Awareness of Hypertension Increases Blood Pressure and Sympathetic Responses to Cold Pressor Test
Morten Rostrup, Sverre E. Kjeldsen, and Ivar K. Eide

The present study was aimed at examining the effects of awareness of hypertension on blood pressure and sympathetic responses to the cold pressor test. Nineteen-year-old men with similarly elevated mean blood pressure at a medical screening, but without knowledge of this, were randomized into two groups. The first group (n = 16) was sent a letter saying that their pressure was too high, and the second (n = 13) was sent a neutral letter. Information increased mean blood pressure both after 15 min sitting, by an average of 11.5 mm Hg (P < .01), and after 30 min supine rest, by an average of 4.5 mm Hg (P < .05). Changes in heart rate (8.4 ± 2.4 v 1.9 ± 1.7 beats/min) and plasma epinephrine (0.11 ± 0.04 v 0.01 ± 0.03 nmol/L) during execution of a cold pressor test were significantly greater in the informed group (P < .05). Plasma dopamine was lower in the informed group (P < .05). Thus, psychological stress caused by the awareness of hypertension may increase blood pressure and sympathetic responses to a provocative maneuver. Ideally, studies on sympathetic function in essential hypertension should be undertaken on subjects unaware of their blood pressure status. Am J Hypertens 1990;3:912-917

KEY WORDS: Epinephrine, awareness of hypertension, dopamine, catecholamines, heart rate, hypertension labeling, norepinephrine, sympathetic tone.

Studies on young subjects with essential hypertension demonstrate increased concentrations of resting plasma catecholamines, and increased sympathetic responsiveness to a provocative maneuver such as mental stress, suggesting a hyperadrenergic state in the early phase of essential hypertension. However, in most studies the hypertensive subjects have all been aware of their high blood pressure. Thus, it might be questioned whether increased sympathetic tone and responsiveness are genuine characteristics of the early hypertensive state, or whether they are caused by emotional tension related to awareness of hypertension by the hypertensive subject himself.

In the present study we wanted to test the hypothesis that awareness of high blood pressure per se in young subjects may influence physiological parameters such as blood pressure, heart rate, and plasma catecholamines during a laboratory examination. Subjects with one previous high blood pressure measurement were considered particularly well suited, and they were therefore all recruited from a high (98th) blood pressure percentile of an ongoing screening study.

SUBJECTS AND METHODS

Subjects As a part of the military draft procedure, blood pressure measurements for all 19-year old men in the city of Oslo (n = 3861) in 1986 were standardized and performed once after 5 min quiet sitting by an automatic auscultatory device with a hidden printer (Boso, digital II S, Bosh & Soho GmbH U. Co., Jungingen, West Germany). The automatic device measured blood pres-
TABLE 1. BLOOD PRESSURE (BP), HEART RATE, AND BODY MASS INDEX AT THE SCREENING STUDY AND CHANGES IN MEAN BLOOD PRESSURE, HEART RATE, PLASMA EPINEPHRINE AND PLASMA NOREPINEPHRINE DURING COLD PRESSOR TEST (CPT) AT THE SECOND EXAMINATION

<table>
<thead>
<tr>
<th></th>
<th>Uninformed group (n = 13)</th>
<th>Informed group (n = 16)</th>
<th>P</th>
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<tbody>
<tr>
<td><strong>Screening</strong></td>
<td></td>
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<tr>
<td>Mean BP (mm Hg)</td>
<td>116.1 ± 0.4</td>
<td>116.2 ± 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>155.8 ± 3.8</td>
<td>158.6 ± 2.8</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>96.2 ± 2.2</td>
<td>95.0 ± 1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>77.9 ± 3.4</td>
<td>77.4 ± 3.0</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.4 ± 0.2</td>
<td>24.5 ± 0.2</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Changes during CPT</strong></td>
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<tr>
<td>Mean BP (mm Hg)</td>
<td>17.6 ± 4.7</td>
<td>16.3 ± 3.4</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>1.9 ± 1.7</td>
<td>8.3 ± 2.3</td>
<td>*</td>
</tr>
<tr>
<td>Norepinephrine (nmol/L)</td>
<td>0.22 ± 0.1</td>
<td>0.33 ± 0.08</td>
<td>NS</td>
</tr>
<tr>
<td>Epinephrine (nmol/L)</td>
<td>0.01 ± 0.03</td>
<td>0.11 ± 0.04</td>
<td>*</td>
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* P < .05; NS = not significant between groups.

Sure 3.9 ± 1.4/4.9 ± 1.5 mm Hg lower than a mercury sphygmomanometer, but the pressure correlations were highly significant (systolic, \( r = 0.95 \); diastolic, \( r = 0.91 \)). Neither physicians nor subjects could read the results of the blood pressure recordings during the medical examinations. The subjects were not informed about their blood pressures, but it was pretended that they had normal blood pressures. Therefore, they all got their final military physical fitness score and medical evaluation independently of their blood pressure recording. This was done deliberately to avoid the possibility of group differences due to secondary gain later in the study.

Thirty-two white men above the 98th percentile of mean blood pressure at the military medical examination were selected for the present study. They were randomized into two groups matched by height and weight, and invited by letter 1 year after the initial screening to attend a second examination. Sixteen subjects were informed that their blood pressures had been elevated at the screening study. They all completed the protocol. The remaining 16 subjects were sent a neutral letter inviting them to take part in a coronary heart disease prevention program. Thirteen completed the protocol.

Protocol The subjects were examined 2 weeks after receiving the letter. They were all previously healthy without any history of hypertension. They had a normal physical examination and normal results of electrocardiogram, routine blood tests and urinalysis. None of the subjects were on any kind of medical treatment or addicted to drugs or alcohol. There were no differences in blood pressure, heart rate or body mass index between the two groups at the screening study one year earlier (Table 1).

The study was approved by the Ethics Committee of Ulleval Hospital, and informed consent was obtained from each subject. All subjects were examined by the same physician. The examinations were carried out at randomized hours between 8 AM and 4 PM following a 4 h fast, with at least 8 h abstinence from nicotine and caffeine, and at least 24-h abstinence from alcohol.

Blood pressure was recorded, after 15 min quiet sitting, by a Hawksley random-zero sphygmomanometer with hidden figures and zero-level, and by the same auscultatory automatic device (Boso Digital II S) used in the initial screening one year earlier. All blood pressures were recorded three times, and the average of the last two measurements was used in the statistical analysis. A short Teflon catheter (Venflon R, 19G, Viggo AB, Helsingborg, Sweden) was then introduced into the left median cubital vein, and the subjects rested supine for 30 min in the presence of the examining physician only. Mean blood pressure and heart rate were recorded every 0.12 min lower than the mercury sphygmomanometer. The correlation between the two techniques was \( r = 0.76 \) (P < .01). However, the same device was used in all subjects to exclude a systematic error in intraindividual or between-group differences. Following the 30 min period, a cold pressor test was announced to the subjects, and thereafter the right hand was completely immersed in ice water (4°C) for 1 min. Mean blood pressure and heart rate were systematically recorded when the cold pressor test was announced, throughout the test, and during an 8 min recovery period.

Blood for a catecholamine assay was collected three times, ie, after 30 min supine rest (before information about the forthcoming cold pressor test), during the last 15 sec of the cold pressor test and 5 min later.
Analytical Methods  The plasma catecholamines were measured by a radioenzymatic technique according to Peuler & Johnson as previously reported. On all the samples the assay was performed by the same technician, who did not know about the subjects’ group status.

Statistical Methods  The data were analyzed using the statistical package SPSS-PC+ (SPSS-PC+, Inc., Chicago, IL). Two-tailed statistical analyses of results, with approximately normal distribution according to Kolmogorov-Smirnov tests, were carried out using Student’s t test for paired and unpaired samples (P) and Pearson’s correlation coefficient (r). For samples not normally distributed, Wilcoxon’s rank sum and signed rank tests were used. Data are presented as means ± SEM. χ² test with Yates correction was used to compare the proportions of hypertensive subjects in the two groups. Mean blood pressure, heart rate and plasma catecholamines were also analyzed by repeated measures ANOVA for between-group differences. The level of statistical significance was set at P = .05.

RESULTS

Blood Pressure  There was a significant reduction in systolic blood pressure in both the uninformed (P < .001) and informed (P < .02) group after 15 min sitting compared to the measurements after 5 min sitting at the screening one year earlier with the same automatic device (Figure 1). However, there was a significant decrease in diastolic blood pressure in the uninformed group only (P < .001). The decrease in systolic and diastolic blood pressure was greater in the uninformed than in the informed group (22.1/15.1 ± 4.2/3.3 v 9.9/6.0 ± 3.8/3.0 mm Hg, P < .05/P = .05).

The informed group had significantly higher systolic (P < .01) and diastolic blood pressures (P < .05) after 15 min sitting measured by the random zero sphygmomanometer (147.8 ± 4.6/87.0 ± 3.5 v 132.0 ± 2.4/77.5 ± 2.7 mm Hg). Systolic blood pressure measured by the auscultatory automatic device was significantly higher (P < .01) as well, whereas the increase in diastolic blood pressure nearly reached significance (P = .07, Figure 1). Mean blood pressure after 30 min supine rest measured by the oscillometric device was significantly higher in the informed group (90.3 ± 1.8 mm Hg v 86.0 ± 0.9 mm Hg, P < .05). An overall consideration of the 30 min supine resting period (ANOVA) showed significantly (P < .05) higher mean blood pressure in the informed group (Figure 2).

The proportion of subjects with systolic blood pressure above 140 mm Hg and/or diastolic blood pressure above 90 mm Hg after 15 min sitting was significantly higher in the informed group, both when measured by
the random zero sphygmomanometer (13/16 ν 2/13, \( P < .005 \)) and the automatic auscultatory device (13/16 ν 3/13, \( P < .01 \)). In both groups, mean blood pressure increased significantly above baseline during the cold pressor test (Figure 2), with no significant difference between the groups (Table 1).

There was an overall higher (\( P < .05 \)) mean blood pressure in the informed group in the recovery period (Figure 2).

**Heart Rate** Heart rate increased significantly during the cold pressor test (\( P < .005 \)) in the informed group only (Figure 2) and the increase in heart rate in the informed group was significantly greater (\( P < .05 \)) than in the uninformed group. In the informed group, most of the increase in heart rate (\( P < .005 \)) became apparent at the outset of the cold pressor test (Figure 2).

There was no significant difference in baseline heart rate between the two groups (Figure 2).

**Plasma Catecholamines** There was no difference in baseline plasma epinephrine or norepinephrine (Figure 3) between the two groups. However, baseline plasma dopamine was significantly lower (\( P < .05 \)) in the informed group (Figure 3).

Plasma epinephrine increased significantly (\( P < .05 \)) above baseline in the informed group during the cold pressor test (Figure 3), whereas there was no significant change in the uninformed group. There was a significantly higher increase in plasma epinephrine (\( P < .05 \)) in the informed than in the uninformed group (Table 1).

In the recovery phase, plasma epinephrine returned to baseline in the informed group.

There was a positive correlation between plasma epinephrine and heart rate during the cold pressor test in the informed group (\( r = 0.58, P < .05 \), Figure 4), but no significant correlation in the uninformed group (\( r = 0.31, P = .3 \)).

Plasma norepinephrine increased significantly in the informed group only (\( P = .001 \)) during the cold pressor test (Figure 3).

Plasma dopamine tended to be lower in the informed group (Figure 3), both during the test (\( P < .06 \)) and at recovery (\( P < .07 \)). Considering all three blood samples by repeated measures ANOVA, plasma dopamine was significantly lower in the informed group (\( P < .05 \)).

**DISCUSSION**

In the present study, young men who had been informed about one single previously elevated blood pressure recording had higher baseline blood pressure, increased heart rate and plasma epinephrine responses and lower plasma dopamine during a cold pressor test, than an uninformed control group. The study shows that awareness of hypertension or hypertension labeling per se may influence physiological parameters to a clinically significant degree.

Previous studies have been focused almost exclusively on the effect of hypertension labeling on psychosocial function and the sense of well-being. Hypertensive subjects informed about their condition show increased illness absenteeism from work\(^{6-9}\) and more psychological distress,\(^{10-12}\) whereas hypertension labeling does not seem to influence absenteeism from school.\(^{13}\) Mislabeling of normotensive subjects may also influence the sense of well-being.\(^{14,15}\)

Rudd et al\(^{16}\) found that the way people were informed about their hypertension at a screening, by naming high blood pressure “the silent killer” instead of emphasizing blood pressure’s natural variability, increased the prevalence of sustained hypertension. Thus, the hypertension diagnosis based on measurements on three different occasions may at least partly depend on whether the patient was informed about his high blood pressure on the
FIGURE 4. Correlation between plasma adrenaline (epinephrine) and heart rate during cold pressor test in the informed (■, \( r = 0.58, P < .05 \)) and uninformed (□, \( r = 0.31, P = \text{NS} \)) groups.

first occasion, or, according to Rudd et al,16 how the patient was informed.

In this study, we have described another important psychological factor which to some extent may be different from the well known "white coat effect." 17,18 Patients informed about hypertension, ie, a potentially harmful disease, seem to have an exaggerated alerting reaction during clinical examination. Since neither of our groups were in fact exposed to the "white coat" in a similar manner, the effects of awareness of high blood pressure can be distinguished from the "white coat effect." However, during a clinical examination of hypertensive patients, there will always be a combination of both "the white coat" and real awareness of hypertension. Thus it is possible that "white coat hypertension" may originate from anxiety related to the patient’s knowledge of high blood pressure as suggested by Pickering et al. 18

The informed group in the present study showed exaggerated responses to the cold pressor test with concomitantly higher increases in heart rate and plasma adrenaline and there was a significant correlation between these two variables during the test. Furthermore, the increase in heart rate mostly occurred before the hand was immersed in ice water. This may also have been the case for plasma epinephrine, although no measurement was undertaken during the announcement of the cold pressor test. However, the responses observed are compatible with arousal or enhanced neurogenic activity as associated with the defense reaction.2,19

Information about high blood pressure did not increase baseline venous plasma epinephrine or plasma norepinephrine despite the increase in baseline blood pressure. However, it is possible that the differences in blood pressure seen after 30 min between the two groups is the residual effect of an elevated catecholamine level in the informed group, which normalized within the 30 min supine resting period. In addition, arterial measurements may be a more sensitive tool than peripheral venous measurements for detecting increased plasma catecholamines in essential hypertension.20 It is therefore still unknown whether awareness of hypertension per se may increase baseline plasma catecholamines as found in studies on young hypertensive subjects.1

Plasma dopamine was significantly lower in the informed group. This finding is in accordance with a previous report of an inverse relationship between blood pressure and plasma dopamine.5 We did not aim to diagnose hypertension in the present study. This would have implemented additional blood pressure examinations. Most of the present subjects would probably have been classified as borderline hypertensive.21 We do not know whether the blood pressure and sympathetic responses detected in the present study are characteristic of such individuals only. For ethical reasons, misinforming normotensive subjects was not undertaken. However, studies on normotensives mislabeled as hypertensives reveal a similar psychosocial effect as that reported in hypertensives correctly labeled,13,14 indicating that normotensives may also experience labeling as mental stress.

In conclusion, awareness of hypertension per se may influence blood pressure and certain sympathetic responses to provocative maneuvers. These results may have importance for the interpretation of previous stud-
ies of sympathetic function. Ideally, studies of the pathophysiology in essential hypertension should be undertaken on subjects who are unaware of their blood pressure status.

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