Blood Pressure Variability and Organ Damage in a General Population

Results from the PAMELA Study

Roberto Sega, Giovanni Corrao, Michele Bombelli, Luca Beltrame, Rita Facchetti, Guido Grassi, Marco Ferrario, Giuseppe Mancia

Abstract—In hypertensive patients, 24-hour blood pressure (BP) variability (V) shows a positive relationship with organ damage, organ damage progression, and cardiovascular morbidity. The clinical relevance of BPV in the population has never been investigated. In a sample of 3200 individuals, randomly selected from the general population of Monza (Milan, Italy), we evaluated BP by an automatic oscillometric device every 20 minutes for 24 hours and left ventricular mass index (LVMI) by echocardiography. In each subject, individual systolic and diastolic BP readings were averaged to obtain a 24-hour mean. Systolic BPV was obtained by calculating (1) the standard deviation of the 24-hour mean, which was taken as the overall BPV, (2) the cyclic components (Fourier spectral analysis) that in the population as a whole explained >95% of the overall BPV, and (3) the fraction of the overall BPV that in each subject was not accounted for by the 2 cyclic components, termed individual residual BPV. A similar procedure was used for diastolic BP and heart rate. Participation rate was 64.1%. Patients receiving antihypertensive therapy (n = 403) were excluded from the analysis, which was therefore limited to 1648 participants. In the population as a whole, LVMI significantly related to 24-hour systolic and diastolic BP mean (β = 0.40 and β = 0.37, respectively, P < 0.001 for both) but not to the 2 cyclic components that accounted for most of the BPV. On the other hand, the individual residual BPV (which accounts on average for about 50% of overall BPV) showed a significant positive relationship with LVMI (β = 0.38 and β = 0.88 for systolic and diastolic BP, respectively, P < 0.05 and P < 0.01). No relationship was found between LVMI and heart rate values. These findings provide evidence that there is a relationship between LVMI and 24-hour average BP values in the population. They also provide the first demonstration that in the population there is also a positive independent association between LVMI and BPV. This association, however, can be exclusively seen with the BPV component that has an erratic rather than a cyclic nature. (Hypertension. 2002;39[part 2]:710-714.)

Key Words: blood pressure ■ blood pressure monitoring, ambulatory ■ blood pressure determination ■ ventricular function, left

Recent studies suggest that in hypertensive subjects, 24-hour blood pressure (BP) variability may be clinically important. (1) In these patients, 24-hour BP standard deviation (i.e., an overall measure of BP variability) has been found to be related to organ damage independently on the 24-hour mean BP values.1–3 (2) The 24-hour BP standard deviation has been shown to be related to the progression of organ damage over the years.4–5 (3) Cardiovascular morbidity has been reported to be greater in subjects with a greater BP variability than in those with a similar BP variability.6

With the exception of the aforementioned study (performed on a Japanese population),6 no information has ever been collected on the possible clinical relevance of 24-hour BP variability in the general population. The present study has addressed this issue by measuring 24-hour BP variability in a large sample representative of the population of Monza, a town in the northeast outskirts of Milan. The measured values were correlated with left ventricular mass (LVM) as derived from echocardiographic measurements because, in the population, this value has been shown to have prognostic significance.7

Methods

The present study is based on the cross-sectional examination of subjects included in the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study.8–10 A sample of 3200 subjects of both genders was randomly selected within 10-year age stratum from the residents of Monza, aged 25 to 74 years (about 70 000) according to the criteria of the World Health Organization (WHO) Monitor Trends in Cardiovascular Diseases (MONICA) Project.11 The subjects were informed of their selection by letter or phone calls and
invited to come to a special outpatient clinic established at the San Gerardo University Hospital in the morning of a working day to undergo a medical visit and a variety of measurements planned in the study protocol. These included a 24-hour ambulatory BP monitoring and an echocardiogram. The ambulatory BP monitoring was performed with oscillometric equipment (Spacelabs 90207) whose cuff was applied to the nondominant arm at the end of the visit. The device was set to obtain ambulatory BP and heart rate (HR) readings at 20 minutes intervals for 24 hours during which the subjects were sent back home and asked to attend their usual activities. The subjects were only invited to (1) hold the arm immobile at the time of the measurements, (2) keep a diary of daily activities and quality of night sleep, and (3) return to the hospital 24 hours later. Details of the procedures employed to check the accuracy of the device in each subject and over time have been previously reported.8–10 The echocardiogram was obtained after the device removal using a 2D, M-mode and pulsed Doppler Accuson 128 Computer Sonography system and a 3.2 MHz mechanical transducer. Left ventricular septal wall and posterior wall thickness measurements were obtained according to the recommendations of the American Society of Echocardiography,12 and LVM was calculated according to the formula of Devereux et al.13 LVM index (LVMI) was calculated as the ratio of LVM in grams and body surface area in square meters.

In each individual, calculation was made of 24-hour average systolic BP, diastolic BP, and HR average and standard deviation (taken as index of the corresponding variability), the overall 24-hour variability being taken as the corresponding standard deviation around the average.14 In addition, (1) each single systolic BP reading collected over the 24 hours (total: 72 recordings) was averaged for all individuals, (2) the Fast Fourier transform spectral analysis15 was applied to the overall circadian BP profile so obtained to identify the cyclic components that accounted for most (>95%) of the systolic BP standard deviation, (3) these components were thereafter tested for their ability to fit the systolic BP profile in each subject, and (4) the sum squared of the differences between the observed and the fitted profile was taken as reflecting in each individual the systolic BP variability unexplained by the cyclic components, accounting for nearly all the systolic BP variability in the population as a whole. This was termed the individual residual variability. A similar procedure was employed for diastolic BP and HR. The 24-hour average values, standard deviation, cyclic components of variability, and individual residual variability were examined for their relationship to LVMI by bivariate regression analysis, separately for systolic

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**Figure 1.** The left panels show the 24-hour systolic BP, diastolic BP, and HR profiles as observed by averaging each 20-minute reading in the 1648 subjects and as obtained by considering, through spectral analysis, the first 2 cyclic components. The right panels show the contribution of all cyclic components to the 24-hour standard deviation or overall variability. The first 2 components accounted for most of the variability, with little or no contribution from the remaining faster components.

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**TABLE 1. Demographics and LVMI, BP, and HR Values of the Subjects (n=1648) Included in the Analysis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/F, n</td>
<td>848/800</td>
</tr>
<tr>
<td>Age, y</td>
<td>48.2±13.1</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.0±4.1</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>83.4±18.2</td>
</tr>
<tr>
<td>24h SBP, mm Hg</td>
<td>118.7±11.1</td>
</tr>
<tr>
<td>24h SBP SD, mm Hg</td>
<td>13.4±3.3</td>
</tr>
<tr>
<td>24h DBP, mm Hg</td>
<td>73.9±7.4</td>
</tr>
<tr>
<td>24h DBP SD, mm Hg</td>
<td>11.7±2.5</td>
</tr>
<tr>
<td>24h HR, bpm</td>
<td>76.3±8.2</td>
</tr>
<tr>
<td>24h HR SD, bpm</td>
<td>13.0±3.7</td>
</tr>
</tbody>
</table>

Data are shown as mean±SD. Twenty-four-hour values are shown as average of the individual 24h mean and standard deviations (SD). SD was taken as measure of overall 24h variability. S indicates systolic; D, diastolic; BP, blood pressure; BMI, body mass index; LVMI, left ventricular mass index; HR, heart rate; M, males; F, females.
TABLE 2. Percentage of the Overall Twenty-Four-Hour BP and HR Variability Accounted for in Individual Subjects by Two Cyclic Components

<table>
<thead>
<tr>
<th>Variable</th>
<th>First Cyclic Component</th>
<th>Second Cyclic Component</th>
<th>Individual Residual Variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>36.3 ± 17.8</td>
<td>12.3 ± 9.7</td>
<td>51.4 ± 16.3</td>
</tr>
<tr>
<td>DBP</td>
<td>39.4 ± 17.2</td>
<td>11.5 ± 9.0</td>
<td>49.1 ± 15.5</td>
</tr>
<tr>
<td>HR</td>
<td>41.1 ± 18.1</td>
<td>7.5 ± 7.2</td>
<td>51.3 ± 17.1</td>
</tr>
</tbody>
</table>

Data are shown as mean (±SD) of individual data.

BP, diastolic BP, and HR. Linear regression models were used because they were found to represent the best fitting models. Data obtained in bivariate analysis always were checked by multivariate analysis after adjustment for age, gender, and 24-hour mean values.14 The last adjustment was made because 24-hour BP variability is related to the mean values.14,17 The regression coefficient (β) and its 95% confidence interval was always taken as an index of association between variables. A P < 0.05 was taken as the level of statistical significance. The symbol ± always refers to the standard deviation of the group mean.

Results
Two thousand fifty-one subjects agreed to participate in the study, a participation rate of 64.1%. There were no differences between participants and nonparticipants in the percentage of the hypertension awareness, antihypertensive drugs on LVM, BP, and HR variability. The demographic, LVMI, BP, HR average and variability values of the 1648 subjects included in the analysis are shown in Table 1.

Table 1 shows the results by fitting the spectral models that accurately reproduce the circadian variations, and thus they accounted for most of the overall variability phenomena, with little or no contribution of the other faster components (Figure 1, right panels). For systolic BP the contribution of the first and the second cyclic components were 77.4% and 19.5%, respectively. The corresponding contributions for diastolic BP were 80.5% and 15.9%, and for HR were 88.7% and 6.9%.

Table 2 shows the results by fitting the spectral models that accounted for most of the variability phenomena in the group as a whole to individual subjects. It is clear that, at variance from the whole population, in the individual subjects the first 2 cyclic components accounted for a much lower fraction of the overall variability, and that, thus, on average the individual residual variability had a substantial magnitude (51.4% for systolic BP, 49.1% for diastolic BP, and 51.3% for HR).

As shown in Table 3, in the whole group of subjects there was a significant positive association between LVMI and gender (on average LVMI was greater in males), age, and 24-hour systolic and diastolic BP averages and standard deviations (LVMI was progressively greater with increasing 24-hour values). LVMI did not correlate with the 2 cyclic components of systolic and diastolic BP variability, but it showed, however, a significant positive relationship with the individual residual variability. The correlations between LVMI and 24-hour systolic BP mean and residual variability are shown in Figure 2.

Table 4 shows the relationship between LVMI and variability phenomena derived by multivariate analysis after LVMI adjustment is made for gender, age, and 24-hour average systolic and diastolic BP values. LVMI did not correlate with the 24-hour standard deviation and the 2 cyclic components of the systolic and diastolic BP variability, but it maintained a significant correlation with systolic and diastolic individual residual BP variability. In both bivariate and multivariate analyses, no association was found between LVMI and 24-hour mean standard deviation, cyclic variability components, and individual residual HR variability.

Discussion
In the subjects recruited for the PAMELA Study, LVMI showed greater values in males than in females and a progressive increase with aging, thereby confirming what has been found in other populations in which, as in the PAMELA population, LVMI was echocardiographically quantified.7-18 Our study, however, provides 2 new sets of data. First, LVMI was also positively related to 24-hour average BP. This is in line with the observation that, in hypertensive patients, cardiac structure depends, among other factors, on average 24-hour BP values.19-20 It extends previous information, however, by showing that, because it relates to LVMI also in the population as a whole, daily life BP participates in the...
and BP variability also holds for a general white population. That is, that BP variability may represent a determinant of organ damage,6 independent of and in addition to, daily life average BP levels. It again expands these findings, however, through the novel evidence that the relationship between organ damage and BP variability also holds for a general white population. That is, that BP variability may represent a determinant of cardiac structure also in individuals in whom both BP and the heart are still normal.

In previous studies on hypertensive patients, alterations in cardiac structure (as well as other types of organ damage) have been reported to be related to overall 24-hour BP variability as quantified by the standard deviation around the mean of all 24-hour BP values.1 This has not been the case with the present study, in which there was no relationship between LVMI, 24-hour BP standard deviation, and the first 2 cyclic components that explained most of the variability value in the population as a whole. Instead, LVMI was related to what we called the individual residual BP variability, ie, the respectable fraction (about 50%) of 24-hour BP variations that could not be explained by the above cyclic components in individual subjects. This suggests that this residual variability is by no means just “noise.” On the contrary, it may represent the tendency for BP to vary in a rather “erratic” fashion that may influence the structure of the heart (and possibly that of the other organs as well) across the heterogeneous characteristics typical of the population. We can speculate that this “erratic” variability is the first to play such a role and that only when BP or LVM values become elevated is this complemented by the participation of the 2 large cyclic variability components and, thus, by the overall BP variability. Because these components reflected, respectively, the regularly occurring day and night BP difference and postprandial hypotension, their later contribution may reflect the intervention of disturbances in BP regulation and homeostasis.

Three additional points deserve to be mentioned. (1) In our study LVMI was similarly related to systolic and diastolic 24-hour BP means, thereby failing to provide any additional population evidence of the clinical superiority of the former over the latter value.21 (2) Because no relationship was found between LVMI and 24-hour HR mean and variability, there was no population evidence of the clinical importance of HR values.22 (3) Our results are in favor of the importance of performing spectral analysis of ambulatory BP monitoring data, despite the limitation represented by their rarefied sampling rate typical of this procedure. By identifying noncyclic components of 24-hour BP, this approach may contribute to the understanding of the BP phenomena involved in the origin and progression of organ damage.

References


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Hypertension. 2002;39:710-714
doi: 10.1161/hy0202.104376

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/39/2/710

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