Relationship Between Urinary Salt Excretion and Pulse Pressure and Central Aortic Hemodynamics Independent of Steady State Pressure in the General Population

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Abstract—Although central pulse pressure (P Pc) is strongly related to central mean arterial pressure (MAPc), P Pc predicts cardiovascular outcomes beyond MAPc. Whether modifiable risk factors for hypertension contribute to P Pc and its determinants, independent of MAPc, is uncertain. In 635 randomly recruited participants, we assessed the independent relationship between 24-hour urinary sodium (Na+) or potassium (K+) excretion and brachial artery PP (in office or 24-hour; n=487), P Pc, the forward (P1) and augmented (Paug) pressure wave components of P Pc, central augmentation index, and determinants of central pressure waves, including aortic pulse wave velocity, effective reflecting distance, and reflective wave transit time. Central dynamics were determined using applanation tonometry of the carotid, femoral, and radial arteries. With adjustments for potential confounders, urinary Na+/K+ was independently associated with in-office, central, and 24-hour PP, as well as Paug, P1, and central augmentation index (P<0.05 to P<0.005). With further adjustments for MAPc (or diastolic BP), urinary Na+/K+ was independently associated with P Pc, 24-hour PP, Paug, P1, and central augmentation index (P<0.05 to P=0.005) but not with in-office PP, pulse wave velocity, effective reflecting distance, or reflective wave transit time. In conclusion, in a population of African ancestry, urinary salt excretion is independently related to central and 24-hour PP independent of MAPc or diastolic BP, effects that are attributed to increases in both P1 and Paug but not to pulse wave velocity. Hence, modifying salt intake could influence cardiovascular risk through effects on 24-hour and central PPs, as well as P1 and Paug, independent of steady-state pressure (MAP or diastolic BP) or pulse wave velocity. (Hypertension. 2010;56:584-590.)

Key Words: pulse pressure ▪ arterial stiffness ▪ central blood pressure ▪ salt intake

Pulse pressure (PP) predicts cardiovascular outcomes beyond other measures of blood pressure (BP), including measures of steady-state pressure, such as mean arterial pressure (MAP).1-14 Moreover, central PP may be more closely associated with cardiovascular outcomes than peripheral PP.15-19 Thus, contemporary notions of the adverse actions of BP are viewed in terms of steady-state effects, indexed by MAP, and dynamic or pulsatile effects, indexed by PP, with central PP receiving the most attention. The effects of PP independent of MAP on cardiovascular outcomes1-14 are particularly impressive considering the close relationship between MAP and PP. Developing strategies that decrease PP, particularly central PP, without necessarily influencing MAP, is, therefore, of considerable interest, and in this regard understanding the mechanisms responsible for these changes is of importance. Although aging has been identified as the major determinant of PP, with increases in both the augmented and the forward pressure wave contributing to central PP,20-23 the impact of modifiable risk factors for hypertension on PP and the component waves through MAP-independent effects is unclear.

Although a number of studies suggest that reductions in sodium (Na+) intake and increases in potassium (K+) intake influence BP and the risk for hypertension,24-29 whether salt intake modifies PP, particularly central PP, the forward and augmented pressure wave components and their determinants independent of MAP are uncertain. This is particularly pertinent for groups of African descent in whom the response to modifications in salt intake may be more profound than in other ethnic groups.26,28 Therefore, we aimed to assess whether, independent of MAP, urinary indexes of Na+ and K+ intake are associated with peripheral in-office, 24-hour, and central PP and the forward and augmented pressure wave components of central PP and their determinants in a population sample of African ancestry with average Na+ and K+ excretion is independently related to central and 24-hour PP independent of MAPc or diastolic BP, effects that are attributed to increases in both P1 and Paug but not to pulse wave velocity. Hence, modifying salt intake could influence cardiovascular risk through effects on 24-hour and central PPs, as well as P1 and Paug, independent of steady-state pressure (MAP or diastolic BP) or pulse wave velocity. (Hypertension. 2010;56:584-590.)
intakes that differ markedly from the recommended daily allowance.\textsuperscript{30}

**Methods**

**Study Group**

The present study was initiated in 2002 and conducted according to the principles outlined in the Helsinki declaration. The committee for research on human subjects of the University of the Witwatersrand approved the protocol (approval No. M02-04-72 and renewed as M07-04-69). Participants gave informed, written consent. The present study design has been described previously.\textsuperscript{31,32} Briefly, nuclear families of black African descent (Nguni and Sotho chiefdoms) with siblings older than 16 years were randomly recruited from the South West Township of Johannesburg, South Africa, using the population census figure of 2001. Of the 971 participants with central hemodynamic assessments, 635 participants had 24-hour urine samples that met with prespecified quality control criteria described previously.\textsuperscript{30} To confirm the outcomes of relationships between urinary indexes of Na\textsuperscript{+} or K\textsuperscript{+} intake and brachial artery in-office PP, we obtained 24-hour BP measurements that met with prespecified quality control criteria (>20 hours and >10 and 5 readings for the computation of day and night means, respectively) in 487 participants. Eighty-three participants were too obese to obtain acceptable femoral pulse waves to determine carotid-femoral (aortic) pulse wave velocity (PWV).

**Clinical, Demographic, and Anthropometric Measurements**

A standardized questionnaire was administered to obtain demographic and clinical data.\textsuperscript{31,32} Height and weight were measured using standard approaches, and participants were identified as being overweight if their body mass index (BMI) was ≥25 kg/m\textsuperscript{2} and obese if their BMI was ≥30 kg/m\textsuperscript{2}. High-quality conventional in-office BP measurements were obtained by a trained nurse technician using a standard mercury sphygmomanometer.\textsuperscript{32} Standard laboratory blood tests of renal function, liver function, blood glucose, hematologic parameters, and percentage glycohemoglobin (HbA1c) were performed. Diabetes mellitus or abnormal blood glucose control was defined as the use of insulin or oral hypoglycemic agents or an HbA1c value >6.1%.\textsuperscript{33}

**Urinary Electrolyte Excretion Rates**

Timed urine samples were obtained over at least a 24-hour period after discarding urine obtained immediately before the collection period. Urine Na\textsuperscript{+}, K\textsuperscript{+}, and creatinine concentrations were measured, as well as 24-hour urine Na\textsuperscript{+} and K\textsuperscript{+} excretion rates calculated from the product of urine volume and urine electrolyte concentration. For the description of the quality assessments of urine samples please see the online Data Supplement at http://hyper.ahajournals.org.

**Pulse Wave Analysis**

Central hemodynamics and carotid-femoral PWV were estimated using techniques described previously.\textsuperscript{31,32,34} Briefly, after participants had rested for 15 minutes in the supine position, arterial waveforms at the radial (dominant arm), carotid, and femoral pulses were recorded by applanation tonometry, each during an 8-second period using a high-fidelity SPC-301 micromanometer (Millar Instrument, Inc) interfaced with a computer using SphygmoCor, version 6.21 software (AtCor Medical Pty Ltd). Recordings where the systolic or diastolic variability of consecutive waveforms exceed 5% or the amplitude of the pulse wave signal was <80 mV were discarded. The pulse wave was calibrated by manual measurement (auscultation) of BP taken immediately before the recordings. All of the measurements were made by a single experienced trained technician unaware of the clinical history of the participants. For further details of the pulse wave analysis please see the online Data Supplement.

**Ambulatory BP**

Twenty-four–hour ambulatory BP monitoring was performed on the same day as conventional BP measurements using oscillometric monitors (SpaceLabs, model 90207) as described previously.\textsuperscript{32} For further details of the ambulatory BP monitoring and analysis please see the online Data Supplement.

**Data Analysis**

For database management and statistical analysis, SAS software, version 9.1 (SAS Institute, Inc) was used. Data are shown as mean±SD. Regression analysis with relevant confounders included in the regression models was used to determine independent relations. For the derivation of \( P \) values, further adjustments were made for nonindependence of family members using the mixed procedure as outlined in the SAS package. Because the majority of treated hypertensives were receiving thiazide diuretic therapy, which in the initial phase of therapy may affect urinary electrolyte excretion rates, sensitivity analysis was conducted in participants not receiving diuretics.

**Results**

**Characteristics of the Participants**

Table 1 gives the demographic and clinical characteristics of the study group. More women than men participated. In general the study group had a high BMI, with ≈67% of participants being either overweight (≥24%) or obese (≥43%). Approximately one quarter of the sample was receiving antihypertensive therapy, and the majority of treated participants (21.3% of the total sample) were receiving thiazide diuretics. The general characteristics of participants who did not have 24-hour urinary samples that met with prespecified quality control were no different from the characteristics of the participants whose data are shown in Table 1 (please see Table S1 in the online Data Supplement at http://hyper.ahajournals.org). Of the participants not receiving diuretic therapy, only 4.2% were receiving alternative antihypertensive agents, and they were younger, had a lower BMI, a lower BP, PP, augmented pressure (Paug), effective reflecting distance and aortic PWV. The average 24-hour urinary Na\textsuperscript{+} excretion rate was well above the recommended daily allowance for Na\textsuperscript{+} intake of 65 mmol/d, with most of the study group (68%) ingesting more than the recommended daily allowance for Na\textsuperscript{+} intake. All of the participants had 24-hour urinary K\textsuperscript{+} excretion rates less than the recommended daily allowance for K\textsuperscript{+} intake of 120 mmol/d.

**Relationships Between Urinary Indices of Salt Intake and Steady-State or Pulsatile BP**

As shown in Table 2, with adjustments for age, BMI, sex, treatment for hypertension, regular tobacco use, regular alcohol intake, and diabetes mellitus or an HbA1c >6.1%, an independent relationship between the ratio of urinary Na\textsuperscript{+}/K\textsuperscript{+} and in-office brachial artery, central artery, 24-hour, day or night PP was noted. Importantly, the independent relationships between urinary Na\textsuperscript{+}/K\textsuperscript{+} and central and ambulatory PPs were noted both before and after adjustments for MAP (Table 2). Similar outcomes were noted after adjustments for diastolic BP rather than MAP (data not shown). Urinary Na\textsuperscript{+}/K\textsuperscript{+} was also independently associated with systolic BP, but no independent relations with diastolic BP were noted (Table 2). In sex-specific analyses, a relationship
between urinary Na+/K+ and central PP was noted after adjustments for central MAP and other confounders both in men (partial $r=0.16; P<0.05$) and in women (partial $r=0.12; P<0.05$). Sensitivity analysis conducted in participants not receiving diuretic therapy revealed similar outcomes (please see Table S2 and description of these data in the online Data Supplement).

In contrast to the independent relationships between urinary Na+/K+ and BP, neither 24-hour urinary Na+ nor 24-hour urinary K+ excretion was independently associated with in-office brachial, central artery, 24-hour, day, or night systolic BP, diastolic BP, or PP (data not shown). In addition, although the urinary K+ corrected for urine creatinine concentrations was modestly associated with central PP and central systolic BP ($P<0.05$ both), and urinary Na+ excretion corrected for urine creatinine concentrations was modestly associated with central PP and systolic BP, 24-hour urinary Na+ corrected for urine creatinine concentrations was modestly associated with central PP and systolic BP, 24-hour systolic BP, diastolic BP, or PP (data not shown). Sensitivity analysis conducted in participants not receiving diuretic therapy revealed similar outcomes (please see Table S2 and description of these data in the online Data Supplement).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean±SD or %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, % women</td>
<td>65.2</td>
</tr>
<tr>
<td>Age, y</td>
<td>45.1±18.4</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.8±8.2</td>
</tr>
<tr>
<td>Regular tobacco intake, %</td>
<td>14.2</td>
</tr>
<tr>
<td>Regular alcohol intake, %</td>
<td>23.0</td>
</tr>
<tr>
<td>% with diabetes mellitus or HbA1C &gt;6.1%</td>
<td>25.5</td>
</tr>
<tr>
<td>% treated for hypertension</td>
<td>24.6</td>
</tr>
<tr>
<td>% receiving thiazide diuretics</td>
<td>21.3</td>
</tr>
<tr>
<td>24-h urinary Na+, mmol</td>
<td>105.4±72.9</td>
</tr>
<tr>
<td>24-h urinary K+, mmol</td>
<td>28.1±18.7</td>
</tr>
<tr>
<td>24-h urine volume, mL</td>
<td>1382±724</td>
</tr>
<tr>
<td>Urinary Na+/K+ ratio</td>
<td>4.27±2.22</td>
</tr>
<tr>
<td>Urinary Na+/creatinine</td>
<td>14.0±8.3</td>
</tr>
<tr>
<td>Urinary K+/creatinine</td>
<td>3.65±1.93</td>
</tr>
<tr>
<td>Conventional SBP/DBP, mm Hg</td>
<td>132±23/85±13</td>
</tr>
<tr>
<td>Conventional PP, mm Hg</td>
<td>47±16</td>
</tr>
<tr>
<td>Pulse rate, bpm</td>
<td>65±12</td>
</tr>
<tr>
<td>Central SBP/DBP, mm Hg</td>
<td>124±24/86±13</td>
</tr>
<tr>
<td>Central MAP, mm Hg</td>
<td>102±17</td>
</tr>
<tr>
<td>Central PP, mm Hg</td>
<td>38±16</td>
</tr>
<tr>
<td>Forward wave pressure (P1), mm Hg</td>
<td>26±10</td>
</tr>
<tr>
<td>P1g, mm Hg</td>
<td>12±9</td>
</tr>
<tr>
<td>Central augmentation index, %</td>
<td>28±13</td>
</tr>
<tr>
<td>PP amplification, mm Hg</td>
<td>9.4±6.8</td>
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<tr>
<td>Effective reflecting distance, cm</td>
<td>37.0±15.6</td>
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<tr>
<td>Reflected wave transit time, ms</td>
<td>106±13</td>
</tr>
<tr>
<td>Aortic PWV, m/s (n=552)</td>
<td>7.03±2.97</td>
</tr>
<tr>
<td>24-h SBP/DBP, mm Hg (n=487)</td>
<td>119±15/73±10</td>
</tr>
<tr>
<td>24-h PP, mm Hg (n=487)</td>
<td>46±10</td>
</tr>
<tr>
<td>Day SBP/DBP, mm Hg (n=487)</td>
<td>123±14/78±10</td>
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<tr>
<td>Day PP, mm Hg (n=487)</td>
<td>45±9</td>
</tr>
<tr>
<td>Night SBP/DBP, mm Hg (n=487)</td>
<td>112±17/85±11</td>
</tr>
<tr>
<td>Night PP, mm Hg (n=487)</td>
<td>47±11</td>
</tr>
</tbody>
</table>

Table 2. Multivariate Adjusted Relationships Between the Ratio of Urinary Na+/K+ and BPs

<table>
<thead>
<tr>
<th>Urinary Na+/K+ vs</th>
<th>Partial $r^*$</th>
<th>CIs</th>
<th>$P^†$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP without adjustments for MAP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central (n=635)</td>
<td>0.18</td>
<td>0.10 to 0.26</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Conventional (n=635)</td>
<td>0.11</td>
<td>0.03 to 0.18</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>24-h (n=487)</td>
<td>0.14</td>
<td>0.05 to 0.23</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Day (n=487)</td>
<td>0.13</td>
<td>0.04 to 0.22</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Night (n=487)</td>
<td>0.14</td>
<td>0.05 to 0.23</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>PP with adjustments for MAP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central (n=635)</td>
<td>0.14</td>
<td>0.06 to 0.21</td>
<td>0.005</td>
</tr>
<tr>
<td>Conventional (n=635)</td>
<td>0.07</td>
<td>−0.01 to 0.15</td>
<td>0.07</td>
</tr>
<tr>
<td>24-h (n=487)</td>
<td>0.12</td>
<td>0.03 to 0.21</td>
<td>0.005</td>
</tr>
<tr>
<td>Day (n=487)</td>
<td>0.12</td>
<td>0.03 to 0.20</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Night (n=487)</td>
<td>0.12</td>
<td>0.03 to 0.21</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Systolic BP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central (n=635)</td>
<td>0.17</td>
<td>0.09 to 0.24</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Conventional (n=635)</td>
<td>0.12</td>
<td>0.04 to 0.20</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>24-h (n=487)</td>
<td>0.12</td>
<td>0.03 to 0.21</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Day (n=487)</td>
<td>0.11</td>
<td>0.02 to 0.20</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Night (n=487)</td>
<td>0.12</td>
<td>0.03 to 0.20</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central (n=635)</td>
<td>0.07</td>
<td>−0.01 to 0.14</td>
<td>0.09</td>
</tr>
<tr>
<td>Conventional (n=635)</td>
<td>0.07</td>
<td>−0.01 to 0.15</td>
<td>0.08</td>
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<tr>
<td>24-h (n=487)</td>
<td>0.04</td>
<td>−0.05 to 0.13</td>
<td>0.36</td>
</tr>
<tr>
<td>Day (n=487)</td>
<td>0.03</td>
<td>−0.06 to 0.12</td>
<td>0.52</td>
</tr>
<tr>
<td>Night (n=487)</td>
<td>0.04</td>
<td>−0.06 to 0.12</td>
<td>0.44</td>
</tr>
</tbody>
</table>

*Data were determined from regression analysis with adjustments for age, BMI, sex, diabetes mellitus, or an HbA1C >6.1%, regular tobacco intake, regular alcohol intake, and treatment for hypertension.

†$P$ values are further adjusted for nonindependence of family members.

PP and systolic BP, and night PP and systolic BP ($P<0.05$ for all), these relations did not survive adjustments for MAP.

Relationships Between Urinary Indices of Salt Intake and PP Amplification

With adjustments for age, BMI, sex, treatment for hypertension, regular tobacco use, regular alcohol intake, and diabetes mellitus or an HbA1C >6.1%, no independent relationship between urinary Na+/K+ and PP amplification was noted (partial $r=−0.03; P=0.49$).

Relationships Between Urinary Indices of Salt Intake and P1, Paug, Central Augmentation Index, and Their Determinants

With adjustments for potential confounders, urinary Na+/K+ was independently associated with P1g, P1, and central augmentation index (AIc) but not with aortic PWV, reflected wave transit time, or the effective reflecting distance (Table 3). The independent relationships between urinary Na+/K+ and P1g, P1, and AIc were noted both before and after adjustments for central MAP (Table 3). Similar outcomes were noted after adjustments for diastolic BP rather than MAP (data not shown). The independent relationship between urinary Na+/K+ and P1 was no different from the
relationship between urinary Na\(^+\)/K\(^+\) and Alc (P=0.98 for comparison of the partial r values after adjustments for MAP). Sensitivity analysis conducted in participants not receiving diuretic therapy revealed similar outcomes (please see Table S3 and description of these data in the online Data Supplement).

Twenty-four–hour urinary Na\(^+\), 24-hour Na\(^+\) corrected for creatinine concentrations, and 24-hour urinary K\(^+\) excretion rates were not independently associated with P1, Paug, Alc, aortic PWV, reflected wave transit time, effective reflecting distance, or stroke volume (data not shown). Although urinary K\(^+\) corrected for urine creatinine concentrations was modestly associated with P1 (P<0.05), this relationship did not survive adjustments for MAP.

**Survival of the Relationship Between Urinary Na\(^+\)/K\(^+\) and Paug or Alc With Adjustments for Potential Determinants**

To identify the potential factors that contribute toward the relationship between urinary Na\(^+\)/K\(^+\) and Paug or Alc, we evaluated the impact of adjustments for a number of potential factors on these relationships. As indicated in Table 4, adjustments for the aortic PWV, reflected wave transit time, and the effective reflecting distance did not affect the relationship between urinary Na\(^+\)/K\(^+\) and either Paug or Alc. Sensitivity analysis conducted in participants not receiving diuretic therapy revealed similar outcomes (please see Table S4 and description of these data in the online Data Supplement).

**Discussion**

The novel findings of the present study are as follows. In a randomly selected community sample of African ancestry, salt intake as indexed by urinary Na\(^+\)/K\(^+\) was associated with the dynamic (BP) component of BP for central (P=0.005), 24-hour (P=0.005), day (P<0.01), and night (P<0.01) but not in-office measurements independent of steady-state (static) BP (MAP or diastolic BP) and other confounders. The relationship with central PP could be reproduced both in women and in men and in participants not receiving diuretic therapy, the predominant antihypertensive used in this population. The relationship between urinary Na\(^+\)/K\(^+\) and central PP was accounted for by the augmented and the incident pressure waves but not by arterial stiffness (as indexed by aortic PWV), the reflected wave transit time, or the site of wave reflection.

Although there are reports indicating that salt intake is associated with brachial artery PP\(^+\) and that alterations in salt intake modify PP,38,39 in only one study was the relationship demonstrated after adjustments for MAP, and this was sex and age specific. Moreover, in none of these studies\(^+\) was central PP evaluated, and the central hemodynamic mechanisms responsible for this effect were not identified. The present study clearly extends these studies by demonstrating a strong MAP-independent relationship between a urinary index of salt intake and central PP in a relatively large randomly selected population sample in both men and women and the central hemodynamic changes that may explain this relationship. Importantly, these independent relationships were noted for in-office central PP, but the relations with in-office brachial artery PP did not achieve significance. Moreover, although urinary salt excretion was not associated with
in-office PP independent of MAP, it was nevertheless associated with 24-hour, day, and night PP independent of MAP.

The relationship between an index of Na\(^+\) intake and systolic but not diastolic BP in the present study, although in contrast to a number of studies showing relationships of indices of Na\(^+\) intake with both systolic and diastolic BPs,\(^{28,40,41}\) is nevertheless in keeping with data obtained in 4919 participants of the Supplementation en Vitamines et Minéraux Antioxydants Study, where Na\(^+\) intake was independently related to PP but not to other measures of BP.\(^{36}\)

Consistent with the stronger relations noted between urinary Na\(^+\)/K\(^+\) and BP than between 24-hour Na\(^+\) excretion rates and BP in the Intersalt\(^{40}\) and the Scottish Heart\(^{41}\) studies, in the present study urinary Na\(^+\)/K\(^+\) but not 24-hour Na\(^+\) excretion was associated with PP and SBP. Although speculative, this effect could be explained by the relationship that exists between Na\(^+\) intake and K\(^+\) excretion in groups of African ancestry where urinary K\(^+\) excretion decreases on a high-Na\(^+\) diet in salt-sensitive individuals.\(^{42}\) This effect may occur as a consequence of an enhanced activity of the Na-K-2Cl cotransporter in the distal tubule.\(^{43}\) Consequently, it is possible that Na\(^+\) excretion is more likely to be associated with an increase in BP in those individuals whose K\(^+\) excretion decreases, thus indicating the presence of an active Na-K-2Cl cotransporter in response to Na\(^+\) intake.

The mechanism that explains the relationship between urinary Na\(^+\)/K\(^+\) and central PP independent of MAP is through an impact of the forward (or incident) pressure wave, as well as the augmented pressure wave, which is largely determined by wave reflection. In this regard, the reflected wave may be determined by the timing of wave reflection (earlier waves may increase the chance of the forward and reflected wave coinciding), the site of wave reflection (if the site is closer to the central arteries, this may increase the chance that the reflected wave returns earlier), the speed of wave conduction (a greater speed increases the chances of earlier reflection), and the magnitude of wave reflection. In the present study, urinary Na\(^+\)/K\(^+\) was not related to reflective wave transit time, effective reflecting distance, or aortic PWV, and adjustments for these variables failed to modify the relationship between the urinary Na\(^+\)/K\(^+\) and either the augmented (and, hence, possibly the reflected) pressure wave or augmentation index. Hence, the relationship between urinary Na\(^+\)/K\(^+\) and either central PP or the augmented pressure wave or augmentation index may not be explained by changes in the timing or site of wave reflection, nor in the speed of wave conduction. Consequently, we assume that the relationship between urinary Na\(^+\)/K\(^+\) and central PP and the augmented pressure wave is in part mediated by the magnitude of wave reflection, possibly by altering vascular smooth muscle tone in medium-sized arteries, a mechanism proposed recently as mediating age-induced changes in central PP.\(^{21}\)

This has important clinical implications because, unlike age, salt intake is a modifiable risk factor for cardiovascular disease. Hence, if population-wide decreases in salt intake could be achieved, this may considerably reduce cardiovascular disease at a population level by decreasing the dynamic component of central BP.

The lack of relationship between indices of Na\(^+\) and K\(^+\) intake or urinary Na\(^+\)/K\(^+\) and aortic PWV in the present study is in apparent contrast to the decrease in aortic PWV noted in response to a reduction in salt intake in a group of African ancestry, as demonstrated previously.\(^{39}\) However, in that study,\(^{39}\) diastolic BP also decreased in response to a reduction in salt intake, a change that could have contributed to changes in large artery stiffness and, hence, aortic PWV. In contrast, in the present study no relationship between urinary indices of salt intake and diastolic BP was noted.

The limitations of the present study include the cross-sectional nature of the study, and, hence, conclusions regarding causality of the relations cannot be drawn. Moreover, we assessed 24-hour urinary excretion rates only once, and this is subject to inaccuracies in urine collection and does not account for daily variations in salt intake. However, the mean 24-hour urine volumes noted in the present study are higher than those reported on in 23 of 52 sites of the Intersalt Study,\(^{40}\) and the electrolyte excretion rates in the present study are the same as that reported on in an alternative study conducted in the same population group and region in South Africa (South West Township, Johannesburg)\(^{44}\) as the present study and in other “salt-sensitive” populations.\(^{45}\) Moreover, assuming there was a degree of inaccuracy of urine collection, under these circumstances we are likely to have underestimated the impact of salt intake on PP independent of MAP. Despite the convincing independent relations between urinary Na\(^+\)/K\(^+\) but not urinary Na\(^+\) excretion rate and central hemodynamics, the explanation provided for this conundrum that urinary K\(^+\) excretion decreases on a high-Na\(^+\) diet in salt-sensitive individuals\(^{42}\) neverthless remains speculative. This hypothesis requires further substantiation by assessing central hemodynamics and PP while modifying Na\(^+\) and maintaining K\(^+\) intake. It is also important to note that an additional limitation of the present study is that, although the use of a transfer function and radial tonometry accurately estimates central aortic pressures, the reconstructed waveform underestimates the central augmentation pressure and augmentation index.\(^{46}\) Again, however, this is likely to have biased against the outcomes of the present study.

**Perspectives**

Although PP predicts cardiovascular outcomes beyond other measures of BP,\(^{1–14}\) and central PP may be more closely associated with cardiovascular outcomes than peripheral PP,\(^{15–19}\) whether these changes can be modified by alterations in lifestyle is uncertain. In this regard, the most important determinant of central PP is age,\(^{20–22}\) and the factors contributing to age-related changes in central PP are possibly an increase in both the incident and the augmented (or reflected) pressure wave, whereas the contribution from alterations in aortic PWV is controversial.\(^{21}\) In the present study we show that urinary Na\(^+\)/K\(^+\) ratios are independently associated with central PP, as well as peripheral 24-hour, day, and night PP independent of MAP, and that the central PP effect is mediated by both forward and augmented pressure wave effects but not through changes in aortic PWV. Thus, the present study suggests that alterations in salt intake may...
modify cardiovascular risk at a population level through an impact on central and 24-hour peripheral dynamic rather than static BPs.

Acknowledgments
This study would not have been possible without the voluntary collaboration of the participants and the excellent technical assistance of Mthuthuzeli Kiviet, Nomonde Molebatsi, and Nkele Maseko.

Sources of Funding
This work was supported by the Medical Research Council of South Africa, the Circulatory Disorders Research Trust, the Hypertension Society of Southern Africa, the University Research Council of the University of the Witwatersrand, the South African National Foundation for Research (Focus Areas, Women in Research and the Thuthuka Program), and the Carnegie Corporation.

Disclosures
None.

References


Hypertension

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ON-LINE SUPPLEMENT

Relationship Between Urinary Salt Excretion and Pulse Pressure and Central Aortic Hemodynamics Independent of Steady State Pressure in the General Population.

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Running title: Urinary salt excretion and pulse pressure.

This work was supported by the Medical Research Council of South Africa, the Circulatory Disorders Research Trust, The Hypertension Society of Southern Africa, the University Research Council of the University of the Witwatersrand, the South African National Foundation for Research and the Carnegie Corporation.

Michelle Redelinghuys, Gavin R Norton and Angela J Woodiwiss contributed equally to this work.

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Methods

Urinary electrolyte excretion rates continued. The quality of urine samples was determined by constructing regression relations between 24-hour urine creatinine and body weight and 24-hour urine volume and age in gender-specific groups. Based upon the 95% confidence intervals for each group, a 24-hour urine sample was considered acceptable if 24-hour urine creatinine (mmol) was >3.5 and <35 for males and >3.5 and <30 for females. Samples with urine volumes <300 ml/day were also assumed to be incomplete urine collections.

Pulse wave analysis continued. From an inbuilt transfer function an aortic waveform was generated from which central systolic, diastolic and mean arterial BP were derived. The magnitude of the forward wave (P1) was determined as the difference between the inflection point at the end of the first systolic shoulder and central diastolic BP.1-3 The magnitude of the augmented pressure wave (aortic augmentation pressure-Paug) was determined as the difference between central systolic blood pressure and the inflection point at the end of the first systolic shoulder.1-3 Central augmentation index was calculated as a percentage of Paug/central PP. Pulse pressure amplification was calculated as peripheral-central PP. The reflected wave transit time was determined from the beginning of the incident wave to the inflection point at the end of the first systolic shoulder.1-3 The effective reflecting distance was calculated as (reflected wave transit time x PWV)/2.4

Ambulatory BP continued. Monitors were programmed to measure BP at 15-minute intervals from 06:00 to 22:00 and at 30-minute intervals from 22:00 to 06:00. The calibration was checked monthly against a mercury manometer. The cuff size was the same as that used for conventional BP measurements. Participants kept a diary card for the duration of the recordings to note the time of going to bed in the evening and getting up in the morning. Diary cards were employed to identify the actual in-bed and out-of-bed periods. These periods were used to calculate the average in-bed and out-of-bed periods and thus the average transition periods during which BP changes rapidly in most participants. These average transition periods were then eliminated. The remaining periods were considered to be the night or day fixed-clock time periods. Fixed-clock time periods rather than actual in bed and out of bed periods were statistically analysed to ensure that similar day and night time periods were selected for comparisons between individuals. These fixed-clock time periods were identified as ranging from 09:00 to 19:00 h and from 23:00 to 05:00 h respectively. Intra-individual means of the ambulatory measurements were weighted by the time-interval between successive recordings.5

Results

Relationships between urinary indexes of salt intake and steady state or pulsatile BP in participants not receiving diuretic therapy. As shown in Table S2, with adjustments for age, BMI, sex, regular tobacco use, regular alcohol intake, treatment for hypertension and diabetes mellitus or an HbA1c>6.1%, an independent relationship between the ratio of urinary Na⁺-to-K⁺ (urinary Na⁺/K⁺) and either in-office brachial artery, central artery, 24 hour, day or night PP was also noted in participants not receiving diuretic therapy. The independent relationships between urinary Na⁺/K⁺ and central PP in these participants were noted both before and after adjustments for MAP (Table S2). In participants not receiving diuretic
therapy urinary Na⁺/K⁺ was also independently associated with systolic BP, but no independent relations with diastolic BP were noted (Table S2).

**Relationships between urinary indexes of salt intake and P1, Paug, Alc and their determinants in participants not receiving diuretic therapy.** As shown in Table S3, with adjustments for potential confounders, urinary Na⁺/K⁺ was independently associated with Paug, P1, and Alc, but not with aortic PWV, reflected wave transit time, or the effective reflecting distance in participants not receiving diuretic therapy. The independent relationships between urinary Na⁺/K⁺ and Paug, P1 and Alc in participants not receiving diuretic therapy were noted both before and after adjustments for central MAP (Table S3) and similar outcomes were noted after adjustments for diastolic BP rather than MAP (data not shown).

**Survival of the relationship between urinary Na⁺/K⁺ and Paug or Alc with adjustments for potential determinants in participants not receiving diuretic therapy.** As indicated in Table S4, in participants not receiving diuretic therapy, adjustments for the neither aortic PWV, reflected wave transit time, nor the effective reflecting distance affected the relationship between urinary Na⁺/K⁺ and either Paug or Alc.

References
Table S1. Comparison of the general characteristics of study participants with and without quality urine samples.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>With</th>
<th>Without</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=635</td>
<td>n=336</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>65.2</td>
<td>64.8</td>
</tr>
<tr>
<td>Age (years)</td>
<td>45.1±18.4</td>
<td>43.1±18.3</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29.8±8.2</td>
<td>28.8±7.9</td>
</tr>
<tr>
<td>Regular tobacco intake (%)</td>
<td>14.2</td>
<td>13.1</td>
</tr>
<tr>
<td>Regular alcohol intake (%)</td>
<td>23.0</td>
<td>21.5</td>
</tr>
<tr>
<td>% with diabetes mellitus</td>
<td>8.8</td>
<td>7.4</td>
</tr>
<tr>
<td>% with hypertension</td>
<td>43.6</td>
<td>40.6</td>
</tr>
<tr>
<td>% treated for hypertension</td>
<td>24.6</td>
<td>22.4</td>
</tr>
</tbody>
</table>
Table S2. Multivariate adjusted relationships between the ratio of urinary Na\(^+\) and K\(^+\) concentrations (urinary Na\(^+\)/K\(^+\)) and blood pressures in the 500 participants not receiving diuretic therapy.

<table>
<thead>
<tr>
<th>Urinary Na(^+)/K(^+) versus</th>
<th>partial r*</th>
<th>confidence intervals</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulse pressure without adjustments for mean arterial pressure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central (n=500)</td>
<td>0.18</td>
<td>0.10-0.27</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Conventional (n=500)</td>
<td>0.10</td>
<td>0.01-0.18</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>24-hour (n=383)</td>
<td>0.13</td>
<td>0.03-0.23</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Day (n=383)</td>
<td>0.13</td>
<td>0.03-0.23</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Night (n=383)</td>
<td>0.12</td>
<td>0.02-0.22</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Pulse pressure with adjustments for mean arterial pressure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central (n=500)</td>
<td>0.14</td>
<td>0.05-0.23</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Conventional (n=500)</td>
<td>0.05</td>
<td>-0.04-0.13</td>
<td>=0.26</td>
</tr>
<tr>
<td>24-hour (n=383)</td>
<td>0.10</td>
<td>-0.00-0.20</td>
<td>=0.051</td>
</tr>
<tr>
<td>Day (n=383)</td>
<td>0.10</td>
<td>-0.00-0.20</td>
<td>=0.052</td>
</tr>
<tr>
<td>Night (n=383)</td>
<td>0.10</td>
<td>-0.01-0.19</td>
<td>=0.068</td>
</tr>
<tr>
<td><strong>Systolic blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central (n=500)</td>
<td>0.16</td>
<td>0.07-0.25</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Conventional (n=500)</td>
<td>0.09</td>
<td>0.01-0.18</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>24-hour (n=383)</td>
<td>0.11</td>
<td>0.01-0.21</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Day (n=383)</td>
<td>0.09</td>
<td>-0.01-0.19</td>
<td>=0.07</td>
</tr>
<tr>
<td>Night (n=383)</td>
<td>0.10</td>
<td>-0.00-0.19</td>
<td>=0.08</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central (n=500)</td>
<td>0.05</td>
<td>-0.04-0.14</td>
<td>=0.16</td>
</tr>
<tr>
<td>Conventional (n=500)</td>
<td>0.04</td>
<td>-0.05-0.13</td>
<td>=0.30</td>
</tr>
<tr>
<td>24-hour (n=383)</td>
<td>0.03</td>
<td>-0.07-0.13</td>
<td>=0.68</td>
</tr>
<tr>
<td>Day (n=383)</td>
<td>0.01</td>
<td>-0.09-0.11</td>
<td>=0.85</td>
</tr>
<tr>
<td>Night (n=383)</td>
<td>0.02</td>
<td>-0.08-0.12</td>
<td>=0.20</td>
</tr>
</tbody>
</table>

* Determined from regression analysis with adjustments for age, body mass index, sex, diabetes mellitus or an HbA1c>6.1%, regular tobacco intake, regular alcohol intake, and treatment for hypertension. †Probability values are further adjusted for non-independence of family members. Significant p values are indicated in bold type.
Table S3. Multivariate adjusted relationships between the ratio of urinary Na\(^+\) and K\(^+\) concentrations (urinary Na\(^+\)/K\(^+\)) and central hemodynamics in the 500 participants not receiving diuretic therapy.

<table>
<thead>
<tr>
<th>Urinary Na(^+)/K(^+) versus</th>
<th>partial r*</th>
<th>confidence intervals</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Without adjustments for mean arterial pressure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forward wave (P1) (n=500)</td>
<td>0.14</td>
<td>0.06-0.23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Augmentation pressure (Paug) (n=500)</td>
<td>0.19</td>
<td>0.10-0.27</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Central augmentation index (n=500)</td>
<td>0.14</td>
<td>0.05-0.23</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Aortic PWV (n=435)</td>
<td>-0.09</td>
<td>-0.18-0.01</td>
<td>0.13</td>
</tr>
<tr>
<td>ERD (n=435)</td>
<td>-0.09</td>
<td>-0.19-0.00</td>
<td>0.11</td>
</tr>
<tr>
<td>RWTT (n=500)</td>
<td>-0.05</td>
<td>-0.13-0.04</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>With adjustments for mean arterial pressure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forward wave (P1) (n=500)</td>
<td>0.10</td>
<td>0.01-0.19</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Augmentation pressure (Paug) (n=500)</td>
<td>0.15</td>
<td>0.06-0.23</td>
<td>&lt;0.005</td>
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<tr>
<td>Central augmentation index (n=500)</td>
<td>0.11</td>
<td>0.02-0.20</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Aortic PWV (n=435)</td>
<td>-0.13</td>
<td>-0.22-0.03</td>
<td>0.06</td>
</tr>
<tr>
<td>ERD (n=435)</td>
<td>-0.13</td>
<td>-0.22-0.03</td>
<td>0.06</td>
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<tr>
<td>RWTT (n=500)</td>
<td>-0.03</td>
<td>-0.11-0.06</td>
<td>0.58</td>
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</tbody>
</table>

* Determined from regression analysis with adjustments for age, body mass index, sex, diabetes mellitus or an HbA1c>6.1%, regular tobacco intake, regular alcohol intake, and treatment for hypertension. † Probability values are further adjusted for non-independence of family members. PWV, pulse wave velocity; ERD, effective reflecting distance; RWTT, reflective wave transit time. Significant p values are indicated in bold type.
Table S4. Independent relationships between the ratio of urinary Na\(^+\) and K\(^+\) concentrations (urinary Na\(^+\)/K\(^+\)) and aortic augmentation pressure (reflected pressure wave) and aortic (central) augmentation index (AIC) before and after adjustments for potential determinants in the 500 participants not receiving diuretic therapy.

<table>
<thead>
<tr>
<th>Urinary Na(^+)/K(^+) versus</th>
<th>partial r*</th>
<th>confidence intervals</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic augmentation pressure (Paug) with adjustments for</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Covariates as listed below* (n=500)</td>
<td>0.19</td>
<td>0.10-0.27</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Covariates* + aortic PWV (n=435)</td>
<td>0.21</td>
<td>0.12-0.30</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Covariates* + ERD (n=435)</td>
<td>0.20</td>
<td>0.11-0.29</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Covariates* + RWTT (n=500)</td>
<td>0.18</td>
<td>0.10-0.27</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Aortic augmentation index (AIC) with adjustments for</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Covariates as listed below* (n=500)</td>
<td>0.14</td>
<td>0.05-0.23</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Covariates* + aortic PWV (n=435)</td>
<td>0.14</td>
<td>0.04-0.23</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Covariates* + ERD (n=435)</td>
<td>0.13</td>
<td>0.04-0.23</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Covariates* + RWTT (n=500)</td>
<td>0.13</td>
<td>0.05-0.22</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* Determined from regression analysis with adjustments for age, body mass index, sex, diabetes mellitus or an HbA1c>6.1%, regular tobacco intake, regular alcohol intake, and treatment for hypertension. † Probability values are further adjusted for non-independence of family members. PWV, pulse wave velocity; ERD, effective reflecting distance; RWTT, reflective wave transit time.