Long-Term Prognostic Value of Blood Pressure Variability in the General Population
Results of the Pressioni Arteriose Monitorate e Loro Associazioni Study

Giuseppe Mancia, Michele Bombelli, Rita Facchetti, Fabiana Madotto, Giovanni Corrao, Fosca Quarti Trevano, Guido Grassi, Roberto Sega

Abstract—The hypothesis has been advanced that cardiovascular prognosis is related not only to 24-hour mean blood pressure but also to blood pressure variability. Data, however, are inconsistent, and no long-term prognostic study is available. In 2012 individuals randomly selected from the population of Monza (Milan), 24-hour ambulatory blood pressure (Spacelabs 90207) was measured via readings spaced by 20 minutes. Systolic and diastolic blood pressure variability was obtained by calculating the following: (1) the SD of 24-hour, day, and night mean values; (2) the day–night blood pressure difference; and (3) the residual or erratic blood pressure variability (Fourier spectral analysis). Fatal cardiovascular and noncardiovascular events were registered for 148 months. When adjusted for age, sex, 24-hour mean blood pressure, and other risk factors, there was no relationship between the risk of death and 24-hour, day, and night blood pressure SDs. In contrast, the adjusted risk of cardiovascular death was inversely related to day–night diastolic BP difference ($\beta$ coefficient $-0.040; P<0.02$) and showed a significant positive relationship with residual diastolic blood pressure variability ($\beta$ coefficient $0.175; P<0.002$). Twenty-four–hour mean blood pressure attenuation of nocturnal hypotension and erratic diastolic blood pressure variability all independently predicted the mortality risk, with the erratic variability being the most important factor. Our data show that the relationship of blood pressure to prognosis is complex and that phenomena other than 24-hour mean values are involved. They also provide the first evidence that short-term erratic components of blood pressure variability play a prognostic role, with their increase being accompanied by an increased cardiovascular risk. (Hypertension. 2007;49:1-6.)

Key Words: population science ■ risk factors ■ blood pressure monitoring ■ blood pressure variability ■ morbidity ■ mortality

Several years ago, the hypothesis was advanced that the deleterious effects of hypertension on the cardiovascular (CV) system depend not only on the increase in average blood pressure (BP) but also on an increase in the magnitude of the BP variability throughout the day and night.1–3 This found support in the studies that have measured the SD of average BP over the 24 hours or shorter time intervals and showed that BP variability is greater in hypertensive than in normotensive individuals4–7 and that for the same increase in mean 24-hour BP, its magnitude is related to the degree of CV damage.1–3 However, in other studies, the correlation between BP variability and organ damage disappeared after adjustment for other CV and/or metabolic and demographic variables.8,9 Furthermore, and more importantly, the prognostic value of BP variability has never been tested by proper longitudinal studies, the few available ones2,3 being limited by a small study size, a short follow-up, or a conclusion based on surrogate prognostic markers (progression of left ventricular hypertrophy or arterial wall thickening) rather than on the incidence of hard end points, such as CV events.

In the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) Study, we measured 24-hour ambulatory BP in a large sample representative of the population of a town (Monza) in the northeast outskirts of Milan.10 Subjects were followed for 148 months during which fatal events were registered. This allowed us to address for the first time whether in the population BP variability predicts the long-term risk of death.

Methods

The methodology used in the PAMELA Study has been reported in detail elsewhere.10 Briefly, 3200 individuals were randomly selected from the Monza residents to represent the town population within the age decades from 25 to 74 years. The overall participation rate was 64%, that is, 2051 subjects.
Subjects, the residual variance accounted for 49.1% of the DBP variations. Two cyclic components were found to account for 95% of the DBP SD, one related to the day and night SBP and DBP SDs (data not shown). However, as reported above, the day/night BP difference, except for the day/night BP SDs, as well as cyclic and residual or erratic BP variability components derived from Fourier analysis of the 24-hour BP tracing, except for the day/night BP difference, which was smaller in subjects who had died as compared with the alive ones. The non-CV death group resembled the CV death group in terms of the age, sex, and other CV risk factors (see above). The log-rank test was used to compare the curves. Differences in proportions and means were calculated using a Student’s t test or a \( \chi^2 \) test. A \( P < 0.05 \) was taken as the level of statistical significance. Throughout the text the symbol “\( \hat{\beta} \)” refers to the SEM, for which it refers to the Student’s \( t \) test. A \( \hat{\beta} \) coefficient, for which it refers to the SEM.

Data Analysis

As reported previously, in each subject ambulatory BP values were edited from artifacts according to preselected criteria and averaged for the 24 hours, the day (7:00 AM to 11:00 PM), and the night (11:00 PM to 7:00 AM). Valid ambulatory BP readings were >95% of the expected readings (n = 72) with a homogeneous distribution through the entire recording time (2.9 readings per hour). Calculation was made of several indices of diastolic (D) BP variability. First was the D SD of the mean 24-hour, day, and night values. Second was the difference mean in DBP day and night values. Third was the DBP variability derived from spectral analysis of the 24-hour BP tracing. That is, individual DBP readings were averaged for all of the subjects to obtain the circadian DBP profile for the group as a whole, and the fast Fourier transform spectral analysis was applied to the data obtained to identify the cyclic components that accounted for most of the DBP variations. Two cyclic components were found to account for >95% of the DBP SD, one related to the day and night and the other to the preprandial and postprandial DBP difference. These 2 components were tested for their overall ability to fit the circadian DBP profile in each subject, and the sum of squared of the difference between the observed and the fitted profile was taken as the individual residual variability derived from spectral analysis of the circadian DBP profile in each subject, and the sum squared of the

Results

During the 148-month follow-up period, there were 233 deaths, (ie, 11.4% of the sample) of which 69 (29.6%) were reported as CV. Table 1 shows that, compared with subjects alive at the end of the follow-up, those who died of CV disease were older, more likely to be male, and more likely to have a history of CV disease. Prevalence of smoking was similar in the 2 groups, whereas body mass index, serum cholesterol, plasma glucose, history of diabetes and CV disease, and clinic, home, and 24-hour ambulatory BP values were greater in those who had a fatal CV event. This was the case also for all of the indices of BP variability (24-hour, day, and night BP SDs, as well as cyclic and residual or erratic BP variability components derived from Fourier analysis of the 24-hour BP tracing), except for the day/night BP difference, which was smaller in subjects who had died as compared with the alive ones. The non-CV death group resembled the CV death one, although the differences with alive subjects were less pronounced.

Cox proportional hazard models were fitted to explore the relationship between each DBP or SBP variability index and the natural logarithm of the relative risk of CV or all-cause death. \( \hat{\beta} \) Coefficients (the average change in the natural logarithm of the relative risk of death per 1-mm Hg increase in a variability index) were estimated by maximizing the logarithm of the practical likelihood function. For each index, the likelihood ratio was computed to evaluate the goodness of fit of the data to the model used to estimate the risk of death. Data were subjected to multivariate analysis, which included 24-hour average BP, sex, and age plus history of CV disease, smoking, plasma glucose, and total serum cholesterol. This was done because most of the above factors bear a positive relationship with BP variability, and in part because of a stiffening influence on large- and middle-size arteries, with an increase in the pressure excursions within the arterial compartment. The variability indices that predicted the risk of death after the above analysis were further subjected to a step procedure to establish the relative importance of their predictive value (\( \chi^2 \) in relation to 24-hour mean BP. Kaplan–Meier survival curves (CV or all-cause death) were constructed for each BP variability index by stratifying subjects according to its value above and below the median 1, after adjustment for age, sex, 24-hour average BP, and other CV risk factors (see above). The log-rank test was used to compare the curves. Differences in proportions and means were calculated using a \( \chi^2 \) test or a Student’s \( t \) test. A \( P < 0.05 \) was taken as the level of statistical significance. Throughout the text the symbol “\( \hat{\beta} \)” refers to the SD of the mean except for the \( \hat{\beta} \) coefficients, for which it refers to the SEM.
section) the relationship was almost invariably lost. This was not the case, however, for other indices of BP variability. The adjusted risk of CV and all-cause death showed a significant inverse relationship with almost all of the day/night BP differences, as well as in several instances with the first cyclic component, derived from the Fourier analysis of the 24-hour BP tracing. It showed, in contrast, a significant positive relationship with the Fourier analysis-derived residual com-

**TABLE 2.** \(\beta\) Coefficients and Goodness of Fit of the Relationships Between SBP and DBP Variability and CV and All-Cause Death Risk

<table>
<thead>
<tr>
<th>Variable</th>
<th>(\beta) Coefficient</th>
<th>(P)</th>
<th>Goodness of Fit (LRT)</th>
<th>(P)</th>
<th>(\beta) Coefficient</th>
<th>(P)</th>
<th>Goodness of Fit (LRT)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>SD 24 h</td>
<td>-0.0184±0.033</td>
<td>0.5752</td>
<td>0.321</td>
<td>0.571</td>
<td>0.0005±0.018</td>
<td>0.9759</td>
<td>0.001</td>
<td>0.9748</td>
</tr>
<tr>
<td>SD day</td>
<td>0.0383±0.032</td>
<td>0.2257</td>
<td>1.371</td>
<td>0.241</td>
<td>0.0313±0.017</td>
<td>0.0659</td>
<td>3.179</td>
<td>0.0746</td>
</tr>
<tr>
<td>SD night</td>
<td>0.0103±0.033</td>
<td>0.7577</td>
<td>0.093</td>
<td>0.7604</td>
<td>0.0180±0.019</td>
<td>0.3396</td>
<td>0.887</td>
<td>0.3463</td>
</tr>
<tr>
<td>(\Delta) day/night</td>
<td>-0.0245±0.012</td>
<td>0.0385</td>
<td>4.281</td>
<td>0.0385</td>
<td>-0.0154±0.007</td>
<td>0.0268</td>
<td>4.900</td>
<td>0.0269</td>
</tr>
<tr>
<td>First cyclic component</td>
<td>-0.0497±0.024</td>
<td>0.0351</td>
<td>-0.0158±0.013</td>
<td>0.2155</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second cyclic component</td>
<td>0.0323±0.035</td>
<td>0.3531</td>
<td>5.384</td>
<td>0.1457</td>
<td>-0.0024±0.020</td>
<td>0.9056</td>
<td>3.569</td>
<td>0.3119</td>
</tr>
<tr>
<td>Residual component</td>
<td>0.0488±0.051</td>
<td>0.3363</td>
<td>0.0465±0.028</td>
<td>0.0948</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD 24 h</td>
<td>0.0287±0.043</td>
<td>0.5053</td>
<td>0.440</td>
<td>0.5071</td>
<td>0.0356±0.024</td>
<td>0.1379</td>
<td>2.180</td>
<td>0.1398</td>
</tr>
<tr>
<td>SD day</td>
<td>0.1029±0.040</td>
<td>0.0108</td>
<td>6.269</td>
<td>0.0123</td>
<td>0.0690±0.022</td>
<td>0.0018</td>
<td>9.440</td>
<td>0.0021</td>
</tr>
<tr>
<td>SD night</td>
<td>0.0509±0.041</td>
<td>0.2198</td>
<td>1.447</td>
<td>0.2290</td>
<td>0.0471±0.023</td>
<td>0.0418</td>
<td>3.396</td>
<td>0.0456</td>
</tr>
<tr>
<td>(\Delta) day/night</td>
<td>-0.0395±0.017</td>
<td>0.0187</td>
<td>5.260</td>
<td>0.0218</td>
<td>-0.0186±0.010</td>
<td>0.0593</td>
<td>3.503</td>
<td>0.0613</td>
</tr>
<tr>
<td>First cyclic component</td>
<td>-0.0832±0.033</td>
<td>0.0109</td>
<td>-0.0285±0.017</td>
<td>0.0987</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second cyclic component</td>
<td>0.0263±0.027</td>
<td>0.5724</td>
<td>14.009</td>
<td>0.0029</td>
<td>-0.0046±0.026</td>
<td>0.8591</td>
<td>14.416</td>
<td>0.0024</td>
</tr>
<tr>
<td>Residual component</td>
<td>0.1752±0.056</td>
<td>0.0016</td>
<td>0.1180±0.031</td>
<td>0.0002</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data adjusted for 24-hour average BP, age, sex, previous CV events, smoking, serum cholesterol, and plasma glucose. LRT indicates likelihood ratio test.
ponent of BP variability. After adjustment for confounders, the residual component of DBP variability was the best predictor of both CV and all-cause death, followed by the alteration of the day/night DBP difference and the 24-hour mean DBP values (Table 3). The adjusted relationship between the risk of CV and all-cause death with the erratic variability, day–night difference, and 24-hour mean is shown in Figure 2 for the actual range of values occurring in the population. As shown by the adjusted (see Methods section) Kaplan–Meier curves of Figure 3 (top), in subjects with a residual DBP variability above the median value, CV mortality was significantly greater than in those with a residual BP variability below the median value, with the 2 curves showing an early and progressive divergence. This was also the case for subjects with a day/night DBP difference below as compared with above the median value. The trends were similar for all-cause mortality (Figure 3, bottom), although the between-curve differences did not achieve statistical significance.

Discussion

In the PAMELA population, the long-term risk of CV mortality showed a positive relationship with 24-hour, day, and night SBP and DBP SDs. However, in most instances, the relationship disappeared after adjustment for 24-hour average BP, age, and other CV risk factors, thus providing no solid longitudinal evidence in favor of their independent adverse prognostic role. However, this was not the case for 2 other indices of BP variability that were used in the study, that is, the BP difference between day and night and the 24-hour BP variations that were not accounted for by the cyclic components of the 24-hour BP profile identified by the Fourier analysis of the 24-hour BP tracing, thus expressing the tendency of BP to vary erratically throughout the day and night. The day/night BP difference was inversely related to the risk of fatal CV events, which means that subjects in whom the nocturnal BP reduction from the higher daytime value was less had a greater probability of dying from CV disease. On the contrary, residual BP variability was positively related to the risk of fatal CV events, which means that CV death was more likely in subjects in whom erratic BP variations were more pronounced. For both indices, the relationship with the risk of CV death remained significant in a multivariate analysis that included 24-hour mean BP values, age, sex, and major CV risk factors, thereby documenting their independent contribution to patients’ prognosis. This was reinforced by the evidence that, in several instances, these indices of BP variability showed an independent relationship also with the risk of all-cause death.

Several other results of our study deserve to be mentioned. First, in addition to providing the first demonstration of an adverse long-term prognostic role of erratic BP variability, our data suggest that this role is by no means marginal. This is because the increase in the risk of CV death with an increase in erratic DBP variability was steep (Figure 2). Furthermore, in the stepwise procedure reported in Table 3, the ability of erratic DBP variability to predict both all-cause and CV death was superior to that related to an alteration of the day/night BP difference, as well as of 24-hour mean BP values. Thus, the probability of dying appears to independently originate from a variety of BP-related phenomena, with a substantial contribution of erratic BP changes.

<table>
<thead>
<tr>
<th></th>
<th>DBP</th>
<th>( \chi^2 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual</td>
<td>30.8035</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>( \Delta ) day/night</td>
<td>21.3414</td>
<td>0.0010</td>
<td></td>
</tr>
<tr>
<td>24-h</td>
<td>16.1096</td>
<td>0.0029</td>
<td></td>
</tr>
<tr>
<td>All-cause death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual</td>
<td>31.6911</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>( \Delta ) day/night</td>
<td>19.8714</td>
<td>0.0013</td>
<td></td>
</tr>
<tr>
<td>24-h</td>
<td>16.4492</td>
<td>0.0025</td>
<td></td>
</tr>
</tbody>
</table>

Data adjusted for confounders (see Table 2). Symbols as in the preceding figures and tables.
Second, previous studies have reported that hypertensive nondippers, that is, individuals with a high BP and an attenuation of the nocturnal BP fall, have, on average, a greater degree of progression of organ damage, as well as a greater risk of a cerebrovascular or CV events than hypertensive dippers, that is, individuals with no or less attenuation of the nighttime BP fall. It has also been reported that nocturnal BP values are prognostically more important than the diurnal ones. This is in line with our present data, which, in addition, show that the adverse prognostic influence of the nondipping phenomenon is also evident when quantified indirectly by the first cyclic component of the Fourier analysis of the 24-hour BP tracing. Furthermore, and more importantly, the greater risk of death associated with an attenuation of the nighttime BP fall is manifest also at a general population level over a much longer follow-up than that explored previously. Finally, the relationship between the risk of death and the day/night BP difference holds also when adjustment is made in a multivariate analysis for differences in 24-hour average BP. This provides strong support for the concept that a greater BP reduction at night protects the CV system, presumably by reducing for a considerable fraction of the 24-hour period the load to the heart and vessels.

Third, in the subjects of the PAMELA Study, the increased risk of CV death associated with an increased magnitude of erratic BP variability was more evident for DBP than for SBP, of which the contribution to patient prognosis did not usually survive adjustment for other potentially confounding factors. We do not have an explanation for this finding, which is not in line with the importance of SBP documented in several epidemiological studies. We may speculate, however, that 2 factors are involved. First is the relatively high number of young and middle-age subjects in the PAMELA Study, because the prognostic significance of SBP and DBP increases and decreases, respectively, with aging. Second is the greater dependence of overall BP variability on DBP rather than on SBP, given that DBP covers a much greater part of the cardiac cycle.

Fourth, the reasons why the erratic BP variability adversely affects survival can only be a matter of speculation. A plausible hypothesis, however, is that the relatively fast BP changes that are quantified by this approach exert a traumatic effect on the CV system, favoring the development and progression of atherosclerosis.

Our results have limitations that need to be mentioned. First, the intermittent BP readings (every 20 minutes) that can be obtained by noninvasive BP monitoring did not allow the fastest and shortest BP changes to be measured, thereby offering an incomplete picture of the multifold components that characterize day and night BP variations. This can only be obtained by intra-arterial BP monitoring or by complex finger beat-to-beat BP monitoring devices that can hardly be used in large-scale studies, particularly when the general population is involved. Second, our population was characterized by a limited number of CV deaths. This limited the power of the study to statistically demonstrate the relationship between the variability phenomena under investigation and fatal CV events. However, the results on the importance...
of erratic BP variability for the risk of CV death were reflected by those on all-cause death, of which the number was 4 times as large.

**Perspectives**

Our data show that the relationship of BP to prognosis is complex and that phenomena other than 24-hour mean values are significantly involved. These phenomena consist of 24-hour variability, of which the components, however, have opposite effects on the risk of mortality. An increase in variability because of greater day/night BP differences is associated with CV protection, which, in contrast, is reduced when there is an increase in erratic BP variability.

**Disclosures**

None.

**References**

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