Homocysteine, Vitamin B6, and Endothelial Dysfunction in Circulatory Disorders

To the Editor:

We read with interest the recent article by Kelly and colleagues1 dealing with the relationship between serum vitamin B6 measured as pyridoxal 5'-phosphate (PLP), serum total homocysteine (tHcy), and C-reactive protein (CRP) in patients after ischemic stroke. The results of their study with univariate and multivariable analyses demonstrated that among stroke patients, CRP was a predictor of PLP. In addition, they indicated that among control subjects, both CRP and tHcy were independent predictors of PLP, although there was no association between CRP and tHcy. The authors proposed that vitamin B6 but not tHcy might be a marker of inflammatory status and vascular diseases.

There is evidence that homocysteines might disturb the bioavailability of nitric oxide (NO), which would, at least in part, contribute to the pathophysiology of circulatory disorders. Stühlinger et al2 examined the relationship among homocysteine, NO, and endothelial function in patients with peripheral arterial disease, and demonstrated that experimentally-induced hyperhomocysteinemia increased plasma asymmetric dimethylarginine (ADMA), an endogenous NO synthase inhibitor, an effect that was temporally related to a decline in endothelial vasodilator function. This is an important mechanism for the endothelial dysfunction that occurs in hyperhomocysteinemia.3 In a study presented earlier, we demonstrated that estrogen-induced improvement of membrane fluidity (a reciprocal value of microviscosity) of erythrocytes was counteracted by ADMA, suggesting that ADMA might actively participate in the regulation of rheologic behavior of cell membranes and microcirculation in postmenopausal women.4 In this context, we speculate that ADMA, suggesting that ADMA might actively participate in the regulation of rheologic behavior of cell membranes and microcirculation in postmenopausal women.4 In this context, we speculate that ADMA, an endogenous NO synthase inhibitor, an effect that was temporally related to a decline in endothelial vasodilator function. 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Response:

We thank Drs Tsuda and Nishio for their interest in our paper. We agree that both experimental and clinical evidence suggests that accumulation of asymmetric dimethylarginine (ADMA) may be an important mediator of homocysteine-related systemic and cerebral endothelial dysfunction, likely via inhibition of endothelial nitric oxide synthase (eNOS).3–4 These data add to previous studies suggesting that homocysteine may cause endothelial injury and dysfunction by other mechanisms, including free radical-induced membrane lipid peroxidation, reduced nitric oxide production, and impaired expression and activity of the antioxidant enzyme glutathione peroxidase.5

In population health terms, these mechanisms are likely to be most relevant in individuals with plasma total homocyst(e)ine (tHcy) in the mild-to-moderate range (15 to 100 µmol/L). Internationally, the reported prevalence of elevated tHcy varies according to the nutritional status of the specific population. In the United States, data from the Framingham cohort and other sources indicate that the prevalence of elevated tHcy has fallen by approximately 50% since the introduction of folic acid grain fortification in 1998, with greatest benefit observed among individuals with higher prefortification tHcy levels.5

In our postfortification sample, we found identical tHcy distributions among individuals with stroke and matched controls, perhaps reflecting a disproportionate benefit of fortification among patients with vascular disease and higher prefortification tHcy. In our study, low B6 status was associated with stroke independent of established risk factors, a relationship that was partly mediated via inflammation as measured by C-reactive protein.6,7 We did not measure ADMA in this sample, but we are investigating the relationships between inflammation, nutritional status, and oxidant stress following acute ischemic stroke in ongoing studies.

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Blood Pressure in Acute Stroke and Its Prognostic Value

To the Editor:

We read with interest the recent paper by Castillo and colleagues evaluating the prognostic relevance of admission blood pressure (BP) values and describing a U-shaped effect in patients with acute ischemic stroke, as well as Boysen’s editorial comment on this issue.1,2 The study’s conclusion was that both high and low admission BP values are associated with poor prognosis regarding early neurological deterioration, infarct volume, and mortality at 3 months. After adjustment for the use of antihypertensive drugs and BP drop >20 mmHg, the authors found that the latter was the most important prognostic factor for poor outcome.

Before accepting these important conclusions, we think that some comments are needed. We have also evaluated the prognostic value of admission BP values in an unselected collective of acute stroke patients. Our findings demonstrated that early and late mortality in patients with ischemic stroke as well as in patients with intracerebral hemorrhage followed a U-shaped pattern in relation to systolic and diastolic BP at admission.3 Low admission BP values were associated with heart failure and coronary artery disease, whereas high BP values were associated with history of hypertension and lacunar stroke. Death due to cardiovascular disease was significantly more frequent among patients with admission BP values beneath the U-point of 130 mmHg, whereas death due to brain edema was significantly more frequent above this U-point.3 We also demonstrated by means of 24-hour BP monitoring that persisting elevated systolic 24-hour BP values during the acute phase of stroke are associated with subsequent brain edema formation in patients not receiving antihypertensive medication during the BP monitoring.4 Investigating the relationship of 24-hour BP to baseline characteristics in stroke subtypes of different etiopathogenic mechanisms, we found that high and low 24-hour BP values correlated with brain edema and heart failure, respectively, in patients with cardioembolic stroke; whereas low BP values correlated with coronary artery disease in lacunar patients.5

The study of Castillo and colleagues differs from our own work in several aspects that deserve attention. Castillo et al suggest that both low and high admission BP values are associated with a higher mortality. However, with the exception of atrial fibrillation, no other data concerning concomitant diseases are given. In addition, details about the exact causes of death in deceased patients would be useful. Such data would be interesting and, if in accordance with ours,3,5 they would then support Boysen’s thesis that the U-shape relationship may reflect cardiac failure being more important in stroke patients with low systolic BP.2 Another issue, which probably needs further discussion, is whether not only ischemic but also edematous tissue was included in the hypodense zone, which was used for infarct volume calculation. Should that be the case, it would be in accordance with our results.3,4 Moreover, the International Stroke Trial (IST) described an independent association between death resulting from presumed cerebral edema and high systolic BP.6 We therefore support Boysen’s assumption that the U-shape relationship may reflect an adverse effect on brain edema in those with very high BP values.2 Additionally, the finding that a BP drop >20 mmHg within the first day is the most important prognostic factor of poor outcome should be faced with caution. Christensen et al have reported that an early spontaneous BP decline is associated with good outcome.7 Furthermore, elevated weighted mean arterial blood pressure values were associated with poor outcome in the GAIN Trial.8 Finally, according to our data, the lower incidence of brain edema observed in hyperacute stroke patients who sustained a spontaneous BP decline could be attributed to an earlier normalization of poststroke hypertension.4

The fact that in Castillo’s study the physicians of the emergency department treated 22% of all patients with antihypertensive agents without following specific guidelines for BP management raises the question whether that was really indicated in all these cases. It is obvious that the described BP drop is not spontaneous and at least in part drug-induced. It also remains unclear if some or all of the patients who received antihypertensive medication in the stroke unit were already premedicated in the emergency department. This might have caused an excessive BP decline leading to hypoperfusion and clinical deterioration, especially in cases of lacunar stroke.

In conclusion, we agree that high and low BP correlates with poor prognosis and that it is unlikely that there will be one treatment for all stroke patients.1,2 Prospective randomized clinical trials with sufficient size and power to include representative patient groups of different age, concomitant diseases, severity, and etiology are required to clarify the issue of optimal BP management in the acute stroke setting.

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Response:

We appreciate the interest of Tsivgoulis et al in our article on the association of high and low systolic and diastolic blood pressure (BP), as well as a relevant drop in BP, with poor prognosis in patients with ischemic stroke.1 We think that their letter raises some interesting points that may help clarify the issue of optimal BP management in the acute stroke setting. Although we did an observational study without the aim of investigating the etiopathogenic mechanisms linked to stroke prognosis, a further exploratory analysis of our data allows us to give some light to the several mechanisms that have been proposed to explain the association between both high and low BP and outcome.
According to the findings reported by Tsivgoulis et al and to the Boysen’s editorial comment, our data support the notion that the U-shape mortality pattern reflects cardiovascular diseases being more frequent in stroke patients with low systolic BP. In the 9 patients with cardiac causes of death (acute myocardial infarction, n = 5; heart failure, n = 4) median [range] admission systolic BP (126 [108–162] versus 166 [130–218] mm Hg, P < 0.001) and diastolic BP (67 [55–81] versus 83 [70–120] mm Hg, P < 0.001) were lower than in those with stroke- or infection-related death (n = 16 and n = 11, respectively).

As Tsivgoulis et al mention, part of the hypodensity volume on CT may reflect brain edema instead of definitive necrosis. Although we did not evaluate the potential mass effect of the ultimate infarct volume, systolic BP (171 [190–234] versus 168 [144–181] mm Hg, P < 0.001) and diastolic BP (117 [108–132] versus 86 [75–102] mm Hg, P < 0.0001) were higher in the 98 patients with early hypodensity on CT. Systolic BP was also significantly higher in the 12 patients who died because of brain edema compared with those with other causes of mortality (226 [184–240] versus 140 [122–175] mm Hg, P < 0.001). Therefore, high systolic BP above the U-point of 180 mm Hg could have adverse effects on brain edema, and consequently increase early neurological deterioration and mortality.

A further point of interest is that high BP may also produce basal lamina disturbances, promoting hemorrhagic transformation (HT) of the cerebral infarct. In our study, HT was seen in 27% of patients with systolic BP > 180 mm Hg, whereas it was present in 7% of patients with systolic BP below these values (P < 0.001). HT was associated with neurological worsening and poor outcome, although the poor prognosis could be attributed to the HT itself in only 8 patients with parenchymal hemorrhage.

As we recognize in our study, the wrong use of antihypertensive drugs in many instances could lead to hypoperfusion and clinical deterioration. The administration of these agents in the emergency unit was associated with a greater reduction in BP in comparison with that observed when therapy was given by neurologists in the stroke unit (Table). Accordingly, early neurological deterioration was more frequent in patients who received the treatment in the emergency unit than in those treated in the stroke unit. This effect was of more particular importance in patients with cardioembolic stroke than in those with lacunar stroke. This finding is consistent with the idea that a drop in BP might have a less detrimental effect in lacunar infarctions or in large territorial ischemia where a penumbral area is more likely, a hypothesis that has been suggested to explain the different outcome in patients with lacunar and territorial infarctions in the IMAGES Trial.6

**Spasticity After Stroke: Why Bother?**

*To the Editor:* Perseveration of behavior is a significant clinical symptom among intentional disorders of organic brain disease, attributed by some authors especially to prefrontal brain impairment. However, the perseverative preoccupation of professional neurologists and therapists with the purpose of overpowering the spasticity ogle seems to be an endemic, intractably-taught delusion that afflicts both academic scholars and clinicians.1,2

In 1951, Thomas Twitchell published a 37-page analysis of the clinical course of recovery of 121 acute hemiplegic stroke patients in the Boston City Hospital.3 Early on they were examined daily, and 25 were carefully followed for weeks or months until they reached a stable status of recovery or disability. Twitchell described in great detail both the usual and exceptional patterns of functional recovery, along with the associated patterns of reflex phenomena. Following transient flaccidity associated with acute paralysis, resistance to passive stretch evolved during the first several days.
Twitchell concluded, “The great disability which results when recovery is halted in the phase of heightened proprioceptive activity has prompted many earlier investigations. Walsh (1919) clarified the previously confused views as to the nature of spasticity, and showed its identity with the type of exaggeration of postural reflexes seen in decerebrate rigidity. The analysis of Sherrington and his collaborators subsequently identified the stretch reflex as the fundamental reaction of such disorder. It has often been assumed that if spasticity could be abolished, willed movement could be more effectively performed. The present study indicates that the first movements to appear following hemiplegia are themselves facilitated stretch reflexes. The problem at that stage is not so much to abolish the spastic reaction, as to harness its diffuse hyperactivity.” Burke’s extensive neurophysiological analysis points out that spasticity may be a functionally useful adaptation to pyramidal tract injury. The only substantive clinical performance accomplishment of baclofen is partial diminution of phasic flexor spasms. Tizanidine does no better.

Like the nociceptive extensor plantar reflex of Babinski and tendon jerk proprioceptive hyperreflexia, spasticity is also a release phenomenon. There are no data or rationale to suggest that severing the extensor hallucis longus tendon may improve recovery from stroke. Similarly, regarding spasticity, I have yet to find any adequately controlled demonstration that the steadfast fad of fixing this phantom facilitates functional recovery from hemiplegia; there is much evidence to the contrary. The integrated forebrain and hindbrain organizations that accomplish fine adaptive coordination, as in handwriting, piano playing, walking down steps, or ballet dancing, are orders of magnitude beyond the simplistic spinal reflex concept of competitive force between agonist and antagonist about a single joint.

I do applaud the rediscovery by Sommerfeld et al that the “focus on spasticity in stroke rehabilitation is out of step with its clinical importance.” I hope, too, that the editorial reviewer, Dr Kramer, may cease to search for “additional studies needed to refine guidelines for treating spasticity after stroke.” George Leigh Mallory’s personal rationale for climbing to the peak of Everest was “because it is there.” Mallory failed. “Because it is there” constitutes neither scientific nor ethical rationale for the reflex temptation to treat this reflex.

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Response:
We thank Professor Landau for his appreciated comment on our article about spasticity after stroke. In the reported and commented study we found spasticity in only a minority of the hemiparetic patients assessed 3 months after acute stroke. The results from our population-based study provide an original clinical support of the theories proposed by Professor Landau in his comment of our article. Additional data, including the number of patients presenting with possible spasticity, ie, exaggerated reflexes as well as intrinsic changes of the muscles, according to the modified Ashworth scale, 18 months after stroke, will soon be presented.

In the spiritual reflection on spasticity, Professor Landau points out the lack of scientific proof supporting the common interest in spasticity after stroke. Considering available scientific proof, both theoretical and clinical, the former assumption that hemiparesis depends on the lesion of the upper motor neuron with accompanying spasticity can no longer remain the basis for physiotherapy assessments or interventions in stroke rehabilitation. Physiotherapists “treating spasticity” most certainly do not treat any exaggerated reflexes but possibly the intrinsic changes of the muscles. As Professor Landau suggests: let us restrain the reflex temptation to treat this reflex.

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Neurobiology of Poststroke Depression

To the Editor:

Eriksson et al. find that the substantial proportion of stroke patients reporting depressive mood but not using treatment with antidepressants suggests that patient selection for treatment should be more precise. This may be accomplished by monitoring speech hesitation pauses (SHPs), which are behavioral correlates of mood. Neurobiological features are demonstrated by (1) the correlation of rate and variability in duration of SHPs 4.79 ± 2.48 per minute, 1.50 ± 0.33 seconds (mean ± SD) with the left and right hemisphere, respectively; and (2) the association of the reduction of blood pressure with longer, less recurrent SHPs of about 2 seconds.

These responses are linked to the feeling of rhythmical and prefrontal cortex modulation of dopamine lateralized to the right hemisphere during the delayed alternation task. This hypothesis is supported by (1) optimum response organization and working memory at intermediate dopamine tone in a mediofrontalstriatal activation system, a study demonstrating that auditory training induces asymmetrical changes in cortical neural activity; (2) a report that pauses convey meaning beyond words; (3) the role of silence in expressing the inexpressible (Aldous Huxley); and (4) the much-quoted “Heard melodies are sweet, but those unheard are sweeter” (John Keats). Therefore, the analysis of SHPs on a time-base may be included in the development of a comprehensive measure of poststroke depression, optimal poststroke assessment intervals, and determination of a representative population reference.

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