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Evaluation of the Placebo Effect and Reproducibility of Blood Pressure Measurement in Hypertension

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Pharmacologic studies in hypertension often describe blood pressure (BP) reductions in placebo control groups. This placebo effect is currently debated, as it seems to be related to BP measurement methods and as a regression to the mean phenomenon may lead to misinterpretation. Furthermore, data on pulse pressure are lacking. This study was designed to evaluate the placebo effect on BP and to differentiate it from regression to the mean. According to a crossover design, 26 mild-to-moderate hypertensive patients who were treated with placebo or given no treatment were followed-up for 1 month. Clinic and ambulatory BP was assessed at baseline and at the end of each 1-month period.

Placebo administration resulted in significant reductions in clinic systolic, diastolic, and mean BP ($P < .01$), ambulatory 24-h SBP ($P < .05$), and daytime systolic, diastolic, and mean BP ($P < .01$, $P < .05$, $P < .01$, respectively). No significant differences were noted for pulse pressure and heart rate or between BP values measured at baseline and after 1 month without treatment. Despite a significant correlation between changes in clinic and ambulatory BP, the scatter of individual data suggests that the placebo response observed with one method cannot be systematically extrapolated to the other method.

This study conclusively shows the effect of placebo in mild-to-moderate hypertension on both clinic and ambulatory systolic, diastolic, and mean BP, in which it has been shown to differ from the regression to the mean phenomenon. This effect was not observed for pulse pressure or heart rate. Am J Hypertens 2001;14:546–552

Key Words: Blood pressure, placebo, ambulatory blood pressure monitoring, regression to the mean, reproducibility.

Pharmacologic studies in mild-to-moderate hypertension often show that hypertensive patients included in the placebo control groups have lower blood pressure (BP) values postdose, suggesting an effect due to placebo administration.[1,2] This variable effect depends on many factors, including the methods used for BP measurements. In fact, higher sensitivity to placebo has been described with clinic BP measurements when compared to ambulatory BP monitoring (ABPM), driving a controversy as to the existence of the placebo effect on ABPM.[3–7] It has also been highlighted that the observation of a placebo effect in clinic settings should be managed with caution, as many other factors may induce a false interpretation of the observed results. These factors may be related to the natural course of the disease, spontaneous improvement, fluctuation of symptoms, regression to the mean, and observer bias.[8]

Considering that the primary reason for misinterpretation in identifying the placebo effect is its differentiation from the "time effect" or regression to the mean phenomenon, and that most studies that have analyzed the placebo effect were not designed in a manner to allow this differentiation, we conducted a study appropriately designed to evaluate the effect of placebo on clinic and ambulatory BP measurements, including not only systolic blood pressure (SBP), diastolic blood pressure (SBP), and mean arterial pressure (MAP), but also pulse pressure (PP).

Patients and Methods

Study Design

The study protocol was designed to assess the placebo effect and to differentiate it from the regression to the mean phenomenon; this differentiation was possible because of the randomized, crossover design. After a 1-month run-in period without any treatment, patients were randomized into two groups, either to receive placebo or to remain without treatment for 1 month. At the end of this period, untreated patients

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received placebo and placebo-treated patients were followed with no treatment for another 1-month period. At each visit (day 0, day 30, day 60), a clinical examination with an assessment of clinic SBP, DBP, MAP, PP, and heart rate (HR) were performed in addition to 24-h ABPM.

Patients

A total of 30 patients with untreated mild-to-moderate hypertension were to be included in the study. Both male and female patients, aged ≥ 18 years, were eligible for inclusion provided that they had a DBP ≥ 90 and ≤ 115 mm Hg or a SBP ≥ 140 and ≤ 200 mm Hg. The main exclusion criteria were severe or symptomatic hypertension, and cardiovascular complications or treatment.

Procedures

Clinic BP measurements were performed in compliance with the World Health Organization recommendations: three successive measurements in patients resting for 10 min in the sitting position, using a mercury sphygmomanometer and the auscultatory method (Korotkoff phase I and V for SBP and DBP, respectively). The last two measurements were averaged for data analysis.

The ABPM was performed according to rigorous methodological requirements to optimize its reproducibility. The same device (Diasys; Novacor, Rueil-Malmaison, France) was employed for the same patient for each of the three ABPM recordings, and fitted at approximately the same time. The devices were programmed to perform one measurement every 15 min during the daytime (7 AM to 10 PM) and one measurement every 30 min during the nighttime (10 PM to 7 AM). Each subject was given a patient diary for recording measurements. All recordings were controlled for quality and were eligible for statistical analysis provided that they met the following criteria: ≥ 60 measures distributed throughout the whole 24-h period, and ≤2 h (consecutively) of missing data.

Statistical Analysis

Data were transferred to a database (Excel 5.0 for PC Microsoft). The quality of the data acquisition was double-checked by two different observers before its transfer to statistical software. Statistical analysis was performed using the NCSS program (Number Cruncher Statistical Systems, Kaysville, UT). Descriptive tests were used to express the range of values, means, and standard deviations. Analysis of variance for repeated measurements was performed to analyze the group and treatment factors. Data from each treatment group were pooled for the two periods after testing the absence of the period effect in each group. A value of $P < .05$ was considered statistically significant.

Results

After controlling for recordings quality for all ABPM, data from 26 patients (62% male) were available for statistical analysis at each of the three evaluation times (D0, D30, and D60). At inclusion, the study population had a mean age of 43 ± 9 years, a mean weight of 72 ± 13 kg, and a mean height of 169 ± 8 cm. The principal baseline BP and biologic characteristics of the study population are presented in Table 1.

Table 1. Baseline clinical characteristics of the study population

Variable	Baseline
n	26
Age (years)	43 ± 9
Weight (kg)	72 ± 13
Height (cm)	169 ± 8
Clinic SBP (mm Hg)	148.8 ± 12
Clinic DBP (mm Hg)	97.8 ± 6.6
Clinic MAP (mm Hg)	115 ± 6.3
Clinic PP (mm Hg)	51.0 ± 13.5
Heart rate (beats/min)	72.4 ± 10.7
Sodium (mmol/L)	140 ± 2.6
Kalemia (mmol/L)	4.1 ± 0.5
Creatinine (mmol/L)	86.2 ± 16.9
Total cholesterol (mmol/L)	5.3 ± 1
HDL (mmol/L)	1.4 ± 0.5
Triglycerides (mmol/L)	1.2 ± 0.8
γ-GT (UI/L)	28.2 ± 19.4

SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; PP = pulse pressure.
Data are given as mean ± SD.

Analysis of the Placebo Effect

Analysis of clinic BP data showed significant decreases from baseline in SBP, DBP, and MAP after placebo therapy: −6.5 ± 11.1, −5 ± 8.4, and −5.6 ± 8.4 mm Hg, respectively ($P < .01$ *v* baseline) (Table 2). No significant changes were observed for PP or HR.

The study results showed a significant placebo effect on ambulatory mean values, with BP reductions in the 24-h SBP and MAP: −2.9 ± 6.2 and −2.6 ± 5.5 mm Hg, respectively; $P < .05$. This 24-h ambulatory BP reduction from baseline appears to be related principally to a significant reduction during the daytime of SBP (−3.7 ± 6.8; $P < .01$), DBP (−3.3 ± 6.9; $P < .05$), and MAP (−3.5 ± 5.8; $P < .01$) (Table 2), whereas BP reduction during the nighttime period was less important than that observed during the daytime and did not reach statistical significant level (Fig. 1, Table 2). No significant changes were observed for PP or HR in any of the 24-h, daytime, or nighttime periods.

On the whole, the results observed with clinic and ambulatory measurements are in agreement and show a significant placebo effect on SBP, DBP, and MAP but not on PP or HR.

Table 2. Clinic and ambulatory blood pressure (BP) mean values and changes (Δ) from baseline after 1 month without treatment, and 1 month of placebo therapy

	Baseline	No Treatment	Placebo	Δ No Treatment, Baseline	Δ Placebo, Baseline
Clinic BP					
SBP (mm Hg)	148.9 ± 12.2	146.7 ± 14.5	142.4 ± 15.7	−2.2 ± 10.5	−6.5 ± 11.1†
DBP (mm Hg)	97.9 ± 6.5	97.6 ± 9.5	92.9 ± 11.3	−0.3 ± 8.2	−5 ± 8.4†
MAP (mm Hg)	115.0 ± 6.1	114 ± 10	109.3 ± 11.2	−1.1 ± 7.0	−5.7 ± 8.4†
PP (mm Hg)	51.0 ± 13.3	49.0 ± 13.5	49.5 ± 13.3	−2 ± 12.3	−1.5 ± 9.9
HR (beats/min)	72.6 ± 10.6	72.6 ± 11.3	71.6 ± 10	0 ± 8.2	−1.0 ± 8.6
Ambulatory BP, 24-h					
SBP (mm Hg)	134.5 ± 10.1	134.9 ± 107	131.7 ± 12.4	+0.3 ± 7.5	−2.9 ± 6.2*
DBP (mm Hg)	87.4 ± 8.6	87.9 ± 9.1	85.4 ± 8.5	+0.4 ± 6.2	−2.1 ± 6.3
MAP (mm Hg)	103.2 ± 7.5	103.5 ± 8.5	100.7 ± 8.6*	+0.3 ± 6.1	−2.6 ± 5.5
PP (mm Hg)	47.1 ± 11	47.1 ± 9.6	46.4 ± 10.7	0 ± 5.1	−0.7 ± 6.6
HR (beats/min)	74.9 ± 10.1	73.7 ± 8.7	73.1 ± 9.8	−1.2 ± 5.5	−1.8 ± 4.8
Ambulatory BP, daytime					
SBP (mm Hg)	140.0 ± 9.5	140.8 ± 10.7	136.3 ± 12.1	+0.7 ± 8.6	−3.7 ± 6.8†
DBP (mm Hg)	93 ± 8.4	92.7 ± 8.2	89.7 ± 8	−0.3 ± 6.6	−3.3 ± 6.9*
MAP (mm Hg)	108.7 ± 7.3	108.8 ± 7.9	105.3 ± 7.9	0 ± 6.6	−3.5 ± 5.8†
PP (mm Hg)	47 ± 10.8	48.1 ± 10.1	46.7 ± 11.3	+1.1 ± 6.2	−0.3 ± 7.9
HR (beats/min)	79.3 ± 10.4	78.3 ± 9.5	78 ± 10.2	−1 ± 6.1	−1.3 ± 4.5
Ambulatory BP, nighttime					
SBP (mm Hg)	125.8 ± 11.7	125.8 ± 12.2	124 ± 13.7	0 ± 8	−1.8 ± 6.5
DBP (mm Hg)	79.3 ± 9.7	80.4 ± 11.0	78.3 ± 10.2	+1.0 ± 6.9	−1.1 ± 6.5
MAP (mm Hg)	94.9 ± 8.9	95.5 ± 10.6	93.4 ± 10.3	+0.6 ± 7.2	−1.5 ± 5.8
PP (mm Hg)	46.5 ± 11.7	45.5 ± 9.8	45.8 ± 10.7	−1.0 ± 5.4	−0.7 ± 6.2
HR (beats/min)	67.8 ± 10.7	66.6 ± 8.5	65.9 ± 9.2	0 ± 2.0	−1.9 ± 6.1

DBP = diastolic blood pressure; HR = heart rate; MAP = mean arterial pressure; PP = pulse pressure; SBP = systolic blood pressure.
Data are given as mean ± SD.
* $P < .05$ *v* baseline.
† $P < .01$ v baseline.

Analysis of the Regression to the Mean Phenomenon

The comparison between mean values of clinic BP measured at baseline and after 1 month with no treatment showed a small but statistically nonsignificant change in BP and HR (Table 2).

The comparison between mean values of ambulatory BP measured at baseline and after 1 month with no treatment showed no significant changes in BP or HR (Table 2). Taken together, the results show that both clinic and ambulatory measurements present satisfactory reproducibility, with better values for ABPM than for clinic BP measurement.

Predictivity of the Placebo Response

To verify whether the placebo effect observed by either clinic measurement or ABPM may be predicted by the other technique, correlations between the clinic BP variations and those observed using ABPM were analyzed. Significant linear correlations were found between the BP changes observed by clinic BP measurements and those observed with the ABPM method, for both SBP and DBP changes (correlation 0.378, $P < .05$; and correlation 0.475, $P < .01$, for SBP and DBP, respectively). However, the corresponding correlation coefficients did not exceed r = 0.50, which is a relatively low value considering the evaluation of a same parameter using two different methods. Moreover, the scatter of individual data suggests that the placebo response observed with one method may not be predicted accurately by extrapolation of the results observed with the other method (Fig. 2).

Discussion

The major findings of this study are the following: 1) in hypertensive patients, there is a placebo effect that differs from the regression to the mean phenomenon; 2) this effect is independent of the BP measurement method used, inasmuch as similar results were obtained with both clinic and ABPM; and 3) the placebo effect is observed for SBP, DBP, and MAP but not for PP or HR.

Several aspects of this last result need discussion. Although some previous studies have reported the absence of placebo effect on HR, data on the effects of PP are lacking. Hypotheses include the following:

1. One explanation for the lack of placebo effect on PP (SBP minus DBP) may be the parallel decrease of

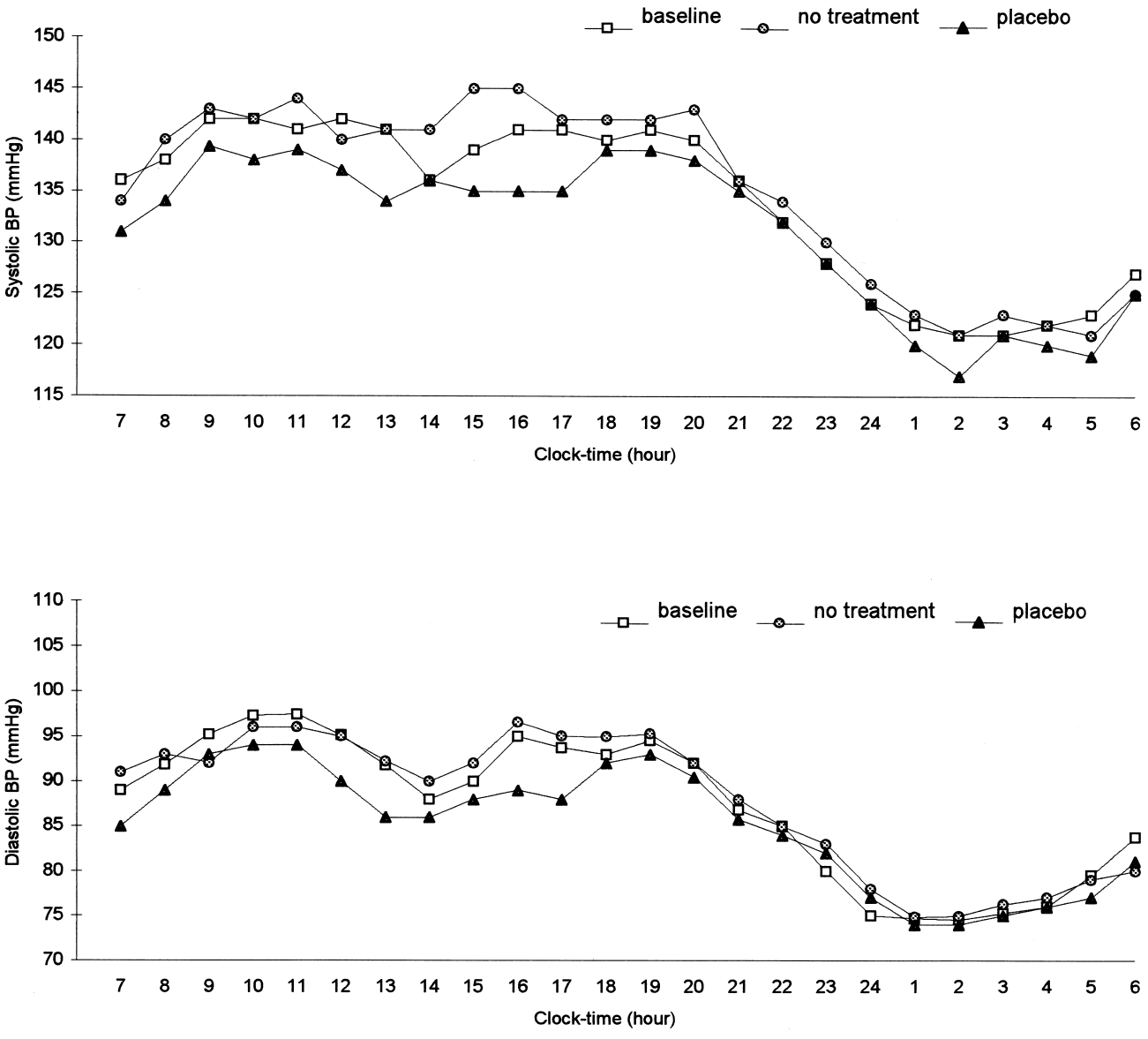


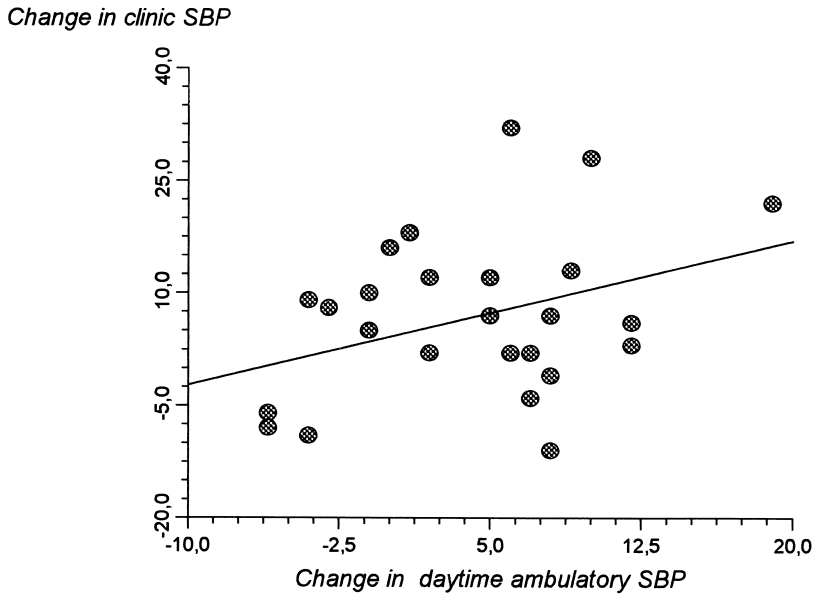
FIG. 1. Mean hourly values and circadian variations of ambulatory systolic and diastolic blood pressure (BP) recorded at baseline, after 1 month without treatment and after 1 month of placebo in the total population.

SBP and DBP. In fact, an analysis of the relationship of the changes in SBP and DBP showed a significant linear correlation between these two parameters ($r = 0.378$; $P < .05$, and 0.475; $P < .01$, for SBP and DBP, respectively). Nevertheless, this may only partly explain the observed results, given the scatter of individual data.

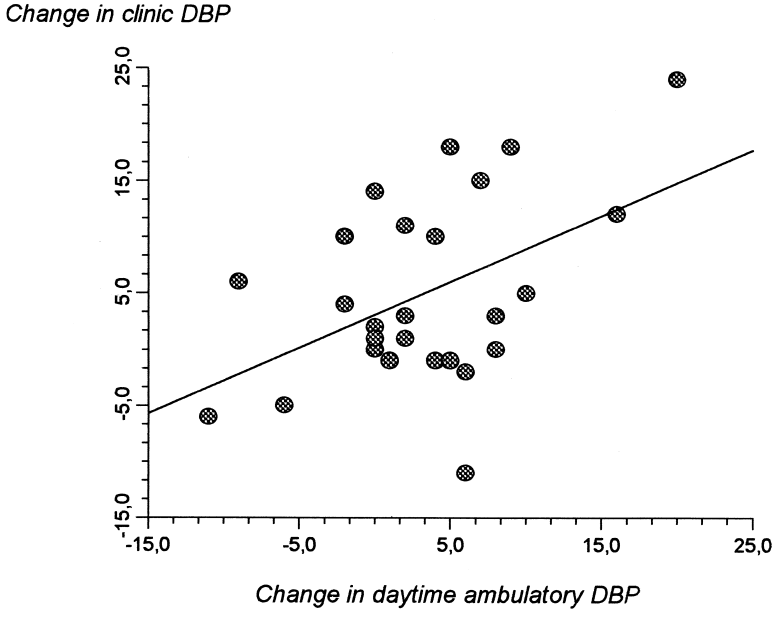
2. Another explanation for the unchanged PP may be the absence of a placebo effect on PP determinants. In fact, the major hemodynamic determinants of SBP, DBP, MAP, and PP are different; thus, the results obtained on PP may be related to its unchanged hemodynamic parameters under the influence of placebo.

The differences in clinic SBP, DBP, and MAP from baseline that were found after treatment ($P < .01$) confirm a placebo effect on clinic BP, which is currently well established. The placebo effect was also observed on ambulatory BP measurements, with significant BP reductions in 24-h SBP and MAP mean values ($P < .05$) due principally to a significant decrease in daytime BP values ($P < .05$ for DBP and $P < .01$ for SBP and MAP).

These findings should to be considered with respect to the current controversy concerning the placebo effect. In fact, the existence of the placebo effect has recently been questioned by Kienle and Kiene[8] who reviewed the meta-analysis of Beecher[9] that highlights the placebo effect as an important part of the total therapeutic effect. Kienle and Kiene suggested that most of the observed improvements were independent of placebo administration, and that the



Equation : Y = 4.134895 + 0.6405493 * X ; correlation : 0.377849 ; p < 0.05



Equation : Y = 3.082471 + 0.5865381 * X ; correlation : 0.4752904 ; p < 0.01

FIG. 2. Correlations observed between the placebo response on clinic systolic blood pressure (SBP) and diastolic blood pressure (DBP), and diurnal ambulatory SBP and DBP.

so-called placebo effect might be a "fiction" related to different factors that are likely to make a clinical effect misinterpreted as an effect of placebo. According to these investigators, these confusing factors are either methodological aspects (observer bias) or are related to the natural course of the disease (spontaneous improvement, regression to the mean). Regarding arterial hypertension, these arguments are of great interest. In fact, it appears that the observation of a placebo effect in hypertension is closely dependent on the method for measuring BP: with clinic BP, the placebo effect is currently observed,[3–5,10–12] whereas ABPM seems to be less affected by placebo.[3–5,13]

The observation bias underlined by Kienle and Kiene[8] is a well known risk related to the clinic measurement of BP. It was also shown by Sassano et al[7] that observer expectations regarding a treatment may have an influence on evaluation of the placebo effect when assessed using clinic BP measurements: no significant difference was noted after single-blind treatment with placebo, whereas a double-blind placebo or active treatment showed lower values of clinic SBP and DBP. When ABPM data were considered, lower values of both SBP and DBP were shown in these patients at the end of the two periods (single-blind and double-blind therapeutic periods). These workers suggested that clinician expectation had an effect on BP measurements.[7]

Another factor that may alter the reliability of the placebo effect evaluation on clinic BP measurement is the well known interaction that exists between the clinic BP response and the influence of psychologic factors such as the medical environment or the relation between the patient and the physician. This interaction is likely to make the BP values either increase ("white coat effect") or significantly decrease (therapeutic effect enhanced by the patient's sensation of confidence). Regarding the evaluation of a placebo effect, ABPM—which is performed out of the medical environment and influence—is likely to provide more objective information. Furthermore, ABPM is more reproducible and sensitive than clinic BP measurement. In our study, both methods of measurements were used for the detection and analysis of the placebo effect, with rigorous conditions regarding ABPM methodology and quality control to ensure its reproducibility and reliability.

The placebo effect on ABPM is controversial because in some studies, ambulatory BP levels seem less affected by placebo than are clinic BP values, leading some researchers to state that the placebo effect may be either limited or eliminated when BP is assessed by ambulatory BP mean values.[3,5–13] This assertion, however, must be considered with caution. In other studies, a placebo effect on ABPM in hypertensive populations has been observed.[5–7,14–16] In addition, this observation can be argued, mainly on the basis of methodological aspects of placebo effect evaluation, including 1) study designs that cannot identify the effect of the placebo and do not consider the risk of confounding factors, as underlined by Kienle and Kiene,[8] and 2) the lack of untreated control patients to provide data that reflect the natural course of the disease.

Our study was designed to identify the effect of placebo on BP and to differentiate it from the "time effect" (regression to the mean). Placebo therapy was compared with no treatment, with each patient as his or her own control. During the no-treatment period, clinic and ambulatory BP values did not differ from those of baseline, indicating that the BP changes observed after placebo were due to an actual effect of the placebo, independent of any regression to the mean or spontaneous improvement. This placebo effect was observed on SBP, DBP, and MAP after administration of the placebo, independent of any therapeutic sequence effect, as BP levels were reduced by placebo whichever was the sequence of administration.

All of the previously mentioned factors that may influence the placebo effect on BP concern SBP, DBP, and MAP but not PP, which remained unchanged under placebo. This lack of placebo effect on PP may be important to consider in clinic settings. In fact, a number of studies[17–23] have shown that brachial PP is an independent predictor of cardiovascular risk, particularly for myocardial infarction[18,19] or congestive heart failure,[20] and that in some populations, PP is apparently a more accurate predictor of cardiovascular mortality than either SBP or DBP or MAP alone.[21–23]

To determinate the ability of each of clinic measurements and ABPM to predict the placebo response observed by the other method, we analyzed the correlations existing between the placebo-induced modifications in BP assessed by both methods. Daytime variations of ambulatory BP were found to correlate with clinic variations but with a relatively low correlation coefficient (< 0.50). Moreover, the scatter of individual data suggests that the placebo response observed with one method cannot be systematically extrapolated to the other method. These observations indicate that different factors may affect each of the two methods of BP measurement.

In conclusion, the results of this study conclusively demonstrate the existence of the placebo effect in the treatment of mild-to-moderate hypertension, on clinic as well as ambulatory BP measurement. This effect of placebo is different from a regression to the mean phenomenon and does not depend on the method used for BP assessment. The placebo effect was observed on SBP, DBP, and MAP but not on PP or HR.

These findings highlight the need for control groups in trials on hypertension. In the absence of a comparison with placebo-treated patients to delineate the role of a placebo effect in the therapeutic effect of antihypertensive drugs, the therapeutic evaluation may overestimate the pharmacologic effect of the medication and lead to an inappropriate use of the treatment.

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