Race and Sex Differences in the Effects of Dietary Potassium Intake on the Risk of Stroke

To the Editor:

We read with great interest the 2 articles by Fang et al and Bazzano et al on the association between dietary potassium intake and stroke mortality. The study by Fang et al has revealed an inverse association between hazard of stroke death and dietary potassium intake in hypertensive men and black men only. On the other hand, Bazzano et al have shown that there was no significant difference in the relation of dietary potassium intake to hazard of stroke that was due to ethnicity or hypertensive status. We would agree with Bazzano et al that their findings of an independent relationship between low potassium intake and increased hazard of stroke in a representative sample of the US population have important clinical and public health implications. However, we believe that the race and sex differences in the effects of dietary potassium intake on the risk of stroke, which was reported by Fang et al, also have important clinical implications as mentioned below.

Recent clinical, experimental, and epidemiologic evidences suggested that dietary potassium intake is inversely related to blood pressure. Therefore, considering that hypertension is the most important known risk factor for stroke, dietary potassium intake may be inversely related to the risk of stroke via blood pressure.

Clegg et al showed that the sodium concentration of erythrocytes from patients with untreated essential hypertension was higher than that of normotensive control subjects. Furthermore, recent evidence has demonstrated that the high dietary potassium intake lowered the blood pressure in the hypertensive rats, associated with the increase of erythrocyte Na⁺-K⁺-ATPase activity. These findings indicate that high dietary potassium intake decreases intracellular sodium concentration, which will result in lowering of blood pressure. An intracellular sodium concentration is thought to have a paramount role in the contractility of vascular smooth muscle cells; an increase in its concentration favors the contraction process. However, erythrocytes have been used routinely to examine the intracellular sodium homeostasis of hypertensive patients because human vascular smooth muscle cells are not readily available.

Several studies showed that the sodium concentration in erythrocytes from normotensive blacks was higher than that of their white counterparts and that erythrocytes of normotensive men had a higher sodium concentration than those from women. Since essential hypertension is more common in blacks and men as compared with whites and women of premenopausal age, and because increased sodium concentration has frequently been demonstrated in erythrocytes of hypertensive patients, it is possible that the higher erythrocyte sodium concentration in blacks and men reflects differences in the cellular regulation of sodium, which increase the likelihood of developing hypertension. Lasker et al revealed that the erythrocyte Na⁺-K⁺-ATPase activity was lower in blacks and men as compared with their counterparts, namely, whites and women, while the sodium concentration in erythrocytes from blacks and men was higher than that of their counterparts, and that there was a significant inverse correlation between the Na⁺-K⁺-ATPase activity and erythrocyte sodium concentration.

These differences based on race and sex in the erythrocyte sodium concentration may have important clinical implications in establishing the useful indication of high dietary potassium intake in the future. We think that a high potassium diet should be indicated for hypertensive patients whose erythrocytes demonstrate a high sodium concentration. However, further studies are required to assess the optimal sodium concentration in erythrocytes of hypertensive patients that can be applied to the indication of high dietary potassium intake.

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Response

We thank Dr Fukui and colleagues for their interest in our work. Their discussion of possible mechanisms for race and sex differences in the blood pressure–lowering effect of dietary potassium intake is intriguing. In a meta-analysis of 33 randomized controlled trials, we found that oral potassium supplementation reduced blood pressure significantly in both hypertensive and normotensive participants and in both black and white subjects. Moreover, the blood pressure reduction was greater in hypertensives compared with normotensives and in blacks compared with whites. Most studies included in the meta-analysis did not show gender differences in blood pressure reduction related to potassium supplementation.

Very few prospective cohort studies have examined the relationship between dietary potassium intake and stroke incidence and mortality. Khaw and Barret-Connor conducted one of the earliest population-based prospective cohort studies to report
a significant inverse relationship between dietary potassium intake and stroke mortality among 859 male and female white retirees in Southern California. They found a slightly stronger relationship between dietary intake of potassium and stroke mortality in women than in men, irrespective of hypertensive status. In the Health Professionals’ Follow-up Study that included 43 738 middle-aged, predominantly-white men, Ascherio and colleagues documented an inverse relationship between the risk of stroke and dietary potassium intake. Fang and colleagues examined the relationship between dietary potassium intake and stroke mortality in the First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study (NHHEFS) and found an inverse association between dietary potassium intake and stroke mortality in black men and hypertensive men. In our analysis, we reported a significantly increased stroke incidence among participants who consumed less than 34.6 mmol of potassium per day. This relationship was independent of age, gender, race, and other important risk factors for stroke.

Findings from our study and from other prospective cohort studies suggest that dietary potassium intake may be related to a lower risk of stroke in blacks and whites and in men and women. However, definitive evidence of a causal relationship between potassium intake and a reduced risk of stroke should come from randomized controlled trials. On the basis of current evidence, high-potassium foods, such as fruits and vegetables, to the pressure lowers stroke risk, it is reasonable to recommend randomization controlled trials. On the basis of current evidence that potassium lowers blood pressure and that reduced blood pressure lowers stroke risk, it is reasonable to recommend high-potassium foods, such as fruits and vegetables, to the general population with the aim of reducing the societal burden of stroke in the United States and worldwide.

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To the Editor:
We read with interest the study reported by Vermeer et al on the prevalence and risk factors for silent brain infarcts in the Rotterdam scan study.1

We were, however, very surprised that the authors neither commented on nor investigated the presence of associated atrial fibrillation (AF) as a risk factor in this study population. As we already know, AF is an independent risk factor for stroke,2 and many other investigators have firmly established the presence of silent cerebral infarction (SCI) in patients with atrial fibrillation.3,4 For example, the Veteran Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators reported that 14.7% of neurologically normal male patients with nonvalvular AF had evidence of cerebral infarction on CT scanning.3 As with Vermeer et al,4 they too reported that an increasing age and a history of hypertension was associated with silent cerebral infarction at entry into the study. Angina was also a risk factor for SCI and was the only independent predictor for later development of symptomatic stroke. Nevertheless, SCI was not an independent predictor of subsequent (symptomatic) stroke in this AF population, although it must be noted that half of the study population were receiving warfarin as part of an intervention study.

Another study from Japan reported a much higher prevalence of SCI in lone AF patients examined with MRI: of 79 patients with lone AF (57 male, 22 female) on no anticoagulant therapy, silent cerebral infarcts were detected in 88% of patients. This high prevalence of SCI increased with age, and, importantly, there was no difference between those patients with paroxysmal and continuous AF.4 These observations are in contrast to a Danish report, which shows a low prevalence of SCI on CT in 30 patients with paroxysmal AF.5 We accept that there are no population studies to indicate whether AF is an independent risk factor for SCI, although the evidence above would suggest that there is a strong association between SCI and AF may exist.

Vermeer et al suggest that the odds ratio of both silent and symptomatic SCI increases with age, at 8% per year—but this could best be explained by an important risk factor from stroke that also increases with age, as is the case with AF.6 Another area of interest would be the relationship of SCI to cognitive function in the affected patients. Indeed, in the Rotterdam study population, an association between dementia and AF has been noted, and SCI would seem to be a likely mechanism.7

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Response
Drs Freestone and Lip suggest that the rise in prevalence of silent brain infarcts with increasing age could be well explained by atrial fibrillation (AF), which also increases with age. We agree that it is indeed very interesting to examine the relationship between AF and silent brain infarcts in the general population. The high prevalence of silent brain infarcts in AF patients, who often suffer from small- and large-vessel disease as well, is insufficient proof of a direct relationship between AF and silent
brain infarcts, of which the majority are lacunes. This relationship has not been examined in the general population. In patients with lacunar stroke, however, atrial fibrillation is rarely the causative factor. In our population-based study, a 12-lead ECG was recorded in all participants a few weeks before MRI scanning from 1995 to 1996. The presence of atrial fibrillation was diagnosed with a computer program, Modular ECG Analysis System (MEANS). In total, 32 participants had AF, of whom 22 had no infarcts on MRI, 8 had silent brain infarcts, and 2 had symptomatic infarcts. AF was not associated with the presence of silent brain infarcts (age- and sex-adjusted odds ratio 1.0, 95% CI 0.4 to 2.3). However, the number of participants with AF in our study was lower than expected in an elderly population. The use of MEANS to detect AF might have led to a misclassification of participants with AF. Moreover, we will certainly miss people with paroxysmal atrial fibrillation, especially because we recorded for only 10 seconds. If anything, this misclassification will have resulted in an underestimation of the association. Nevertheless, the absence of a relationship in our study and our finding that the vast majority of silent lesions were lacunes make it unlikely that AF is a contributing factor in the age-related increase in the prevalence of silent brain infarcts in the general population.

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Cerebral Atherosclerosis Causes Neurogenic Hypertension

To the Editor:

Su et al presented an excellent report regarding “the hypothesis that hypertension has a major role in the pathogenesis of atherosclerosis.” The results of their study were very similar to other findings previously reported. Both groups defended that essential arterial hypertension (EAH) is the major risk factor in the development of atherosclerosis. However, I offer some opposing comments upheld by many authors, based on clinical and neurosurgical evidences. First, EAH represents 90% to 95% of all cases of hypertension and is the main factor of risk in the generation of cerebrovascular and cardiovascular diseases. Second, generally there is a close correlation between age (about 35 years) and the incidence of essential hypertension as well as the onset of cerebral atherosclerosis. Third, 5 areas are associated with EAH—but: derangement of the baroreceptors from the carotid sinus and aortic arc by atherosclerosis, and ischemia in the posterior hypothalamus and medulla oblongata (A1/C1 cell column, commissural portion of the nucleus solitary, and A1/C2 cell column). Fourth, microvascular decompression of the left rostral ventralateral medulla or the omental transplantation on the anterior perforated space can improve or normalize EAH—by restitution of the blood flow in the A1/C1 cell column using the first surgical technique, and because of revascularization in the lateral and posterior hypothalamus produced with the last technique. Therefore, ischemia in the posterior hypothalamus and nuclei of the medulla oblongata are the specific causes of neurogenic hypertension.

Based on the above-mentioned factors and the efficacy of both neurosurgical techniques in the treatment of EAH, we think that neurogenic hypertension represents the great majority of patients with essential hypertension. Therefore, as the specific cause is proven, this neurogenic hypertension type is defined as secondary. Moreover, as the onset of neurogenic hypertension and cerebral atherosclerosis are associated with age (about 35 years), these clinical findings suggest that in the pathogenesis of atherosclerosis, there exist a primary factor and a secondary factor. In my opinion, the primary factor is the main cause of atherosclerosis during the first decades of life; mechanical stresses generated by blood flow provoke a reactive biological response of the intima, i.e., atherosclerotic changes.

For these reasons, we believe that the primary cause of neurogenic hypertension is of microvascular origin related to vascular anomalies and that atherosclerotic plaques located at the mouths of the arterial branches vascularize to the posterior hypothalamus and medulla oblongata. In other words, neurogenic hypertension is caused by atherosclerosis, and later on, arterial hypertension constitutes the most important risk factor that accelerates the development of atherosclerosis.

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Response

We would like to thank Dr Rafael for his interest and valuable comments on our recent article in Stroke.1 In our article, we did not address the mechanism of essential hypertension and the relationship between carotid atherosclerosis with neurogenic hypertension. We agree that neurogenic mechanisms may be important for the maintenance of most forms of hypertension. However, there are still insufficient evidences to implicate abnormal central nervous system (CNS) function as the primary cause of essential hypertension.2 The effect of lowering blood pressure by microvascular decompression of the left rostral ventrolateral medulla3 may be similar to blockade of the sympathetic nervous system, leading to vasodilatation. Our previous study revealed that thoracic sympathectomy might reduce blood pressure and elevate blood flow volume of carotid arteries; that may partly explain one of the neurogenic mechanisms. However, the etiologies of essential hypertension are multifactorial: environmental, genetic, pathological, and so on.5 The relief of hypertension from microvascular decompression surgery at the rostral ventrolateral medulla does not indicate CNS atherosclerosis as the unique cause of essential hypertension. The immediate postprocedural hemodynamic complications in patients receiving carotid stenting for severe carotid stenosis, including hypotension (22.4%) and hypertension (38.8%),6 indicate that release of compression from severe internal carotid artery stenosis does not always reduce blood pressure.

The causal relationship between hypertension and carotid atherosclerosis was reinforced by the findings of the dose-response effect of hypertension on carotid intima-media thickness and carotid atherosclerosis.1 Furthermore, the analysis of subjects with extracranial carotid atherosclerotic plaque scores ≥4 showed that 27.6% cases are normotensives.1 There are bodies of evidence demonstrating that hypertension may play a major role in carotid atherosclerosis1,7 and its progression.8,9 A recent study provided convincing data that treatment for hypertension by microvascular decompression of the left rostral ventrolateral medulla4 may be similar to blockade of the sympathetic nervous system, leading to vasodilatation. Our previous study revealed that thoracic sympathectomy might reduce blood pressure and elevate blood flow volume of carotid arteries; that may partly explain one of the neurogenic mechanisms. However, the etiologies of essential hypertension are multifactorial: environmental, genetic, pathological, and so on.5 The relief of hypertension from microvascular decompression surgery at the rostral ventrolateral medulla does not indicate CNS atherosclerosis as the unique cause of essential hypertension. The immediate postprocedural hemodynamic complications in patients receiving carotid stenting for severe carotid stenosis, including hypotension (22.4%) and hypertension (38.8%),6 indicate that release of compression from severe internal carotid artery stenosis does not always reduce blood pressure.

Thus, the hypothesis raised by Dr Rafael that neurogenic hypertension is caused by atherosclerosis, which is considered to be the primary cause of essential hypertension, seems to lack strong and direct evidence. Further studies by cohort and prospective designs may be conducted to delineate the sequential and causal relationship between hypertension and atherosclerosis at the vascular beds of CNS.

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Multiple Panel of Biomarkers for TIA/Stroke Evaluation

To the Editor:

Brey et al1 reported what is to their knowledge the first study to demonstrate a prospective association between sera cofactor-dependent antiphospholipid antibodies and stroke independent of other risk factors as well as myocardial infarction (MI). In addition to lending support to basic research that has shown the pathogenicity of antiphospholipid-protein antibodies (aPL) in thrombosis,2 this well-conducted epidemiological study of Japanese-American men enrolled in the Honolulu Heart Program and followed for up to 20 years provides evidence for the role of aPL as potentially important markers and/or causes of increased vascular risk associated with ischemic stroke and MI.

It is known that stroke is a multisystemic disorder involving mechanisms of thrombotic and neurotoxic coupling.3 Biochemical markers including glutamate, homocysteine (a sulfinic analog of aspartate4), and N-methyl-D-aspartate (NMDA) receptor autoantibodies (aAb) are independently associated with neurotoxicity and can be measured in blood.5 The aPLs are a part of the structural components of excitatory membranes containing glutamate receptors and may be involved in the neurotoxicity process as well.5 Consequently, the appearance of elevated levels of aPL in blood represents an additional indicator of NMDA receptor damage under ischemic conditions.

The development of a multiple panel of biomarkers for stroke analogous to that now in use for MI would be beneficial for the emergency bedside diagnosis of stroke and may help differentiate ischemic from hemorrhagic stroke. We assessed 3 proposed biomarkers: glutamate and homocysteine as correlates of large and middle artery dysfunction, and NR2A aAb as a criterion of microvascular damage independently associated with neurotoxicity and thrombosis in patients with transient ischemic attack (TIA)/stroke. We studied 92 patients with high blood pressure, prestroke, and TIA, subdivided according to symptom severity, including patients with left hemispheric stroke admitted within 6 hours of stroke onset (30.4 ± 3.2 score on the Orgogozo Stroke Scale) and patients with intracerebral hemorrhage located in the left hemisphere (Table 1). Patients underwent neurological examination and neuroimaging (computed tomography, T2-weighted MRI, diffusion-weighted imaging, and Doppler angiography).6,7 After informed consent, blood samples were collected on the day of admission from all subjects. Plasma levels of glutamate and homocysteine and serum levels of the NMDA receptor NR2A subtype were assessed by high-performance liquid chromatography and enzyme-linked immunosorbent assay.6

Plasma glutamate concentrations were highest in patients with TIA (Table 1). Homocysteine levels increased in patients with

1181
TABLE 1. Plasma Concentrations of Glutamate and Homocysteine and Serum Concentrations of NR2A Autoantibodies in Patients and Control Subjects

<table>
<thead>
<tr>
<th>Subjects</th>
<th>n</th>
<th>Age, y</th>
<th>M</th>
<th>F</th>
<th>Glutamate*</th>
<th>Homocysteine*</th>
<th>NR2A aAb†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>30</td>
<td>51.6±4.6</td>
<td>12</td>
<td>18</td>
<td>32.0±3.8</td>
<td>8.3±0.5</td>
<td>1.4±0.3</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>25</td>
<td>36.9±2.3</td>
<td>8</td>
<td>17</td>
<td>32.8±0.9</td>
<td>11.5±0.4</td>
<td>1.9±0.1</td>
</tr>
<tr>
<td>Prestroke</td>
<td>12</td>
<td>59.9±4.7</td>
<td>5</td>
<td>7</td>
<td>37.5±1.2</td>
<td>12.3±0.6</td>
<td>2.5±0.1</td>
</tr>
<tr>
<td>TIA</td>
<td>14</td>
<td>58.9±1.7</td>
<td>7</td>
<td>7</td>
<td>40.4±1.1</td>
<td>12.9±0.5</td>
<td>4.2±0.2</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>23</td>
<td>54.7±1.4</td>
<td>14</td>
<td>9</td>
<td>30.8±1.2</td>
<td>13.0±0.7</td>
<td>4.9±0.8</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>18</td>
<td>53.0±4.4</td>
<td>12</td>
<td>6</td>
<td>33.3±3.5</td>
<td>9.2±0.3</td>
<td>1.7±0.1</td>
</tr>
</tbody>
</table>

aAb indicates autoantibodies.

Data are mean±SEM, *expressed in micromoles per liter; †expressed in nanogram per milliliter; ‡P<0.05 and §P<0.01 compared with controls.

cerebrovascular abnormalities, pre-stroke, TIA, and ischemic stroke (in that order) and depended on stroke severity, whereas amino acid contents did not show such a correlation (Table 1). We did not observe any changes in the dynamic of glutamate and homocysteine for patients with hemorrhage during the first 3 hours of hospitalization (Table 1). Detailed T2-weighted MRI and DWI in 9 patients with TIA were analyzed on the third hour of admission. Regional ischemia was clearly depicted as hyperintensity on DWI, while T2-weighted imaging showed no changes. T2-weighted MRI showed an area of infarction in 4 patients that developed to day 7 of observation and was accompanied by neurological worsening.

Excessive activation of NMDA receptors is the result of glutamate and homocysteine neurotoxicity. Level of NR2A aAb was lower in patients with cerebrovascular abnormalities, prestroke, TIA, and ischemic stroke (in that order) and depended on stroke severity, whereas amino acid contents did not show such a correlation (Table 1). Different profiles of elevated NR2A aAb were revealed in the blood of patients with ischemic stroke, while no changes in sera of patients with hemorrhage were detected (Table 2). The appearance of NR2A autoantibodies elevated above control depended on the severity of disorder, with the same tendency as homocysteine. The correlation between infarct volume and the level of NR2A aAb was demonstrated by CT and MRI. Concentration of aAb was lower in patients with infarcts localized in the posterior region (4 to 5 cm²) and significantly higher in infarcts with a cortical topography (>25 cm²). When neuroprotective glycine was administered, we observed NR2A aAb reduction in patients with acute stroke that was accompanied by an improvement in neurological function.

Our experimental and clinical research data have demonstrated that simultaneous assessment of these 3 biomarkers allows neurotoxicity and thrombosis to be correlated with severity of cerebral ischemia and as such represents a promising additional tool for use with neuroimaging for the diagnosis of TIA/stroke. Development of a blood test that would also detect the thrombotic marker (anticardioplin antibodies) observed by Brey et al would, when used in conjunction with our proposed biomarkers, help evaluate the thrombotic and neurotoxic contributions in stroke: guide antplatelet, antithrombotic, and neuroprotective therapy; and assess patient follow-up and recovery after ischemic events.

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TABLE 2. NR2A Autoantibody Monitoring in Patients with Ischemic and Hemorrhagic Stroke

<table>
<thead>
<tr>
<th>Time (on admission)</th>
<th>NR2A Autoantibody, ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ischemic Stroke*</td>
</tr>
<tr>
<td>0 (on admission)</td>
<td>5.04±0.91</td>
</tr>
<tr>
<td>3</td>
<td>4.96±0.32</td>
</tr>
<tr>
<td>6</td>
<td>5.10±0.71</td>
</tr>
<tr>
<td>9</td>
<td>7.90±1.23</td>
</tr>
<tr>
<td>12</td>
<td>7.30±1.53</td>
</tr>
<tr>
<td>24</td>
<td>3.20±0.62</td>
</tr>
<tr>
<td>72</td>
<td>3.50±0.50</td>
</tr>
</tbody>
</table>

*P<0.001, versus control (1.4±0.3 ng/ml).
Multiple Panel of Biomarkers for TIA/Stroke Evaluation
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