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Hypertension. 1986;8:267-271
doi: 10.1161/01.HYP.8.4.267

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

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An Evaluation of Self-Recorded Blood Pressure During Drug Trials

BRIAN A. GOULD, ROBERT S. HORNUNG, HASSAN KIESO, PETER M. M. CASHMAN, AND EDWARD B. RAFTERY

SUMMARY To our knowledge, there have been no published comparisons of different techniques for measuring blood pressure during clinical trials. We undertook a comparison during clinical trials with verapamil and prazosin. During an open trial of verapamil we compared the treatment-induced blood pressure reductions as measured by clinic, intra-arterial, and self-recorded methods. The mean reduction in blood pressure was 38 ± 13.6/20 ± 10.1 mm Hg for clinic blood pressure, 24 ± 17.9/16 ± 7.3 mm Hg for self-recorded blood pressure, and 23 ± 12.3/19 ± 10.1 mm Hg for mean daytime intra-arterial blood pressure. During prazosin treatment the mean reduction in blood pressure was 28 ± 21.5/18 ± 8.5 mm Hg for clinic blood pressure, 21 ± 20.5/6 ± 13.7 mm Hg for self-recorded blood pressure, and 18 ± 19.2/5 ± 9.6 mm Hg for mean daytime intra-arterial blood pressure. There was little agreement between methods within individual patients and for group comparisons of intra-arterial or clinic methods. There was, however, good agreement between intra-arterial and self-recorded methods. This study suggests that self-recorded blood pressure recording is suitable for monitoring efficacy of antihypertensive agents in a group of patients, although caution must be exercised when interpreting the effects of therapy when measured by indirect methods in an individual patient. (Hypertension 8: 267–271, 1986)

KEY WORDS • self-recorded blood pressure • drug trial methods • intra-arterial blood pressure • blood pressure monitoring

CLINIC blood pressure measurements are limited in scope as they are recorded at a similar time of day at each visit and therefore give no information about the behavior and response of the blood pressure at other times of day. This information may be obtained from home blood pressure measurements using either noninvasive semiautomatic recorders or patients’ own measurements, and we have reported on the accuracy and possible role of self-recorded blood pressure in clinical trials of antihypertensive agents. However, it remains to be established that self-recorded blood pressure (measured at home) provides information on the degree of blood pressure reduction that is significantly different from that provided by clinic readings. In this study two antihypertensive agents, verapamil and prazosin, were assessed in separate groups of patients. The antihypertensive efficacy of these agents has been reported in earlier publications. The object of this report is to compare the blood pressure response as observed by different methods. Measurement of the blood pressure response by intra-arterial, clinic, and self-recorded pressures allowed a direct comparison of the three methods of blood pressure measurement during two clinical trials.

Subjects and Methods

Verapamil Trial

Ten patients were recruited from the hypertension clinic. The group consisted of five women and five men with a mean age of 47 years (range, 33–67 years). Five were newly diagnosed as hypertensive, and the mean length of diagnosed hypertension in the other five was 4.8 years. Six patients were not receiving antihypertensive therapy at the time of the first clinic visit. All patients had essential hypertension, having undergone routine testing to exclude causes of secondary hypertension. After 6 weeks without therapy the patients were taught to measure their blood pressure. The patients attended a special session of...
the clinic, during which an indirect measurement was recorded. The Hawksley random-zero sphygmomanometer (Lancing, Sussex, England) was used to avoid bias and digit preference. The patients were taught the technique of home blood pressure measurement, a previously calibrated aneroid gauge and standard techniques of measurement were used, but Korotkoff phase V was used for diastolic pressure. An average of 30 minutes was spent in instruction. Each patient's technique of recording was checked using a double-listening stethoscope, but none of our patients were excluded from the study on the grounds of inaccurate recordings.

Self-recorded blood pressure was then obtained four times daily at set times for 10 days. During the 10 days, intra-arterial ambulatory blood-pressure monitoring was performed over 48 hours using a technique that has been fully described. During intra-arterial monitoring the patients attended the hospital at 12-hour intervals for calibration and equipment checks. At these visits the blood pressure was recorded by the physician using the random-zero sphygmomanometer, after which the accuracy of the patients' technique was assessed using a double-listening stethoscope. The intra-arterial tape recording was marked with an event signal at the start of each indirect recording, both at home and in the hospital, although the data from these individual observations are not analyzed in this report. In the week following intra-arterial blood pressure monitoring, the patients attended the outpatient clinic where verapamil, 120 mg t.i.d., was prescribed. Two patients subsequently had their dosage increased to 160 mg t.i.d. due to inadequate response in terms of the clinic blood pressure levels. After 6 weeks at a constant dosage with regular visits to the outpatient clinic, intra-arterial and home blood pressure monitoring were repeated exactly as in the first study.

Prazosin Trial

The protocol for prazosin was identical to that for verapamil except that two groups of patients were recruited. In the first group of seven patients prazosin was prescribed as the sole therapy. The mean age of this group was 48 years (range, 38—64 years). Four of the patients were newly diagnosed as hypertensive, and the mean length of known hypertension in the other three was 3 years. The second group consisted of five patients whose hypertension was inadequately controlled with β-adrenergic receptor blocking agents (propranolol, 80 mg t.i.d., or its equivalent), inadequate control was defined as an average of three clinic blood pressure measurements in excess of 160 mm Hg for systolic or 95 mm Hg for diastolic blood pressure or both. The mean age of this group was 58 years (range, 44—69 years). Intra-arterial and self-recorded blood pressure monitoring were undertaken in both groups of patients before and after prazosin therapy. The second group continued to take β-adrenergic receptor blocking agents throughout the trial. The dosage of prazosin was titrated by dose-doubling from 0.5 mg b.i.d. daily to 8 mg b.i.d. In the group of seven patients receiving prazosin monotherapy, six received a dosage of 8 mg b.i.d. and one received 4 mg b.i.d. In the group of five patients receiving prazosin in addition to β-adrenergic receptor blocking agents, one received 8 mg, three received 3 mg, and one received 1 mg in a twice-daily dosage.

Both studies were approved by the hospital ethical committee, and informed consent was obtained from all subjects.

Data Analysis

The self-recorded blood pressure measurements for each patient were averaged over the 2 days of intra-arterial monitoring, and the clinic blood pressure measurements were assessed by taking the mean of the pressures at two clinic visits, immediately before and after intra-arterial monitoring. A hybrid computer was used to compute mean hourly pressure from the direct recordings. Intra-arterial blood pressure was computed in hourly sections. The data were pooled for each hour of the day, and mean daytime intra-arterial pressure was calculated by averaging the hourly means from 1200 to 1800.

Since the comparisons include different numbers of measurements by each method, we have presented the results recorded by each method as group means before and after treatment. For each patient the change in blood pressure was calculated for each method of measurement. These values were averaged for each method to obtain a mean reduction in blood pressure. Scatter plots, paired t tests, and correlation coefficients were used to compare the intrapatient changes in blood pressure obtained by the different methods of measurement.

Results

Verapamil

A detailed account of the intra-arterial profile of verapamil-induced blood pressure reduction has been reported previously. Both systolic and diastolic blood pressure fell with verapamil treatment, and the reductions were significant with all three methods of measurement (Table 1; p < 0.001). The systolic pressure reductions obtained in clinic readings were significantly greater than those assessed by intra-arterial or self-recorded blood pressure methods (see Table 1). Mean diastolic

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Reduction (mm Hg)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-arterial</td>
<td>23/19 ± 12 3/10 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinic</td>
<td>38/20 ± 13 6/10 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>24/16 ± 17 9/7 3</td>
<td></td>
<td></td>
</tr>
<tr>
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<tr>
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<td>&gt;0.5/0.2</td>
<td></td>
</tr>
<tr>
<td>Home vs clinic</td>
<td>2 7/1 5</td>
<td>&lt;0.05/0.1</td>
<td></td>
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</tbody>
</table>

Values are means ± SD

The mean change in blood pressure, as recorded by each method of measurement in each patient, was compared using a two-tailed Student's paired t test.
reductions were very similar with all three methods of measurement. There was a large individual variation for both systolic and diastolic pressure, as shown in the scatter plots (Figures 1–3).

Prazosin

A report on the efficacy of prazosin has been published previously. Analysis of results from the combined groups showed that systolic blood pressure fell with prazosin treatment but diastolic blood pressure showed only a small reduction, except when measured by clinic methods, and these reductions were statistically significant (Table 2; p < 0.001). The recorded mean systolic reductions were similar with each of the three methods of measurement, although clinic readings showed the greatest reduction. The reductions in diastolic pressure assessed by clinic readings were significantly greater than those obtained by intra-arterial

Figure 1 Scatter plot of change in mean systolic (A) and diastolic (B) blood pressure (BP) recorded by intra-arterial BP (mean daytime) and by clinic BP (mean). Correlation coefficients were 0.30 during studies with verapamil (*) and 0.20 with prazosin (o) for systolic BP and −0.15 and 0.21, respectively, for diastolic BP.

Figure 2. Scatter plot of change in mean systolic (A) and diastolic (B) blood pressure (BP) recorded by home BP (2-day mean) and by intra-arterial BP (mean daytime). Correlation coefficients were 0.44 during studies with verapamil (*) and 0.44 with prazosin (o) for systolic BP and 0.29 and 0.15, respectively, for diastolic BP.

Figure 3 Scatter plot of change in mean systolic (A) and diastolic (B) blood pressure (BP) recorded by home BP (2-day mean) and by clinic BP (mean). Correlation coefficients were 0.52 during studies with verapamil (*) and 0.60 with prazosin (o) for systolic BP and 0.53 and 0.26, respectively, for diastolic BP.
TABLE 2  Change in Blood Pressure and Comparison of Changes Recorded by Different Methods in 12 Patients After Treatment with Prazosin

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Reduction (mm Hg)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-arterial</td>
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<td>&gt;0.2/0.01</td>
</tr>
<tr>
<td>Clinic</td>
<td>28/18 ± 21 5/8 5</td>
<td>0</td>
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<tr>
<td>Home</td>
<td>21/6 ± 20 5/13 7</td>
<td>0</td>
<td>&gt;0.2/0.05</td>
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<tr>
<td>Intra-arterial vs clinic</td>
<td>1 2/4 1</td>
<td>&gt;0.2/0.01</td>
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</tr>
<tr>
<td>Intra-arterial vs home</td>
<td>0 4/0 1</td>
<td>&gt;0.5/0.9</td>
<td></td>
</tr>
<tr>
<td>Home vs clinic</td>
<td>0 9/2 3</td>
<td>&gt;0.2/0.05</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD

The mean change in blood pressure, as recorded by each method of measurement in each patient, was compared using a two-tailed Student's paired t test

or home-recorded blood pressure (see Table 2). The scatter plots and frequency histograms showed that all the methods of blood pressure measurement exhibited marked intraindividual variation (see Figures 1–3).

Discussion

The relative accuracy of intra-arterial, clinic, and self-recorded blood pressure measurements has been examined previously.7 That study compared simultaneous measurements recorded with the different methods. The aim of this study was to compare the blood pressure reduction, induced by antihypertensive agents as recorded by the different techniques. Since the earlier study focused on simultaneous comparisons, we concluded that the mean reductions recorded by each method for each patient would be appropriate. In clinical practice it is the mean reduction, not one isolated recording, that is important.

In our earlier study, self-recorded systolic blood pressure measurements showed good agreement with clinic and intra-arterial pressures, but self-recorded and clinic diastolic blood pressures overestimated those obtained with intra-arterial methods. The clinic and self-recorded measurements of diastolic pressure showed good average agreement, but considerable variability in intraindividual differences was evident in comparing the indirect and intra-arterial methods.

In the verapamil study clinic systolic blood pressure showed a significantly greater mean reduction than did that obtained with either intra-arterial or self-recorded pressure. This difference may result because clinic pressure measurement is subject to a "placebo response" or to a greater regression toward the mean, or to both, than is self-recorded pressure. This effect could be explained by a marked reduction in the arousal response12 during clinic blood pressure measurements than during self-recorded or intra-arterial measurements. We have previously reported the absence of this effect when intra-arterial pressure measurements were performed.13 Mean reductions in clinic blood pressure were otherwise similar to those obtained using home (self-recorded) and intra-arterial methods, but there was a wide range of individual differences in pressure recorded by the three methods (see Figures 1–3). If the discrepancies were due to a lack of a placebo period in the noninvasive studies, there would have been evidence of a systematic error. The absence of such an error suggests that the wide variations between methods are inherent in the indirect methods of measurements, rather than due to a lack of placebo control.

In the study with prazosin, the mean reduction observed using clinic systolic pressure was again greater than that obtained with the other two methods, although not significantly so; the mean change in clinic diastolic pressure was significantly greater than that shown by intra-arterial or self-recorded pressure. Mean changes in intra-arterial and self-recorded pressure measurements were similar (see Table 2), but there was wide individual variability, as recorded by each method (see Figures 1–3).

Gordon et al.14 measured blood pressure reduction in response to a thiazide diuretic using both clinic and self-recorded measurements. The average reductions in supine daytime self-recorded blood pressure and clinic blood pressure during the first treatment period with the thiazide were 11/7 and 5/6 mm Hg, respectively. Their findings differ from ours in that the clinic systolic pressure measurements indicated a smaller reduction in the blood pressure than did the self-recorded pressures.

In the present study the intra-arterial and self-recorded home methods of recording blood pressure produced similar results when measuring the mean change in blood pressure in a group of patients after antihypertensive treatment. However, the scatter plots comparing the intraindividual blood pressure changes for the two techniques showed poor agreement. Thus, we conclude that self-recorded blood pressure recording and clinic measurement of blood pressure do not accurately reflect an individual patient's intra-arterial changes in blood pressure resulting from antihypertensive therapy. When used to estimate the antihypertensive effect of a drug in a group of patients, self-recorded blood pressure measurement appears to give valid results, whereas clinic blood pressure measurement overestimates the reduction. As discussed previously, the overestimation by clinic methods probably would be reduced by inclusion of a placebo control group.13 For any given subject, however, the reduction of intra-arterial blood pressure may not (with any trial design) be accurately recorded by the use of indirect techniques. It is important to standardize the technique of self-recorded blood pressure measurement as well as the circumstances under which pressure is measured. This approach may help to reduce some of the technique's inaccuracies.

The use of semiautomated or automated blood pressure recorders is unlikely to improve these results. We have evaluated the Remler M2000 (Brisbane, CA, USA) and the Avionics 1978 Pressureometer (Del Mar Avionics, Irvine, CA, USA) using intra-arterial pressures as the "gold standard." The accuracy of the
Remler M2000 was similar to that of the self-recorded method\(^{15, 16}\) whereas the accuracy of Avionics Pressurometer was not.\(^{15}\) Although the Remler M2000 could be used for drug trials, the self-recorded method has the advantage of following the changing trends in blood pressure over prolonged periods, enabling comparisons of several antihypertensive agents.

In conclusion, the present study compared the relative performance of three methods of recording blood pressure changes during a clinical trial, namely clinic, intra-arterial, and self-recorded pressure measurement. Self-recorded and intra-arterial blood pressure measurements indicated similar reductions in pressure, while clinic measurements recorded reductions that were significantly larger. Self-recorded blood pressure measurement is suitable for daytime monitoring of the average efficacy of antihypertensive agents within a group of patients. Reductions recorded in the clinic by physicians or nurses and at home by patients did not agree closely with those recorded by the intra-arterial method. The indirect method of blood pressure measurement does not, therefore, accurately reflect what is happening to the intra-arterial blood pressure in an individual patient. Since self-recorded blood pressure measurement is similarly deficient, a more sensitive method of indirect measurement is required. Until a more accurate indirect blood pressure recorder is available, however, self-recorded blood pressure measurement should be the method of choice for clinical trials. Intra-arterial blood pressure monitoring is still required to assess the 24-hour profile of blood pressure reduction.

**Acknowledgment**

The authors thank Mr. D. Altman for advice on statistical methods.

**References**