

# Variability of office, 24-hour ambulatory, and self-monitored blood pressure measurements

Roderick E Warren, Tom Marshall, Paul L Padfield and Sigrun Chrubasik

## ABSTRACT

### Background

The diagnosis of hypertension is difficult when faced with several different blood pressure measurements in an individual. Using the average of several office measurements is recommended, although considerable uncertainty remains. Twenty-four-hour ambulatory monitoring is often considered the gold standard, but self-monitoring of blood pressure has been proposed as a superior method.

### Aim

Determination of within-individual variability of blood pressure measured in the office, by ambulatory monitoring, and by a week of self-monitoring.

### Design of study

Retrospective analysis of a clinical trial of 163 subjects.

### Method

Within-patient variability of office and ambulatory blood pressure was determined from measurements at 0 and 6 weeks. Subjects had performed self-monitoring of blood pressure twice each morning and evening, for at least 6 weeks; variability was determined from the means of week 1 and week 6.

### Results

The within-individual coefficients of variation (CVs) for systolic blood pressure were: office, 8.6%; ambulatory, 5.5%; self, 4.2%. Equivalent values for diastolic blood pressure were 8.6%, 4.9%, and 3.9%. CVs tended to be lower with longer self-monitoring duration, and higher with longer intervals between self-monitoring.

### Conclusion

Office blood pressure is impractical for precise assessment, as 10–13 measurements are required to give the accuracy required for rational titration of antihypertensive drugs. Twenty-four-hour ambulatory monitoring is better than a single office measurement, but considerable uncertainty remains around the estimate. A week of self-monitoring appears to be the most accurate method of measuring blood pressure, but remains imperfect. Further research may identify superior self-monitoring schedules. Given the inherent accuracy in blood pressure measurement, the importance of considering overall cardiovascular risk is emphasised.

### Keywords

ambulatory; blood pressure; blood pressure monitoring; home; hypertension; self.

## INTRODUCTION

The usual approach to high blood pressure begins with assessment of need for pharmacologic or other therapy, followed by titration of therapy according to response. Implicitly, an accurate measurement of an individual's blood pressure is required at each stage. But blood pressure is variable: it is unlikely that two measurements in the same individual will be identical, whether taken minutes, days, or months apart, and the range of measured values may be quite wide. This variation is partly due to inaccuracies in the measurement process (which may be irreducible), but blood pressure may also genuinely change between day and night, weekend and working day, stress and relaxation, and illness and health, to list but a few possibilities.

This natural variability makes the apparently simple question 'Is this patient's blood pressure too high?' rather complex. Taking the mean of several blood pressure measurements improves the accuracy of the estimate of 'true underlying' blood pressure. In recognition of this, the current Joint British Societies guidelines recommend that 'the average of two

*RE Warren, MRCP, MD, consultant physician, Macleod Diabetes & Endocrine Centre, Royal Devon & Exeter Hospital, Exeter. PL Padfield, FRCP, professor of hypertension, Metabolic Unit, Western General Hospital, Edinburgh. T Marshall, MSc, PhD, MRCP, FFPH, senior lecturer, Health & Population Sciences, Unit of Public Health, Epidemiology and Biostatistics, University of Birmingham, Edgbaston, Birmingham. S Chrubasik, MD, professor, Institute of Forensic Medicine, University of Freiburg, Freiburg, Germany.*

### Address for correspondence

Roderick Warren, Macleod Diabetes & Endocrine Centre, Royal Devon & Exeter Hospital, Barrack Road, Exeter.  
E-mail: roderick.warren@nhs.net

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## How this fits in

This study has quantified the variability, or reproducibility, of blood pressure measured in the office, by 24-hour ambulatory monitoring, and by self-monitoring at home. A week of self-monitoring was found to be the most reproducible method, and was well-tolerated by patients, but no method could provide an accuracy better than about  $\pm 8$ – $10$  mmHg. This suggests that some common practices are illogical, such as making small adjustments in antihypertensive drug doses, or classifying individual patients as non-responders to individual drugs.

readings at each of several measurements should be used to guide the decision to treat,<sup>1</sup> but a precise number of measurements is not specified. However, the number of measurements that ought to be made can be calculated if we decide (i) how variable blood pressure is in a typical individual; (ii) how accurate we wish our estimate to be; and (iii) how confident we wish to be that the estimate is within the specified accuracy range.

It would be impractical to measure the variability of blood pressure in an individual, because a tremendously large number of measurements would be required. However, when a large number of individuals have had blood pressure measured two or more times, such as in a clinical trial, variability for the 'average patient' can be accurately computed. Assuming that repeat blood pressure measurements show a normal distribution around a mean value, the variability can be represented by the standard deviation (SD). Since the SD is likely to be greater in people with a higher mean blood pressure, the coefficient of variation (CV) is preferable. The CV expresses the SD as a percentage of the mean.

The desired accuracy of a blood pressure estimate is somewhat arbitrary. Antihypertensive drugs in standard dose reduce systolic blood pressure by about 9 mmHg.<sup>2</sup> The authors suggest that for rational drug titration, the minimum accuracy for blood pressure estimates is about half that, or  $\pm 5$  mmHg. This permits identification of the number of different drugs that are required to achieve a blood pressure target, although is not sufficient for precise dose adjustment of individual drugs. The desired confidence level is also arbitrary, but the authors suggest that 80% confidence is reasonable.

The difficulties inherent in office (or clinic) blood pressure measurement are well recognised, and 24-hour ambulatory blood pressure monitoring is often considered the gold standard alternative. However, average blood pressure may vary from day to day, meaning that a single 24-hour ambulatory result may not be a good estimate of a patient's 'true underlying' blood pressure. This, again, can be quantified using data from clinical trials where subjects have had two or more ambulatory monitorings performed.

Self-monitoring (also referred to as home monitoring) of blood pressure holds promise as a method that is free of the 'white coat' effect, is convenient to patients, and permits multiple measurements over a longer period at low resource and financial cost.<sup>3</sup> The European Society of Hypertension recommends 7 days of self-monitoring with two measurements taken twice daily and the first day's data discarded, that is, the mean of 24 measurements.<sup>4</sup>

This study sought to determine the within-individual CV, as a measure of variability or reproducibility, of three methods of blood pressure measurement: (i) office blood pressure repeated 6 weeks apart; (ii) daytime average from 24-hour ambulatory monitoring repeated 6 weeks apart; and (iii) self-monitoring of blood pressure as recommended by the European Society for Hypertension. A specific question was whether any method can offer 80% probability of accuracy within  $\pm 5$  mmHg for an individual with a 'true' systolic blood pressure of 140 mmHg.

## METHOD

Blood pressure data from a previously published trial of a herbal preparation, *Asparagus P*, were analysed.<sup>5</sup> This was a single-group study intended as proof of concept. In fact, no persuasive evidence of a clinically useful blood pressure-lowering effect was seen, and for this reason, along with a suggestion of undesirable side-effects, further studies of *Asparagus P* were not arranged.

## Subjects

Subjects ( $n = 163$ ) were recruited in Freiburg, Germany, partly on the basis of experience in other trials conducted by one of the authors, and partly through word of mouth. The former group of subjects had originally been recruited by advertisements in local newspapers and radio stations. Inclusion criteria were somewhat loosely drawn, but aimed to identify individuals between the ages of 25 and 79 years who were perceived to be at increased cardiovascular risk on the basis of: (i) reported previous diagnosis of hypertension, or (ii) body mass index greater than 27 kg/m<sup>2</sup>. Exclusion criteria were (i) assessed need for urgent antihypertensive treatment; (ii) angina pectoris; (iii) atrial fibrillation; (iv) cardiac failure; and (v) pregnancy, or actively seeking pregnancy. Subjects therefore represent a mixture of general public and primary care patients. Some characteristics are shown in Table 1.

Study assessments took place in a small city-centre clinic. All subjects took the study product (*Asparagus P*) for 6 weeks, with other medications unchanged.

### Blood pressure measurement

Office blood pressure was measured by a nurse, initially and after 6 weeks. A Boso-Medicus Prestige device (Bosch+Sohn GmbH u. Co KG, Jungingen), graded A/A (British Hypertension Society protocol), was used to obtain triplicate measurements at 2-minute intervals in each arm, after sitting for 5 minutes. The averages of the second and third measurements in the left arm are used here.

Twenty-four-hour ambulatory blood pressure recordings were performed initially and after 6 weeks, using Boso TM-2430 PC oscillometric devices (graded A/A) on the non-dominant arm. Blood pressure measurements were taken every 15 minutes from 0800 to 2100 and every 30 minutes from 2100 to 0800. Daytime measurements were defined as 0700 to 2300.

Self-monitoring of blood pressure was performed every day for at least 6 weeks, although some subjects continued for up to 12 weeks. Duplicate measurements were taken morning and evening, preceded by at least 5 minutes of rest, and abstinence from coffee or tobacco. Most (151 subjects) were supplied with the Boso-Medicus Prestige device that was also used for office measurements. Subjects were trained in the use of the device until they were able to perform measurements correctly under supervision. Eleven subjects used their own devices, provided they had also been suitably validated.

### Statistical methods

Comparisons were made between (i) mean daytime ambulatory blood pressure at baseline and after 6 weeks; (ii) office blood pressure at baseline and after 6 weeks; (iii) mean self-monitored blood pressure during the first and sixth weeks, calculated from days 2 to 7 each week, and ignoring measurements during intervening weeks. Coefficients of variation and 95% confidence intervals were computed in Microsoft Excel 2007 for Windows, using the logarithmic method described by Bland and Altman.<sup>6</sup> For self-monitoring, analyses were restricted to those weeks in which at least 12 of 14 scheduled duplicate measurements were made. Weeks with fewer measurements were treated as 'data missing'.

A further analysis was carried out of the effects of increasing the duration of self-monitoring, and varying the interval between repeat episodes. No additional studies were performed for this: self-monitored blood pressure was measured every day for 6–12 weeks, and different segments were simply selected for analysis. For example, to assess the reproducibility of self-monitored blood pressure performed for 2 weeks (with the first day discarded) and repeated after an interval of 2 weeks, mean

**Table 1. Subject characteristics.**

Personal characteristics	
Mean age, years (SD)	46.9 (11.7)
Sex, males:females	76:87
Mean weight, kg (SD)	86.8 (15.7)
Mean BMI, kg/m <sup>2</sup> (SD)	29.8 (4.4)
Medical history, <i>n</i> (%)	
Hypertension	74 (45.4)
Diabetes	10 (6.1)
Hypercholesterolaemia	52 (31.9)
Family history of cardiovascular disease, <i>n</i> (%)	24 (14.7)
Medication, <i>n</i> (%)	
Aspirin	20 (12.3)
Antihypertensives	51 (31.3)
Diabetes medication	8 (4.9)

BMI = body mass index. SD = standard deviation.

blood pressure was compared from days 2–14 and from days 30–42. Many subjects continued self-monitoring for up to 12 weeks, allowing assessment of longer monitoring episodes and intervals between repeat episodes.

### RESULTS

Of the 163 subjects, 141 attended for office measurements, and 107 completed 24-hour ambulatory monitoring, at both baseline and 6 weeks. Self-monitoring was abandoned by 19 subjects before 6 weeks were up; the remaining 144 subjects completed 95% of scheduled measurements during weeks 1–6. Compliance tailed off slightly, such that only 109 subjects completed the minimum number of measurements in both weeks 1 and 6. No subject required re-education in the use of the device.

Table 2 shows the results of blood pressure measurements at baseline and 6 weeks. Mean office systolic blood pressure fell from 135.4 to 131.3 mmHg ( $P < 0.001$ ). Mean self-monitored systolic blood pressure fell from 135.2 to 133.0 mmHg ( $P =$

**Table 2. Office, ambulatory, and self-monitored blood pressure. Baseline and 6-week data, and calculated coefficients of variation.**

	Baseline BP, mmHg	6 week BP, mmHg	CV, % (95% CI)	<i>n</i>
Systolic				
Office	135.4	131.3	8.6 (7.6 to 9.6)	141
Ambulatory day	142.0	142.7	5.5 (4.8 to 6.3)	107
Self-monitored	135.1	133.0	4.2 (3.6 to 4.7)	109
Diastolic				
Office	85.9	84.1	8.6 (7.5 to 9.6)	141
Ambulatory day	82.2	81.8	4.9 (4.3 to 5.6)	107
Self-monitored	83.2	82.8	3.9 (3.7 to 4.1)	109

BP = blood pressure. CV = coefficient of variation.

**Table 3. Self-monitored systolic blood pressure: coefficients of variation (%) from different combinations of monitoring duration, and interval between monitoring.**

Interval, weeks	Duration of monitoring, weeks			
	1	2	3	4
0	3.0	2.7	2.3	2.7
1	3.7	2.8	2.7	3.4
2	3.9	2.9	3.3	4.0
3	4.0	3.6	4.9	4.8
4	4.2	4.1	4.6	5.0
5	4.4	5.1	5.0	
6	5.2	5.0	5.2	
7	5.6	5.2		
8	5.5	5.7		
9	6.1			
10	6.6			

*Note that the interval is the period between the end of the first monitoring period and the start of the second.*

0.004). Mean daytime ambulatory blood pressure did not change significantly, from 142.0 to 142.7 mmHg (not significant).

Office and self-monitored blood pressure measurements gave very similar results, with an absolute difference in systolic means of 0–2 mmHg. Surprisingly, ambulatory measurements yielded daytime means that were 7–9 mmHg higher than office and self measurements. Even the 24-hour ambulatory means (138.1 mmHg at baseline, 138.7 mmHg at 6 weeks) were 3–7 mmHg higher than office and self-monitored means.

The CVs for systolic office, ambulatory, and self-monitored blood pressure, compared at baseline and 6 weeks, were 8.6%, 5.5%, and 4.2% respectively. Table 3 shows CVs for self-monitoring for varying durations, and repeated at varying intervals. There is a clear trend for higher CVs with longer intervals between repeated monitoring, and a possible trend for lower CVs with longer durations of monitoring.

## DISCUSSION

### *Summary of main findings*

It is implicit that blood pressure-lowering treatments should be directed at an individual's average, or 'true underlying' blood pressure, rather than a measurement which, by the play of chance, is unrepresentatively high or low. There is no universally accepted method for estimating 'true' blood pressure, but the ideal method should have minimal within-individual variability: in other words, if repeated, the second estimate should not be very different from the first.

This study yielded a CV of 8.6% for systolic office blood pressure measurements. The implications are calculated as follows. Suppose an individual has a 'true' mean systolic office blood pressure of 150 mmHg and a CV of 8%, and that their blood pressure measurements will be normally distributed:

- the SD of repeated measurements is  $150 \times 0.08$ , or 12 mmHg;
- 80% of measurements will be within 1.28 SD of the mean, that is, 135–165 mmHg; and
- 95% of measurements will be within 2 SD, that is, 126–174 mmHg.

If the mean of three measurements is taken, the variability should be reduced by  $\sqrt{3}$ :

- 80% of estimates will be within 141–159 mmHg
- 95% of estimates will be within 136–164 mmHg.

In simplified terms, this means that in usual practice office blood pressure measurements cannot identify an individual's 'true' blood pressure with an accuracy better than about  $\pm 10$  mmHg. The authors suggest that 80% confidence that the estimate is within  $\pm 5$  mmHg of the 'true' blood pressure is desirable. To achieve this, 10–13 office measurements are required. If this is impractical, then office blood pressure measurement is not fit for this purpose.

Results from 24-hour ambulatory monitoring were more reproducible than single office measurements, but remained imperfect (CV 5.5%). For an individual with a 'true mean' ambulatory systolic blood pressure of 150 mmHg, a single 24-hour monitoring only permits 80% confidence that the result is accurate within  $\pm 10$  mmHg. This may seem paradoxical, as ambulatory monitoring here comprised some 54 daytime measurements, whereas 10–13 office measurements ought to provide good accuracy. The authors suggest this is because average blood pressure varies from day to day: people have good days and bad days, and a single 24-hour monitoring cannot capture this.

Self-monitoring by European Society for Hypertension guidelines achieved slightly better reproducibility (CV 4.2%). For a hypothetical individual with a 'true' self-monitored systolic blood pressure of 150 mmHg, a week of self-monitoring provides 80% confidence that the measured mean is within  $\pm 8$  mmHg of the true mean. With the decreasing cost and improving accuracy of portable devices, self-monitoring is likely to be the favoured method for more and more clinicians and patients. In this study it was well tolerated, with 88% of subjects monitoring for at least 6 weeks, and completing 95% of scheduled measurements during this time.

### **Strengths and limitations of the study**

Strengths include the prospective nature of the study, the number of subjects (which has permitted reasonably narrow confidence intervals), and the use of all three methods of blood pressure monitoring in the same subjects.

Some study limitations must be acknowledged. There were small falls in office and self-monitored blood pressure, but not ambulatory blood pressure, which could have been due to an antihypertensive effect of the trial product. Other explanations include a placebo effect, tolerance of blood pressure measurement, or regression to the mean, but the data would be more robust had the herbal product not been given.

The finding that ambulatory measurements were higher than both office and self-monitored measurements is unusual. This cannot be confidently explained, but in this study office blood pressure measurements were performed by a nurse, and it is known that measurements by nurses are about 10 mmHg lower than those of physicians.<sup>7</sup> Furthermore, restricting self-measured blood pressure to the morning and evening after resting may have eliminated higher readings associated with daily stress.

### **Comparison with existing literature**

The CV of 8.6% calculated in this study for systolic office blood pressure measurements 6 weeks apart is consistent with previous estimates. A review of randomised controlled trials found an overall CV of 9.9% for office systolic blood pressure.<sup>8</sup> In a recent re-analysis of the PROGRESS trial, a CV of 7.2% was reported.<sup>9</sup> The authors' own unpublished analysis of data from the MRC Mild Hypertension Trial<sup>10</sup> yielded a CV of 7.2% over 11 months.

For ambulatory blood pressure monitoring, this study's CV estimate of 5.5% is lower than previously reported estimates of 7.7% and 7.5%.<sup>11,12</sup> Ambulatory blood pressure measurement may be helpful in identification of diurnal variation or 'white coat hypertension', but cannot be considered the gold standard.

### **Implications for clinical practice and future research**

The following implications for clinical practice can be suggested. First, it is unlikely that blood pressure can be estimated with the accuracy that is often implied. This study suggests that three office measurements, or one 24-hour ambulatory measurement, or 1 week of self-monitoring, only give 80% confidence that the average obtained is within about 8–10 mmHg of the patient's 'true average' blood pressure. Subjects in this study were not older or unwell, and blood

pressure estimates may be even less accurate in some patient groups.

Second, attempting to fine-tune drug doses is probably pointless. Antihypertensive drugs in standard dose reduce systolic blood pressure by about 9 mmHg<sup>2</sup> and so the mean of three office measurements carries an uncertainty two- to threefold greater than the effect of a drug. Thus, there is limited ability even to identify the number of different drugs a patient requires. Increasing the dose of an individual drug is likely to reduce average systolic blood pressure by 2–5 mmHg, and there is no practical ability to estimate average blood pressure with this accuracy. Attempts to fine-tune therapy may waste clinical time and opportunities to effectively reduce cardiovascular risk. Using antihypertensive drugs as a treatment for overall cardiovascular risk, perhaps lowering blood pressure well below standard targets, but without needing to be precise about the exact level achieved, is more logical.<sup>13</sup>

Third, clinicians cannot identify individuals who have good or poor responses to drugs. A sample size calculation reveals that some 40 office blood pressure measurements are required both before and after prescription to be reasonably confident of detecting a true reduction of 5 mmHg. Clearly, this is impractical. Classifying individuals as 'non-responders' or 'good responders' on the basis of two or three measurements will, in the great majority of cases, be misinterpretation of random variation.

Fourth, self-monitoring of blood pressure is an attractive option for obtaining the best estimate of an individual's true average blood pressure, although it does not negate the problems described above. Self-monitored blood pressure showed lower variability than 24-hour ambulatory monitoring, which has traditionally been considered the gold standard. Little training or re-education was required in this study.

Future research should take account of the fact that blood pressure appears to vary not just from hour to hour, or day to day, but also over longer periods. The data presented in Table 2 show that the reproducibility of self-monitored blood pressure declined with increasing interval between measurements. This may be because factors affecting blood pressure (for example, psychosocial stresses, illness, and exercise habits) are more likely to have changed over a longer interval. Table 2 also suggests that better accuracy may be achievable with self-monitoring for longer than 1 week. A seasonal difference of 8 mmHg has been demonstrated between warm (>22°C) and cold (<8°C) days in France.<sup>14</sup> Thus, no matter how many blood pressure measurements are made during a week or a month, the average obtained cannot be

definitive, because repeating the same process 6 months later is likely to yield a significantly different result.

The authors suggest estimating blood pressure over a longer period than is currently normal practice. One possible schedule would be a week of self-monitoring every 3 months for a year. If this can be shown to have good year-to-year reproducibility, then frequent repeat measurements would be unnecessary for most patients. Age-related blood pressure change is typically of the order of 0.5–0.8 mmHg per year,<sup>15</sup> which would mandate repeat estimation after 5–10 years in the absence of any new cause for concern. Further study of this approach is warranted.

#### Ethical approval

Committee of Human Ethics, University of Freiburg.

#### Competing interests

The authors have stated that there are none.

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