated with a 39% increase in the odds of having an elevated CRP level (odds ratio [OR]=1.39, 95% confidence intervals [CI] 1.21 to 1.61, P<0.0001). When the same model was re-run adjusted for diastolic blood pressure instead of systolic blood pressure, a 10 mm Hg rise in diastolic blood pressure was associated with a significant 42% increase in the odds of having an elevated CRP level (OR=1.42, 95% CI 1.17 to 1.73, P=0.0004).

In conclusion, our preliminary results suggest that elevated levels of systolic or diastolic blood pressure in the acute phase after an ischemic stroke are associated with elevated CRP levels. An acute increase of blood pressure more than a history of arterial hypertension determine higher levels of CRP after stroke. Probably, the levels of blood pressure after an ischemic stroke are one of underlying processes related to inflammation and they are relevant in the inflammatory response after an ischemic stroke. These data confirm the recent observation by Engström and colleagues that the high pressure values are associated with the production of inflammation-sensitive plasma protein. Many speculative hypotheses could be made regarding the relationship between blood pressure and the inflammatory mechanism in ischemic stroke. From this point of view, because higher CRP levels are an independent prognostic factor after stroke and, apparently, high blood pressure increases CRP levels, the current idea on the acute hypertension and its treatment after stroke probably should be revisited.

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AICA Infarction and Hearing Loss: Is it Peripheral or Central?
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