Potassium Chloride Supplementation Diminishes Platelet Reactivity in Humans

Masayuki Kimura, Xiaobin Lu, Joan Skurnick, Girgis Awad, John Bogden, Francis Kemp, Abraham Aviv

Abstract—The prevalence of occlusive stroke is inversely correlated with potassium intake. We explored the hypothesis that a high potassium intake attenuates platelet reactivity, as expressed in ADP-evoked platelet aggregation. We studied healthy men (n = 31) and women (n = 42), blacks (n = 33) and whites (n = 40). In this cohort, we supplemented the habitual intake of 17 men and 21 women with 60 mmol KCl/70 kg body weight per day for 3 days and maintained 14 men and 21 women on their habitual intake. We then compared the change in ADP concentration causing 50% of the maximal initial rate (EC50) of platelet aggregation in the potassium-supplemented versus control groups. Potassium supplementation attenuated platelet reactivity, expressed by an increase in EC50 of platelet aggregation (P = 0.0005), which was primarily attributable to an increase in EC50 in whites (P = 0.0004). Urinary potassium excretion was significantly lower in blacks than in whites under basal conditions and after potassium supplementation. We conclude that potassium supplementation diminishes platelet reactivity, a phenomenon that provides a link between platelet biology and occlusive stroke. (Hypertension. 2004;44:1-5.)

Key Words: stroke ■ cardiovascular disease ■ atherosclerosis

The potential cardiovascular benefits of dietary potassium in the general population have been considered primarily from the perspectives that potassium may serve as a sodium substitute in the diet and that a high potassium intake enhances natriuresis.1 Accordingly, the beneficial effect of a high potassium intake on blood pressure.2 The question that follows is whether or not the cardiovascular effect of a high potassium intake may also be mediated through blood pressure-independent mechanisms, given that large-scale studies strongly suggest that dietary potassium intake is inversely correlated with stroke and myocardial infarction, was significantly higher in subjects with hypokalemia (serum potassium <3.5 mmol/L) associated with diuretic use.8 Collectively, these findings suggest a link between systemic potassium homeostasis and atherosclerosis and thrombosis.9,10 We note, however, that potassium is primarily an intracellular ion, so that dietary intake and diuretic use are likely to have an effect on intracellular potassium pool even without detectable changes in serum potassium. Because thromboembolic processes largely depend on platelet biology, we hypothesized that a high potassium intake would diminish platelet reactivity. This concept was explored in the present work.

Materials and Methods

Subjects
We studied healthy men (n = 31) and women (n = 42), blacks (n = 33) and whites (n = 40), whose general characteristics at the start of the study are described in Table 1. Subjects were not on any prescribed drugs and were instructed to avoid over-the-counter pain and anti-inflammatory medications (except acetaminophen) for 2 weeks before the study. Women on oral contraceptives or hormonal replacement and blacks with sickle cell traits were excluded from the study. Women were studied 2 days after the end of their menses. Subjects were randomly assigned to control and potassium-supplemented groups. All subjects gave informed consent approved by the institutional review board of the University of Medicine and Dentistry of New Jersey, New Jersey Medical School.

General Procedures
We obtained blood pressure (3 measurements after a 5-minute rest, separated by 2-minute intervals in a sitting position) and collected fasting blood immediately thereafter between 8 and 9 AM on 2 occasions: at the beginning (first visit) and 3 days later, at the end of the study (second visit). We supplemented the diet of experimental subjects with 60 mmol KCl/70 kg body weight in the form of tablets (KLOREX extended release, containing 750 mg KCl; Upsher-Smith). We had estimated that this dose would approximately double...
the average potassium intake of subjects and thus their urinary potassium excretion. We instructed experimental subjects to take the tablets after meals, each time with 2 glasses of water. Control subjects were instructed to maintain their habitual diet and drink 2 glasses of water with each meal. To assess compliance with potassium supplementation, 2 24-hour urine collections were obtained: 1 before the first visit and the other before the second visit.

Blood was collected from the antecubital vein into vials with and without 0.129 mol/L sodium citrate. Serum was used for measurements of potassium concentration in serum and urine samples were determined by flame atomic absorption spectrophotometry.

### Platelet Reactivity

By monitoring ADP-mediated platelet aggregation, we assessed platelet reactivity (Figure 1). This was performed in an aggregometer (model 560CA; Chrono-Log) in which an infrared light shines through a cuvette containing the subject’s plasma, which serves as a reference. Initial rates (IRs) of the downward deflection in light transmission, which reflects the rate of platelet aggregation instantaneously after addition of different concentrations of ADP (0.4 to 20 μmol/L) to the PRP, are computed using AGGRO/LINK software. To improve sensitivity, we computed EC$_{50}$ of platelet aggregation as follows: $\text{IR} = \text{IR}_{\text{max}} \cdot (\text{ADP}_0)/(\text{EC}_{50} + (\text{ADP}_0))$, where $\text{IR}_{\text{max}}$ = maximal IR; ADP$_0$ = ADP concentration; $a_0$ = slope of the curve; and EC$_{50}$ = ADP concentration causing 50% of the IR$_{\text{max}}$. A higher EC$_{50}$ denotes less platelet reactivity.

### Statistical Analysis

Data are presented as mean±SD. Baseline (first visit) characteristics of control and potassium-supplemented subjects were compared by ANOVA. Comparisons of whites and blacks included gender as an adjustment factor, and gender comparisons were adjusted for race. Pearson’s linear correlation coefficient $r$ was computed to measure strength of association. Within control and potassium-supplemented subgroups, paired $t$ tests were used to compare first- and second-visit measurements of EC$_{50}$, urinary potassium, and sodium excretion using within-subject differences. To compare the magnitude of changes between subject groups, repeated-measures ANOVAs were performed with models that incorporated within-subject effects. Gender and race were evaluated as adjustment factors and included in analyses when so indicated. The criterion for statistical significance was 2-tailed $P<0.05$; 2-tailed $P$ values are presented throughout. Analyses were performed using SAS software packages.

### Results

#### Subject Characteristics

At the first visit, there was no difference in age, body mass index (BMI), systolic blood pressure (SBP), and diastolic blood pressure (DBP) between control and potassium-supplemented groups. There was no significant race- or gender-related variation in age, SBP, and DBP. BMI was higher in blacks than in whites, primarily because of a higher potassium excretion. At the first visit, age was significantly correlated with SBP ($r = 0.26; P = 0.024$), DBP ($r = 0.43; P = 0.0002$), and BMI ($r = 0.26; P = 0.024$). BMI was significantly correlated with DBP ($r = 0.24; P = 0.044$).

For the control group, basal SBP/DBP was 109±9.57/73.3±9.47 mm Hg in the first visit and 106±10.4/70.4±8.65 mm Hg in the second visit. Basal SBP/DBP for the potassium-supplemented group was 109±14.0/73.3±8.65 mm Hg in the first visit and 107±10.9/70.4±8.65 mm Hg in the second visit. The change in SBP between the first and second visits was not significant. For DBP, the first visit was 9.47 mm Hg in the first visit and 10.4 mm Hg in the second visit, and the difference was not significant. For BMI, the first visit was 26.7±5.36 in the first visit and 26.7±5.36 in the second visit, and the difference was not significant.

### Figure 1

Illustration of ADP-induced platelet aggregation. A, Platelet aggregation was monitored using 0.4 to 20 μmol/L ADP. Arrow denotes addition of ADP to PRP. The upward deflection reflects platelet shape change, whereas the downward deflection denotes platelet aggregation. B, Dose response depicting IIRs of ADP-induced platelet aggregation and EC$_{50}$ as delineated in Methods and Results.
Table 2. Urinary Electrolytes Excretion (mmol/70 kg per day)

<table>
<thead>
<tr>
<th>Subject Group</th>
<th>KCl Supplement K excretion</th>
<th>Control K excretion</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>First 53.5±23.4 97.0±62.4</td>
<td>Second 48.8±27.4 46.0±19.0</td>
<td>34 &lt;0.0001</td>
</tr>
<tr>
<td>Whites</td>
<td>First 62±22.7 119±71.5</td>
<td>Second 57.4±31.4 51.3±20.1</td>
<td>20 0.0002</td>
</tr>
<tr>
<td>Blacks</td>
<td>First 43.5±20.5 72.0±38.9</td>
<td>Second 36.5±14.0 38.5±14.9</td>
<td>14 0.021</td>
</tr>
<tr>
<td>Men</td>
<td>First 57.2±26.4 102±81.7</td>
<td>Second 57.0±32.4 53.2±22.4</td>
<td>14 0.021</td>
</tr>
<tr>
<td>Women</td>
<td>First 50.5±20.9 92.6±42.8</td>
<td>Second 43.1±22.5 41.0±14.8</td>
<td>20 &lt;0.0001</td>
</tr>
</tbody>
</table>

*P values are for within-subject change between first and second collections by repeated-measures ANOVA.

73.8±10.9 mm Hg in the first visit and 108±11.3/73.2±8.48 mm Hg in the second visit.

**Twenty-Four–Hour Urinary Electrolyte Excretion**

For the control group, no significant differences were observed in excretion of potassium and sodium between the first and second collections (Table 2). For the potassium-supplemented group, urinary potassium excretion was significantly higher in the second than the first collection by 43.5 mmol/70 kg body weight, but there was no significant increase in urinary sodium excretion between the 2 collection periods (Table 2). Urinary potassium excretion was significantly lower in blacks than whites during the first collection (Table 1). For the second collection, within the potassium-supplemented group, blacks raised their urinary potassium excretion in the second visit, but had still significantly lower urinary potassium excretion than whites (P=0.021).

**Serum Electrolytes**

There were no statistically significant differences in serum sodium and potassium concentrations between control and potassium-supplemented subjects. In the first visit, serum sodium/potassium concentrations (in mmol/L) were: control=136.7±3.78/4.09±0.348, potassium-supplemented=136±4.10/4.23±0.337. In the second visit 3 days later, serum sodium/potassium concentrations (in mmol/L) were: control=137±4.08/4.10±0.363, potassium supplemented=135±0.37/4.38±0.399.

**Platelet Reactivity**

There was considerable variation in platelet reactivity, as expressed by EC50 of the ADP-mediated platelet aggregation. Potassium supplementation increased EC50 from 1.06±0.357 μmol/L in the first visit to 1.18±0.383 μmol/L in the second visit (P=0.0017 by paired t test). In the control group, EC50 was slightly higher in the first than the second visit (1.07±0.322 μmol/L and 1.02±0.289 μmol/L), but this difference was not statistically significant. Figure 2 depicts the difference in the change (second minus first visits) in EC50 between potassium supplementation and control for all subjects: whites, blacks, men, and women. Significant differences were observed in EC50 changes between the potassium-supplemented group and control for all subjects: whites (P=0.0005), blacks (P=0.0004), men (P=0.0033), and women (P=0.016). Potassium-supplemented blacks exhibited an increase in EC50 between the first and second visits (1.18±0.393 μmol/L and 1.27±0.442 μmol/L), whereas control blacks showed little change in the first and second visits (1.02±0.352 μmol/L and 1.01±0.305 μmol/L). However, the difference in EC50 change between potassium-supplemented and control blacks did not reach statistical significance (P=0.17; Figure 2).

**Discussion**

Our study shows that potassium supplementation for 3 days diminished platelet reactivity, as expressed in an increase in EC50 of the ADP-evoked platelet aggregation. The finding of
diminished ADP-evoked platelet aggregation with potassium supplementation suggests that high dietary potassium is associated with diminished platelet reactivity. Given that platelets are a major factor in vascular occlusion, our findings are in line with epidemiological studies linking potassium intake with occlusive stroke.3-7

The lower urinary potassium excretion in blacks in our cohort could be attributable to: (1) poor compliance with potassium supplementation, (2) incomplete urine collections, and (3) racial differences in primary potassium excretion. A poor compliance with potassium supplementation may explain the nonsignificant EC50 change in potassium-supplemented blacks, although, like whites, blacks showed an increase in EC50. We note, however, that it is well established that without and with potassium supplementation, urinary excretion of potassium is lower in blacks than in whites.11-15

This racial difference has been attributed to low potassium intake in blacks, albeit no data have been provided to substantiate this idea. This topic is addressed in detail in a recent communication.16

The mechanism that accounts for the effect of potassium supplementation on ADP-evoked platelet aggregation is unclear. We suspect that this phenomenon may ultimately relate to the link between the sodium/potassium gradients across the platelet plasma membrane and platelet cytosolic calcium, which is the penultimate platelet activator. The sodium/potassium gradients are crucial for maintaining platelet calcium homeostasis through the platelet sodium–calcium exchanger. This exchanger is a major regulator of cellular calcium in a variety of cells, including platelets. The platelet sodium–calcium exchanger is driven by the transmembrane gradient of not only sodium but also potassium, rendering this unique calcium transporter, and therefore platelets, highly sensitive to perturbations in cellular sodium/potassium concentrations.17,18 Lin and Young19 found that raising the extracellular potassium concentration to 6 mmol/L in vitro diminished the thrombin-evoked aggregation of human platelets. In and of itself, a rise in extracellular potassium would diminish the outward K gradient across the platelet plasma membrane and retard the forward (calcium extrusion) mode of the platelet sodium–calcium exchanger. However, a rise in the extracellular K can also stimulate the Na pump and thereby diminish cytosolic sodium and increase cytosolic K concentrations.

In the present study, potassium supplementation did not significantly change serum sodium/potassium concentrations. If potassium supplementation increased the inward sodium gradient, the outward potassium gradient, or both across the platelet plasma membrane, this was accomplished without raising the extracellular potassium. The outcome of increased sodium and potassium gradient would be an increase of the forward mode of the platelet sodium–calcium exchange and attenuation of the ADP-evoked increase in the cytosolic-free calcium and platelet aggregation.

Increased platelet reactivity may be a determinant not only in thrombosis but also atherosclerosis.20 In addition, previous studies have reported that hypertension is associated with an increase in platelet reactivity.21,22 However, it is unlikely that diminished platelet reactivity in the potassium-supplemented group was mediated through blood pressure because potassium supplementation for 3 days had no significant effect on blood pressure.

Perspectives

The present study demonstrates that potassium supplementation diminishes platelet reactivity, pointing to a new and heretofore unexplored mechanism in the development of vascular occlusions in the brain and perhaps other anatomic regions in humans. The debate about the links between nutrition and cardiovascular disease has focused on the excess salt (in the form of sodium chloride), calories, and saturated fats in the American diet. Yet the connection between dietary potassium and cardiovascular disease has attracted only rudimentary attention. Most Americans would experience considerable difficulties in taking measures to reduce their intake of salt and saturated fats because processed foods, high in these ingredients, are a major staple of the average American diet. However, Americans would have little difficulty to reconfigure their diet to raise their potassium intake, which may be an inexpensive and safe preventive modality in the campaign against cardiovascular disease.

Acknowledgments

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References


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