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 B$_12$ 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 B$_12$. Methyl-tetrahydrofolate and cobalamine metabolism are important cofactors in the biochemical conversion of homocysteine and both are readily oxidized.7,8 Chronic immune activation has been discussed to be crucially involved in the pathogenesis of AD9 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 al.12 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 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). 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). This type of retrospective study can hardly be used to dispute the results of a prospective, randomized trial, such as the NASCET, 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 trials 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 posited.

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. 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. 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, or who have significant medical co-morbidities, or specific anatomical features associated with a worse outcome. Since the term “high-risk” does not imply that CEA is “absolutely contra-indicated” in such patients, we, like other investigators, 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 CEAs were performed in 363 patients: all CEAs involved carotid eversion 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/or high ipsilateral turbulence). Of the 126 CEAs, 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. Of the remainder, none of the clinical conditions or particular anatomical features considered in our study emerged as predictors of neurological events. Age and gender had no significant impact on stroke incidence. Although no asymptomatic patients developed a perioperative stroke, the presence of symptoms did not adversely affect the stroke rate. These findings correlate closely with two recently-published reports dealing specifically with the high-risk patient population, showing that high-risk patients can undergo CEA with a stroke rate equivalent to that of non-high-risk patients.

The alarming 9.5% peri-procedural stroke rate reported by Fox et al in their high-risk patient population consequently seems unacceptable when compared with the 0.8% (1/126) perioperative stroke incidence emerging from our own study, or the 4.4% (3/68) and the 2.0% (2/98) recorded in similar case series after CEAs or the 3.6% (1/28) peri-procedural stroke rate described in other CAS experiences dealing with NASCET-ineligible patients. Moreover, the claim that a comparable peri-procedural disabling stroke rate (9.9%) was observed in the CAS group of the only completed randomized clinical trial comparing CEA with CAS, ie, the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), is a lame excuse. Indeed, the CAVATAS trial showed similar major risks and effectiveness for surgical and stenting procedures, yielding peri-procedural stroke and death rates of about 10% in each.
group - much higher than those of the large CEA trials\(^2\)\(^4\) on which treatment recommendations are based. In conclusion, 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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4. European Carotid Surgery Trialists Collaborators Group, MRC European Carotid Surgery Trial. Interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) carotid stenosis. Lancet. 1991;337:1235–1243.


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 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.
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.3 ASPECTS has excellent reliability and prognostic capability.4 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,5 even ten minutes delay to complete the CT angiogram may be disadvantageous by delaying the application of thrombolytic therapy. 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 to be discouraged. The patient with a disabling stroke, a hyperdense artery sign and a favorable delay in thrombolytic therapy. 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.

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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 dangerously 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.1,2 While the HMCAS highly correlates with occlusion of the proximal MCA,3,4 it 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,5 however DWI should be considered as the present gold standard for the imaging assessment in acute stroke.6

In keeping with the scientific progress, the optimum diagnostic tools should be applied to improve patient management.7 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*) should be applied to improve patient management. In most instances the expert is not available 24 hours a day.

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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 al 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. 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 auditory response in the brain stem. The latter describes the modality and response in the brain stem. The former would imply a generation of the entire auditory evoked response type. It has become increasingly clear that the wave I of the AEP is generated outside the brain stem, and probably represents a 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 pathophysiologies. The I-III interval may thus reflect a sensorineural lesion (delayed or abolished wave I/II) as well as a central lesion (wave III, interval may thus reflect a sensorineural lesion (delayed or abolished wave III).4 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.5 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 cochlear 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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criticism of major meta-analysis published. In addition, promi-
nent 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
depth 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 manage-
ment in major European and North American hospitals. These
standards include high-quality brain and vascular imaging (CCT,
MRI, ECD, TCD), cardial 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 transfor-
mation and bleeding complications in patients treated with rtPA
in acute stroke trials even if the time window was extended
beyond 3 hours.3 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 anticoag-
ulation although we disagree with his conclusion: adapting to the
downhill skiing with modern technology combined with training
resulted in both breathtaking records and a substantial reduc-
tion in the ‘complication’ rate of this discipline. Similarly
potential risks of anticoagulation should be minimized by appro-
priate 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 Canada4,4 as well as our country surveyed in 33
dedicated stroke centers, mostly university hospitals,5 reflect a
pathophysiologically driven, widespread careful use of anticoag-
ulation in selected patients and the use of heparinoids for the
prevention of deep vein thrombosis in most immobilized pa-
ents. In all patients individual therapy decisions are dynami-
cally 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
all not 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 anticoagu-
ulant 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 antico-
gulation 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.”1 However, the focus on my review was
the issue is 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,2 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 al2 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
written 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.3

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 manage-
ment, and an adequate sample size to avoid false-negative 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 antico-
gulation 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 factors 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 increase in blood pressure and the increased risk of stroke may be inflammation. Engström et al⁴ demonstrated in a recent Stroke article that increased levels 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 level.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±9 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 to the history of arterial hypertension.

The association between blood pressure and the odds of having an elevated CRP level⁶ (≥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,⁷ 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.⁴ 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 stroke⁶,⁸ and, apparently, high blood pressure increases CRP levels, the current idea⁴ on the acute hypertension and its treatment after stroke probably should be revisited.

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