Influence of Hospitalization and Placebo Therapy on Blood Pressure and Sympathetic Function in Essential Hypertension


SUMMARY The decline in blood pressure (BP) in essential hypertensives following hospitalization may result from: 1) regression toward the mean; 2) reduction of anxiety as patients habituate to a new environment; 3) the placebo effect of medication; and 4) an independent effect of hospitalization itself. A randomized crossover study of 12 essential hypertensives demonstrated a fall in supine blood pressure from 165.0/97.9 ± 2.3/1.1 mm Hg to 154.3/89.6 ± 2.7/1.1 mm Hg (p < 0.005) due to hospitalization. A similar reduction in BP from 164.9/99.5 ± 8.4/4.1 mm Hg to 151.9/93.4 ± 4.5/1.9 mm Hg (p < 0.005) resulted from regression toward the mean and habituation during the study period. Urinary catecholamines fell from 68.7 ± 5.0 to 55.1 ± 4.3 µg/g creatinine/24 hours (p < 0.05) due to hospitalization and from 56.1 ± 5.4 to 49.7 ± 4.3 µg/g creatinine/24 hours (p < 0.05) with time. Although placebo therapy tended to reduce BP, it failed to do so significantly. When expressed as a percentage of the individual's overall mean, urinary catecholamine excretion fell from 110.5% ± 3.7% to 89.5% ± 3.7% (p < 0.001) during hospitalization and from 105.8% ± 3.9% to 94.2% ± 3.9% (p < 0.05) during the outpatient period. Blood pressure and sympathetic activity rapidly returned to prehospitalization values on discharge. These factors may confound the analysis of drug effects on BP and sympathetic activity in essential hypertensives following admission to hospital. (Hypertension 3: 113-118, 1981)

KEY WORDS • blood pressure • hospitalization effect • sympathetic activity • placebo effect

PATIENTS with elevated blood pressure (BP) are usually stabilized on antihypertensive therapy either in the hospital or when attending the outpatient clinic. However, the BP of hypertensive patients often shows a marked fall from outpatient levels during a period of hospitalization. Hecht et al. noted a 10% to 20% decline in both systolic and diastolic pressure in almost 85% of their 91 patients following admission to hospital. The maximum decrease had occurred by the tenth day in 60% of these patients, but in some did not reach a minimum until they had spent 80 days in hospital.

At least four factors may contribute to the reported BP decline. The first is regression upon the mean. If patients are selected from a population because their BP lies toward the high end of their personal variation, restudy on a further occasion is likely to find them closer to their personal mean; thus, the average of the group will fall toward the population mean.

The second, a closely related factor, is habituation to the medical environment. Blood pressure tends to fall from the first to the second and the second to the third visit to a physician. It is likely the main reason that familiarization leads to less anxiety.

The third factor, again closely related, but distinguishable, may be the placebo effect of treatment rather than the active component of the drug. The act of ingesting a placebo may carry a concomitant feeling that something is being done about one's problems, and thus lessen anxiety; it may even activate other central nervous system (CNS) mechanisms such as the encephalin-endorphin system, thereby leading to a fall in BP.
The fourth factor is that resting in a hospital bed, isolated from the stress of the patient's normal occupation and environment, may exert a further independent BP-lowering effect. The aim of the present study was to examine the independent effect of these four factors in a randomized controlled trial. Sympathetic tone was assessed by measuring plasma norepinephrine and urinary catecholamine excretion.

There is conflicting information as to whether BP recordings obtained in outpatient clinics are indicative of ambulant readings outside the hospital. An additional objective of this study was to compare the BP as recorded by a physician in the outpatient clinic with readings recorded by the patient at home.

Materials and Methods

Subjects

Twelve untreated essential hypertensives (six women, six men) whose mean age (± SEM) was 53.9 ± 9.2 years (range, 41–69 years) participated in the study. Their mean supine BP following 10 minutes of rest on their first visit to the clinic was 184.1 ± 25.1/101.0 ± 7.5 mm Hg, and their mean weight was 77.3 ± 4.2 kg. None had previously received antihypertensive medication, and all abstained from medications during the study. Ten patients were non-smokers; two smoked between 5 and 10 cigarettes per day. The subjects were not requested to abstain from caffeinated drinks during the investigation. Ten patients performed a urinary collection for vanillylmandelic acid (VMA) which would have excluded them retrospectively if it had been elevated. However, all urinary VMA levels were normal. The study was limited to the first 12 patients who satisfied these criteria.

Study Design

The patients were randomly assigned to one of four groups (fig. 1). Group A received 1 week of outpatient placebo treatment, and then no treatment the second week. Group B reversed this procedure, and then had hospitalization with 4 days of placebo and 4 days of no treatment. The other two groups were hospitalized the day after the clinic visit; Group C patients received placebo for Days 1 to 4 and then no treatment for Days 5 to 8. Group D reversed this procedure, followed by 2 weeks of outpatient monitoring. Compliance with placebo (oval pink tablet, 1 × 0.4 cm) was assessed by tablet counts.

The patients received instruction in self-monitoring of BP by a nurse technician on the day of admission to the study with the aid of a simulated BP recording. During the outpatient period they recorded their BP after 5 minutes of reclining and 1 minute of standing at 0900, 1300 and 1700 hours. A corresponding minute count of heart rate was made at the radial pulse with each reading.

![Diagram of the study protocol](http://hyper.ahajournals.org/...)

**Figure 1.** Diagram of the study protocol. Patients were randomized into one of four groups. Groups C and D were immediately hospitalized, Groups A and B following a 2-week period of outpatient follow-up. Subjects were randomized between placebo and no therapy within and outside hospital. Supine and standing blood pressure (at 1300 hours) were significantly lowered by hospitalization (p < 0.01) although not by placebo alone. Measurements performed at 0900 and 1700 hours did not differ significantly from those recorded at 1300 hours.
The patients attended the outpatient clinic once weekly (Thursday afternoons) when not hospitalized. Following entry to the physician's room, the patients were asked to lie down, and had their BP recorded immediately after lying for 5 minutes and again after standing for 1 minute, by a physician with a standard sphygmomanometer. The patient was then interviewed by the physician, followed by another 5 minutes in the supine position after which the blood was sampled for estimation of plasma norepinephrine and plasma renin activity (PRA).

During hospitalization, the nurse technician performed corresponding BP recordings at 0900, 1300, and 1700 hours. Patients who attended the outpatient clinic were seen between 1230 and 1400 hours. Recordings at the clinic were thus compared with measurements performed at 1300 hours at home and hospital to minimize the influence of circadian variability in BP. Continuous 24-hour urine collections were carried out throughout the study for catecholamine, electrolyte, and creatinine determinations. Urinary catecholamines were measured fluorimetrically, creatinine with the picric acid method, and urinary sodium and potassium by flame photometry.

Plasma norepinephrine and PRA were measured from blood withdrawn by venipuncture in subjects after 5 minutes of lying down on the outpatient visits and on Days 1, 3, 5, and 7 of hospitalization. Plasma norepinephrine was measured by radioenzymatic assay. In addition, the subjects estimated anxiety with a self-rating anxiety scale on alternate days during hospitalization and during the outpatient period.

Analysis of variance and pairwise comparisons were performed by distribution-free methods. Two-tailed probabilities were employed throughout the analysis. The allocation code was not broken by the investigators until completion of the study and the biochemical analysis.

**Results**

The BP fell significantly during hospitalization (fig. 2). The mean (1300 hours) supine BP during the outpatient periods (all groups) fell from 165.0 ± 2.3/97.9 ± 1.1 mm Hg (mean ± SEM) to 154.3 ± 2.7/89.6 ± 1.1 mm Hg during hospitalization (p < 0.005). Standing BP fell from 171.3 ± 2.2/106 ± 1.2 mm Hg to 145.4 ± 2.6/98.1 ± 1.0 mm Hg (p < 0.005). Heart rate did not change significantly, being 75.5 ± 0.8 beats/min during hospitalization and 76.0 ± 0.7 beats/min during the outpatient period in the supine position, and 84.9 ± 1.0 during hospitalization and 81.9 ± 0.8 beats/min during the outpatient period on standing. There was no significant difference between placebo or nil treatment, either during the outpatient period or during the hospitalization (table 1). The BP and heart rate changes recorded at 0900, 1300, and 1700 did not significantly differ from each other.

The BP fell as the study progressed in all four groups. When therapeutic or hospitalization status was ignored, the mean (1300 hours) supine BP fell from 164.9 ± 8.4/99.5 ± 4.1 mm Hg supine and 170.6 ± 9.2/108.9 ± 3.3 mm Hg standing during the first week, to 151.9 ± 4.5/93.4 ± 1.9 mm Hg supine and 156.1 ± 4.4/101.9 ± 2.0 mm Hg standing during the third (and last) week in which all four groups were included in the study. This trend was more marked in Groups A and B, whose mean BP (184 ± 5.6/110 ± 3.4 mm Hg supine) was higher than that (171 ± 4.3/105 ± 2.3 mm Hg) of Groups C and D. Heart rate, however, did not change, being 73.2 ± 3.1 beats/min supine and 79.2 ± 3.7 beats/min during the first week and 72.2 ± 2.4 beats/min supine and 80.4 ± 2.9 beats/min during the third week.

In Groups A and B, BP recorded in the clinic was compared with the mean of the home readings performed (at 1300 hours) on the 6 days preceding the third clinic visit. The comparison was confined to these groups to avoid the influence of measurements taken preceding hospitalization, and delayed until the third clinic visit to allow for the initial effects of habituation. The results are shown in table 2.

The alterations in the sympathetic nervous system were estimated by measuring plasma norepinephrine and urinary catecholamine excretion. Urinary catecholamines fell significantly (p < 0.05) during hospitalization. A further significant reduction was observed during placebo treatment (p < 0.05). Plasma norepinephrine did not alter with hospitalization or placebo therapy.
During the outpatient treatment, the decline on placebo failed to attain significance. However, when expressed as a percentage of the individual overall mean, catecholamine excretion was significantly lower on placebo than on no treatment during both the hospitalization (89.5% ± 3.7%, 110.5% ± 3.7%, p < 0.001) and the outpatient periods respectively (94.2% ± 3.9%, 105.8% ± 3.9%, p < 0.05). Urinary catecholamines also fell significantly with hospitalization (table 3) and with time from 56.1 ± 5.4 μg/g creatinine/24 hours during the first week to 49.7 ± 4.3 μg/g creatinine/24 hours during the third (p < 0.05) (table 4). Expressed as a percentage of the individual's overall mean, this difference (109.6% ± 4.5% vs 90.4% ± 4.8%) was also significant (p < 0.01).

The decline in plasma norepinephrine and PRA during the placebo treatment and during hospitalization did not attain statistical significance (table 3). The subjective estimation of anxiety as measured by the self-rating scale did not show any evidence of subjective relief during hospitalization or placebo treatment.

Although the patients were not maintained on a strict salt balance, urinary sodium and potassium did not alter during the study.

### Discussion

This study demonstrates that a fall in BP occurred upon the hospitalization of patients with essential hypertension. This was independent of the fall in pressure that occurred as the study progressed and the patients became used both to their physician and to medical procedures. The decline in BP upon hospital admission may result from regression toward the mean, habituation to a new environment, the placebo effect of medication, and an independent effect of hospitalization itself.

Both regression toward the mean and acclimatization to medical surroundings contributed to the fall in BP that occurred as a function of time. The slight reduction of pressure with placebo therapy failed to attain significance. Previous studies have documented that placebo therapy reduces BP from pretreatment levels. The exclusion of regression toward the mean and of habituation from the comparison in this investigation may explain this discrepancy.

### Table 1. Influence of Hospitalization and Placebo Therapy on Blood Pressure and Heart Rate

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Clock hours</th>
<th>No treatment</th>
<th>Placebo</th>
<th>No treatment</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>0900</td>
<td>163.1 ± 2.9</td>
<td>163.0 ± 3.4</td>
<td>149.9 ± 3.3</td>
<td>146.9 ± 3.4</td>
</tr>
<tr>
<td>1200</td>
<td>162.5 ± 3.2</td>
<td>165.3 ± 3.4</td>
<td>148.9 ± 2.9</td>
<td>150.1 ± 3.2</td>
<td></td>
</tr>
<tr>
<td>1700</td>
<td>164.4 ± 2.8</td>
<td>163.7 ± 3.1</td>
<td>165.7 ± 2.7</td>
<td>156.9 ± 3.0</td>
<td></td>
</tr>
<tr>
<td>Diastolic pressure (mm Hg)</td>
<td>0900</td>
<td>99.6 ± 1.3</td>
<td>100.3 ± 1.5</td>
<td>90.5 ± 1.5</td>
<td>88.0 ± 1.3</td>
</tr>
<tr>
<td>1200</td>
<td>99.0 ± 1.4</td>
<td>100.4 ± 1.9</td>
<td>89.9 ± 1.4</td>
<td>88.7 ± 1.3</td>
<td></td>
</tr>
<tr>
<td>1700</td>
<td>99.5 ± 1.4</td>
<td>99.9 ± 1.6</td>
<td>96.1 ± 1.0</td>
<td>95.9 ± 1.2</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>0900</td>
<td>72.4 ± 1.1</td>
<td>71.6 ± 1.5</td>
<td>76.0 ± 1.6</td>
<td>74.2 ± 1.4</td>
</tr>
<tr>
<td>1200</td>
<td>73.1 ± 1.2</td>
<td>73.6 ± 1.3</td>
<td>74.2 ± 1.5</td>
<td>73.3 ± 1.5</td>
<td></td>
</tr>
<tr>
<td>1700</td>
<td>71.8 ± 1.1</td>
<td>73.4 ± 1.2</td>
<td>69.4 ± 2.2</td>
<td>71.5 ± 1.6</td>
<td></td>
</tr>
<tr>
<td>Standing:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>0900</td>
<td>170.4 ± 3.1</td>
<td>168.8 ± 3.5</td>
<td>153.0 ± 3.0</td>
<td>155.3 ± 3.2</td>
</tr>
<tr>
<td>1200</td>
<td>170.6 ± 3.2</td>
<td>170.9 ± 3.8</td>
<td>154.3 ± 2.5</td>
<td>153.6 ± 3.2</td>
<td></td>
</tr>
<tr>
<td>1700</td>
<td>170.7 ± 3.2</td>
<td>169.2 ± 3.4</td>
<td>157.7 ± 2.7</td>
<td>157.8 ± 3.3</td>
<td></td>
</tr>
<tr>
<td>Diastolic pressure (mm Hg)</td>
<td>0900</td>
<td>109.5 ± 1.4</td>
<td>109.3 ± 1.5</td>
<td>101.2 ± 1.5</td>
<td>97.6 ± 1.5</td>
</tr>
<tr>
<td>1200</td>
<td>109.4 ± 1.4</td>
<td>107.5 ± 1.6</td>
<td>99.2 ± 1.6</td>
<td>98.1 ± 1.3</td>
<td></td>
</tr>
<tr>
<td>1700</td>
<td>108.2 ± 1.4</td>
<td>107.0 ± 1.6</td>
<td>104.0 ± 1.2</td>
<td>104.5 ± 1.2</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>0900</td>
<td>78.5 ± 1.4</td>
<td>79.1 ± 1.5</td>
<td>82.8 ± 2.0</td>
<td>82.8 ± 1.9</td>
</tr>
<tr>
<td>1200</td>
<td>78.4 ± 1.5</td>
<td>78.3 ± 1.5</td>
<td>81.5 ± 1.9</td>
<td>81.0 ± 1.9</td>
<td></td>
</tr>
<tr>
<td>1700</td>
<td>78.2 ± 1.5</td>
<td>80.1 ± 1.5</td>
<td>80.1 ± 1.5</td>
<td>78.5 ± 1.7</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM.

---

### Table 2. Comparison of Blood Pressure and Heart Rate Measurements Done in the Outpatient Department by a Physician and at Home During the Preceding Week at the Same Time

<table>
<thead>
<tr>
<th>Reading</th>
<th>Blood Pressure (mm Hg)</th>
<th>Heart Rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician readings:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine (1 min)</td>
<td>181.3 ± 6.5</td>
<td>98.4 ± 1.9</td>
</tr>
<tr>
<td>Supine (5 min)</td>
<td>166.4 ± 4.6</td>
<td>98.4 ± 1.4</td>
</tr>
<tr>
<td>Standing (1 min)</td>
<td>162.6 ± 4.5</td>
<td>104.6 ± 4.5</td>
</tr>
<tr>
<td>Home readings:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine (5 min)</td>
<td>162.8 ± 5.4</td>
<td>96.4 ± 2.3</td>
</tr>
<tr>
<td>Standing (1 min)</td>
<td>169.5 ± 5.5</td>
<td>108.3 ± 2.1</td>
</tr>
</tbody>
</table>

All values are mean ± SEM. Recordings performed by the physician when the patient lay supine for 1 and 5 minutes were each compared with home supine readings. Corresponding measurements in the standing position were also compared.

* p < 0.05.
† p < 0.01.
The hypotensive effect was most marked in the first days in the hospital may cause anxiety, patients partly attributed to reassurance. Although the initial (156-164/96-99 mm Hg) being conducted by the Medical Research Council (MRC) in the United Kingdom. The reduction in systolic pressure attributable to both hospitalization and habituation was similar to that attained with a beta blocker or a thiazide diuretic in the MRC investigation.

The influence of hospitalization on BP has been gradual readjustment of sympathetic tone over days rather than minutes. It is more appropriate to study sympathetic function with a time-integrated index, such as urinary catecholamines, rather than a dynamic index such as plasma norepinephrine. However, one would have expected such an adjustment to be reflected in the plasma concentrations of both norepinephrine and renin activity. Although plasma norepinephrine tended to decline upon placebo therapy and on hospitalization, this trend failed to attain significance.

Blood was obtained for plasma norepinephrine following 5 minutes of supine rest, whereas it may take up to 10 minutes for plasma concentration to reflect an altered steady state of noradrenaline release. Thus, it is possible that an insufficient period from rest to sampling obscured the effects of hospitalization upon plasma norepinephrine. Additionally, blood was taken by direct venipuncture. Lake et al. suggest that the stress of venipuncture may significantly elevate plasma noradrenaline, although this experience has not been confirmed by others.

A recent study demonstrated that a fall in BP that occurred with both hospitalization and habituation was accompanied by a reduction in the rate of urinary catecholamine excretion. The objective of this study was to detect a gradual readjustment of sympathetic tone over days rather than minutes. It is more appropriate to study sympathetic function with a time-integrated index, such as urinary catecholamines, rather than a dynamic index such as plasma norepinephrine. However, one would have expected such an adjustment to be reflected in the plasma concentrations of both norepinephrine and renin activity. Although plasma norepinephrine tended to decline upon placebo therapy and on hospitalization, this trend failed to attain significance.

Blood was obtained for plasma norepinephrine following 5 minutes of supine rest, whereas it may take up to 10 minutes for plasma concentration to reflect an altered steady state of noradrenaline release. Thus, it is possible that an insufficient period from rest to sampling obscured the effects of hospitalization upon plasma norepinephrine. Additionally, blood was taken by direct venipuncture. Lake et al. suggest that the stress of venipuncture may significantly elevate plasma noradrenaline, although this experience has not been confirmed by others.

A recent study demonstrated that a fall in BP that occurred with both hospitalization and habituation was accompanied by a reduction in the rate of urinary catecholamine excretion. The objective of this study was to detect a gradual readjustment of sympathetic tone over days rather than minutes. It is more appropriate to study sympathetic function with a time-integrated index, such as urinary catecholamines, rather than a dynamic index such as plasma norepinephrine. However, one would have expected such an adjustment to be reflected in the plasma concentrations of both norepinephrine and renin activity. Although plasma norepinephrine tended to decline upon placebo therapy and on hospitalization, this trend failed to attain significance.

Blood was obtained for plasma norepinephrine following 5 minutes of supine rest, whereas it may take up to 10 minutes for plasma concentration to reflect an altered steady state of noradrenaline release. Thus, it is possible that an insufficient period from rest to sampling obscured the effects of hospitalization upon plasma norepinephrine. Additionally, blood was taken by direct venipuncture. Lake et al. suggest that the stress of venipuncture may significantly elevate plasma noradrenaline, although this experience has not been confirmed by others.

A recent study demonstrated that a fall in BP that occurred with both hospitalization and habituation was accompanied by a reduction in the rate of urinary catecholamine excretion. The objective of this study was to detect a gradual readjustment of sympathetic tone over days rather than minutes. It is more appropriate to study sympathetic function with a time-integrated index, such as urinary catecholamines, rather than a dynamic index such as plasma norepinephrine. However, one would have expected such an adjustment to be reflected in the plasma concentrations of both norepinephrine and renin activity. Although plasma norepinephrine tended to decline upon placebo therapy and on hospitalization, this trend failed to attain significance.

Blood was obtained for plasma norepinephrine following 5 minutes of supine rest, whereas it may take up to 10 minutes for plasma concentration to reflect an altered steady state of noradrenaline release. Thus, it is possible that an insufficient period from rest to sampling obscured the effects of hospitalization upon plasma norepinephrine. Additionally, blood was taken by direct venipuncture. Lake et al. suggest that the stress of venipuncture may significantly elevate plasma noradrenaline, although this experience has not been confirmed by others.
The patients in this study were not placed on a sodium balance. However, urinary sodium did not alter either on hospitalization or with the duration of the study. Although urinary catecholamines fell significantly on placebo therapy, both inside and outside the hospital, the BP did not fall. This dissociation might not have been present had the BP been monitored continuously during the periods of these urine collections rather than at three discrete time points. Alternatively, it is possible that the sympatholytic effect of placebo tablets is similar to that of anxiolytics such as benzodiazepines, which may reduce stress-induced peaks of sympathetic activity without altering basal sympathetic tone. Both BP and plasma norepinephrine were measured under basal conditions at discrete time points, and thus the sympatholytic potency of placebo might not be evident. Urinary catecholamines, however, represent an index of sympathetic activity that is integrated across the time of the collection period, thus incorporating the peaks of stress, and would be a more sensitive measure of the postulated placebo effect.

Finally, there was a close approximation of BP recordings in the clinic to an integrated index of home readings. Although the motivation required by self-monitoring may enhance compliance with antihypertensive therapy and improve BP control, these effects appear to be modest. As long as the patient lay supine for 5 minutes prior to the recording, BP at the clinic corresponded well to that recorded by the patient at rest outside hospital.

This investigation has several important clinical implications. First, many patients are admitted to hospital for stabilization of their BP. Owing to the hypertensive effects of both hospitalization and habituation, control may deteriorate on discharge. In all four groups in this study, BP rose on leaving the hospital. The evaluation of drug effects on BP and sympathetic function following hospitalization may thus also be confounded.

References

Influence of hospitalization and placebo therapy on blood pressure and sympathetic function in essential hypertension.

V Hossmann, G A FitzGerald and C T Dollery

Hypertension. 1981;3:113-118
doi: 10.1161/01.HYP.3.1.113

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1981 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/3/1/113