Nighttime Blood Pressure and New-Onset Left Ventricular Hypertrophy
Findings From the Pamela Population

Cesare Cuspidi, Rita Facchetti, Michele Bombelli, Carla Sala, Francesca Negri, Guido Grassi, Giuseppe Mancia

Abstract—The relationship between circadian blood pressure (BP) variations and the extent of subclinical cardiac organ damage is still debated. In a general population, we investigated the association of night-to-day BP fall, as well as nocturnal BP level (mean and lowest values), with left ventricular (LV) hypertrophy and the value of both BP parameters in predicting new-onset LV hypertrophy. Office BP, 24-hour ambulatory BP values, and laboratory investigations were assessed on entry in 1682 subjects (50.2% men; mean age, 50.2±13.7 years) of the Pressioni Arteriose Monitorate E Loro Associazioni. Echocardiographic LV mass was measured at the initial evaluation and 10 years later. Multiple regression analyses, including daytime systolic BP (SBP), age, sex, and body mass index, showed that the lowest SBP level and the extent of nocturnal SBP decline were independently related to baseline LV mass. After adjustment for several confounders, both mean nocturnal SBP (relative risk for each 10-mm Hg increase in SBP, 1.15; 95% confidence interval, 1.01–1.23; P<0.0001) and the lowest SBP level (relative risk for each 10-mm Hg increase in SBP, 1.10; 95% confidence interval, 1.02–1.19; P=0.01) were independent predictors of new-onset LV hypertrophy. This was not the case for the magnitude of nighttime SBP fall (hazard ratio for each 10% decrease in SBP, 0.91; 95% confidence interval, 0.80–1.04; P=0.18). In a general population, nighttime BP level rather than the nocturnal BP decline may be regarded as a reliable parameter for predicting the development of LV hypertrophy in subjects with normal LV mass. This finding may have important implications for optimizing cardiovascular prevention in the general population. (Hypertension. 2013;62:78-84.)

Key Words: left ventricular hypertrophy  ■  nighttime blood pressure  ■  nocturnal blood pressure fall

Extensive echocardiographic investigations performed in the past 3 decades have shown that hypertensive heart disease includes a variety of anatomic and functional alterations, such as left ventricular hypertrophy (LVH), systolic/diastolic dysfunction, myocardial fibrosis, and left atrial and aortic dilatations.1-5 Among these manifestations of cardiac damage, particular attention has been devoted to LVH because this phenotype has been reported to be a powerful, independent predictor of cardiovascular (CV) events and all-cause mortality either in the general population or in hypertensive cohorts.6,7

Although the pathogenesis of hypertensive LVH is not fully understood, a consistent body of evidence indicates that the severity of pressure overload, as better reflected by out-of-office than by in-office blood pressure (BP) levels, in combination with nonhemodynamic variables, including genetic, ethnic, and humoral factors, plays a pivotal role in its development.8,9 Nonetheless, numerous reports have also shown that circadian variations in BP correlate to LVH independently of 24-hour ambulatory BP monitoring (ABPM) values. Furthermore, earlier studies suggested that daytime BP, in particular BP values recorded during working hours, is more closely associated with LVH compared with nighttime BP.10 More recently, however, numerous studies have shown that nighttime BP and nocturnal BP fall are stronger correlates of LVH than daytime or average 24-hour BP.11,12

Although a blunted decrease in nighttime BP (ie, nondipping status) has been associated with unhealthy conditions, including diabetes mellitus, metabolic syndrome, sleep apnea, cardiac or extracardiac organ damage, resistant hypertension, and an increased risk of CV morbidity and mortality,13-15 this issue remains a source of debate. It is worthy of mention that a systematic review by Hansen et al16 which included 25856 hypertensive patients and 9641 individuals randomly recruited from the population revealed that nondipping status and increased night-to-day BP ratio were associated with higher all-cause mortality and CV events but added a marginal prognostic value over and beyond 24-hour BP. Thus, whether intermediate and hard end points are better related to
nocturnal BP levels or to the degree of nocturnal BP decline remains unsettled.

So far, only a few population-based studies investigated the cross-sectional relationship of circadian BP variations and nighttime BP levels with LVH; more importantly, no studies examined the value of such ambulatory BP parameters in predicting new-onset LVH in the general population. To provide a comprehensive investigation of these associations, we analyzed the data from the Pressioni Arteriosi Monitorate E Loro Associazioni (PAMELA) study, a population-based longitudinal survey performed in Italy in which ambulatory BP data, together with echocardiographic LV mass measurements, were obtained in each individual at the initial evaluation and during a long-term follow-up period.

Methods

Population

The PAMELA Study was performed on a sample of 3200 subjects representative of the population of Monza (a town near Milan, Italy) for sex and age decades (25–74 years). The participation rate was 64%, which means that data were collected in 2051 subjects. The demographic characteristics of nonparticipants were similar to those of participants; this was also the case for CV risk assessed by data collected via phone interview. Of the 2051 participants, 208 died during the follow-up period. Among the 1843 participants still alive at the end of follow-up, 1402 were actually reexamined. Nonparticipants (unwilling to participate or moved from the town of Monza) were older, had higher systolic BP (SBP), cholesterol, fasting blood glucose, LV mass index, and were more frequently men than women (data not shown).

Entry Data

Methods used in the PAMELA study have been previously described in detail. Before 1990 and 1992, after an informed consent, subjects were invited to undergo a comprehensive clinical evaluation at the outpatient clinic of the S. Gerardo University Hospital of Monza on the morning of a working day. The data obtained consisted of full medical history, blood and urine samples, physical examination, and 3 sphygmomanometric BP measurements in the sitting position. Body weight was recorded to the nearest 0.1 kg using a calibrated electronic scale, with subjects wearing indoor clothing without shoes. Height was recorded to the nearest 0.5 cm using a standardized wall-mounted height board.

Ambulatory BP Monitoring

Subjects were then fitted with an ABPM device (Spacelabs 90207) set to obtain automated BP and heart rate oscillometric readings every 20 minutes during the 24 hours. The subjects were asked to pursue their normal activities during the monitoring period, with the precaution of holding the arm still at time of BP reading and going to bed no later than 11:00 pm and to arise not before 7:00 am. All ABPMs were performed on a working day (Monday to Friday). Recordings were analyzed to obtain 24-hour, daytime (7:00 am to 11:00 pm), and nighttime (11:00 pm to 7:00 am) average SBP/diastolic BP (DBP) values, nocturnal SBP decrease (%), and heart rate. Nocturnal nondipping pattern was defined as a nighttime reduction in SBP <10% compared with daytime values.

Echocardiography

Echocardiography was performed according to standardized procedures, as previously reported. In brief, M-mode and 2-dimensional echo examinations were performed with a commercially available instrument (Acuson 128 CF, Computer Sonography). End-diastolic (d) and end-systolic (s) LV internal diameters (LVID), interventricular septum (IVS) thickness, and posterior wall (PW) thickness were measured from 2-dimensionally guided M-mode tracings recorded at 50 to 100 cm/s speed during ≥3 consecutive cycles according to the Penn convention. Relative wall thickness was defined as the ratio of PW plus IVS thickness to LVIDd; LV mass was estimated by using the corrected American Society of Echocardiography method: 0.8×(1.04×[(IVSd+LVIDd+PWTd)/2]−LVIDd)−0.620 and normalized to body surface area. Echocardiographic tracings were obtained by 2 skilled operators and read by a third independent observer: the intraobserver coefficient of variation was 0.6% for LVIDd, 3.1% for IVSd thickness, and 3.2% for PWd thickness.

LVH was defined as LV mass index ≥115 g/m² in men and 99 g/m² in women; these cutoffs are derived from sex-specific upper limits of normality (mean+1.96 SD) for LV mass indexed to body surface area in 675 healthy individuals with sustained normotension.

Follow-Up

The outcome retained for the present analysis was the new-onset echocardiographic LVH according to the above-mentioned criteria. In addition, participants were contacted 10 years later (from 2001 to 2003), and survivors willing to be reexamined were asked to attend the San Gerardo Hospital for a second clinical and echocardiographic examination, as well as collection of data set.

Data Analysis

In each subject, the 3 clinical BP values were averaged; also 24-hour ambulatory BP values were averaged after artifactual readings had been eliminated according to preselected criteria. Valid ambulatory SBP and DBP readings were 95.2% and 94.8%, respectively, of the planned 72 readings. Statistical analysis was performed by SAS System (version 9.12; SAS Institute, Inc, Cary, NC).

Values were expressed as means±SD or as percentages. Means were compared by the Student t test for independent samples, and categorical data were analyzed by the χ² test or Fisher exact test when appropriate. The strength of linear correlation between variables was tested by the Pearson correlation coefficient. The relationship between nocturnal BP fall or nighttime SBP values (ie, mean nocturnal SBP and the lowest nocturnal SBP value) and LV mass was evaluated using a multiple linear regression model. The independent variables considered were age, sex, height, weight, waist circumference, daytime and clinical SBP, use of antihypertensive drugs, total serum cholesterol, fasting serum glucose, and creatinine. We selected variable with stepwise selection (p≤0.05).

The relative risk (RR) of developing LVH was calculated using a modified Poisson approach, with robust error variance; RR was calculated for a 10% increment of nocturnal fall and 10 mm Hg increase of average nighttime SBP and lowest SBP values. Data were adjusted for confounding factors (ie, age, sex, use of antihypertensive drugs, and baseline LV mass index [LVMI]). All tests were 2-sided, and a p <0.05 was considered statistically significant.

Results

As reported on Table 1, a total of 1682 subjects (50.4% men; mean age, 50.2±13.7 years) with a good quality echocardiographic examination were included in the baseline analysis (of these, 1184 had a valuable echocardiogram at the end of follow-up). Mean office BP at baseline was 132±21/83±10 mm Hg, and mean 24-hour BP was 119±11/74±7 mm Hg. Average body mass index and waist circumference were 25.5±4.4 kg/m² and 85±12 cm, respectively.

Correlation Analyses

Table 2 reports univariate correlations among the percent SBP decrease at night, average nighttime SBP values, and the lowest SBP values with clinical variables in the study population. The extent of SBP decrease at night showed significant, albeit weak, inverse correlations with average nighttime SBP,
Hypertension

July 2013

24-hour SBP, LVMI, age, fasting blood glucose, and a direct correlation with average daytime BP.

Average and lowest SBP nocturnal values exhibited significant positive correlations with average night SBP, 24-hour SBP, LV mass, age, body mass index, waist circumference, blood fasting glucose, and total cholesterol.

In multiple regression analyses, the extent of nocturnal SBP decline, lowest SBP level, and average nighttime SBP turned out to be independently correlated with LV mass (Table 3).

Comparison of Patients With and Without New-Onset LVH

Of the 978 subjects with normal LVMI, 243 developed LVH during the follow-up; compared with those with persistently normal LV mass they were older, had higher BMI, waist circumference, office BP, 24-hour, daytime, and nighttime SBP/DBP values, lower nocturnal SBP/DBP falls, and greater nocturnal SBP values at night in comparison with their counterparts.

Comparison of Patients With and Without Baseline LVH

Table 4 shows clinical differences between subjects without and with LVH at the initial evaluation. Patients with LVH were older, had higher BMI, waist circumference, office BP, 24-hour, daytime, and nighttime SBP/DBP values, lower nocturnal SBP/DBP falls, and greater nocturnal SBP values at night in comparison with their counterparts.

Table 1. Clinical Characteristics of the Study Population at the Initial Evaluation (n=1682) and at the End of Follow-Up (n=978)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Initial Study (n=1682)</th>
<th>End Study (n=978)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, men %</td>
<td>50.4</td>
<td>49.9</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.5±4.4</td>
<td>26.4±4.3</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>85.1±12.3</td>
<td>89±12.2</td>
</tr>
<tr>
<td>Clinical SBP/DBP, mm Hg</td>
<td>131.8±20.8/83.4±10.4</td>
<td>134.9±21.6/83.2±10.5</td>
</tr>
<tr>
<td>Clinical heart rate, bpm</td>
<td>71.0±10.2</td>
<td>73.7±10.5</td>
</tr>
<tr>
<td>24-h SBP/DBP, mm Hg</td>
<td>119.4±11.4/74.0±7.2</td>
<td>122.6±11.5/74.4±7.5</td>
</tr>
<tr>
<td>Daytime SBP/DBP, mm Hg</td>
<td>124.4±11.8/78.6±7.7</td>
<td>127.1±11.7/78.5±8.2</td>
</tr>
<tr>
<td>Nighttime SBP/DBP, mm Hg</td>
<td>109.6±12.4/64.7±7.9</td>
<td>113.2±12.7/66.1±7.6</td>
</tr>
<tr>
<td>Nocturnal SBP/DBP fall, %</td>
<td>11.8±6.3/17.7±7.4</td>
<td>10.8±6.3/15.6±7.4</td>
</tr>
<tr>
<td>Serum fasting glucose, mg/dL</td>
<td>90.3±20.9</td>
<td>94.3±25.4</td>
</tr>
<tr>
<td>Serum total cholesterol, mg/dL</td>
<td>222.1±42.9</td>
<td>204.8±36</td>
</tr>
<tr>
<td>LVMI/BSA, g/m²</td>
<td>86.7±21.1</td>
<td>94.2±22.6</td>
</tr>
<tr>
<td>LVMI/height², g/height²</td>
<td>39.9±11.2</td>
<td>44±11.9</td>
</tr>
<tr>
<td>LVM, g</td>
<td>152.2±44.7</td>
<td>168.6±49</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>3.4</td>
<td>6.3</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.9±0.2</td>
<td>0.9±0.2</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>44.1</td>
<td>54.7</td>
</tr>
<tr>
<td>Use of antihypertensive drugs, %</td>
<td>18.2</td>
<td>27.6</td>
</tr>
</tbody>
</table>

Data are shown as mean±SD, percentages, or absolute numbers. Hypertension=office BP ≥140/90 mm Hg or use of antihypertensive drugs. BSA indicates body surface area; DBP, diastolic blood pressure; h, height; LVMI, left ventricular mass index; and SBP, systolic blood pressure.

Table 2. Univariate Correlations Among Percent Nighttime SBP Decrease, Lowest Nighttime SBP, and Mean Nighttime SBP Values With Clinical or Demographic Variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Nighttime SBP Decrease, %</th>
<th>Lowest Nighttime SBP</th>
<th>Mean Nighttime SBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>−0.065</td>
<td>0.003</td>
<td>0.317</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>−0.026</td>
<td>0.23</td>
<td>0.149</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>0.002</td>
<td>0.94</td>
<td>0.176</td>
</tr>
<tr>
<td>24-h SBP, mm Hg</td>
<td>−0.115</td>
<td>0.0001</td>
<td>0.788</td>
</tr>
<tr>
<td>Daytime SBP, mm Hg</td>
<td>0.109</td>
<td>0.0001</td>
<td>0.675</td>
</tr>
<tr>
<td>Fasting blood glucose, mg/dL</td>
<td>−0.049</td>
<td>0.03</td>
<td>0.173</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>0.025</td>
<td>0.26</td>
<td>0.115</td>
</tr>
<tr>
<td>LV mass/BSA, g/m²</td>
<td>−0.063</td>
<td>0.001</td>
<td>0.323</td>
</tr>
<tr>
<td>LV mass/height², g/height²</td>
<td>−0.061</td>
<td>0.02</td>
<td>0.317</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>−0.061</td>
<td>0.01</td>
<td>0.311</td>
</tr>
</tbody>
</table>

BSA indicates body surface area; LV mass, left ventricular mass; and SBP, systolic blood pressure.
Nocturnal BP and Risk of New-Onset LVH

To determine the impact of different ABPM parameters on new-onset LVH, a Poisson regression analysis was performed, including nocturnal SBP decrease and average and lowest nighttime SBP. After adjustment for age, sex, baseline LV mass, and use of antihypertensive drugs, mean SBP at night (RR for each 10-mmHg increase in SBP, 1.15; 95% confidence interval [CI], 1.01–1.23; P<0.0001) and lowest SBP (RR for each 10-mmHg increase in SBP, 1.10; 95% CI, 1.02–1.19; P=0.0001) were risk factors for development of LVH; this was not the case for the extent of nocturnal BP fall (RR for each 10% decrease in SBP, 0.91; 95% CI, 0.96–1.01; P=0.17; Figure). Similar results were obtained when variations in cardiac structure of the 978 subjects were analyzed as a continuous (ie, LV mass) rather than a dichotomous variable (data not shown).

Although the lowest SBP at night represents a single BP measurement potentially confounded by multiple sources of error, this value (which may reflect the extent of sympathetic inhibition at night) was strongly related to average nighttime SBP (r=0.89; P<0.0001). Of note, further analyses based on the average of 3 nighttime SBP values, namely the lowest SBP and the adjacent SBP values (preceding and successive value), provided similar results. In additional analyses aimed to investigate the value of office SBP in predicting LVH, no correlation was found between this parameter (P=0.11) with incident LVH. Finally, because ambulatory BP changes during the follow-up could have an important impact on LV mass variations, we analyzed the predictive value of changes in average nighttime SBP, lowest SBP, and day–night SBP fall. None of these variations, adjusted for age, sex, LV mass, and use of antihypertensive drugs at baseline, was independently correlated with new-onset LVH: Δ mean SBP (RR for each 10-mmHg increase in SBP, 1.04; 95% CI, 0.97–1.13; P=0.27), Δ lowest SBP (RR for each 10-mmHg increase in SBP, 0.97; 95% CI, 0.90–1.04; P=0.33), and Δ nocturnal SBP fall (RR for each 10% decrease in SBP, 0.98; 95% CI, 0.86–1.11; P=0.71).

Discussion

This study for the first time, to our knowledge, investigated the association of either night-to-day BP fall or nocturnal BP level with LVH, as assessed by echocardiography; and the value of these variables in predicting new-onset LVH over a long-term follow-up in a large sample of the general population. Our main findings can be summarized as follows: (1) nighttime SBP values (ie, average, lowest SBP, and the extent of night-to-day SBP fall) were significantly correlated to LV mass measured at baseline evaluation; (2) both average and lowest nocturnal SBP levels were significantly higher in subjects who
We recently showed that in the presence of elevated nighttime BP values (ie, 120/70 mm Hg), LVMI and LVH prevalence were not different between dippers and nondippers; in particular, neither group had a more pronounced subclinical cardiac involvement after adjustment for confounders.23 This observation was strengthened by the fact that (1) the study compared individuals with similar clinical/demographic characteristics and reproducible dipping/nondipping patterns, and (2) no correlation was found between LVMI and the magnitude of nocturnal BP fall in the entire study population.

Although a blunted decrease in BP during nighttime may have unfavorable effects on cardiac structure, available evidence on subclinical cardiac damage in dipper and nondipper hypertensives remains inconclusive, so far. A meta-analysis by Fagard et al26 based on 19 comparative studies encompassing 1223 normotensive and hypertensive individuals showed that the relationship of LV mass to daytime BP difference was not a consistent finding and, when present, was weakly significant. More recently, we reviewed data provided by 26 studies published in the past 12 years: 17 studies including 2497 of the 3877 subjects reported a positive association between nondipping status and LVH, whereas the remaining 9 studies did not.29 Several methodological problems may explain these conflicting findings. The 10% threshold separating dippers from nondippers is an arbitrary value because the extent of nocturnal BP fall in a population sample has been documented to be normally distributed.22 An additional critical issue concerns the definition of nighttime dipping.
and daytime periods. Henskens et al\textsuperscript{22} documented that awake–asleep time defined by different duration periods (wide or narrow fixed time periods) caused significant variations in the magnitude of BP dip, as well as in the prevalence of dippers and nondippers. Finally, classification of dippers and nondippers has a limited short- and long-term reproducibility. Accordingly, categorization of dipping/nondipping status based on a single ABPM may not reflect a definite clinical trait in a relevant fraction of the hypertensive population, ranging from one fifth to one third.\textsuperscript{30} To minimize potential methodological limitations related to the dichotomous classification of dipping/nondipping, we analyzed the circadian variations in BP as a continuous variable. Despite this more reliable approach, we failed to observe an independent relationship between nocturnal BP decrease and new-onset LVH. Some further general considerations may be useful to explain this finding. The magnitude of the nocturnal dip is markedly affected by erratic factors, including the degree of physical activity during daytime, afternoon nap, nicturia, and nocturnal activity. More importantly, a fully preserved BP fall at night in dipper hypertensives may not result in a normal nighttime BP profile because nocturnal hypertension may occur independently from the dipping status.\textsuperscript{23,31}

In the present study, we found that nocturnal SBP levels (ie, average nighttime, lowest SBP, and the extent of day-to-night SBP decline) contributed to explain the variance of baseline LV mass value and, more importantly, that the level of nighttime SBP, but not day-to-night SBP fall, was predictive of new-onset LVH during a 10-year follow-up period. Some few points and limitations of our study need to be mentioned. First, in line with previous evidence supporting the superiority of SBP over DBP levels\textsuperscript{14} in predicting prognosis, as well as the closer relationship between SBP and cardiac remodeling,\textsuperscript{32} our analysis was restricted to SBP values because the strength of the relationship among DBP, pulse pressure, and heart rate with LV mass in the PAMELA population was weaker than that of SBP (data not shown). Second, in accordance with the established notion that subjects with low nocturnal BP are at low CV risk, our findings add the information that the lower the SBP at night the lower the risk of having or developing LVH. Third, LVH was defined according to sex-specific upper limits of normality in 675 healthy sustained normotensives from the PAMELA population.\textsuperscript{21} Nonetheless, different partition values or LV mass indexation methods did not change our results.

In conclusion, our study offers a new piece of evidence on the controversial association between circadian BP variations and cardiac damage by showing that the absolute nighttime SBP level rather than the degree of nocturnal SBP decline is a reliable ABPM parameter for predicting the development of LVH.

**Perspectives**

The dipping status is regarded as a clinical trait associated with a less pronounced target organ damage and a more favorable prognosis. However, it is worth noting that a fully preserved BP fall at night in hypertensive subjects may not result in a normal nighttime BP profile. Our findings focusing on the relationship between different nocturnal BP parameters and LVH indicate that nighttime SBP levels may be more important in the progression of subclinical cardiac organ damage than the extent of day-to-night BP variations. In a clinical perspective, our data support the hypothesis that tight control of nighttime SBP over and beyond the dipping status may have a key role in preventing LVH. Further studies are needed to confirm this hypothesis.

**Disclosures**

None.

**References**

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