Sodium Sensitivity

Detecting Sodium-Sensitivity in Hypertensive Patients
Information From 24-Hour Ambulatory Blood Pressure Monitoring

Paolo Castiglioni, Gianfranco Parati, Lorenzo Brambilla, Valerio Brambilla, Massimo Gualerzi, Marco Di Rienzo, Paolo Coruzzi

See Editorial Commentary, pp 156–157

Abstract—Sodium sensitivity is an important cardiovascular risk factor for which a diagnosis requires a time-consuming protocol, the implementation of which is often challenging for patients and physicians. Our aim was to assess the reliability of an easier approach based on data from 24-hour ambulatory blood pressure monitoring performed in hypertensive subjects during daily-life conditions and habitual diet. We enrolled 46 mild to moderate hypertensive subjects who underwent 24-hour ambulatory blood pressure monitoring during usual sodium intake. Patients were divided into 3 classes of sodium sensitivity risk on the basis of ambulatory blood pressure monitoring data: low risk if dippers and a 24-hour heart rate ≤70 bpm; high risk if nondippers and a 24-hour heart rate of >70 bpm; intermediate risk with the remaining combinations (dippers with heart rate >70 bpm or nondippers with heart rate ≤70 bpm). Then patients underwent a traditional sodium sensitivity test for the dichotomous classification as sodium sensitive or sodium resistant and for evaluating the sodium sensitivity index. Prevalence of sodium-sensitive patients and mean value of sodium sensitivity index were calculated in the 3 risk classes. The sodium sensitivity index markedly and significantly increased from the low-risk to the high-risk class, being equal to 19.9±14.4, 37.8±8.3, and 68.3±17.0 mm Hg/(mol/day) in the low-risk, intermediate-risk, and high-risk classes, respectively (M±SEM). Also, the prevalence of sodium-sensitive patients increased significantly from the low-risk class (25%) to the intermediate-risk (40%) and high-risk (70%) classes. Thus, performance of 24-hour ambulatory blood pressure monitoring in daily-life conditions and habitual diet may give useful information on the sodium sensitivity condition of hypertensive subjects in an easier manner than with the traditional sodium sensitivity test approach. (Hypertension. 2011;57:180-185.)

Key Words: salt sensitivity ■ hypertension ■ ambulatory blood pressure monitoring

The stratification of cardiovascular risk in patients with arterial hypertension can be more accurately performed through use of 24-hour ambulatory blood pressure monitoring (ABPM) data than by focusing on isolated office blood pressure readings. Because the cardiovascular risk of hypertensive patients increases in presence of sodium sensitivity at any blood pressure level, it would be important to also identify the presence of a sodium sensitivity condition in these patients.

Unlike the diagnosis of hypertension, the evaluation of a sodium sensitivity status requires a time-consuming protocol that is often challenging for both patients and physicians, its confirmation depending on blood pressure changes significantly greater at the end of a high-salt diet (over 1 week) than at the end of a low-salt diet (over 1 additional week). The emerging evidence of a relationship between sensitivity to sodium and alterations of the cardiovascular control mechanisms influencing the 24-hour profile of blood pressure suggests that information on the sodium sensitivity condition of a given hypertensive subject could be indirectly derived from 24-hour ABPM data, possibly without need to perform the sodium sensitivity test.

In this context, 2 ABPM parameters appear particularly promising, one of which is the blood pressure “dipping pattern” at night because loss of such a dipping pattern has been observed in sodium-sensitive hypertensive subjects during a high-sodium diet. This allows speculation that an altered dipping pattern could be a marker of a sodium sensitivity condition even when observed during everyday diet.

The other parameter is mean heart rate (HR) computed over the 24 hours. In fact, during sodium load, HR increases proportionally to the degree of sodium sensitivity in hypertensive patients, suggesting an altered cardiac autonomic regulation in this condition. Changes in both HR and sodium

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From the Don C. Gnocchi Foundation (P.Ca., L.B., V.B., M.G., M.D., P.Co.), Milan, Italy; Department of Clinical Medicine and Prevention (G.P.), University of Milano-Bicocca, Milan, Italy; Department of Cardiology (G.P.), Istituto Auxologico Italiano, Milan, Italy; and Department of Clinical Sciences (P.Co.), University of Parma, Parma, Italy.

Correspondence to Gianfranco Parati, MD, Department of Cardiology, Ospedale San Luca, Istituto Auxologico Italiano via Spagnaletto 3, 20149 Milan, Italy. E-mail gianfranco.parati@unimib.it

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sensitivity have been also described in subjects with metabolic syndrome and insulin resistance.\textsuperscript{6–8} In particular, a 24-hour mean HR >70 bpm has been reported in a population with elevated body mass index, a condition clearly associated not only with insulin resistance\textsuperscript{9} but also with salt sensitivity. All of these findings also contribute to suggest that an elevated 24-hour mean HR might represent a marker of a sodium sensitivity condition.

The aim of this work was thus to explore whether identification of a condition of cardiovascular risk associated with sodium sensitivity can be obtained through analysis of parameters derived from routine 24-hour ABPM performed in hypertensive patients following their usual diet (ie, through a much easier approach than the implementation of classic sodium sensitivity tests). For this purpose, we studied a population of mild to moderate hypertensive subjects in whom both a 24-hour ABPM and a conventional sodium sensitivity test were performed. Following the suggestions provided by previous studies, we focused our attention on the blood pressure dipping pattern at night and on the mean 24-hour HR level. However, we also explored whether other ABPM parameters might provide information on the sodium sensitivity condition.

**Methods**

The experimental protocol was approved by the ethics committee of our institution (Don Gnocchi Foundation). Patients gave their written informed consent after having received a detailed explanation of the study procedures and purposes.

**Subjects**

The study included 46 outpatients (30 males) selected among those who had been consecutively referred to our cardiology clinic with a diagnosis of hypertension and who fulfilled our inclusion criteria. Patients had never treated mild or moderate uncomplicated essential hypertension, with repeated office auscultatory diastolic blood pressure (DBP) measurements, in the seated position, between 95 and 109 mm Hg. During all office visits, conventional measurements of blood pressure were performed in sitting and standing positions according to the recommendations of the European Society of Hypertension.\textsuperscript{10} No patient had orthostatic hypotension based on data from history and from blood pressure measurements at the time of patient recruitment. Patients had neither history nor physical or laboratory evidence of cardiovascular disease. They were free from target organ damage at the heart and vascular level, as assessed by echocardiography and by renal vascular Doppler ultrasound examination. Renal disease was excluded by the finding of normal urinalysis, creatinine clearance assessment, and echographic evaluation. Diabetes was also excluded. Subjects under concomitant treatment with estrogens or nonsteroidal anti-inflammatory agents, or with drugs known to influence salt, potassium, calcium, water, hemodynamic, or neural regulation, were excluded. Subjects were nonsmokers with a body mass index between 16.9 and 31 kg/m\textsuperscript{2}, were between 28 and 62 years of age, had a sedentary lifestyle, and had no history of excessive alcohol consumption. Screening of patients for excluding the presence of sleep-disordered breathing was accomplished by administering the Epworth sleepiness scale test.\textsuperscript{11}

**Blood Pressure Monitoring**

Before starting the controlled sodium diets, 24-hour ABPM was performed with a validated oscillometric automated device (Spacelabs model 90207). The inflatable cuff was wrapped around the nondominant arm after excluding between-arm differences in blood pressure of >5 mm Hg. The local accuracy of the oscillometric device was assessed in each patient by comparison with 3 auscultatory readings simultaneously taken from the same arm with a Y tube connection between the Spacelabs device pump and a mercury column. The Spacelabs device was programmed to provide one measure of systolic blood pressure (SBP), DBP, mean arterial pressure (MAP), and HR every 15 minutes during the day and every 30 minutes at night. Patients were asked to carefully fill in a diary of their main activities during ABPM, including information on the occurrence of daytime naps and on whether and how many times they woke up or got up at night.

Pulse pressure (PP) was computed as SBP-DBP difference. Values were averaged over the whole 24-hour recording and, separately, over daytime (8 AM to 10 PM) and nighttime (0:00 to 6 AM) periods, defined based on the narrow fixed interval approach.\textsuperscript{12} The standard deviation (SD) of 24-hour HR values was calculated in each subject as index of long-term HR variability. To obtain indexes of long-term blood pressure variability devoid of the contribution of the nocturnal fall of blood pressure, the SDs of SBP and DBP were calculated in a weighted fashion (wSD).\textsuperscript{13} (ie, as the mean of day [SD\textsubscript{D}] and night [SD\textsubscript{N}] values of SD, corrected for the number of hours included in each of these subperiods). Because daytime and nighttime periods lasted 14 and 6 hours, respectively, the following formula was used to calculate weighted SD of both SBP (SBP\textsubscript{wSD}) and DBP (DBP\textsubscript{wSD}):

\[
\text{wSD} = (14/20) \times SD_D + (6/20) \times SD_N.
\]

The nocturnal fall of MAP (MAP\textsubscript{NF}) was calculated as MAP\textsubscript{NF} = (MAP\textsubscript{P} - MAP\textsubscript{NF})/MAP\textsubscript{P}, where MAP\textsubscript{P} and MAP\textsubscript{NF} are daytime and nighttime mean values of MAP. This quantity was also calculated for SBP (SBP\textsubscript{NF}) and DBP (DBP\textsubscript{NF}). Ratios between nighttime and daytime mean values of SBP (SBP\textsubscript{NF/D}), DBP (DBP\textsubscript{NF/D}), and PP (PP\textsubscript{NF/D}) were also calculated. Like the nocturnal fall of blood pressure, SBP\textsubscript{NF/D}, DBP\textsubscript{NF/D}, and PP\textsubscript{NF/D} also describe the dipping pattern at night. In particular, SBP\textsubscript{NF/D} and DBP\textsubscript{NF/D} have been reported to have prognostic value in hypertensive patients.\textsuperscript{14}

**Classes of Salt Sensitivity Risk From ABPM**

Following standard criteria,\textsuperscript{4} patients were classified as “dippers” when MAP\textsubscript{NF} >10% and “nondippers” otherwise. We made use of MAP, rather than SBP or DBP, for 2 reasons. First, MAP is directly measured by oscillometric devices, whereas SBP and DBP are computed, making MAP preferable for classifying the dipping status.\textsuperscript{15} Second, most of the literature on sodium sensitivity quantifies the dipping phenomenon in terms of percentage decrease of MAP.\textsuperscript{4} However, it should also be considered that other criteria have been proposed for dichotomously classifying subjects in dippers and nondippers. A popular one is based on defining as nondippers those subjects with SBP\textsubscript{NF} <10%.\textsuperscript{16} Because dipping classification may vary largely with the selected criteria,\textsuperscript{17} we also evaluated whether a classification based on SBP\textsubscript{NF} rather than on MAP\textsubscript{NF} may influence the results.

The same subjects were also classified as high HR whenever their mean HR over the 24 hours (HR\textsubscript{24H}) was >70 bpm and as low HR otherwise. The HR cutoff was set at 70 bpm on the basis of the reported differences in HR\textsubscript{24H} between subjects with and without metabolic syndrome.\textsuperscript{8} These classification criteria, based on ABPM data only, allowed us to define 3 subgroups of patients in whom we hypothesize a different degree of sodium sensitivity: a group at low risk for sodium sensitivity (SSLR), including patients classified both as dippers and low HR at 24-hour ABPM; a group at high risk of sodium sensitivity (SSHR), including patients classified both as nondippers and high HR at ABPM; and a group at intermediate sodium sensitivity risk, including patients belonging neither to SSLR nor to SSSHR groups because they were classified as dippers and high HR or as nondippers and low HR at ABPM.

**Assessment of Salt Sensitivity**

After the 24-hour ABPM, patients followed a high-sodium (200 mmol NaCl per day) and a low-sodium (30 mmol NaCl per day) diet, each for 1 week, in randomized order. The 24-hour urinary sodium excretion was quantified on the last day of each diet week. This assessment was also used to verify the patients’ compliance with the dietary regimen. Patients were also asked to follow a diet with controlled caloric content. Compliance with caloric intake was
assessed through repeated phone calls, aimed at ensuring that patients were indeed following the prescribed dietary regimen. After overnight fasting, at 7:30 AM on days 7 and 14 (ie, at the end of each weekly diet period), patients came to our laboratory, where they were asked to remain quietly seated. After a 30-minute period of familiarization with the environment, blood pressure was measured at 15-minute intervals, over the following 2 hours, from 8 to 10 AM, by the Spacelabs 90207 automated device. Patients were diagnosed as sodium sensitive (SS) whenever the change in brachial oscillometric MAP between the high-sodium and the low-sodium diet periods (ΔMAP) was >8 mm Hg and as sodium resistant (SR) otherwise.4

The sodium sensitivity degree was also evaluated on a continuous basis through use of the sodium sensitivity index (SSI). The SSI was calculated as the ratio between ΔMAP, in mm Hg, and the difference between urinary sodium excretion rates (ΔUNaV) in the high-sodium and low-sodium diet periods, expressed in mmol/day. The ratio was multiplied by a factor of 1000 to facilitate readability of results;18 SSI=ΔMAP/ΔUNaV×1000 [mm Hg/(mol/day)].

Statistical Analysis
Differences between SS and SR groups in mean values of ABPM parameters and of anthropometric variables were tested by the nonparametric Mann–Whitney U test,19 whereas differences in gender and in prevalence of dipper subjects were tested by the z test. Significance of differences in SSI among the 3 classes of sodium sensitivity was assessed by the median test and between the SSLR class and each of the other 2 risk classes by the Mann–Whitney U test. Differences in the prevalence of SS subjects and between urinary sodium excretion rates (UNaV) in the high-sodium and low-sodium diet periods (ΔUNaV) was >8 mmol/day and as sodium resistant (SR) otherwise.4

Table 1. Demographic and Sodium Sensitivity Test Data in the Study Population Separately for SS and SR Subjects: Mean (SD)

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>SR</th>
<th>SS</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (males/females)</td>
<td>20/7</td>
<td>10/9</td>
<td>0.13</td>
</tr>
<tr>
<td>Age (y)</td>
<td>45 (7)</td>
<td>45 (8)</td>
<td>0.89</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.7 (2.5)</td>
<td>24.2 (2.3)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sodium sensitivity test</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>SSI (mm Hg/[mol/day])</td>
<td>8 (36)</td>
<td>81 (36)</td>
<td>&lt;10⁻⁴</td>
</tr>
<tr>
<td>MAP after high-sodium diet (mm Hg)</td>
<td>103.4 (8.7)</td>
<td>108.6 (9.2)</td>
<td>0.06</td>
</tr>
<tr>
<td>MAP after low-sodium diet (mm Hg)</td>
<td>101.9 (8.8)</td>
<td>96.0 (9.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>UNaV after high-sodium diet (mmol/day)</td>
<td>219 (71)</td>
<td>206 (46)</td>
<td>0.77</td>
</tr>
<tr>
<td>UNaV after low-sodium diet (mmol/day)</td>
<td>42 (18)</td>
<td>38 (16)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Table 2. ABPM Data in the Study Population Separately for SS and SR Subjects: Mean (SD)

<table>
<thead>
<tr>
<th>ABPM Parameters</th>
<th>SR</th>
<th>SS</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR24H (bpm)</td>
<td>69.1 (7.6)</td>
<td>72.4 (6.4)</td>
<td>0.12</td>
</tr>
<tr>
<td>SBP24H (mm Hg)</td>
<td>137 (11)</td>
<td>137 (13)</td>
<td>0.86</td>
</tr>
<tr>
<td>DBP24H (mm Hg)</td>
<td>88 (8)</td>
<td>89 (9)</td>
<td>0.84</td>
</tr>
<tr>
<td>PP24H (mm Hg)</td>
<td>49 (6)</td>
<td>48 (6)</td>
<td>0.60</td>
</tr>
<tr>
<td>HRSD (bpm)</td>
<td>10.6 (2.9)</td>
<td>11.6 (3.2)</td>
<td>0.13</td>
</tr>
<tr>
<td>SBPwSD (mm Hg)</td>
<td>10.8 (2.0)</td>
<td>11.6 (2.8)</td>
<td>0.45</td>
</tr>
<tr>
<td>DBPwSD (mm Hg)</td>
<td>9.3 (1.9)</td>
<td>10.1 (2.4)</td>
<td>0.32</td>
</tr>
<tr>
<td>MAPwSD (%)</td>
<td>15.5 (5.6)</td>
<td>12.5 (5.2)</td>
<td>0.06</td>
</tr>
<tr>
<td>Prevalence of dippers (MAPNF &gt;10%)</td>
<td>78% (8%)</td>
<td>53% (11%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Prevalence of extreme dippers (MAPNF &gt;20%)</td>
<td>19% (7%)</td>
<td>17% (7%)</td>
<td>0.45</td>
</tr>
<tr>
<td>PP24H</td>
<td>0.91 (0.07)</td>
<td>0.97 (0.05)</td>
<td>0.008*</td>
</tr>
</tbody>
</table>

Table 3. Spearman Rank Correlation Coefficient, R, With Corresponding Level of Statistical Significance (P), Between SSI and ABPM Parameters

<table>
<thead>
<tr>
<th>ABPM Parameters</th>
<th>R</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR24H</td>
<td>0.32</td>
<td>0.03</td>
</tr>
<tr>
<td>SBPwSD</td>
<td>0.30</td>
<td>0.04</td>
</tr>
<tr>
<td>SBPwSD</td>
<td>0.30</td>
<td>0.04</td>
</tr>
<tr>
<td>PPwSD</td>
<td>0.28</td>
<td>0.06</td>
</tr>
<tr>
<td>MAPwSD</td>
<td>-0.23</td>
<td>0.13</td>
</tr>
<tr>
<td>PP24H</td>
<td>0.18</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Table 1. They were of similar age and similar body mass index. The prevalence of males tended to be higher in the SR group but not significantly. Table 2 compares ABPM parameters in the SR and SS groups. SR and SS patients had the same values of ambulatory SBP, DBP, and PP over the 24 hours. The nocturnal fall of blood pressure tended to be greater in the SR group, but it was differently quantified by the 3 blood pressure parameters, being larger for DBP than for MAPNF or SBPwSD. However, only for SBPwSD it was significantly different between SS and SR patients. The prevalence of nocturnal blood pressure dippers tended to be higher in the SR group, whereas the mean 24-hour HR tended to be lower; however, these differences fell short of statistical significance. In contrast, night:day ratios of SBP and PP were significantly lower in SR subjects.

Correlations between ABPM parameters and the index of sodium sensitivity are shown in Table 3. The strongest correlations were with 24-hour SBP, DBP, and PP. HR24H correlated with SBPwSD, DBPwSD, and PPwSD. "wSD" indicates weighted SD values, being larger for DBPwSD than for MAPNF or SBPwSD. However, only for SBPwSD was it significantly different between SS and SR patients. The prevalence of nocturnal blood pressure dippers tended to be higher in the SR group, whereas the mean 24-hour HR tended to be lower; however, these differences fell short of statistical significance. In contrast, night:day ratios of SBP and PP were significantly lower in SR subjects.
of sodium sensitivity, as defined by the proposed 3 classes (SSI/HR11005) being equal to 28.3 (9.1) in dippers and to 58.7 (12.1) in SSHR. The trend was also similar after correction of the means to 24.6 (11.3) and to 49.7 (9.7) in the low-HR and high-HR groups, respectively (P=NS). Similar results were obtained when classification was based on MAPNF only, with SSI being equal to 28.3 (9.1) in dippers and to 58.7 (12.1) in nondippers (P = NS).

Also, the prevalence of SS patients increased with the risk of sodium sensitivity, as defined by the proposed 3 classes (Figure, right). Although only 25% of patients were SS in the SSLR class, the prevalence of SS subjects increased up to 70% in the SSHR class (P=0.043).

Results may be influenced by the criteria used for classifying patients in dippers or nondippers. Defining nondippers as those with SBP_{NF} <10%,16 the prevalence of dippers would decrease (from 78% to 67% in the SR group and from 53% to 37% in the SS group), and the difference between SR and SS groups in dipper prevalence would reach the significance threshold (P<0.05). Moreover, compared with the classification based on MAPNF, the difference between sodium sensitivity risk classes would be more marked (P=0.036). In fact, the prevalence of SS subjects would result as slightly lower in the SSHR class, being equal to 67%, and more substantially lower in the SSLR class, being equal to 18%.

Other ABPM-Derived Predictors of SSI

The ABPM parameters considered in the multivariate analysis were 24-hour HR and PP mean values and 4 indexes of dipping pattern: SBP_{ND}, PP_{ND}, SBP_{NF}, and MAPNF. No other ABPM parameter showed correlation coefficients with SSI at univariate analysis high enough to be included in the multivariate model (Table 3; Methods). In the forward-stepwise method, the regression model is built by adding at each step the predictor with the larger effect on the dependent variable; stepping stops when all the predictors are included or when no new predictor significantly improves the model. In our study, after having included HR_{24H}, PP_{ND}, and PP_{24H}, the forward-stepwise method did not include any other predictor in the model, which reached a multiple correlation coefficient R equal to 0.46. However, only 2 predictors had beta coefficients significantly different from 0: HR_{24H} (beta=0.34) and PP_{ND} (beta=0.29).

Discussion

Our study offers novel information on the possibility to identify a condition of increased cardiovascular risk associated with the sodium sensitivity status in mild to moderate hypertensive patients from ABPM parameters obtained under daily-life conditions and habitual diet. This may have important practical implications because it is much easier to perform a 24-hour ABPM, without implementing controlled diets or monitoring salt intake, than a traditional sodium sensitivity test. The reliability of our analysis is strengthened by the fact that patients classified as SS or SR based on sodium load were matched in terms of 24-hour mean blood pressure, age, and body mass index. This allowed us to exclude interference from relevant confounding factors.

The relationship between nocturnal fall of blood pressure and sodium sensitivity of hypertensive patients was also examined in previous articles. However, with the exception of an investigation performed in normotensive black adolescents,20 these studies performed ABPM recordings at the end of high-sodium and low-sodium intake periods.21–23 Thus, to our knowledge, this study provides the first indications on the possibility to predict the sodium sensitivity risk of mild to moderate hypertensive patients based on a 24-hour ABPM performed with unrestricted diet (ie, with a much easier methodological approach compatible with daily practice).
Definition of Sodium Sensitivity Risk From MAP$_{NF}$ and HR$_{24h}$

Based on previous evidence, as a first step, our study focused on the predicting power of MAP$_{NF}$ and HR$_{24h}$. These parameters were shown previously to be altered in SS subjects. With regard to MAP$_{NF}$, a correlation has been reported between loss of dipping pattern at night and sodium sensitivity during high sodium loads. This alteration was also found to be frequently associated with an increased sodium excretion at night in nondipper hypertensive subjects following a high-sodium intake diet. Moreover, it should be noted that adaptation to a low-sodium intake tends to restore both the physiological decline of sodium excretion at night and the blood pressure dipping pattern.

Also, our results suggest that the blood pressure dipping pattern may be partially lost in SS subjects because MAP$_{NF}$ and prevalence of dipper subjects were lower in the SS group. However, under conditions of unrestricted diet, differences in nocturnal fall of blood pressure between SS and SR subjects, although close to the 5% threshold, did not reach statistical significance (Table 2).

Previous articles also suggested a link between sodium sensitivity and high HR levels. In fact, it has been shown that during sodium load, higher SS is associated with higher HR and lower cardiac vagal modulation, these relationships disappearing when shifting to a low sodium intake. Moreover, insulin resistance was found to be associated both with higher 24-hour HR levels and with higher sodium sensitivity. These data further highlighting the existence of a link between elevated HR and sodium sensitivity. In line with our hypothesis, we found a positive correlation between HR$_{24h}$ and SS (Table 3). However, as observed for MAP$_{NF}$, under habitual diet, the difference in HR$_{24h}$ between SR and SS patients did not reach statistical significance levels (Table 2).

Interestingly, HR$_{24h}$ and MAP$_{NF}$ were unrelated to each other. This may be expected if different mechanisms are responsible for their alterations (reduced sodium excretion at night for MAP$_{NF}$, altered autonomic balance, or insulin resistance for HR$_{24h}$). The finding of a lack of correlation between HR$_{24h}$ and MAP$_{NF}$ allowed us to combine the information carried by these parameters aimed at improving the prediction of sodium sensitivity. This was done by defining groups at different risk of sodium sensitivity on the basis of both their dipper/non-dipper classification (ie, MAP$_{NF}$ > 10 mm Hg or < 10 mm Hg) and their mean 24-hour HR values (ie, HR$_{24h}$ < 70 bpm or > 70 bpm). The SSLR and SSHR classes so defined were indeed characterized by marked and significant differences in SSI and in prevalence of SS patients.

Most of our SSHR patients were found to be SS. Thus, information provided by 24-hour ABPM analysis appears sufficient for recommending a substantial reduction of their salt intake in everyday diet. In contrast, most but not all of our patients classified as SSLR by ABPM were found to be SR at the laboratory test. Indeed, a non-negligible fraction of them (25%) actually resulted to be SS. We cannot provide a clear-cut explanation for this finding, but it is possible that SS patients classified as low sodium sensitivity risk by ABPM analysis might already have been following a correct low-salt diet, thus normalizing the nocturnal fall of blood pressure and mean HR in spite of their intrinsic sodium sensitivity condition. In fact, a low-sodium diet has been shown to restore the normal values of sodium excretion at night, the blood pressure dipping pattern, and most of the autonomic alterations, including HR mean levels. If this hypothesis is true, it might be superfluous, in a daily practice perspective, to recommend a sodium sensitivity test in patients classified as SSLR by ABPM parameters. In fact, even if some of them might actually be SS, their current spontaneous diet might already be low enough in sodium to prevent the appearance of important alterations in cardiovascular regulation without any additional dietary recommendation.

Therefore, based on these considerations, our results might suggest the need to perform a traditional sodium sensitivity test only on those patients classified as intermediate sodium sensitivity risk, representative of about half of the population of moderate and mild hypertensive subjects considered in this study.

Sodium Sensitivity Prediction From Other ABPM Parameters

In our study, we also considered a larger group of ABPM parameters as possible predictors of SSI. Indexes of cardiovascular variability over 24 hours, such as weighted SDs, are not related to sodium sensitivity. What is different is the case of specific components of blood pressure variability, which, like MAP$_{NF}$, quantify the nocturnal dipping phenomenon. Indeed, Tables 2 and 3 suggest that SBP$_{NF}$, SBP$_{ND}$, or PP$_{ND}$ may predict the sodium sensitivity condition even better than MAP$_{NF}$. This is confirmed by multivariate analysis, which showed that only HR$_{24h}$ and the log-transformed PP$_{ND}$ are independent predictors of SSI. Interestingly, nighttime changes of DBP, as quantified by DBP$_{NF}$ or DBP$_{ND}$, did not differ significantly between SR and SS groups (Table 2). It is believed that because of their limited capacity to excrete sodium during the day, SS subjects may excrete more sodium during the night by increasing nocturnal blood pressure levels so to stimulate a pressure–natriuresis mechanism.

This nocturnal adjustment of blood pressure would contribute to the disappearance of the dipping phenomenon at night. Our data suggest that in mild or moderate hypertension, the nocturnal adjustment of blood pressure levels, produced to stimulate natriuresis, may not involve DBP, which remains mainly unchanged (Table 2). Consequently, at night, mainly SBP increases, leading to an increase in PP. MAP, which is influenced more by DBP than by SBP, would therefore be less sensitive compared with SBP or PP to reflect the changes of blood pressure levels occurring in SS subjects at night.

These findings would then suggest that a better classification of patients in sodium sensitivity risk classes could be obtained by identifying dippers and nondippers using SBP or PP rather than MAP and by properly selecting the thresholds for their changes during night.

We acknowledge some limitations of our study. First, we did not instrumentally record postural changes at night, which might have helped us in more precisely interpreting differences between subjects in the degree of nocturnal blood pressure changes. Actually, it has been shown that nighttime awakening (eg, for voiding) may influence the identification.
of the dipping status.\textsuperscript{25} Dipping also may be misclassified by daytime naps.\textsuperscript{26,27} However, based on ABPM diaries, none of our patients reported occurrence of daytime sleep periods nor major sleep disturbances produced by the ABPM device. It should also be mentioned that another cause of misclassification of the dipping status is orthostatic hypotension.\textsuperscript{28} Orthostatic hypotension was excluded in our patients, and thus, the conclusions of this study cannot be also applied to such patients. Second, the HR threshold for the classification of subjects into HR groups might change with age, blood pressure level, or gender. Larger studies, including subjects with wider distribution of age and blood pressure levels, are thus needed for selecting more accurately the HR threshold. Consequently, our conclusions can be safely applied only to subjects within the age and blood pressure ranges considered in the present study. Third, the amount of salt intake in the diet during ABPM was not assessed. This information might have allowed us to better interpret our results, although it is not necessary to estimate the degree of “sodium sensitivity-related risk,” which is proposed in our article as a simpler approach to identify SS subjects in absence of information on their sodium intake habits.

**Future Perspectives**

Our study indicates that in about half of mild or moderate hypertensive patients, it is possible to derive information on the additional cardiovascular risk associated with sodium sensitivity simply from the analysis of blood pressure and HR behavior over the 24 hours under unrestricted sodium diet. Future studies might further improve the classification approach proposed in our article by identifying ABPM parameters that could better reflect sodium sensitivity by using more sophisticated algorithms of risk classification or by including subjects with a wider distribution of age and blood pressure level. Future studies might also extend this approach to normotensive populations, in which alterations of the 24-hour blood pressure dynamics associated with sodium sensitivity may also exist.\textsuperscript{20}

**Authors’ Contribution**

P.Ca., G.P., and P.Co. equally contributed to conceiving and designing the study and to analyzing the data. L.B., V.B., and M.G. acquired the data. All authors contributed to interpret the data and to draft the manuscript, discussed results and implications, and commented on the manuscript at all stages.

**Disclosures**

None.

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Detecting Sodium-Sensitivity in Hypertensive Patients: Information From 24-Hour Ambulatory Blood Pressure Monitoring
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