Attenuation of the “White-Coat Effect” by Antihypertensive Treatment and Regression of Target Organ Damage

Gianfranco Parati, Luisa Ulian, Lorena Sampieri, Paolo Palatini, Alessandra Villani, Alessandro Vanasia, Giuseppe Mancia, on behalf of the Study on Ambulatory Monitoring of Blood Pressure and Lisinopril Evaluation (SAMPLE) Study Group

Abstract—This study assessed whether 2 common surrogate measures of the “white-coat effect,” namely the clinic-daytime and the clinic-home differences in blood pressure (BP), were attenuated by long-term antihypertensive treatment and whether this attenuation is relevant to the treatment-induced regression of left ventricular hypertrophy, thus having clinical significance. We considered data from 206 patients with essential hypertension (aged 20 to 65 years) who had a diastolic BP between 95 and 115 mm Hg and echocardiographic evidence of left ventricular hypertrophy. In each patient, clinic BP, 24-hour ambulatory BP, and left ventricular mass index were assessed at baseline, after 3 and 12 months of treatment with an angiotensin-converting enzyme inhibitor, and after a final 4-week placebo run-off period. At baseline, the clinic-daytime differences in systolic and diastolic BP were 12.1 ±15.4 and 6.8±10.1 mm Hg, respectively; the corresponding values for the clinic-home differences were 5.7±10.6 and 2.9±6.1 mm Hg, respectively. These differences were reduced by 57.6% and 77.1% (P<0.01) and by 65.7% and 64.3% (P<0.01), respectively, after 12 months of treatment, with a partial return toward the pretreatment differences after the final placebo period. The observed treatment-induced reductions in left ventricular mass index and those in the clinic-daytime or clinic-home differences for systolic and diastolic BP showed no significant relationship when tested by multiple regression analysis. This provides the first longitudinal evidence that clinic-daytime and clinic-home differences in BP have no substantial value in predicting the regression of target organ damage, such as left ventricular hypertrophy, that has prognostic relevance. (Hypertension. 2000;35:614-620.)

Key Words: blood pressure ■ hypertension, white-coat ■ antihypertensive agents

Clinic blood pressure (BP) is greater than ambulatory or home BP in most hypertensive patients,1,2 and a major current question is whether the condition in which the former value is elevated when the latter ones are not3 is an innocent phenomenon or if it has an adverse prognostic significance. Some studies reported that in subjects with a high clinic but a normal ambulatory BP, little or no end-organ damage4,5 and no increase in the frequency of cardiovascular morbid or fatal events occurs.5 Other studies, however, have shown that this condition is associated with alterations in organ structure and function or, in subjects with a high clinic and a normal home BP, with metabolic risk factors frequently accompanying hypertension.6–9 For this reason, guidelines on hypertension have found it difficult to decide whether isolated clinic hypertension (also widely known as white-coat hypertension) requires immediate treatment or just follow-up with no antihypertensive drug administration.10,11 Although some negative data were recently collected,12 no conclusive evidence exists regarding the clinical relevance of another commonly used BP parameter, ie, the surrogate measure of the “white-coat effect” that is quantified as the absolute difference between clinic and ambulatory or home BP, regardless of whether ambulatory of home values are in the normotensive or the hypertensive range.12,13

The present study focused on 3 questions never addressed before on this matter. (1) Does the clinic-daytime BP difference become attenuated with long-term antihypertensive drug administration? (2) What is the relationship between the 2 means commonly used to obtain a surrogate measure of the white-coat effect in the medical practice, ie, the clinic-daytime and the clinic-home BP differences? (3) Does the attenuation of these differences have any relevance to the treatment-induced improvement of end-organ damage and, thereby, carry prognostic significance?

Addressing these questions was made possible by the data collected in the SAMPLE study, which was a prospective, single-blind, noncomparative study aimed at determining the relationship of long-term reductions in clinic, home, and...
ambulatory BP with the regression of left ventricular hypertrophy in hypertensive patients.\textsuperscript{14}

Methods

Patients

A total of 206 patients with essential hypertension from 11 hypertension centers located in Italy\textsuperscript{13} were included in the present study using the following criteria: (1) age between 20 and 65 years, (2) a diastolic BP (DBP) between 95 and 115 mm Hg after a 4-week washout from antihypertensive drugs (previously treated patients) or a 3-week observation period (previously untreated patients), and (3) a left ventricular mass index $\geq 110$ g/m$^2$ in women and $\geq 131$ g/m$^2$ in men. Exclusion criteria were the occurrence of cardiovascular complications or major cardiovascular or noncardiovascular diseases besides hypertension and previous antihypertensive treatment consisting of $>2$ drugs; these criteria were used to minimize subsequent drop-out because of a lack of BP control (see below). All patients consented to the study after being informed of its nature and purpose. The number of patients dropped slightly from the initial to the final evaluation after 13 months, but it always remained higher than the minimum required to ensure adequate statistical power (158 subjects).\textsuperscript{14} When patients were divided into 2 subgroups based on whether their clinic-daytime and clinic-home BP differences were, respectively, higher or lower than the median value of the whole group, the number of subjects who dropped out over time was evenly distributed: 48.5\% were in the group with higher and 51.5\% were in the group with lower clinic-daytime or clinic-home BP differences. The study protocol was approved by the Ethics Committees of the Centers involved.

BP Measurements

Clinic BP was measured in the morning using a mercury sphygmomanometer; the first and fifth Korotkoff sounds were used to identify systolic and diastolic values, respectively. Two measurements were collected with the patient in the supine position for 5 and 8 minutes, respectively, and the average of the 2 values was taken as the clinic BP for inclusion in the study and for the determination of the efficacy of treatment.

Home BP was measured by a semiambulatory oscillometric device (Model HP 5331, Philips); its accuracy was shown in previous studies.\textsuperscript{10} The patient was asked to obtain a morning and an evening measurement in the sitting position during the same day in which ambulatory BP monitoring was performed. Morning and evening values were averaged.

Ambulatory BP monitoring was performed by oscillometric SpaceLabs 90202 or 90207 equipment.\textsuperscript{15} The cuff of the monitoring device was applied to the nondominant arm at the end of the clinic visit and, for patients satisfying recruitment criteria, at the second medical visit and, for patients satisfying recruitment criteria, in a no-drug condition for 4 weeks if they were previously treated and for 3 weeks if they were untreated. This was followed by a second medical visit and, for patients satisfying recruitment criteria, by the administration of lisinopril at a morning dose of 20 mg. Lisinopril was selected because the administration of an angiotensin-converting enzyme inhibitor guarantees the regression of left ventricular hypertrophy,\textsuperscript{19} which was necessary to compare the relative importance of the effect of treatment on clinic, home, and ambulatory BP in relation to regression of target organ damage. A morning dose of 12.5 or 25 mg of hydrochlorothiazide was added during subsequent visits in nonresponders, ie, in patients in whom clinic DBP at trough had not fallen below 90 mm Hg or by $\geq 10$ mm Hg. Treatment was continued for an overall period of 12 months; after this time, antihypertensive drugs were substituted, in a single-blind fashion, with placebo tablets, which were administered for an additional 4-week period. Home BP, ambulatory BP, and echocardiographic data were collected before the beginning of treatment, after 3 and 12 months of treatment, and at the end of the final placebo period.

Echocardiography

Left ventricular diameter, septal wall thickness, and left posterior wall thickness were assessed by M-mode echocardiography after selecting the measurement section by B-mode echocardiography. Data were averaged over 5 cardiac cycles. Left ventricular mass index was calculated from thickness and diameter values using the Penn convention formula.\textsuperscript{18}

Study Protocol

The study was conducted using a single-blind, noncomparative, prospective design. After an initial medical visit, patients were kept in a no-drug condition for 4 weeks if they were previously treated and for 3 weeks if they were untreated. This was followed by a second medical visit and, for patients satisfying recruitment criteria, by the administration of lisinopril at a morning dose of 20 mg. Lisinopril was selected because the administration of an angiotensin-converting enzyme inhibitor guarantees the regression of left ventricular hypertrophy,\textsuperscript{19} which was necessary to compare the relative importance of the effect of treatment on clinic, home, and ambulatory BP in relation to regression of target organ damage. A morning dose of 12.5 or 25 mg of hydrochlorothiazide was added during subsequent visits in nonresponders, ie, in patients in whom clinic DBP at trough had not fallen below 90 mm Hg or by $\geq 10$ mm Hg. Treatment was continued for an overall period of 12 months; after this time, antihypertensive drugs were substituted, in a single-blind fashion, with placebo tablets, which were administered for an additional 4-week period. Home BP, ambulatory BP, and echocardiographic data were collected before the beginning of treatment, after 3 and 12 months of treatment, and at the end of the final placebo period.

Data Analysis

Data obtained in the longitudinal study were analyzed retrospectively. In each patient, the differences between clinic and home and clinic and average daytime systolic BP (SBP) were computed for the data obtained before treatment, after 3 and 12 months of treatment, and at the end of the final placebo period. Daytime SBP was defined as the average value obtained for the hours in which the subjects reported in their diary as being awake. These waking hours were selected within the time interval ranging from 6 AM to midnight. Results from individual subjects were expressed as means$\pm$SEM for the group as a whole. Similar calculations were made for the differences between clinic and home or daytime average DBP. The reproducibility of these differences was assessed by computing the correlation coefficients between the data obtained in the initial and subsequent periods.

Echocardiographic data were obtained for pretreatment and drug treatment conditions. Both univariate and multivariate linear regression analyses were applied to the changes in left ventricular mass index after 12 months of treatment and the corresponding treatment-induced changes in clinic BP, home BP, and clinic-daytime and clinic-nighttime average BP differences. When multiple regression analysis was performed, the treatment-induced changes in average daytime or home BP and treatment-induced changes in clinic-daytime or clinic-nighttime BP differences were included in the model as independent variables; these data were separated into SBPs and DBPs. Treatment-induced changes in left ventricular mass index or in left ventricular wall thickness (average of septal and left posterior wall thickness) were taken as dependent variables.

The statistical significance of the treatment-induced changes was assessed by ANOVA and by Student’s $t$ test for paired observations, with Bonferroni’s correction for repeated comparisons when necessary, after the determination of the normality of the data distribution by the Shapiro Wilk nonparametric test.\textsuperscript{20} $P<0.05$ was the level of statistical significance.

Results

Clinic-Daytime BP Difference Before and During Treatment

Figure 1 shows that before treatment, the average clinic SBP was higher than the average daytime SBP; both measures fell...
after 3 and 12 months of treatment and returned toward the initial high values after the final placebo period. In all 4 conditions, the clinic-daytime SBP difference showed large between-patient variability. Compared with the pretreatment condition, however, the mean difference decreased after 3 and 12 months of treatment ($P<0.01$), with a return toward the initial higher mean value after the final placebo period (Table 1; Figure 2, top left). Similar findings were obtained for DBP (Figure 2, top right). As shown in Table 2, the clinic-daytime BP differences before treatment were, in general, significantly related to the corresponding differences after the final off-treatment period. This was also the case for the clinic-daytime BP differences after 3 and 12 months of treatment. In no instance, however, were the correlation coefficients $>0.45$.

**Clinic-Home BP Differences Before and During Treatment**

Figure 1 shows that before treatment, home SBP and DBP values were lower than the corresponding clinic values but higher than the corresponding average daytime BP values; the pretreatment clinic-home BP differences were, thus, smaller than the clinic-daytime BP differences. The clinic-home BP differences decreased after 3 and 12 months of treatment (more after 12 than 3 months), with a partial return toward the pretreatment values after the final placebo period; this return was less evident than that observed for the clinic-daytime BP differences (Table 1; Figure 2, bottom). The clinic-home BP differences observed in the periods without treatment (pretreatment and final placebo values) were also usually related (but only to a limited extent and with 1 exception) to those during treatment (3 and 12 months of treatment) (Table 2). Before treatment, the clinic-home BP differences showed a limited, although significant, relationship with the clinic-daytime BP differences. This also occurred when the changes in these 2 measurements induced by treatment were considered (Figure 3); the relationship was closer for SBP than DBP values.

**Clinic-Daytime or Clinic-Home BP Differences and Left Ventricular Mass Index**

As shown in Figure 1, the left ventricular mass index was reduced by 3 months and even more so by 12 months of treatment and returned toward the initial high values after the final placebo period. In all 4 conditions, the clinic-daytime SBP difference showed large between-patient variability. Compared with the pretreatment condition, however, the mean difference decreased after 3 and 12 months of treatment ($P<0.01$), with a return toward the initial higher mean value after the final placebo period (Table 1; Figure 2, top left). Similar findings were obtained for DBP (Figure 2, top right). As shown in Table 2, the clinic-daytime BP differences before treatment were, in general, significantly related to the corresponding differences after the final off-treatment period. This was also the case for the clinic-daytime BP differences after 3 and 12 months of treatment. In no instance, however, were the correlation coefficients $>0.45$.

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treatment, with a significant increase after the final placebo period. The change in left ventricular mass index induced by 12 months of treatment was significantly related to the treatment-induced change in daytime SBP and DBP ($r=0.37$ and 0.36, respectively; $P<0.001$ for both), but not to the treatment-induced modification of the clinic-daytime BP differences (multiple regression analysis, $\beta=-0.10$ and $-0.14$ for the clinic-daytime difference in SBP and DBP, respectively; $P=NS$ for both). The treatment-induced change in left ventricular mass index was also weakly related to the concomitant change in home BP ($r=0.23$ for SBP and 0.19 for DBP; $P<0.05$ for both) but, again, not to the change in the clinic-home BP differences (multiple regression analysis, $\beta=-0.10$ and $-0.20$ for the clinic-home difference in SBP and DBP, respectively; $P=NS$ for both). The results are shown in a tridimensional fashion in Figure 4.

**Discussion**

Our study provides data on all 3 questions mentioned in the introduction. These data will be discussed separately.

Does Antihypertensive Treatment Attenuate the Clinic-Daytime BP Difference?

In our study, the clinic-daytime SBP and DBP differences observed in the initial pretreatment period showed marked between-patient variability. The average differences, however, were reduced after 3 months ($-47\%$ and $-61\%$, respectively, for SBP and DBP; $P<0.01$), and a slight further reduction was observed after 12 months of treatment ($-58\%$ and $-77\%$, respectively, for SBP and DBP; $P<0.01$ versus baseline). A clear-cut, although incomplete, return toward the initial average differences occurred at the end of the final off-treatment period. This extends previous reports of an attenuation of these surrogate measures of the “white-coat effect” after short-term treatment. It further shows, however, that this attenuation tends to progress with the duration of the treatment period and that active treatment is presumably involved. This, of course, pertains to the type of treatment used in the present study. Whether antihypertensive drugs or drug combinations other than angiotensin-converting enzyme inhibitors and beta blockers are also effective in reducing these surrogates remains to be determined.

**Figure 2.** Clinic-daytime differences (top) and clinic-home differences (bottom) for SBP and DBP. Data are shown as individual values for the subjects shown in Figure 1. Differences are separately illustrated for the baseline condition, the 3 (3 mT) and 12 (12 mT) month treatment periods, and the final placebo period. Changes in both clinic-daytime and clinic-home BP differences between baseline and 3 or 12 months of treatment were statistically significant ($P<0.01$). The corresponding changes between baseline and the final placebo values were significant for only the clinic-daytime BP difference ($P<0.05$).

**TABLE 2. Reproducibility of Clinic-Daytime and Clinic-Home BP Differences**

<table>
<thead>
<tr>
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<th>Initial Visit vs Final Placebo</th>
<th>Treatment, 3 vs 12 mo</th>
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<tr>
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<td>$r$</td>
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<tr>
<td>Clinic-daytime</td>
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<tr>
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<tr>
<td>Clinic-home</td>
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<tr>
<td>SBP</td>
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<td>DBP</td>
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enzyme inhibitors and diuretics perform similarly or differently remains to be assessed. Two further points should be mentioned. First, in the final off-treatment period, the clinic-daytime BP differences remained somewhat smaller than in the initial pretreatment period. This may be interpreted as indicating that these surrogate measures of the white-coat effect can indeed be attenuated by time. However, in the final off-treatment period, patients were given a placebo, which may have reduced clinic BP and, thus, the clinic-daytime differences, both during and in the absence of antihypertensive treatment; an attenuation after 3 and 12 months of treatment; and a tendency to return toward baseline values during placebo administration, although the latter occurred to a lesser extent in the clinic-home differences than in the clinic-daytime differences. The discrepancy is that the clinic-home SBP and DBP differences are no more than half of the corresponding clinic-daytime differences, both during and in the absence of treatment. Thus, the white-coat effect is subjected to a highly discordant quantification, depending on which of the 2 surrogate methods is used to determine it.

The reasons why the white-coat effect is so markedly greater when indirectly quantified by the clinic-daytime BP differences instead of the clinic-home differences are not clarified by our study. We speculate that, in this respect, the former difference is more relevant than the latter, because in hypertensive patients, self-measurements of BP at home may elicit an emotionally induced BP rise, which is not elicited when BP is measured automatically or semiautomatically by an ambulatory device. Evidence is available, however, that neither difference accurately reflects the actual pressor effect of BP measurements in a clinical environment, ie, the “true” white-coat effect. Thus, we can also speculate that the clinic-daytime BP difference is greater than the clinic-home one because daytime BP, which is the average of a large number of readings, undergoes an instantaneous regression to the mean, which makes it lower than the average of a few clinic and a few home readings.

Treatment-Induced Attenuation of the Clinic-Daytime and Clinic-Home BP Differences Versus Regression of Left Ventricular Hypertrophy

In the hypertensive patients in the SAMPLE study, the regression of left ventricular hypertrophy induced by 1 year of antihypertensive treatment correlated with the treatment-induced reduction of daytime and (less so) home BP but not with the treatment-induced reduction in clinic BP. The
additional important finding of the present study, however, is that neither the attenuation of the clinic-daytime BP difference nor the attenuation of the clinic-home BP difference induced by antihypertensive drug treatment had any relationship with the treatment-induced regression of left ventricular hypertrophy. This provides the first longitudinal evidence that these commonly used surrogate methods of quantifying the white-coat effect do not predict the treatment-induced improvement of structural cardiac alterations, which is predicted to a significant degree only by the effect of treatment on a BP obtained outside the clinic environment. This supports the hypothesis that surrogate measures of the white-coat effect, such as the clinic-daytime or clinic-home BP differences, are of marginal clinical significance.

It should be emphasized that this conclusion is based on echocardiographic left ventricular hypertrophy, ie, on end-organ damage of prognostic significance. This has been demonstrated in observational studies in which subjects with left ventricular hypertrophy showed an incidence of cardiovascular disease that was greater than that in those without left ventricular hypertrophy. It has also been shown, although less conclusively, in longitudinal studies in which the regression of left ventricular hypertrophy by antihypertensive treatment was accompanied by the reduction of arrhythmias; improvement of cardiac function, coronary reserve, and cardiogenic reflexes; and, in the context of uncontrolled studies, a reduction in cardiovascular mortality. It should also be emphasized, however, that the lack of clinical relevance of the surrogate measures of the white-coat effect may apply to the type of patients involved in our study and that whether these measures have any additional clinical value over ambulatory or home BP values in patients with milder hypertension and no end-organ damage remains to be assessed. Further insight on these issues might benefit from additional longitudinal, controlled studies on both uncomplicated and complicated hypertensive individuals to determine the relevance of treatment-induced modifications of clinic-home or clinic-ambulatory BP differences on other organ damage and on cardiovascular morbidity events. It also remains to be assessed whether the direct quantification of the “true” white coat effect (ie, the actual increase in BP during a visit by a physician) might have a better clinical value than the surrogate measures of this phenomenon considered in our study.

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