Repeated measurements of non-invasive ambulatory blood pressure: distinction between reproducibility and the proper effect of placebo

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Objective To determine whether non-invasive ambulatory blood pressure is more reproducible and less affected by the placebo treatment than are clinic blood pressure measurements.

Method Thirty-four essential hypertensive outpatients were randomly allocated after a 4-week preselection period in two groups in a cross-over study design. One group received placebo for 4 weeks while the other formed the control group (reproducibility), then the treatments were exchanged for another 4 weeks. Clinic and ambulatory blood pressures were measured at three different times for each patient, namely before the random allocation to groups and at the end of each period, using a mercury sphygmomanometer and 24 h non-invasive ambulatory blood pressure monitoring.

Results Administration of placebo was accompanied by a significant reduction in systolic and diastolic clinic blood pressures (by 3.4 ± 13 and 3.6 ± 8 mmHg, respectively), but not in 24 h, daytime and night-time blood pressures. Circadian hourly blood pressure and heart rate curves were virtually superimposable. In the 13 placebo responder patients selected on the basis of clinic blood pressure, placebo decreased the clinic blood pressure and also reduced systolic and diastolic ambulatory blood pressures, mainly during the day period (by 5.2 ± 6.2 and 4.8 ± 7.8 mmHg, respectively). This effect is specific and related to the placebo administration because repetition of the measurements without any treatment showed no significant difference. To characterize at baseline the placebo responder patients, comparison with the non-placebo responders showed lower baseline values of ambulatory systolic blood pressure recorded during 24 h daytime and night-time in the placebo responder group.

Conclusion The 24 h ambulatory blood pressure average is not affected by placebo in the present group of patients but that a placebo effect occurs mainly during the daytime in patients who decreased their clinic blood pressure under placebo (placebo responders); the placebo-induced reduction in blood pressure is related to a specific effect of placebo and is independent from any alerting reaction or reproducibility hypothesis. This study clearly indicates the necessity of including placebo and ambulatory blood pressure monitoring in the therapeutic and pharmacological trials of antihypertensive drugs.

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Introduction

Casual measurement in the clinic is the most common method used to determine blood pressure in clinical trials. Although they are easy to obtain, casual blood pressures have some disadvantages for a variety of reasons: for example, repeated measurements present a significant fall with time and under placebo [1,2]. Elsewhere, several studies have reported that the ambulatory blood pressure is not reduced by treatment with placebo and that it is more reproducible than are the casual measurements [2–5]. The lack of a placebo effect on ambulatory blood pressure was analysed first by Gould *et al.* [6] in 1981 using 24 h intra-arterial monitoring and then several other studies showed similar results with the same method [3,6]. Using the non-invasive ambulatory recording technique, the effect of placebo has never been established clearly. Some studies showed that the average blood pressure over 24 h is not affected by treatment with placebo whereas others reported that the ambulatory blood pressure falls slightly during the initial recording hours. On balance, most publications now favour the hypothesis that non-invasive ambulatory blood pressure is not subject to a placebo effect [7,8], but most of these studies were performed with a small number of patients or included only two blood pressure recordings (before and after

administration of placebo), which did not allow the investigators to analyse the reproducibility separately from the proper and specific effect of placebo. The aim of this study is to analyse the reproducibility and the sensitivity to placebo of non-invasive ambulatory blood pressure by comparison with clinical measurements.

Methods

Study design

After a 4-week preselection period, patients with mild-to-moderate essential hypertension were randomly allocated to two groups: a control group, without any treatment, to analyse the reproducibility; and a placebo group, who received placebo once a day in the morning for 4 weeks. At the end of this first period, the treatment groups were exchanged for a second 4-week period. This cross-over design allowed analysis independently both from the reproducibility and from the proper placebo effect. The study was approved by the Broussais Hospital Ethical Committee.

Patients

The study was performed with 36 patients with mild-to-moderate essential hypertension. They had never been treated or at least not for 4 weeks before the study. They had no organic complications and no clinical evidence of congestive heart failure, coronary insufficiency or any other occlusive artery disease. After their informed consent to participate had been obtained on the basis of a detailed description of the procedure, patients were subjected to three different clinical and 24 h ambulatory blood pressure measurements (see Methods) at the end of the preselection period and after each phase of the cross-over design. Two patients were excluded because of the quality of their ambulatory blood pressure recordings, which showed some technical problems, there being fewer than two available measurements per hour during the 24 h period. This restricted the study population to 34 patients (15 women, 19 men). Their mean age was 45 ± 9 years (mean ± SD), their mean weight was 72 ± 13 kg and their mean height was 169 ± 8 cm.

Casual blood pressure measurements

Casual blood pressure measurements were performed in the morning (before the ambulatory blood pressure monitoring) in triplicate within a 10 min period and after 10 min supine rest by the subject, according to the WHO recommendations, using a mercury sphygmomanometer with an appropriate cuff circumference. Systolic blood pressure was determined by Korotkoff phase I and diastolic by phase V. The means of the triplicate values were used in the statistical analysis.

Ambulatory blood pressure monitoring

Non-invasive ambulatory blood pressure monitoring was performed using either the Diasys model 200 RS device (n = 15; Novacor, Rueil-Malmaison, France) or the SpaceLabs model 90207 device (n = 19; SpaceLabs, Redmond, Washington, USA). In each patient, the same device was used to record the three different ambulatory blood pressure measurements. The monitor was programmed to measure the blood pressure and heart rate every 15 min throughout a 24 h period. Ambulatory blood pressure monitoring was undertaken for a full active day: the patient worked normally during the day and then went home in the evening. Each full day recording was divided into a diurnal period (0700–2200 h) and a nocturnal period (2200–0700 h); the hourly mean values of all the parameters were also expressed. Individual mean values were summed to obtain averages (means ± SD) for the group.

Data analysis

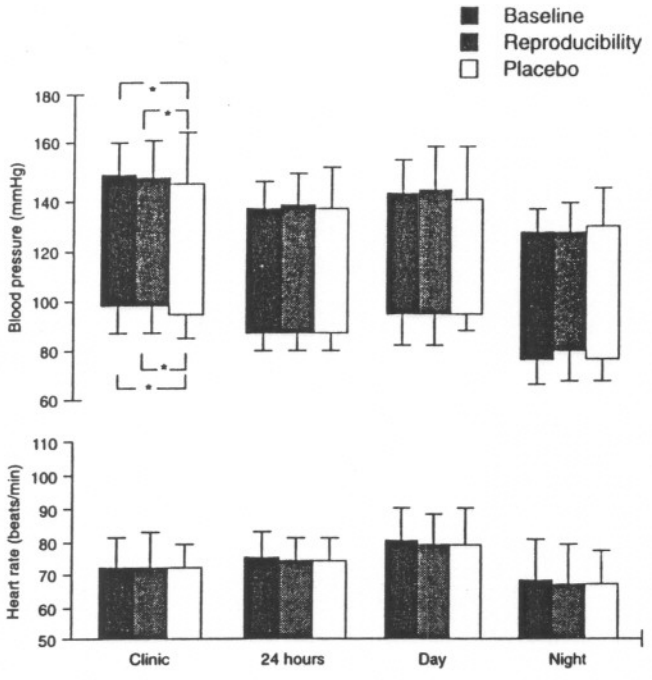
Data were transferred to a spreadsheet program (Excel® version 5.0; Microsoft Corporation, Washington DC, USA) for analysis on a personal computer. The quality of the data acquisition was double checked by two different observers before its transfer to a statistical software. Statistical analysis was performed by the NCSS® program (Number Cruncher Statistical Systems, Kaysville, Utah, USA). Descriptive tests were used to express the range values, their means and standard deviation. Analysis of variance for repeated measurements was performed to analyse the group and treatment factors: data of each treatment group were pooled for the two periods after testing the absence of a period effect in each group. Comparison of the mean values was performed using analysis of variance or Student's paired t-test. F or $P < 0.05$ was considered statistically significant.

Results

Clinical measurements

Figure 1 shows that measurements performed after 1 month without any treatment (reproducibility) were very similar to those observed at baseline both for blood pressure and for heart rate. The mean values were, respectively, at baseline and after 1 month 149 ± 13 versus 148 ± 15 mmHg for systolic blood pressure, 97 ± 7 versus 97 ± 9 mmHg for diastolic blood pressure and 72 ± 10 versus 72 ± 11 beats/min for the heart rate. In contrast, compared with the baseline and the 'reproducibility' values, administration of placebo for 4 weeks was accompanied by a significant reduction in clinic systolic and diastolic blood pressures ($F = 3.24$, $P < 0.05$, Fig. 1). Compared with the baseline values, the mean reductions under placebo were 3.4 ± 13 mmHg for systolic blood pressure (baseline 149 ± 13 mmHg, placebo 146 ± 19 mmHg; $P < 0.05$) and 3.6 ± 8 mmHg for diastolic blood pressure (baseline 97 ± 7 mmHg, placebo 93 ± 10 mmHg; $P < 0.05$). No change in heart rate was noted (baseline 72 ± 10 beats/min, placebo 72 ± 9 beats/min; NS; Table 1).

Fig. 1



Clinical and ambulatory blood pressures and heart rate mean values at baseline after 1 month without treatment (reproducibility) and after 1 month of placebo treatment. *$P < 0.05$, versus placebo.

Non-invasive ambulatory blood pressure monitoring

The mean values of systolic and diastolic blood pressures recorded non-invasively under ambulatory conditions were lower than the clinic blood pressure in the three analysed periods: 24 h, daytime and night-time (Fig. 1). For the heart rate, the mean values recorded over the 24 h and mainly in the daytime (activity) period were higher than the clinic heart rate values measured after 10 min supine rest by the subjects.

Comparison between the ambulatory mean blood pressure and heart rate values recorded at baseline, after 1 month without treatment (reproducibility) and after 1 month of placebo administration showed no significant difference in any of these parameters over the three averaged periods (Fig. 1). Table 1 shows the average changes in ambulatory systolic and diastolic blood pressures and heart rate mean values observed between the baseline and after 1 month without treatment and between the baseline and after 1 month of placebo.

The circadian curves of hourly average values of systolic and diastolic blood pressures and heart rate recorded at baseline, after 1 month without treatment and after 1 month of placebo administration were substantially superimposable and the analysis of variance showed no significant difference in hourly averages for any of the recorded parameters.

Analysis of the placebo effect

In order to evaluate in detail the effect of placebo on the clinic and non-invasive ambulatory blood pressure measurements, and to determine whether the placebo responders with the clinical measurements were also placebo responders with the ambulatory recordings, we used an individual analysis approach. Patients were defined as placebo responders if their systolic or diastolic clinic blood pressure, or both, decreased under placebo by $\geq$10 mmHg or $\geq$10% from the baseline values. On this basis, there were 13 placebo responders (six women, seven men). Their mean age was 41 ± 11 years, their mean weight 74 ± 14 kg and their mean height 170 ± 8 cm.

Clinic measurements

As expected from the selection of placebo responders, Figure 2 shows a significant reduction in clinic systolic and diastolic blood pressures without changes in heart rate. Table 2 shows that, compared with baseline values, the mean reductions under placebo were 13.6 ± 11.4 mmHg for systolic and 11.5 ± 7.1 mmHg for diastolic blood pressure ($P < 0.01$). Concerning the reproducibility, the analysis of variance showed no significant difference between the baseline blood pressure and heart rate values and those recorded after 1 month without any treatment (Fig. 2). It must be noted here that, even in the absence of a statistically significant difference, there was a tendency towards lower clinic values after 1 month, there being a mean reduction of 3.2 ± 8.4 mmHg for systolic and 1.7 ± 7.2 mmHg for diastolic blood pressure (Table 2).

Table 1 Mean changes in clinic and ambulatory systolic blood pressure (SBP) and diastolic blood pressure (DBP), and heart rate observed between baseline and after 1 month without treatment (reproducibility), and between baseline and after 1 month of placebo

	No treatment – baseline				Placebo – baseline			
	Clinic	24 h	Day	Night	Clinic	24 h	Day	Night
SBP (mmHg)	−1.7 ± 10.1	0.5 ± 9.3	1.4 ± 10.5	−0.4 ± 9.1	−3.4 ± 13.2	−0.5 ± 9.7	−1.2 ± 10.2	+0.7 ± 10.6
DBP (mmHg)	+0.1 ± 8.1	0.7 ± 6.5	0.5 ± 7.6	−0.9 ± 6.3	−3.6 ± 8.1	−0.2 ± 7.7	−1.0 ± 8.2	+0.6 ± 8.4
Heart rate (beats/min)	−0.3 ± 8.4	−0.8 ± 4.7	−0.7 ± 5.5	−0.8 ± 5.3	−0.3 ± 8.1	−1.1 ± 4.9	−0.8 ± 4.9	−0.9 ± 6.2

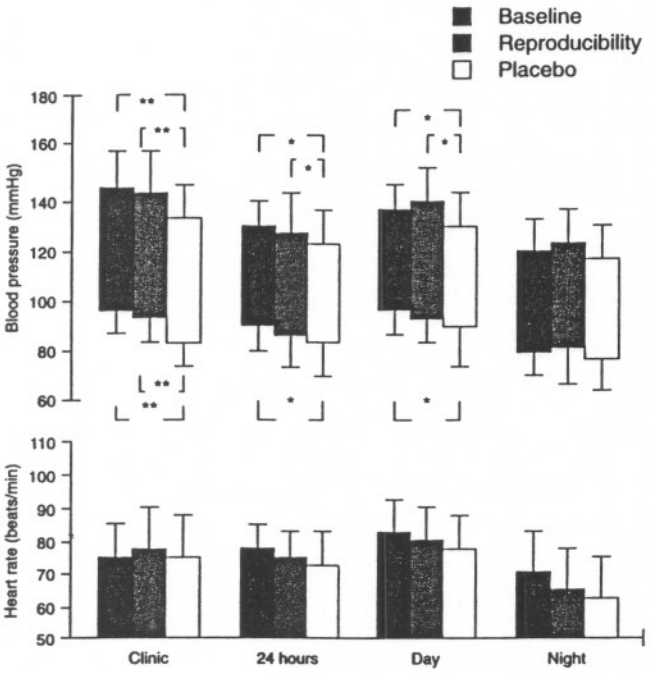
Values are expressed as means ± SD.

Table 2 Mean changes in clinic and ambulatory systolic blood pressure (SBP) and diastolic blood pressure (DBP), and heart rate observed between baseline and after 1 month without treatment (reproducibility) and between baseline and after 1 month of placebo in the 13 placebo responder patients selected on the basis of the clinic measurements

	No treatment – baseline				Placebo – baseline			
	Clinic	24 h	Day	Night	Clinic	24 h	Day	Night
SBP (mmHg)	−3.2 ± 8.4	+1.2 ± 8.4	+1.3 ± 8.8	+0.9 ± 9.8	−13.6 ± 11.4	−4.6 ± 5.7	−5.2 ± 6.2	−3.7 ± 4.4
DBP –mmHg)	−1.7 ± 7.2	−0.3 ± 5.8	−0.8 ± 5.1	+0.6 ± 7.7	−11.5 ± 7.1	−4.1 ± 7.4	−4.8 ± 7.8	−3.4 ± 7.4
Heart rate –beats/min)	+2.0 ± 9.7	−1.8 ± 5.3	−1.2 ± 6.6	−2.7 ± 5.6	+0.3 ± 10.1	−2.8 ± 4.1	−2.1 ± 4.4	−4.0 ± 5.2

Values are expressed as means ± SD.

Fig. 2



Clinic and ambulatory blood pressures and heart rate mean values at baseline after 1 month without treatment (reproducibility) and after 1 month of placebo in the 13 placebo responder patients selected on the basis of the clinic measurements (see text). *$P < 0.05$, **$P < 0.01$, versus placebo.

Non-invasive ambulatory monitoring

Figure 2 shows the blood pressure and heart rate values averaged over three periods (24 h, daytime and night-time) for the 13 placebo responder patients at baseline, after 1 month without treatment and after 1 month of placebo administration. The analysis of variance showed a significant decrease in systolic and diastolic blood pressures under placebo ($P < 0.05$) without modification of the heart rate. This reduction observed during the 24 h period is related mainly to the daytime period, for which the mean reductions were 5.2 ± 6.2 mmHg for systolic and 4.8 ± 7.8 mmHg for diastolic blood pressure (Table 2). The comparison between the ambulatory mean blood pressure and heart rate values recorded at baseline and after 1 month without treatment showed no significant difference (Fig. 2).

Prediction of the placebo response

In order to analyse the placebo responder patients and thus to distinguish them from the non-responders at baseline, comparison between these two groups was performed for all of the clinical and ambulatory parameters measured at baseline. The analysis shows that placebo responder patients had lower baseline values of ambulatory systolic blood pressure recorded during the 24 h period (130 ± 10 versus 138 ± 9 mmHg, $P < 0.05$), daytime (137 ± 11 versus 143 ± 10 mmHg, $P < 0.05$) and night-time (121 ± 11 versus 129 ± 11 mmHg, $P < 0.05$). No significant difference was noted between the two groups for the other measured parameters.

Discussion

Several studies have shown that ambulatory blood pressure monitoring results are more reproducible than are clinic measurements [2,4]. This reproducibility has important implications for assessing blood pressure levels in clinical practice and in trials of antihypertensive therapy. It has been studied on the basis of repetition of measurements over different periods, as short as 48 h and as long as 1 year. It has been analysed in young and in old patients, in normotensives and in hypertensives, with different measurement frequencies (from every 15 min to every 60 min over 24 h), using microphonic or oscillometric devices [9–12]. Most of these studies suggested that the reproducibility of ambulatory blood pressure is as good as or better than that of home or clinic measurements [2]. However, more recent reports showed that the ambulatory blood pressure fell slightly during the initial hours of recording and suggested that this decrease might be related partly to an alerting response to the first application of the device [7,8]. Most of these studies were based on a mere two blood pressure recordings; few, if any, have analysed the reproducibility of blood pressure measurements on the basis of more than two recordings and employed other than an open simple group or parallel-groups study design. In the present study, the reproducibilities of clinic and non-invasive ambulatory blood pressure measurements were analysed and compared according to a double-group cross-over design, which

allowed us to analyse in detail and separately the different phenomena involved. The protocol was intentionally as similar as possible to those usually used in clinical and therapeutical trials.

As shown in Figure 1, the average blood pressure and heart rate values obtained at baseline and after 1 month without any treatment were almost identical and thus reproducible both for the clinic and for the non-invasive ambulatory measurements. This quite good reproducibility analysed in terms of the calculation of the differences and their SD between the two measurements of the same methods showed a slightly higher reproducibility for the non-invasive ambulatory measurements as expressed by the lower SD values of the differences (Table 1).

Several factors, such as the severity of hypertension, type of patient, age and interval between the repeated measurements, have been described that influence the reproducibility of the blood pressure measurements [8–12]. In this way, the analysis of the placebo responder group, which corresponds to a particular type of hypertension, presents different values of reproducibility both for the clinic and for the ambulatory blood pressure and heart rate measurements (Fig. 2, Table 2). In fact, in this population, even though the two methods remain well reproducible, their reproducibilities are less satisfactory than are those observed in the population as a whole (Fig. 1, Tables 1). Thus, these data showed that clinic and ambulatory measurements present good reproducibility after 1 month without treatment, with a slightly higher reproducibility of the ambulatory averages, even, but to a lesser degree, in the placebo responder patients.

Gould *et al.* [6] reported that, in hypertensive patients, administration of placebo caused a decrease in blood pressure measured by the traditional cuff method but not when it was assessed by 24 h intra-arterial monitoring. For safety reasons, studies concerning antihypertensive drugs employ non-invasive automatic ambulatory blood pressure monitoring [11,13,14]. The absence of a placebo effect with this technique is not well established [8,10]. Indeed, several studies have reported that, unlike clinic blood pressure, 24 h average blood pressure is not subject to a placebo effect whereas other reports claim that ambulatory blood pressure fell slightly during the initial hours of recording, which decrease might lead to overestimation of the peak effect on blood pressure of a drug and thus underestimation of its trough : peak ratio [3,7,8,10]. Most of these studies concerned only two blood pressure recordings (before and after administration of placebo) and thus were inadequate to analyse the reproducibility (in terms of the effect of the repetition of measurements) separately from the specific and proper effects of the placebo. In fact, one explanation for the decrease in blood pressure under placebo during the first hours of the recordings of the device was presumably that there was a transient alerting reaction to the first application of the device, which is a typical phenomenon related to the repeatability of the measurements rather than to the placebo. None of the previous studies performed with automatic non-invasive ambulatory monitoring used a cross-over design study with three different recordings for each patient. This design allows us to analyse and compare the effects of placebo on clinic and on non-invasive ambulatory blood pressure measurements and to characterize them separately from reproducibility.

The results showed that administration of a daily placebo tablet for 4 weeks was accompanied by a significant reduction in clinic systolic and diastolic blood pressures but not in the 24 h, daytime, night-time and hourly average systolic and diastolic blood pressures (Fig. 1). This apparent discrepancy in terms of the effect of placebo on the two methods is related mainly to the differences in variability and in sensitivity between the methods themselves.

The placebo effect on clinic blood pressure noted in this study (Fig. 1) in the groups as a whole, and both on clinic and on ambulatory blood pressure (Fig. 2) in the placebo responder patients, is observed independently from the reproducibility of the methods and from any other alerting or familiarization factors. In fact, it is important to note here than no changes were observed for the heart rate and that the blood pressure values noted under placebo differ significantly both from the baseline and from the reproducibility values. The effect of placebo has been defined by Wolf [15,17] and by Wolf and Pinsky [16] as 'any effect attributable to a pill, potion or procedure, but not its pharmacodynamic or specific properties'. This effect can show a high degree of therapeutic effectiveness both in terms of subjective and in terms of objective responses. Lasagna *et al.* [18] showed that the subjective response to a placebo can mimic certain characteristics of 'active' drugs. It has also been shown that the personality of the patient [19] and indeed the colour of the tablet [20] are important. It is therefore reasonable that there should be a placebo-induced reduction in blood pressure. All of these subjective aspects may explain why the observed decrease in clinic and ambulatory blood pressure occurs mainly during the daytime.

The placebo effect can be influenced by the severity of hypertension and by some of the characteristics of the patient. The comparison between the placebo responder and non-responder patients showed that, whereas these two groups did not differ in their clinic baseline blood pressure values, the placebo responders had lower systolic baseline ambulatory values; moreover, their 24 h average values remain within the normal range [21] and thus express mainly the so-called 'white-coat' or 'clinic' hypertension.

In conclusion, this study showed that (1) clinic and automatic non-invasive ambulatory blood pressure measurements present high reproducibility after 4 weeks without any treatment, with a slightly higher degree of reproducibility for the ambulatory method; (2) administration of a daily placebo tablet for 4 weeks decreased only the clinic blood pressure but affected also to a lesser degree the ambulatory blood pressure, mainly during the daytime in the placebo responder patients; (3) this decrease in blood pressure under placebo is related to a proper effect of the placebo, which is independent from the reproducibility of the methods and other alerting reactions [22]; and (4) placebo responder patients showed low systolic baseline ambulatory blood pressure values, which remained within the normal range and thus reflect 'clinic' hypertension. Thus, in order to obtain a precise estimate of any blood pressure intervention, studies using non-invasive ambulatory monitoring, no less than those using conventional measurements, require a placebo-controlled design and may include mainly hypertensive patients selected on the basis of ambulatory blood pressure measurements that seem to be less sensitive to the placebo effect. In addition, such a design is suitable to evaluate the other aspects of antihypertensive treatment [14,23,24].

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