Do Hypertensive Patients Have a Different Diurnal Pattern of Electrolyte Excretion?

ALAN R. DYER, ROSE STAMLER, RICHARD GRIMM, JEREMIAH STAMLER, REUBEN BERMAN, FLORA C. GOSCH, LINDA ANN EMIDY, PATRICIA ELMER, JOAN FISHMAN, NANCY VAN HEEL, AND GINA CIVINELLI

SUMMARY Studies generally indicate that excretion of sodium, potassium, and water is greater during the day than during the night. To determine whether hypertensive patients exhibit this same pattern of excretion, diurnal variations in excretion of sodium, potassium, creatinine, and water were examined in 107 hypertensive men and women from a clinical trial on control of hypertension by nonpharmacological means — the Hypertension Control Program. Each participant provided two carefully timed 24-hour urine collections divided into daytime and overnight specimens. The median ratios of 24-hour to 8-hour overnight excretion were 2.84, 3.95, 2.99, and 2.77 for sodium, potassium, creatinine, and water, respectively. Thus, more than half of this hypertensive group exhibited a greater rate of sodium and water excretion during sleep than during daytime hours, a reversal of the usual pattern. When the group was subdivided based on age, sex, race, trial randomization group, use of diuretics, and hypertension severity, women had significantly lower ratios of 24-hour to overnight excretion for sodium and water than men and blacks had significantly lower 24-hour to overnight ratios for water and potassium than whites. When the 24-hour to overnight ratios for these hypertensive patients were compared with those for a group of 30 men and women with high-normal blood pressure, those with high-normal blood pressure had significantly larger ratios for sodium and water excretion than the hypertensive group. The results of this study suggest that hypertensive patients may have a different diurnal pattern of sodium and water excretion than normotensive subjects and that further research is needed to clarify this issue. (Hypertension 10: 417-424, 1987)

KEY WORDS • hypertension • electrolytes • diurnal patterns

DIURNAL variations in urinary excretion of sodium, chloride, potassium, and water have long been recognized, with excretion of water and electrolytes generally reaching a maximum some time during midday and a minimum sometime during sleep. A reversal of the usual diurnal cycle of sodium, chloride, and water excretion (i.e., higher excretion at night) has been reported for persons with such diseases as cirrhosis of the liver, congestive heart failure, nephrosis, glomerulonephritis, Cushing's disease, and primary hyperaldosteronism. Some investigators have also reported a reversal of the usual cycle of sodium and chloride excretion in hypertensive persons. Because overnight urine specimens are considered easier to obtain than 24-hour specimens, several investigators have proposed and evaluated use of overnight collections for assessing sodium and potassium intake in studies on the relationships of these electrolytes to blood pressure. In contrast to 24-hour specimens, however, overnight specimens do not provide a direct estimate of the actual intake of sodium and potassium. To estimate actual intake from overnight urine, one must generally convert overnight values to 24-hour values (e.g., by multiplying the overnight val-
In a clinical trial to assess ability to control hypertension by nonpharmacological means, all participants were asked to collect seven carefully timed overnight urine specimens at baseline and annually thereafter for measurement of sodium, potassium, and creatinine. To determine the multipliers needed for estimating 24-hour excretion of these variables from overnight values, a substudy was undertaken to estimate the ratios of 24-hour to overnight excretion. The study was also undertaken to determine if the ratios observed among trial participants were similar for men and women, blacks and whites, and other subgroups. This report presents the results of this substudy and their implications for the use of overnight urine specimens for assessing sodium intake.

**Patients and Methods**

**Patients**

Participants in this study were patients in a clinical trial on nonpharmacological control of hypertension — the Hypertension Control Program (HCP). They were men and women, 41 to 80 years of age, 86.0% white, all previously under effective drug treatment for hypertension. Approximately 90% of persons in the HCP had been participants for 5 or more years in the national cooperative Hypertension Detection and Follow-up Program (HDFP) at its Minneapolis and Chicago centers. The primary purpose of the HCP was to test whether hypertensive patients whose blood pressure had previously been well controlled by pharmacological treatment could discontinue drugs and be maintained at normotensive levels by following a nutritional intervention program. Intervention focused on control of overweight and on reduction of sodium and alcohol intakes. Participants were randomly assigned to one of three study groups: Group 1 having intensive nutritional intervention throughout the trial, with withdrawal of medication 2 months postrandomization; Group 2 having no nutritional intervention, with discontinuation of antihypertensive medication at 2 months; and Group 3 having no nutritional intervention, with continued antihypertensive medication. A total of 189 participants were randomized to the three groups, with approximately twice the number of persons assigned to Group 1 as to each of the two control groups, Groups 2 and 3. The procedures followed in this study were in accord with institutional guidelines for studies involving human subjects.

The primary end point of the HCP was comparison of the percentage able to remain without drug treatment during the entire trial in Group 1 (nutritional intervention group) compared with Group 2 (first control group). The results with respect to this primary end point have been described.33

**Procedures**

Substudy participants provided two carefully timed 24-hour urine collections divided into daytime and overnight periods. Special attention was paid to completeness of all specimens. Detailed instructions on methods for collection for each time period were included in each urine collection kit. Each participant was also verbally instructed until it was evident that collection procedures were clearly understood. For overnight collections the participant was told to completely empty his or her bladder at bedtime and to discard that specimen. The time of this voiding was entered on the urine jar label to mark the beginning of the overnight collection. All urine voided during the night and the first specimen passed on rising in the morning constituted the overnight collection. Time of first voiding in the morning was entered on the overnight collection label as well as on the daytime collection label, since the end of the overnight collection also marked the beginning of the daytime collection. The daytime collection included all urine passed during the day as well as the last specimen passed before bedtime. Time of this specimen was added to the label of the daytime collection to mark its end. On return of the collections to the clinic, participants were carefully questioned on completeness of collection.

Participants were asked to collect all urine passed in 24 hours for 1 weekday and 1 weekend day. Because not everyone was able to follow this procedure and because subsequent analysis indicated that ratios did not differ for the group for weekend days and weekdays, day of the week was not taken into account in subsequent analyses.

Urine aliquots from both the Chicago and Minneapolis HCP Centers were analyzed at the Clinical Research Laboratory of Northwestern Memorial Hospital in Chicago. Sodium and potassium were analyzed by ion-selective electrode, using a Nova I instrument (Newton, MA, USA). Creatinine was analyzed by the Jaffe alkaline picrate method, using a Gilford 203S clinical chemistry analyzer (Oberlin, OH, USA).

For the analysis, daytime excretion values were converted to a 16-hour base by multiplying by 16 and dividing by the actual time in hours of the collection. Overnight values were converted to an 8-hour base in a similar fashion. The 24-hour values were then obtained by summing the adjusted overnight and daytime values. The 24-hour to overnight ratio for each variable was obtained by dividing the sum of the two 24-hour excretions by the sum of the two adjusted overnight excretions. This approach was used to define the relationship between the 8-hour overnight and 24-hour values for each variable, rather than taking the average of the ratio for the 2 days for each participant, because it yielded smaller group standard deviations than were obtained with the average of the ratios for the 2 days. A total of 107 HCP participants provided two complete 24-hour collections for use in these analyses.

**Statistical Analysis**

The 24-hour to 8-hour overnight ratios for each variable are presented for the group as a whole and for the group divided into subgroups based on age, sex, race, randomization, use of diuretics, and severity of hypertension. For this analysis, a person is defined as having more severe hypertension if he or she was receiving...
drug treatment before entry into the HDFP (6–8 years before the start of HCP) or if the diastolic pressure at that time was greater than 100 mm Hg. Because the frequency distributions of the ratios of 24-hour to 8-hour overnight excretion were generally highly skewed, making the arithmetic mean a relatively poor measure of central tendency for these distributions, the median and harmonic mean were used to describe the central tendency of the 24-hour to 8-hour overnight ratio for each variable. (The harmonic mean is obtained by computing the average of the ratio of 8-hour overnight to 24-hour values and then dividing that average into 1.0. Because the harmonic mean is calculated from the ratio of 8-hour to 24-hour values, rather than from the ratio of 24-hour to 8-hour values, it is intuitively appealing as an alternative to the arithmetic mean, while at the same time being less susceptible to the influences of outlying values.) For the total group, both medians and harmonic means are presented, while for subgroups only harmonic means are given. For the total group, t tests were used to determine if harmonic means were significantly different from 3.0. Means were compared with 3.0, because a ratio of 3.0 indicates an essentially constant excretion over the 24 hours of collection, with one third excreted in the 8 overnight hours. For subgroups, harmonic means were compared for each pair of subgroups using a two-sample t test.

All tests were two-sided, and results were considered statistically significant at a p level below 0.05. As part of this substudy 30 men and women (age range, 36–49 years) participating in a separate ongoing trial on the primary prevention of hypertension (PPH) also provided two carefully timed 24-hour urine collections divided into 16-hour daytime and 8-hour overnight specimens. PPH participants were normotensive and excreted sodium, potassium, and creatinine than men. Those over 60 years of age also excreted significantly less sodium and creatinine than those 60 years of age or younger. There were no significant differences in water or potassium excretion for the two age groups. Blacks excreted significantly less potassium than whites in both daytime and 24-hour collections. There were no significant differences between blacks and whites for sodium or water. Participants in Group 1, as expected, excreted significantly less sodium than control group participants for all time periods. These subgroups did not differ significantly for the other three variables. None of the four variables differed significantly in any period by diuretic use or severity of hypertension.

Table 2 presents the median, harmonic mean, and standard deviation of the 24-hour to 8-hour overnight ratio for each urinary variable as well as results of tests of hypotheses that mean ratios are equal to 3.0. For both sodium and water, the harmonic mean was significantly less than 3.0. Thus, on average, this group showed higher rates of sodium and water excretion during sleep than during waking hours, a reversal of the usual diurnal pattern. The ratios for sodium and water were also highly correlated within individuals with a rank-order correlation of 0.66. The harmonic mean for potassium was significantly greater than 3.0, indicating that on average an excretion that conforms to the usual diurnal pattern for potassium (i.e., a higher rate of excretion during the day than during the night).
The harmonic mean of the ratio for each variable is given in Table 3 for the various subgroups. For sodium, potassium, creatinine, and urine volume, the means did not differ significantly by age, randomization group, diuretic use, or severity of hypertension. For sodium and urine volume, the means were significantly different for men and women, with women having lower ratios on average than men. For urine volume and potassium, the means were significantly different for blacks and whites, with blacks having lower ratios on average than whites. The ratio for sodium in blacks was also less than that in whites, but the difference was not statistically significant.

Because the lower sodium excretion ratio observed among hypertensive women in this study might be related to their lower sodium output, the ratios for sodium were examined further in relation to the 24-hour output of sodium. In these analyses, which were sex-specific, the ratios were compared for those above and below the median for 24-hour excretion of sodium. In both men and women, the ratios did not differ significantly for the two levels of sodium excretion.

**Primary Prevention Study**

Table 4 presents the medians, harmonic means, and standard deviations of the ratios for the four variables for the 30 PPH participants, along with results of tests of hypotheses that harmonic means are equal to 3.0. As in HCP participants, the mean for potassium was significantly greater than 3.0, while that for creatinine did not differ significantly from 3.0. For both water and sodium, while the means were greater than 3.0, they did not differ significantly from 3.0, as in the HCP patients. The harmonic means for sodium, potassium, and urine volume were all significantly different for this group of 30 compared with values for the 107 HCP participants ($p<0.01$ for sodium and urine volume, $p<0.05$ for potassium). The medians were also significantly different for sodium and urine volume ($p<0.05$), but not for potassium (Figure 1). The age ranges for these two groups were quite different: HCP participants ranged in age from 41 to 80 years, with an average of 60 years, and PPH participants ranged in age from 36 to 49 years, with an average of 42 years. This difference in age does not appear to be a concern, however, since the ratios did not differ significantly by age among HCP participants (see Table 3). In addition, only four of the 30 PPH participants were women. When the comparisons between the two study groups were restricted to the 93 men in the two groups, the mean ratios for sodium, potassium, and water continued to be significantly different.

**Discussion**

The present report examined diurnal variation in urinary excretion of sodium, potassium, creatinine, and water in a group of 107 hypertensive participants from a clinical trial on control of hypertension by non-pharmacological means. Each participant in this substudy provided two carefully timed 24-hour urine collections divided into daytime and overnight specimens. The median ratios of 24-hour to overnight excretion, standardized to 8 hours, were 2.84, 3.95, 2.99, and 2.77 for sodium, potassium, creatinine, and water, respectively. For sodium and water, the harmonic means did not differ significantly by age, randomization group, diuretic use, or severity of hypertension. However, for potassium, the harmonic means were significantly different for black and white hypertensive participants, with blacks having lower ratios on average than whites. The ratio for sodium in blacks was also less than that in whites, but the difference was not statistically significant.

**Table 3. Comparison of Mean Ratios of 24-Hour to 8-Hour Overnight Urine Volume and Excretion of Sodium, Potassium, and Creatinine by Age, Sex, Race, Randomization Group, Diuretic Use, and Severity of Hypertension in 107 Participants from the Hypertension Control Program**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Urine volume</th>
<th>Sodium</th>
<th>Potassium</th>
<th>Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≤ 60 yr (n = 51)</td>
<td>2.77</td>
<td>2.79</td>
<td>3.89</td>
<td>2.97</td>
</tr>
<tr>
<td>Age &gt; 60 yr (n = 56)</td>
<td>2.84</td>
<td>2.82</td>
<td>3.78</td>
<td>3.03</td>
</tr>
<tr>
<td>Male (n = 67)</td>
<td>2.92</td>
<td>2.99</td>
<td>3.85</td>
<td>2.98</td>
</tr>
<tr>
<td>Female (n = 40)</td>
<td>2.62*</td>
<td>2.55†</td>
<td>3.79</td>
<td>3.03</td>
</tr>
<tr>
<td>White (n = 92)</td>
<td>2.89</td>
<td>2.87</td>
<td>3.91</td>
<td>3.02</td>
</tr>
<tr>
<td>Black (n = 11)</td>
<td>2.38*</td>
<td>2.54</td>
<td>3.27*</td>
<td>2.84</td>
</tr>
<tr>
<td>Group 1 (n = 49)</td>
<td>2.75</td>
<td>2.67</td>
<td>3.79</td>
<td>2.97</td>
</tr>
<tr>
<td>Groups 2 and 3 (n = 58)</td>
<td>2.85</td>
<td>2.94</td>
<td>3.87</td>
<td>3.03</td>
</tr>
<tr>
<td>Diuretics (n = 68)</td>
<td>2.81</td>
<td>2.88</td>
<td>3.80</td>
<td>3.04</td>
</tr>
<tr>
<td>No diuretics (n = 39)</td>
<td>2.78</td>
<td>2.69</td>
<td>3.88</td>
<td>2.93</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More severe (n = 52)</td>
<td>2.87</td>
<td>2.83</td>
<td>3.78</td>
<td>3.04</td>
</tr>
<tr>
<td>Less severe (n = 55)</td>
<td>2.74</td>
<td>2.79</td>
<td>3.88</td>
<td>2.96</td>
</tr>
</tbody>
</table>

* $p<0.05$, † $p<0.01$, compared with value in respective counterpart. 
‡ Four persons of other races were excluded.
monic mean was significantly less than 3.0, while that for potassium was significantly greater than 3.0. Thus, for this hypertensive group, there was on average a higher rate of sodium and water excretion at night than during the day, a reversal of the usual pattern. Potassium excretion was consistent with the usual pattern of a higher daytime rate. When the group was subdivided based on age, sex, race, trial randomization, use of diuretics, and severity of hypertension, women had on average higher relative nighttime excretions of sodium and water than men and blacks had higher relative nighttime excretions of potassium and water than whites. When these ratios were compared with the ratios for 30 men and women with high-normal blood pressure, normotensive subjects had on average higher ratios for sodium and water excretion than hypertensive patients (i.e., the normotensive subjects exhibited the expected higher rate of excretion during the day).

For decades excess sodium intake has been implicated in the pathogenesis of high blood pressure.\textsuperscript{31-40} Data from epidemiological, clinical, and animal experimental studies all indicate a direct causal association between excess salt intake and hypertension. Several investigators suggest that hypertension is the result of an inability of the kidney to excrete salt and water normally.\textsuperscript{37, 42, 46-51} It is hypothesized that the development of chronic blood pressure elevation results from the need of the kidneys to increase urine volume and sodium excretion — in the presence of habitual high sodium intake — to maintain homeostasis of the extracellular fluid volume.\textsuperscript{42, 45, 47-49}

Diurnal variations in excretion of sodium, chloride, potassium, and water have been observed in many studies.\textsuperscript{1-16} Creatinine excretion has generally been reported to be fairly constant over the course of 24 hours.\textsuperscript{7, 11} On average, creatinine excretion was constant over the 24 hours in the hypertensive patients and subjects with high-normal blood pressure reported on here. There was, however, a good deal of interindividual variation in the ratio of 24-hour to overnight excretion of creatinine. Water and electrolyte excretion in normal persons generally reaches a maximum sometime around midday, with a minimum toward the end of the sleep period.\textsuperscript{5, 6, 13, 14, 16} Previous studies have suggested that the daytime excretion rate exceeds the nighttime excretion rate by 50 to 100%.\textsuperscript{15} A reversal of the diurnal cycle in the excretion of sodium, chloride, and water has been reported for several diseases including hypertension.\textsuperscript{10, 15-25} In a study of 12 hypertensive patients, Vagnucci and Wesson\textsuperscript{17} found that the maximal chloride excretion occurred during the daytime in seven persons and during sleep in five. There was no reversal in the diurnal pattern of potassium excretion.

To our knowledge, no other studies in the literature have computed 24-hour to overnight ratios for excretion of sodium, potassium, and creatinine in the manner reported here. Several studies, however, have proposed or evaluated use of overnight urine collections for assessment of sodium intake.\textsuperscript{16, 26-31} From six of these studies,\textsuperscript{26-31} it is possible to obtain estimates of the ratio of 24-hour to overnight excretion of sodium and potassium by computing the ratio of the reported means for 24-hour and overnight collections. To make these results comparable with those of the present study, it is necessary, where possible, to correct daytime excretions to 16 hours and overnight excretions to 8 hours.

Table 5 presents the ratios of mean 24-hour to mean overnight excretion of sodium and potassium for the 107 hypertensive patients and the 30 high-normal subjects described in the present report and for the six studies in the literature for which such data are available.\textsuperscript{26-31} The table also gives the sample size, the general blood pressure level of study participants, the age range of the subjects, and other pertinent study features. The table also indicates whether the ratios were adjusted for time of collection. In two of the studies,\textsuperscript{26, 31} ratios were adjusted based on average length of daytime and overnight collections, and in a third study,\textsuperscript{56} ratios were adjusted by the difference between 3.0 and the reported ratio of mean 24-hour to mean overnight creatinine. No data were available to adjust the ratios for three of the studies.\textsuperscript{27, 28, 50} For three studies,\textsuperscript{29-30} since data were provided for more than one level of sodium intake, ratios are given for each level. In addition, for Luft et al.\textsuperscript{46} the means for each diet were computed by taking the average urinary output over 7 days.

For the hypertensive patients of the present study, the estimates of the ratios of 24-hour to overnight excretion of sodium and potassium derived from the ratios of mean 24-hour to mean 8-hour overnight excretion are quite close to the medians of the individual ratios reported in Table 2, suggesting that the ratios computed for the other studies should provide good approximations to the actual average 24-hour to overnight ratios in those studies. The ratio for sodium for the HCP participants is consistent with those studies that have noted a reversal of the diurnal cycle of sodium excretion in hypertensive patients.\textsuperscript{17, 22-25} Both the sodium and potassium ratios for these hypertensive patients appear lower than those for the high-normal subjects in the present study, the borderline hypertensive subjects studied by Tuomilehto et al.,\textsuperscript{31} and the subjects — who generally appear to be normotensive — studied by the other investigators.\textsuperscript{26-30}

Only one of these six studies provided data on urine volume from which a ratio of 24-hour to overnight excretion of water could be estimated.\textsuperscript{28} For the 52 student nurses studied by Watson and Langford,\textsuperscript{26} the ratio of mean 24-hour to mean overnight excretion was 3.57, which is higher than the ratio of 2.87 for the hypertensive patients in the present study and slightly higher than the ratio of 3.39 for the high-normal subjects.

Given the generally older ages of the participants in this study, it is not clear whether the reversal of the diurnal pattern of sodium and water excretion observed in these hypertensive patients is associated with hypertension per se or reflects a deterioration of renal functional capacity with age, since age reportedly modifies
a number of factors that determine renal sodium handling, including glomerular filtration rate and renal hemodynamics. Furthermore, Luft et al. reported that persons over 40 years of age had a lower ratio of mean 24-hour to mean overnight excretion of sodium than did those under 40 years of age. For 30 men and women under 40 years of age, ratios on two diets were 4.35 and 4.54, respectively, after correction for creatinine excretion, while for 13 persons over 40 years of age the ratios were 3.23 and 3.40, ratios similar to those for persons with high-normal diastolic pressures in the present report and the borderline hypertensive subjects described by Tuomilehto et al. In the study by Luft et al., mean systolic and diastolic blood pressures were similar for the two age groups. However, in regard to this possibly confounding factor of age, the ratios for sodium for the hypertensive patients in the present study did not differ significantly when the sample was divided into those over 60 years of age and those 60 years of age or younger.

Another possible explanation of our findings is that long-term use of diuretics alters the diurnal pattern of sodium excretion. Participants in this study were hypertensive patients whose blood pressure had been well controlled for at least 5 years as part of the HDFP. Most of these participants had received diuretics during the HDFP, and most were receiving diuretics at the start of the HCP. Since the ratio of 24-hour to overnight excretion of sodium did not differ on average for those taking diuretics at the time of the collections compared with those not taking diuretics, this seems an unlikely explanation of the observed results. However, one cannot rule out the possibility that long-term diuretic use permanently alters the diurnal pattern of sodium excretion.

The results of this study have serious implications for the use of overnight urine collections in the estimation of sodium intake. If hypertensive and normotensive persons differ on average in the ratio of 24-hour to overnight excretion of sodium, as suggested by the present results, then the use of overnight urine collections in studies on the relationship between sodium and blood pressure would tend to produce an overestimate of the true association. Overnight urine collections would still, however, be a reasonable alternative to 24-hour collections in dietary intervention studies as a means for assessing individual adherence to a low sodium diet.

The findings of this study indicate that further research is needed to clarify whether hypertensive and normotensive persons of the same age have a different pattern of sodium excretion and, if so, whether a reversed or flattened diurnal pattern of excretion is implicated in the pathogenesis of hypertension.

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