Reproducibility and Clinical Value of the Trough-to-Peak Ratio of the Antihypertensive Effect
Evidence From the Sample Study

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Abstract—The objectives of our study were to assess the reproducibility of the trough-to-peak ratio (T/P) and to see whether a high T/P is accompanied by more organ protection or vice versa. The study included 175 (mean±SD age, 51±9 years) subjects with mild-moderate essential hypertension who had echocardiographic evidence of left ventricular (LV) hypertrophy taken from the SAMPLE study (Study on Ambulatory Monitoring of Blood Pressure and Lisinopril Evaluation), an open-label multicenter study. The study included a 3-week washout pretreatment period, a 12-month treatment period with lisinopril (n=84) or lisinopril plus hydrochlorothiazide (n=91) once daily, and a 4-week placebo follow-up period. Results of 24-hour ambulatory blood pressure monitoring and echocardiographic determination of left ventricular mass index (LVMI) were obtained before and after 3 and 12 months of treatment. T/Ps were computed in each patient by dividing the systolic and diastolic blood pressure changes at trough (changes in the last 2 hours of the monitoring period) by those at peak (average of the 2 adjacent hours with the maximal blood pressure reduction between the 2nd and 8th hour from drug intake) after 3 and 12 months of treatment. Average 24-hour blood pressure was similarly reduced at 3 and 12 months. Trough blood pressure changes at 3 and 12 months were closely correlated, as were the corresponding peak blood pressure changes. However, the 3- and 12-month T/Ps correlated to a lesser degree (r<0.42). Furthermore, the reduction of LVMI induced by treatment was similarly correlated with the treatment-induced reduction in 24-hour average, trough, and peak blood pressures but not with the T/Ps. This was also evident when the contribution to LV hypertrophy regression by 24-hour blood pressure changes and T/Ps was assessed in a multivariate regression analysis. In patients with a T/P $\geq 0.5$ or $<0.5$, the regression of LVMI was similar. In conclusion, peak and trough blood pressure changes are reproducible and predict the regression of LVMI induced by treatment as well as average 24-hour blood pressure. T/Ps are less reproducible, and their value does not predict regression of organ damage by antihypertensive treatment. (Hypertension. 1998;32:424-429.)

Key Words: trough-to-peak ratio ■ blood pressure monitoring, ambulatory ■ hypertrophy, left ventricular ■ lisinopril ■ hydrochlorothiazide ■ antihypertensive agents

In 1988, the US Food and Drug Administration stated that for an antihypertensive drug to be acceptable, “. . . the drug effect at trough should be no less than half to two thirds of the peak effect” to guarantee (1) the sustained therapeutic coverage necessary to prevent hypertension-related cardiovascular complications and (2) that this coverage would not be obtained at the price of excessive early hypotension that might endanger perfusion of vital organs. This has meant that all antihypertensive drugs had to be assessed not only by the absolute magnitude of their blood pressure–lowering effect but also by their ability to reduce systolic blood pressure (SBP) or diastolic blood pressure (DBP) at the end of the between-dose interval in relation to the maximal reduction early after administration of the dose(s), an evaluation of their “trough-to-peak ratio” (T/P) thus being an invariable component of the evidence to be obtained. The importance of the antihypertensive effect being not too dissimilar at trough and peak has been emphasized also by the latest report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Three important questions concerning the T/P of antihypertensive drugs have only partly been answered, however. Are trough blood pressure changes, peak blood pressure changes, and T/Ps reproducible over time, thereby making the results obtained in short-term studies valid also for chronic antihypertensive treatments? Are greater T/Ps associated with greater beneficial effects, eg, greater regression of hypertension-related target organ damage? Are new methods...
to assess the duration and homogeneity of the antihypertensive effect over the 24 hours more reproducible and clinically relevant than the T/Ps? We have addressed these questions by analyzing the data collected in the SAMPLE Study (Study on Ambulatory Monitoring of Pressure and Lisinopril Evaluation), which provided strong evidence via a prospective controlled design that in essential hypertension, regression of left ventricular (LV) hypertrophy at the end of 1 year of treatment is more closely predicted by change in average 24-hour than clinic blood pressure.9

Methods

Patients

The methodology used was described in detail previously. Briefly, the study was performed in 11 Italian centers, each of which was instructed to recruit male or female patients according to the following criteria: (1) age between 24 and 65 years; (2) clinic supine DBP (average of 2 consecutive sphygmomanometric readings) between 95 and 115 mm Hg after a 3- or 4-week period without antihypertensive treatment (see below); and (3) “echocardiographic” LV hypertrophy (see below).10 Exclusion criteria were (1) secondary hypertension; (2) history and/or signs of cardiovascular complications (eg, congestive heart failure, myocardial infarction, stroke, angina pectoris) or major target organ damage (eg, serum creatinine >1.5 mg/dL); (3) major cardiovascular or noncardiovascular diseases beside hypertension; (4) pregnancy or lactation; (5) contraindications to the antihypertensive drugs to be used during the treatment period; and (6) conditions preventing collection of technically adequate echocardiograms (eg, obesity or pulmonary emphysema) or ambulatory blood pressure monitoring (ABPM) (eg, atrial fibrillation or other major arrhythmias). Patients also were excluded from the study if previous antihypertensive treatment consisted of more than 2 drugs to minimize patients’ subsequent dropout because of lack of blood pressure control. All patients consented to the study after being informed of its nature and purpose. The study protocol was approved by the ethics committees of the centers involved.

ABPM was performed on the nondominant arm with a Spacelabs 90202 or 90207 device after validation of its readings against a mercury sphygmomanometer. The device was set to obtain automatic blood pressure readings at 15-minute intervals during the day (6 AM to midnight) and at 20-minute intervals during the night (midnight to 6 AM). The monitoring was performed on a work day, starting around 9 to 10 AM. The patient was sent home with instructions to continue with usual daily life activities but to hold the arm still at the time of the measurements, note on a diary the occurrence of unusual events or poor sleep at night, and return 24 hours later. Ambulatory blood pressure data were analyzed by a single center (Milan).

The echocardiograms were obtained with the subject in a left decubitus position. LV internal diameters, LV posterior wall thickness, and interventricular septum thickness were measured monodimensionally on the longitudinal parasternal view previously identified bidimensionally according to the recommendations of the American Society of Echocardiography.11 LV volumes were calculated by the cube formula, while LV mass was calculated according to the Penn Convention10 and indexed to body surface area by the formula of Dubois and Dubois.12 Patients were recruited if LVMi exceeded 110 g/m² in women and 131 g/m² in men.13 All echocardiographic tracings, however, were then centralized (Brescia and Milan) and calculated by 2 independent observers (1 for each center). The within-observer variation coefficients of the LV end-diastolic diameter and posterior wall thickness (ie, the standard deviation of the average of 2 readings obtained by the same observer divided by the average and multiplied by 100) were 0.5% and 3.4%, respectively. The corresponding values for the between-observer variation coefficients were 0.8% and 3.9%. The “central” calculations were those considered for the results.

Study Protocol

The protocol of the study was as follows: (1) After an initial medical visit, previously treated hypertensive patients underwent a 4-week washout period from antihypertensive treatment; previously untreated hypertensive patients underwent a 3-week period of observation. (2) After a second medical visit, patients who met recruitment criteria were given lisinopril in a single morning dose of 20 mg (month 0). (3) One month later, nonresponders to lisinopril (ie, patients in whom clinic supine DBP at trough was not reduced to <90 mm Hg or by at least 10 mm Hg) were given additional treatment with hydrochlorothiazide in a single morning dose of 12.5 mg (month 1). (4) After 1 more month, the dose of hydrochlorothiazide was doubled in patients who were still not responding to treatment (month 2). (5) Treatment was maintained unchanged for the subsequent 10 months (months 2 through month 12). At the end of this treatment period (month 12), antihypertensive drugs were substituted with placebo tablets, which were administered for 4 weeks. As mentioned in the report of the main results of the SAMPLE study,9 this was done to allow blood pressure to return toward pretreatment values and thus allow collection of evidence that their blood pressure reduction seen in the previous 12 months had been due to drug treatment.

Ambulatory blood pressure and echocardiographic data were collected at the end of the pretreatment washout or observation periods, after 3 months (ie, 1 month after the doubling of the hydrochlorothiazide dose in nonresponders) and 12 months of treatment, and at the end of the final placebo period. ABPM was started immediately before drug(s) or placebo administration.

Data Analysis

Each ABPM recording was first automatically scanned to remove artifactual readings according to preselected editing criteria.14 A monitoring was regarded as suitable for further analysis if at least 70% of the expected number of readings and/or 1 valid reading per hour was available. The recording was then analyzed to obtain (1) 24-hour average SBP and DBP before treatment, after 3 and 12 months of treatment, and after the final placebo period; (2) average SBP and DBP for each hour of the monitoring period before treatment and during treatment (3rd and 12th month); and (3) after the final placebo period, peak and trough changes and T/Ps for SBP and DBP after 3 and 12 months of treatment. T/Ps were calculated as described in detail previously. Briefly, peak blood pressure changes were calculated by considering the interval between the 2nd and 8th hour after drug intake (ie, when the peak effect was expected to occur) and by averaging, within this time window, the values for (1) the hour in which the blood pressure fall was maximal and (2) the adjacent hour in which the blood pressure fall was more evident, compared with the corresponding pretreatment values. Trough blood pressure changes were calculated by averaging pretreatment and during-treatment blood pressure differences over the last 2 hours of the monitoring period. Individual T/Ps were obtained by dividing, for each patient, the blood pressure change at trough by the blood pressure change at peak, separately for SBP and DBP. We also calculated the “surface ratio” (SR) of the antihypertensive effect, which has recently been reported to have advantages over the T/P because it is based on the effect of treatment on the whole 24-hour blood pressure profile. This was done by (1) calculating the average blood pressure changes induced by treatment for each hour of the 24-hour monitoring period, (2) dividing the area delimited by the above hourly blood pressure changes by the maximal hourly blood pressure reduction (ie, the maximal treatment effect), and (3) multiplying the results by the dosing interval (ie, 24).

Blood pressure and LVMi values from individual patients were averaged to obtain mean±SD values for the group as a whole. Group T/Ps were obtained by either (1) dividing the average change in trough blood pressure by the average change in peak blood pressure or (2) calculating the median (plus the upper and lower quartile and the extreme values of the distribution) of the individual T/Ps. The latter approach was used also for calculation of group SRs. This was done because the individual T/Ps15 and the SRs16 do not show a normal distribution. The reproducibility of peak and trough blood
pressure changes after 3 and 12 months of treatment (ie, the 2 treatment periods in which treatment was the same) was assessed by the Bland and Altman approach.16 This consisted of calculation of the correlation coefficients ($r$), the mean difference ($\pm 2 SD$), and the percent repeatability coefficients of peak blood pressure changes, trough blood pressure changes, and T/Ps between 3 and 12 months of treatment. The percent repeatability coefficient (ie, the inverse of the reproducibility) was obtained by (1) calculating the difference between the 3- and 12-month data in each individual subject, (2) calculating the SD of the mean difference in all subjects and multiplying it by 2, (3) dividing this value by 4 times the SD of the average value at 3 months of treatment and multiplying the result by 100 to allow it to be compared with other coefficients.7,8,16 A similar approach was used for the T/P and SR, although in these instances the percent repeatability coefficient was calculated using the 5th to 95th percentile interval of the average 3-month value to allow for their not-normal distribution.15 The percent repeatability coefficient allowed cross comparisons of different variables. A high repeatability coefficient indicated a low reproducibility and vice versa.

The effect of treatment on blood pressure and LVMI and correlation between blood pressure and LVMI changes were analyzed by paired Student’s $t$ test and Pearson correlation coefficient, respectively. The Wilcoxon test and the Spearman correlation coefficient were used to compare the T/P and SR at 3 and 12 months and to determine their correlation with LVMI changes. The relative importance of T/P versus 24-hour average blood pressure changes induced by treatment on regression of LVMI was assessed by multivariate regression analysis. Finally, the impact of the T/P values on the regression of LV hypertrophy induced by treatment was analyzed by dividing patients into groups with a more favorable ($\geq 0.5$) systolic and diastolic T/P, based on the T/P indicated by the US Food and Drug Administration1 and recently mentioned by the Joint National Committee Report8 as the median of individual T/Ps. Squares correspond to individual outliers with no reference to their actual value. The same approach was applied to T/Ps.3,4,6,16

TABLE 1. BP Values and LVMI Before Treatment (Entry), After 3 and 12 Months of Treatment (TR), and After Final Placebo Period

<table>
<thead>
<tr>
<th>Entry</th>
<th>TR (3 mo)</th>
<th>TR (12 mo)</th>
<th>Placebo</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic SBP, mm Hg</td>
<td>165±15</td>
<td>140±11*</td>
<td>139±11*</td>
<td>175</td>
</tr>
<tr>
<td>Clinic DBP, mm Hg</td>
<td>105±5</td>
<td>87±6*</td>
<td>87±7*</td>
<td>175</td>
</tr>
<tr>
<td>24-h SBP, mm Hg</td>
<td>149±16</td>
<td>131±12*</td>
<td>130±12*</td>
<td>175</td>
</tr>
<tr>
<td>24-h DBP, mm Hg</td>
<td>95±11</td>
<td>81±8*</td>
<td>82±9*</td>
<td>175</td>
</tr>
<tr>
<td>LVMI, g/m$^2$</td>
<td>160±31</td>
<td>145±29*</td>
<td>134±26†</td>
<td>154</td>
</tr>
</tbody>
</table>

Data are mean±SD.

$^{*}P<0.01$ vs Entry; $^{†}P<0.01$ vs TR (3 mo); $^{‡}P<0.01$ vs TR (12 mo).

Results

Effects of Treatment on Blood Pressure and LVMI

Two hundred and six patients were given antihypertensive treatment. Of these, 175 (113 men, 62 women; aged 51±9 years) had valid ABPM recordings before treatment, at the 3rd month of treatment, and at the 12th month of treatment; 154 patients had both valid ABPM recordings and valid echocardiograms. The number of patients was somewhat less after the final placebo period: 172 had valid ABPM recordings and 151 had both valid ABPM recordings and echocardiograms. Four patients withdrew because of treatment inefficacy, 12 because of side effects; 21 patients did not come in for follow-up examinations. In the evaluable patients, the number of valid blood pressure readings over the 24 hours was on average 95%, 93%, 93%, and 93% of the expected 90 readings in the recordings performed before treatment, at 3 and 12 months of treatment, and in the final placebo period, respectively. The corresponding number of valid hours was 23.8, 23.9, 23.8, and 23.9, respectively. Clinic and 24-hour average blood pressures were similarly reduced after 3 and 12 months of treatment, whereas LVMI was significantly reduced after 3 months and more so after 12 months. Blood pressures, but not LVMI, returned toward pretreatment values after the final placebo period (Table 1).

Reproducibility of T/Ps and SRs

Figure 1 (left panels) shows that SBP and DBP were reduced at both peak and trough after either 3 or 12 months of treatment. The average peak and trough reductions were superimposable at 3 and 12 months. This was the case also for the T/P, both when obtained from average trough and peak changes and when expressed as the median of individual T/Ps (Figure 1, middle panels). Median SRs were also similar at 3 and 12 months of treatment (Figure 1, right panels). As shown in Figure 2, peak blood pressure changes at 3 and 12 months of treatment were closely related; this was even more the case for trough blood pressure changes. In contrast, the 3- and 12-month T/Ps were significantly but less closely related. Furthermore, the repeatability coefficients
between 3 and 12 months of treatment were greater for the T/P and SR than the blood pressure changes at peak and at trough. The mean±2 SD differences and the repeatability coefficients are shown in Table 2.

Regression of LV Hypertrophy
As shown in Figure 3, the reduction of LVMI after 12 months of treatment was not related to the treatment-induced changes in clinic blood pressure, but it showed a significant relationship with the treatment-induced changes in 24-hour average blood pressure. Peak and trough blood pressure changes after 12 months of treatment were related to the reduction of LVMI to an extent similar to that of 24-hour average blood pressure changes. In contrast, the reduction of LVMI showed no relationship with the 12-month T/Ps and a poor even though significant negative relation with SRs. On a multivariate regression analysis, the treatment-induced reduction in 24-hour average SBP was a determinant of the reduction in LVMI ($\beta=0.39$, $P<0.0001$) with a small contribution from the T/P ($\beta=-0.15$, $P=NS$). This was the case also for DBP ($\beta=0.37$, $P<0.0001$ for 24-hour average change; $\beta=-0.10$, $P=NS$ for T/P). Furthermore, when patients were divided into groups with a more (≥0.5) and less (<0.5) favorable systolic and diastolic T/P, only small and nonsignificant differences in the magnitude of the reduction of LVMI were found (Figure 4).

Discussion
In our hypertensive patients, administration of lisinopril alone or in combination with hydrochlorothiazide reduced 24-hour average SBP and DBP to a similar extent after 3 and 12 months. The average peak and trough blood pressure changes induced by 3 and 12 months of treatment were also similar, and in both instances the individual 3- and 12-month values

### Table 2. Difference (Δ) for Peak and Trough Blood Pressure Changes and T/P and SR Between 3 and 12 Months of Treatment

<table>
<thead>
<tr>
<th></th>
<th>SBP</th>
<th></th>
<th>DBP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ</td>
<td></td>
<td>Δ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak, mm Hg</td>
<td>$-0.34±31.4$</td>
<td>44</td>
<td>$+0.58±23.8$</td>
<td>48</td>
</tr>
<tr>
<td>Trough, mm Hg</td>
<td>$+0.07±30.2$</td>
<td>39</td>
<td>$-0.74±23.2$</td>
<td>41</td>
</tr>
<tr>
<td>T/P</td>
<td>$+0.05±2.8$</td>
<td>140</td>
<td>$+0.20±3.6$</td>
<td>167</td>
</tr>
<tr>
<td>SR</td>
<td>$-0.04±1.6$</td>
<td>192</td>
<td>$+0.04±2.4$</td>
<td>291</td>
</tr>
</tbody>
</table>

Data are mean±2 SD. RC indicates repeatability coefficient.
were closely related to each other. Thus, peak and trough blood pressure changes associated with antihypertensive treatment are reproducible, and their magnitude after short-term administration of antihypertensive drugs satisfactorily reflects the magnitude characterizing 12-month antihypertensive treatment.

This is less the case, however, for the T/P of the antihypertensive effect. In our patients, the average T/Ps obtained after the 3-month treatment were similar to the T/Ps obtained when treatment was prolonged to 12 months, both when calculations were based on average trough and peak changes and when they were based on average of individual T/Ps. However, the percent repeatability coefficients (ie, the reciprocal of reproducibility) were higher and the correlation coefficients were lower for the T/Ps than for peak and trough blood pressure changes separately considered. Thus, at variance from trough and peak blood pressure changes, T/Ps of the antihypertensive effect have a limited reproducibility, which may make their individual values after short-term treatment not entirely representative of those after 1 year of treatment. This may originate from the fact that because it is derived from 2 relatively small blood pressure changes, this ratio can be substantially affected by minor alterations of the antihypertensive effect. For example, for a peak change of 10 mm Hg and a trough change of 5 mm Hg, the resulting 0.50 T/P would range from 0.36 for a T/P of 4/11 mm Hg and to 0.67 for a T/P of 6/9 mm Hg (ie, it would show major differences for just 1 mm Hg change in the peak and trough effect from 1 treatment period to another).

The SAMPLE study has previously shown that in hypertensive patients with LV hypertrophy, regression of the hypertrophy is much more closely related to treatment-induced reduction of the 24-hour average than of clinic blood pressure. The present findings additionally show, however, that regression of LV hypertrophy is related to treatment-induced “ambulatory” trough and peak blood pressure reductions as closely as to 24-hour average blood pressure reduction. Thus, 24-hour blood pressure control is superior to clinic blood pressure control in predicting reversal of end-organ damage of documented prognostic significance. Such an advantage is shared, however, by the 2-hour blood pressure values from which trough and peak blood pressure changes induced by antihypertensive treatment can be calculated. This raises the question of whether 24-hour ABPM is truly necessary or, as our data suggest, information of similar clinical importance can be more easily (and cheaply) obtained with shorter monitoring periods within the between-dose interval.

However, the T/P of the antihypertensive effect performed less well than the separate trough and peak changes. In our hypertensive patients, there was no significant relationship between the reduction of LVMI induced by the 12-month treatment and the 12-month T/P of either SBP or DBP. Furthermore, in patients with a systolic or diastolic T/P regarded as favorable (≥0.5), regression of LV hypertrophy was quantitatively similar to that of the patients with an unfavorable (<0.5) T/P. Thus, the reproducibility as well as the clinical relevance of the T/P of the antihypertensive effect do not mirror the trough and peak blood pressure changes from which the ratio is derived. This indicates that these changes, rather than their ratio, should be considered for use in evaluating in a reproducible fashion how large, balanced, and clinically beneficial are the effects of a given antihypertensive drug or drug combination.

Three further results of our study deserve to be mentioned. First, in the present study we calculated the peak blood pressure effect within a fixed time window, ie, between 2 and 8 hours after administration of the drug(s). The question may therefore be raised whether the peak effect may have occurred later. However, this is unlikely because in a previous study with lisinopril in which no “a priori” time window was used, the peak effect in the group occurred around 11 AM and noon, ie, well within the time window we used.

Second, peak blood pressure changes are regarded as difficult to assess when ambulatory blood pressure is used because the sometimes short-lasting peak blood pressure fall may occur during the interval between the automatic blood pressure readings and/or be modified to an unpredictable and erratic degree by behavioral influences on blood pressure. In the present study, however, calculation of peak blood pressure changes by averaging the hour with the maximal blood pressure reduction plus the adjacent hour with the greater blood pressure reduction resulted in highly reproducible values. Thus, these changes can be consistently assessed if calculated over 2 hours within a fixed time window.

Third, our results also provide information on an alternative method to calculate the duration and homogeneity of the antihypertensive effect over the between-dose interval, ie, the “surface ratio.” Theoretically, this method has an advantage because the calculation takes into account all blood pressure changes during the interval between drug consumption, and according to recent findings obtained after 1 and 2 months of treatment, it is more reproducible than the T/P. In our study, however, the reproducibility of the SR after 3 and 12 months of treatment was not better than the T/P. In this study, however, the reproducibility of the SR after 3 and 12 months of treatment was not better than the T/P and worse than the trough and peak blood pressure changes, separately considered. Furthermore, a poor relationship was found between the SR and the magnitude of the LV hypertrophy reduction. Thus, use of this method is not supported by our data on long-term antihypertensive treatment.

References


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Hypertension. 1998;32:424-429
doi: 10.1161/01.HYP.32.3.424

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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