Factors Affecting Ambulatory Blood Pressure Reproducibility
Results of the HARVEST Trial

Paolo Palatini, Paolo Mormino, Cristina Canali, Massimo Santonastaso, Giuseppe De Venuto, Giuseppe Zanata, Achille C. Pessina

Abstract  To assess the reproducibility of ambulatory blood pressure, we recorded 24-hour blood pressure twice 3 months apart in 508 hypertensive subjects participating in the HARVEST trial using a noninvasive technique. Blood pressure was measured every 10 minutes during the daytime and 30 minutes during the nighttime. Reproducibility was better for ambulatory than for office blood pressure. It was greater for 24-hour than for daytime blood pressure and lowest for nighttime blood pressure. The reproducibility of blood pressure variability (standard deviation) was poorer than that of the average values. A small but significant decrease in average daytime blood pressure (−0.8/−1.0 mm Hg) and virtually no change in nighttime blood pressure (+0.5/+0.1 mm Hg) were observed at repeat recording. Reducing the sampling rate by 50% caused only a small impairment of the reproducibility indexes of both the average values and variability. Blood pressure reduction was greater during the first and last hours of the recordings, indicating an effect of the hospital environment on the between-monitoring difference. Changes in body weight (−0.7 kg, P=0.006, at repeat recording) were related to those of 24-hour diastolic blood pressure (P<.05). In conclusion, patient reaction to medical environment and changes of body weight seem to account for most of the change in 24-hour blood pressure that occurs over a 3-month period. (Hypertension. 1994;23:211-216.)

Key Words  • hypertension, essential • blood pressure monitoring, ambulatory • blood pressure • reproducibility of results • clinical trials • blood pressure variability

Methods

Subjects
The study was carried out in 508 consecutive white subjects (375 men and 133 women) who took part in the HARVEST study, a trial on the predictive value of ABPM for the development of fixed hypertension in patients with borderline to mild hypertension. Subjects aged 18 to 45 years with diastolic BP from 90 to 100 mm Hg or isolated systolic hypertension are eligible for the HARVEST study. The protocol was approved by the Ethics Committee of the trial, and the subjects gave informed consent. Mean BP in the 508 subjects considered in this report was 147±11/94±5 mm Hg, their mean age 33±9 years, and their body weight 76.3±13 kg. None of them had ever taken antihypertensive therapy.

Office Blood Pressure
Following the recommendations of the British Society of Hypertension, we measured BP three times after subjects had rested 5 minutes in the supine position. The mean of the three readings was defined as office BP. Phase V Korotkoff sounds were considered as diastolic BP, except in subjects with sounds tending to zero, in whom phase IV was taken. Standard (12×24 cm) cuffs were used in subjects with arm circumference less than 35 cm and large (15×30 cm) cuffs in those with arm circumference of 35 cm or greater. Office BP was measured just before the application of the ABPM device.

Ambulatory Blood Pressure Monitoring
In 455 subjects 24-hour ABPMs were obtained with the A&D TM-2420 model, which uses a microphone to detect Korotkoff sounds, and in the other 53 with the ICR Spacelabs 90207, which uses an oscillometric method. Both of these devices were previously validated. Before starting the study all investigators underwent common training procedures on the use of the recorders to ensure methodological homogeneity. The device was always applied and taken away in the
hospital, using a cuff of the same size as that used to measure office BP. Before the recording was started, the device was checked against a mercury sphygmomanometer by means of a Y tube. Six subsequent measurements provided by the recorder, three with subjects in the supine and three in the standing position, had to agree closely with simultaneous ambulatory measurements performed by the doctor; otherwise, patients were excluded from the study. When the device was in operation, subjects were requested to keep their arm still and to remain motionless. They were invited to follow their ordinary daily routine, to avoid strenuous physical activity, and as far as possible to perform the same pattern of activity during the two recordings. They were asked to go to bed not later than 11 PM. BP was measured every 10 minutes during waking hours (6 AM to 11 PM) and every 30 minutes during the nighttime.

**Data Analysis**

Measurements recorded during the ambulatory period were stored on a personal computer and loaded on a diskette. All ABPMs were sent to the Coordinating Office in Padova where they were screened for editing of artificial values based on previously described criteria. Only recordings containing error measurements of 20% or less were considered acceptable for evaluation. Means of 126±16 unedited readings and 109±20 valid readings were obtained during the 24 hours. The arithmetic average of the edited pressures was used as the ambulatory measurement for each recording period. Average 24-hour BP, daytime BP (6 AM to 11 PM), nighttime BP (11 PM to 6 AM), and day-night BP difference were calculated. The period from midnight to 5 AM was also averaged to obtain a more reliable estimate of a period of sleep. The standard deviation was calculated for each of these periods as an index of BP variability. To ascertain whether reproducibility was better for some periods of the day, we subdivided the 24 hours into eight 3-hour periods, starting from midnight. Moreover, to test the effect of the hospital environment on the reproducibility and adaptation response to ABPM in the 391 subjects in whom the monitoring apparatus was applied and taken away in the morning (from 9 AM to 12:59 PM), we averaged the four 2-hour periods that immediately followed the application of the device and the last 2-hour period just before the end of the recording. Finally, to assess the effect of the frequency of measurements on the results, we calculated average 24-hour BP, daytime BP, and nighttime BP and their standard deviations using 50% of the original readings by sequentially excluding intervening measurements. With this approach one measurement every 20 minutes was considered from 6 AM to 11 PM and one every 60 minutes during the remaining hours. Body mass index was calculated as the ratio of body weight to squared height.

**Statistics**

Baseline and repeat periods of recording were compared with the Student’s t test for paired observations. The other comparisons were made by means of the Student’s t test for unpaired observations or the analysis of variance and Tukey’s post hoc test where indicated. Categorical variables were analyzed with the x² test. For correlations the Pearson test was used. BP reproducibility was assessed using the Bland-Altman approach. Change between duplicate recordings was calculated by subtracting the first from the second recording, taking into account the sign of the difference. Consistency was obtained by calculating the difference between baseline and repeat recording, disregarding the sign of the difference. Repeatability was defined as twice the standard deviation of the changes between the two repeated recordings. Significance was taken as a probability value less than .05.

**Results**

A total of 9.3% of the ABPMs were rejected because the artificial BP readings exceeded 20% of the total measurements. Age, arm size, and BP levels were not different in the subjects with failing recordings and in those with acceptable ABPMs. Instead, rejected ABPMs were more common in women than in men (x²=4.9, P<.03).

Overall, 128 016 BP measurements were obtained in the 508 subjects with acceptable ABPMs during the two recordings. Of these, 13% were automatically rejected by the machine or the observer after inspection of the tracing. An average number of 89±16 valid readings was obtained during the daytime and 20±7 readings during the nighttime. Baseline and repeat ABPM values are reported in Table 1. Correlation coefficients of baseline office with 24-hour and daytime systolic BP were .30 and .31 (P<.0001). For diastolic BP they were both .41 (P<.0001).

Correlation coefficients between baseline and repeat ABPMs are reported in Table 1. They were greater for average values than for the standard deviation and better for 24-hour BP than for daytime or nighttime BP.

**Blood Pressure Reproducibility**

Change, consistency, and repeatability for office BP and the various periods of ABPM are reported in Table 2. All indexes of reproducibility were better for ABPM than for office BP. Within ABPM data all changes from baseline to repeat recording were less than or equal to 1 mm Hg. A small significant decrease was observed for daytime BP and a negligible insignificant increase for

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**Table 1. Average Values, Standard Deviation, and Correlation Coefficients of Ambulatory Blood Pressure in 508 Subjects**

<table>
<thead>
<tr>
<th>Period</th>
<th>Baseline Mean (SD)</th>
<th>Repeat Mean (SD)</th>
<th>CC</th>
<th>Baseline Mean (SD)</th>
<th>Repeat Mean (SD)</th>
<th>CC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average 24-hour</td>
<td>130.1±11</td>
<td>129.7±11</td>
<td>.71*</td>
<td>81.3±8</td>
<td>80.6±8</td>
<td>.68*</td>
</tr>
<tr>
<td>Average daytime</td>
<td>133.3±11</td>
<td>132.5±11</td>
<td>.69*</td>
<td>83.5±8</td>
<td>82.3±8</td>
<td>.66*</td>
</tr>
<tr>
<td>Average nighttime</td>
<td>116.2±11</td>
<td>116.6±12</td>
<td>.61*</td>
<td>73.0±9</td>
<td>73.0±8</td>
<td>.60*</td>
</tr>
</tbody>
</table>

| 24-Hour SD      | 14.7±3             | 14.5±3           | .35*| 10.6±2             | 10.5±2           | .39*|
| Daytime SD      | 13.3±4             | 13.2±3           | .33*| 9.9±2              | 9.9±2            | .34*|
| Nighttime SD    | 11.4±2             | 11.4±4           | .31*| 8.3±2              | 8.6±3            | .161|

BP indicates blood pressure; CC, correlation coefficient; and SD, standard deviation. *P<.0001, tP<.01.
TABLE 2. Reproducibility of Mean Values of Office and Ambulatory Blood Pressures in 508 Subjects

<table>
<thead>
<tr>
<th>Period</th>
<th>Change</th>
<th>P</th>
<th>Consistency</th>
<th>Repeatability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office SBP</td>
<td>-5.9</td>
<td>&lt;.0001</td>
<td>10.6</td>
<td>25.6</td>
</tr>
<tr>
<td>Office DBP</td>
<td>-3.1</td>
<td>&lt;.0001</td>
<td>6.6</td>
<td>16.7</td>
</tr>
<tr>
<td>24-Hour SBP</td>
<td>-0.4</td>
<td>NS</td>
<td>6.3</td>
<td>16.5</td>
</tr>
<tr>
<td>24-Hour DBP</td>
<td>-0.7</td>
<td>.009</td>
<td>4.8</td>
<td>12.8</td>
</tr>
<tr>
<td>Daytime SBP</td>
<td>-0.8</td>
<td>.031</td>
<td>6.9</td>
<td>17.7</td>
</tr>
<tr>
<td>Daytime DBP</td>
<td>-1.0</td>
<td>.001</td>
<td>5.2</td>
<td>13.7</td>
</tr>
<tr>
<td>Nighttime SBP</td>
<td>0.5</td>
<td>NS</td>
<td>8.1</td>
<td>21.0</td>
</tr>
<tr>
<td>Nighttime DBP</td>
<td>0.1</td>
<td>NS</td>
<td>5.7</td>
<td>15.0</td>
</tr>
<tr>
<td>Day-night difference SBP</td>
<td>-1.3</td>
<td>.012</td>
<td>7.8</td>
<td>20.0</td>
</tr>
<tr>
<td>Day-night difference DBP</td>
<td>-1.1</td>
<td>.002</td>
<td>5.6</td>
<td>14.5</td>
</tr>
</tbody>
</table>

SBP Indicates systolic blood pressure in millimeters of mercury; DBP, diastolic blood pressure. The Nighttime period was 11 PM to 6 AM.

nighttime BP. However, a somewhat greater and significant increase in systolic BP was observed when the period from midnight to 5 AM was considered in computing nighttime BP (+1.0±12 mm Hg, \( P=.038 \)). Consistency and repeatability were better for 24-hour BP than for daytime BP. The poorest values were observed for nighttime BP and nighttime BP fall.

The standard deviation was unchanged at the second monitoring (Table 3). Consistency and repeatability values were poorer than those for the mean levels of ABPM.

The BP change from the first to the second recording was similar in the subjects who underwent ABPM with the A&D TM-2420 and in those who used the Spacelabs device. Consistency and repeatability were similar in the two groups for systolic BP, whereas for diastolic BP they were a little better for the Spacelabs device.

The between-monitoring BP change was also analyzed within each of the 16 centers that provided ABPM data. Although a certain variability was present from center to center, Tukey's test showed that the between-monitoring 24-hour systolic and diastolic BP change was not different in the 16 centers regardless of whether the sign was taken into account.

Fifty Percent Reduction of Measurement Frequency

Changes of BP from the first to the second recording and consistency and repeatability values were a little greater when only 50% of the readings were taken into account. The same applies to standard deviation, which also showed negligible increases in the indexes of consistency and repeatability when calculated using 50% of the BP readings, except for the nighttime period, during which the increases were greater.

Three-Hour Periods

Analysis of the eight periods (Fig 1) showed that the greatest decrease in BP from baseline to repeat study was present between 9 AM and noon for both systolic and diastolic BP. On the other hand, a significant

TABLE 3. Reproducibility of Ambulatory Blood Pressure Standard Deviation In 508 Subjects

<table>
<thead>
<tr>
<th>Period</th>
<th>Change</th>
<th>P</th>
<th>Consistency</th>
<th>Repeatability</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-Hour SBP</td>
<td>0.2</td>
<td>NS</td>
<td>2.9</td>
<td>7.5</td>
</tr>
<tr>
<td>24-Hour DBP</td>
<td>0</td>
<td>NS</td>
<td>1.6</td>
<td>4.1</td>
</tr>
<tr>
<td>Daytime SBP</td>
<td>0.1</td>
<td>NS</td>
<td>2.9</td>
<td>8.3</td>
</tr>
<tr>
<td>Daytime DBP</td>
<td>0</td>
<td>NS</td>
<td>1.6</td>
<td>4.4</td>
</tr>
<tr>
<td>Nighttime SBP</td>
<td>-0.4</td>
<td>NS</td>
<td>3.5</td>
<td>9.5</td>
</tr>
<tr>
<td>Nighttime DBP</td>
<td>-0.4</td>
<td>.02</td>
<td>2.4</td>
<td>6.2</td>
</tr>
</tbody>
</table>

SBP Indicates systolic blood pressure in millimeters of mercury; DBP, diastolic blood pressure. The Nighttime period was 11 PM to 6 AM.
increase in systolic BP was observed from midnight to 3 AM. During the other periods of time, BP changes were all within 1 mm Hg. Consistency and repeatability were similar throughout the 24 hours and always poorer than those values shown by 24-hour, daytime, and nighttime BP (consistency range: systolic, 10.1 to 8.5; diastolic, 7.7 to 5.9; repeatability range: systolic, 26.6 to 22.8; diastolic, 20.0 to 15.7).

**Effect of the Hospital Environment**

Comparisons of the 2-hour periods obtained by averaging the values soon after the commencement of the monitoring irrespective of the time of the day in the 391 subjects who underwent ABPM from 9 AM to 12:59 PM showed a clear effect of hospital environment on the between-monitoring BP difference. In fact, changes of systolic and diastolic BP were greater and significant during the first 2 hours after the beginning of the recording (Fig 2). Changes progressively decreased during the following 2-hour periods and increased again at the end of the recording period. Instead, consistency and repeatability showed few changes throughout the five 2-hour periods examined (consistency range: systolic, 10.0 to 11.3; diastolic, 7.3 to 8.8; repeatability range: systolic, 26.5 to 29.8; diastolic, 18.8 to 22.2). The start (and stop) time of recording affected the between-monitoring difference only marginally. In fact, the mean 24-hour BP change with sign was \(-0.7\pm8/0.9\pm2\) mm Hg in the 391 subjects who started the ABPM before 1 PM and \(+0.5\pm8/0.2\pm6\) mm Hg in the 117 who started the ABPM after 1 PM (P=.NS). The mean changes without sign were \(6.3\pm5/4.8\pm4\) mm Hg and \(6.1\pm5/4.7\pm4\) mm Hg, respectively (P=.NS).

**Patient Clinical Characteristics**

Age was not correlated with the reproducibility indexes, which were similar in men and women.

Only 13 subjects required the large-sized cuff. Their indexes of reproducibility did not significantly differ from those of the rest of the population. In the 495 subjects who used the normal-sized cuff there was no correlation between the difference in BP from the first to the second ABPM and the body weight or mass index.

Body weight decreased from 76.2±13 to 75.5±13 kg (P=.006) and body mass index from 25.4±3 to 25.2±3 kg/m² (P=.01) during the 3 months of observation. A significant but weak correlation was found between the changes of 24-hour diastolic BP and body weight (r=-.11) or mass index (r=-.12) from the first to the second ABPM (both P<.05). When the between-monitoring systolic BP difference (without sign) was correlated with the semisum of the two ABPM 24-hour systolic BP averages, a significant but weak correlation was found between the two variables (r=-.17, P<.001).

**Discussion**

Although adaptation to measurement is lower for ABPM than for office BP,1,2,3,15 some authors have reported a substantial decrease in BP at the second of two ABPMs.4,6,14,15 These results were drawn from small samples of subjects ranging from less than 103615 to 84 subjects.1 Only recently were some prospective multicenter studies initiated7-16 with the purpose of also testing the reproducibility of ABPM.

Our results, obtained from the largest population of subjects hitherto studied, show that a small but significant decrease in average daytime BP (within 1 mm Hg) and virtually no change in average nighttime BP occur when ABPM is performed twice 3 months apart. However, when a more restrictive approach was used to compute nighttime BP (from midnight to 5 AM), an increase of 1 mm Hg in systolic BP could be observed at the second monitoring.

Confirming previous results from our group6 and other authors,1,2 ABPM in the present report showed a better reproducibility than office BP, especially for 24-hour BP. Nighttime BP was less reproducible than daytime BP, probably because of sleep disturbance, which has been reported to occur in two thirds of patients.20

In the HARVEST trial BP during daytime is measured every 10 minutes to allow a more reliable assessment of BP variability. Indeed, Di Rienzo et al21 showed with intra-arterial ABPM that by using 10-minute intervals a fairly good quantitation of standard deviation could be obtained, and by using 15-minute or greater intervals the discrepancies with the beat-to-beat analysis became larger. However, in the present report the 10-minute interval approach did not provide a better consistency and repeatability than the 20-minute sam-
sampling except for the nighttime period. In agreement with Kelly et al., reproducibility was lower for nighttime than for daytime standard deviation. Overall, the reproducibility of BP variability appeared to be worse than that of average values, as shown by the lower value of the between-monitoring correlation coefficients, a finding also reported by Des Combes et al. This might be due to the insufficient number of BP readings used to compute standard deviation, as we measured only one of the 500 to 1000 BP values present within a 10-minute period. On the other hand, we cannot exclude the possibility that BP variability is actually less reproducible than the average BP, as it could be influenced to a greater extent by day-to-day variations in the pattern of a subject's activities. To our knowledge no studies performed with intra-arterial recordings have addressed this issue. Finally, the calculation of BP standard deviation may be affected to a greater extent by outliers than average BP and is therefore more influenced by the presence of potential artifacts.

The analysis of the 24-hour curve subdivided into periods of 3 hours showed that by far the largest difference between the two monitorings occurred between 9 AM and noon. In no other daytime period were the differences significant for systolic BP, whereas they barely attained the level of statistical significance for diastolic BP. During the nighttime a significant increase in systolic BP was observed from the first to the second recording during the period from midnight to 3 AM. Although the nighttime rise in BP at the second ABPM is difficult to explain, one could argue that the previous ABPM experience generates in the subject the expectation of a disturbed sleep, thereby limiting his or her ability to fall asleep.

Some authors have suggested that BP recorded over a short period of time can be as adequate as 24-hour recording. This would minimize the cost and the inconvenience of the technique. In agreement with the data by Conway et al., our results indicate that the reproducibility of BP recorded over a short period of time (3 hours) is lower than that of the entire 24-hour period and that such an approach does not have the same clinical value as a 24-hour recording.

It is well known that BP measured in the hospital is higher than at home and that BP steadily decreases when ABPM is performed twice 3 months apart. Subject reaction to the medical environment mostly accounts for the between-monitoring difference. To avoid this drawback, one could advise subjects to switch on the monitor once at home and switch it off before leaving home for the hospital at the end of the 24 hours. The present data further confirm the better reproducibility of ABPM compared with office BP. Reducing the number of readings by 50% affects the reproducibility of both ABPM and BP at the second recording.

It is known that changes in body weight are accompanied by parallel variations in BP. Recent reports indicate that a drop of 0.5 mm Hg or greater in BP occurs for every 1 kg reduction in body weight. Therefore, the 0.7 kg weight loss observed in our population could at least partially account for the slight decline in ABPM found at the second recording. This problem has never been taken into account when ABPM reproducibility was assessed.

Among the other clinical factors explored, only ABPM levels at the second recording affected only to a small extent the mean 24-hour BP change, as the reproducibility indexes were not significantly different in the subjects who started the ABPM in the morning and afternoons.

In conclusion, the present results show that a slight but significant decrease in average daytime BP occurs when ABPM is performed twice 3 months apart. Subject reaction to the medical environment mostly accounts for the between-monitoring difference. To avoid this drawback, one could advise subjects to switch on the monitor once at home and switch it off before leaving home for the hospital at the end of the 24 hours. The present data further confirm the better reproducibility of ABPM compared with office BP. Reducing the number of readings by 50% affects the reproducibility of both mean values and standard deviation only to a negligible extent. Finally, changes in body weight, which may occur during the between-monitoring period, can affect ABPM levels at the second recording.

Acknowledgments

References


Factors affecting ambulatory blood pressure reproducibility. Results of the HARVEST Trial. Hypertension and Ambulatory Recording Venetia Study.
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