Magnitude, Reproducibility, and Components of the Pressor Response to the Clinic

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We investigated the magnitude of the pressor response to the clinic with ambulatory monitors by comparing blood pressure readings related to the medical visit with all clinic-unrelated readings during the day. One hundred studies were conducted on 51 hypertensive patients who were placed either on placebo (67) or on monotherapy with hydrochlorothiazide, atenolol, or the converting enzyme inhibitors captopril or zofenopril. On placebo, clinic-related systolic (162±2), diastolic (101±1), and pulse (61±2) pressures (mm Hg) were significantly higher than the respective clinic-unrelated values (149±2, 93±1, and 56±1 mm Hg). Heart rates were not different. Despite significant reductions of blood pressure, the same pattern was found during treatment. After initiating the monitoring and while in transit to job or home (initial component of the clinic-related readings), systolic (166±2 mm Hg) and pulse (64±2 mm Hg) pressures were higher than those during return to the office the next day (final component, 158±3 and 58±2 mm Hg). Blood pressures of both components, however, were significantly higher than the clinic-unrelated ones. In 19 repeat studies carried out 2–24 months apart on placebo, the average pressor response did not change from the first (13±3/11±2) to the second (13±4/11±2 mm Hg) procedure. No correlation, however, was found between the first and second study responses of individual patients. We conclude that the pressor response to the clinic 1) has a magnitude of 13±2/9±1 mm Hg (p<0.001), 2) is not altered by antihypertensive therapies with different mechanisms of action, 3) is not reproducible, 4) is associated with increased pulse pressure, and 5) has a hitherto undescribed component that differs from the “white coat phenomenon” in that it precedes the encounter with the physician. (Hypertension 1990;15(suppl I):I-161–I-165)

Recording of the blood pressure (BP) by the physician or other medical personnel produces a pressor response, which has long been recognized and is often referred to as the “white coat phenomenon.” This pressor response, by misrepresenting the severity of hypertension, can partially explain the weak association between office BP values and the degree of hypertensive target organ damage. Knowledge of the magnitude of this response can have implications for patient management and for assessment of cardiovascular risk. The magnitude of the white coat phenomenon has been estimated in outpatients by comparison of intra-arterial or noninvasive ambulatory BPs to sphygmomanometric readings in the clinic. These approaches did not take into consideration possible differences attributable to the use of two methods of measurement. Mancia et al analyzed the rise of intra-arterial BPs in response to visits by a physician who inflated a cuff on the contralateral arm. Their patients, however, were hospitalized, which might have modified their unstimulated BPs as well as their pressor response to this maneuver. We hypothesized that the magnitude of the pressor response to the clinic could be estimated by noninvasive ambulatory BP monitoring of outpatients. With this method, we also set out to explore the components and reproducibility of this response.

Methods

Patients

One hundred 24-hour-ambulatory BP monitorings were performed in 51 essential hypertensive patients with the Spacelabs 5200 device (SpaceLabs Inc., Redmond, Washington). Sixty-seven studies were obtained after discontinuation of previous therapy and maintenance on placebo for 3–10 weeks. The remaining studies were conducted after switching 33 patients from placebo to 10 weeks of monotherapy with hydrochlorothiazide (n=6), the β-blocker atenolol (n=8), or the converting enzyme inhibitors captopril or zofenopril (n=19), with a randomized, double-blind protocol. All patients gave informed consent and the study was approved by the Institutional Review Board.
Monitoring Procedure

Patients came to the clinic between midmorning and early afternoon and were instructed in the functioning of the monitor. On triggering of the first reading by the device, a sphygmomanometric reading was simultaneously obtained in the contralateral arm for validation of the procedure. This maneuver was repeated when patients returned to the clinic the next day, before disconnection of the monitor. Studies in which monitor and cuff (Korotkoff phase V) diastolic BPs differed by more than 5 mm Hg were excluded from this report (n = 4). In the remaining studies (n = 100), the mean differences in blood pressures by the two methods were -3±0.8/1±0.3 (not significant for both). The r values for the regression of monitor on simultaneous cuff readings were 0.89 for systolic and 0.95 for diastolic BPs (p<0.001, for both). In each procedure, the monitor recorded BPs every 30 minutes from 6:00 AM to midnight and every 60 minutes from midnight to 6:00 AM.

We designed a diary in which patients provided information regarding events occurring at the time of each automatic reading. Additionally, we specifically asked for 1) the time of arrival to their home or job after leaving the clinic, 2) the time of retiring to bed, 3) the time of awakening the next morning, and 4) the time of departure from home or job to return to the clinic for disconnection of the monitor.

Data Handling

Data were retrieved from the monitor onto magnetic tape by means of the Epson Spacelabs 5300 desktop computer (SpaceLabs Inc.). This information was electronically transferred to the mainframe computer of the City University of New York for statistical analysis. The following commonly used algorithm was used to define erroneous readings for deletion 1) systolic BPs higher than 260 or lower than 70 mm Hg, 2) diastolic BPs higher than 150 or lower than 40 mm Hg, 3) pulse pressures greater than 150 or less than 20 mm Hg, 4) heart rates greater than 150 or less than 40 beats/min, and 5) changes between consecutive readings of more than 30 mm Hg or 30 beats/min unless there was a clear explanation for them in the patients' diaries.

Data Analysis

BP readings were divided into periods using the information requested in the diaries. We defined clinic-related readings (CLIN) as those occurring while the patients were either physically present in the clinic, or in transit from it to the location where their usual activities take place, or returning to it for disconnection of the monitor. The CLIN period was the sum of two components. The initial one (INIT) consisted of all readings obtained from initiation of the monitoring until patients' return to their home or job activities; the final one (FIN) consisted of those obtained the next day, from the time of departure from home or job until return to the clinic and discontinuation of the procedure. Therefore, readings obtained while the patients were in the clinic are included in these components. The mean number of total CLIN readings in the 100 procedures ±SEM (range), was 4.2±0.1 (2-8). Clinic-unrelated readings were defined as those occurring during routine daily activities (ACT), did not include those while bedbound or asleep, and their mean number was 17.4±0.5 (4-30) in the 100 procedures. Bedbound and asleep readings were not used for assessment of the pressor response to the clinic. Their mean number was 10.7±0.3 (2-18). The average systolic, diastolic, mean, and pulse pressures, and the average heart rate were calculated for the periods CLIN and ACT, and the subperiods INIT and FIN, in each study.

All statistical analyses (t tests, correlations, linear regression, and analysis of variance [ANOVA]) were performed using a statistical package (SAS Institute, Inc., Cary, North Carolina). A probability value of less than 0.05 was used to reject the null hypothesis. When paired t tests were done on the difference between average values in two periods, each observation was weighted with the number of readings in each period. Means between three groups were compared with a factorial model two-way ANOVA (general linear model procedure for unbalanced designs) to control for the effects of interpatient variability.

Results

Our 51 essential hypertensive patients were predominantly 1) middle aged: 58.5±1.6 (39-79) years old; 2) minority: Hispanic 41, Black 9, White 1; and 3) female: F/M, 43/8. The duration of their hypertension by history was 12.3±1.0 (1-28) years, and they had been maintained on a variety of antihypertensive agents before study. Retinopathy was present in 92% (grades I or II), left ventricular hypertrophy by electrocardiogram in 16%, and renal dysfunction (creatinine clearance less than 80 cc/min) in 43% of the patients. Major concomitant illnesses included diabetes (31%) and obesity (69%), with average weight of 165±4.9 (116-285) lbs and body mass index (BMI) of 29.6±0.76 (21-42) kg/m². Sphygmomanometric BPs after 3 weeks on placebo averaged 168±3 (130-210)/101±1 (90-110) mm Hg.

In the placebo group, monitor CLIN systolic (162±2 mm Hg), diastolic (101±1 mm Hg), and pulse (61±2 mm Hg) pressures were significantly higher than ACT systolic (149±2 mm Hg), diastolic (93±1 mm Hg), and pulse (56±1 mm Hg) pressures (Figure 1, top). In contrast, heart rates were not different (CLIN, 87±1; ACT, 86±1 beats/min). The magnitude of the pressor response to the clinic visit (CLIN minus ACT) was as follows: systolic 13±2 (-21 to +50) and diastolic 9±1 (-9 to +26) mm Hg (not shown, p<0.001, for both). As the ranges indicate, some patients exhibited depressor responses (18% of the studies for systolic and 12%
FIGURE 1. Bar graphs showing clinic-related (CLIN) and clinic-unrelated (ACT) blood pressures in 67 studies on placebo (top panel), and blood pressures of initial (INIT) and final (FIN) components of CLIN (bottom panel) (see Methods). SYS, systolic; DIAS, diastolic; PP, pulse pressure; HR, heart rate. Standard errors are shown. p values (weighted paired t tests for individual differences between CLIN and ACT or INIT and FIN) are indicated (*p<0.001; †p<0.01; ‡p<0.05; ns, not significant).

for diastolic BPs). BPs during sleep (not used for the comparison above) averaged 136±2/85±1 mm Hg, that is, 9% lower than those of ACT.

The differences between the INIT and FIN components of CLIN are shown in Figure 1, bottom. FIN systolic (158±3 mm Hg) and pulse (58±2 mm Hg) pressures were lower than INIT systolic (166±2 mm Hg) and pulse (64±2 mm Hg) pressures, although FIN systolic was still significantly higher than its respective ACT counterpart (ANOVA). Diastolic pressures were not different between INIT and FIN, whereas heart rate was 4±2 beats/min higher in FIN.

The average pressor response to the clinic visit (CLIN−ACT) did not change in 19 repeat studies on placebo performed 2−24 months apart in 15 patients. Its magnitude was 13±3/11±2 mm Hg in the first study and 13±4/11±2 mm Hg in the second (error bars in Figure 2). Individual responses in the second study, however, could not be predicted from those of the first. This is indicated by the slopes of the lines joining data points for each patient in Figure 2. Accordingly, the correlation coefficients for the regression of second on first study responses (not shown) were 0.21 for systolic (NS) and 0.35 for diastolic (NS).

Significant reductions in ACT BPs were produced by 10 weeks of therapy with hydrochlorothiazide (−11±5−8±2 mm Hg), atenolol (−25±6−13±3 mm Hg), or the converting enzyme inhibitors captopril and zofenopril (−15±3−9±2 mm Hg). BPs before and during treatment are shown in Figure 3 (left). The pressor responses to the clinic were not significantly different before and after reduction of BP by these three classes of agents (Figure 3, right). Atenolol produced a 14±6 beats/min (0.05<p<0.10) reduction in heart rate, which was not observed with the other two agents. The heart rate response (CLIN−ACT) to the visit while on atenolol (1.7±9.0 beats/min), however, was not significantly different from that before treatment (−1.8±3.3 beats/min; not shown).

Discussion

The white coat phenomenon, that is, the pressor response evoked by the physician, can lead to misdiagnosis of hypertension in people with modest elevations of BP and to overestimation of the need for therapy in established hypertensive patients. In the latter, knowledge of the magnitude of individual responses can permit better targeting of treatment, diminishing its untoward effects.
FIGURE 3. Bar graphs showing clinic-unrelated (ACT) blood pressures (left panel) and pressor responses to the clinic (CLIN-ACT) (right panel); systolic (SYS), diastolic (DIAS), before and after monotherapy, in 33 studies. Number of patients on hydrochlorothiazide (HCTZ), atenolol, or converting enzyme inhibitors (captopril and zofenopril [CEI]) is indicated. p values on left are for paired t tests assessing significance of blood pressure reduction produced by these agents (*p<0.001, tp<0.01, #0.05<p<0.10). Symbol ns (not significant) on the right, indicates lack of effect of therapy on pressor responses to clinic.

The response to a physician’s visit in a group of hospitalized patients was 27/15 mm Hg by intra-arterial monitoring. Results in hospitalized patients, however, cannot be extrapolated to conditions of routine medical care. The problem has been addressed by comparing the average of daytime ambulatory intra-arterial recordings (Oxford technique) with office cuff readings. In a group of patients with higher office than ambulatory BPs, the difference in mean arterial pressure was 20 mm Hg. Several factors might have affected this result. Office readings were the average of visits not coincidental with the monitoring procedure, the device was invasive, and the response was calculated by subtraction of BP measurements obtained by two different methods. In another study, noninvasive monitoring was compared with office cuff readings. The magnitude of the pressor response was 29/15 mm Hg. The correlation coefficients for the regression of simultaneous BPs by the monitor and the cuff (the validation test for the monitor) were 0.85–0.90. Hence, a large component of the apparent magnitude of the response could have been due to the use of two methods of measurement. Interestingly, it was observed that monitor-recorded BPs decreased progressively over the first hour after leaving the office.

We measured the pressor response to the clinic using only BPs obtained by a noninvasive monitor. For this purpose we defined clinic-related and unrelated readings assuming that the medical visit is a stressor different from those during daily routine activities at home or job. The magnitude of the response in our study was 13±2/9±1 mm Hg, less than those previously mentioned. We believe our results offer a better estimate of the phenomenon as it occurs in conditions of routine medical care. Our patients were ambulatory, were studied with a noninvasive device, and the response was measured with a single method. One other group reported responses of a magnitude similar to the one we measured. Their study group, however, included a large percentage of patients who exhibited depressor responses, making it not comparable with ours.

The mechanism of the pressor response to the medical visit is not clearly understood. In most studies, this response has been accompanied by an increase in heart rate, supporting a role for rate-related increases in cardiac output. The asso-
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The association between the pressor and heart rate responses to the visit was weak, however, indicating that other factors must be involved. Our patients did not exhibit a heart rate response. The increase in their pulse pressures suggests a role for adrenergic stimulation of stroke volume. Atenolol reduced heart rate as expected but did not modify the pressor and heart rate responses to the clinic. This is analogous to lack of abolition of the hyperkinetic state of borderline hypertensives by β-blockade and could be taken as evidence for parasympathetic contribution to the pressor response to the clinic. We cannot, however, exclude a role for α-adrenergic-mediated vasoconstriction.

In a group of hypertensive patients analyzed as a whole, the pressor response to the physician maintained the same magnitude over four repeat visits in 24 hours. The reproducibility of individual responses was not commented on. This issue has been studied in 84 normotensive individuals who were retested after 3-4 months. The test-retest correlation coefficients for systolic (0.43) and diastolic (0.44) responses were weak but significant. We confirmed maintenance of the average group response in 19 repeat studies conducted 2-24 months apart on placebo. The test-retest correlation coefficients in our hypertensive patients, however, were not significant. We cannot ascertain whether this difference is because of the study of hypertensive versus normotensive persons or to the different number of patients in the two studies. This issue must be further investigated because poor reproducibility of the response, if confirmed, bears directly on its predictability.

Attempts have been made to identify correlates or predictors of the pressor response to the clinic. Results regarding sex and age have been conflicting. No correlation has been found between 24-hour BPs and the magnitude of the response to the encounter with the physician. In our study, several antihypertensive agents decreased BP without altering the response. This also indicates that patients' BPs and responses to the medical visit are not related.

By defining subperiods related to the clinic visit, we were able to identify a new component of the pressor response to the clinic, the one preceding the encounter with the physician. This component was observed 1 day after initiating the procedure and had smaller systolic and pulse pressure elevations than those after the patient-physician interaction of the day before. The reduction in monitor systolic BP is analogous to the decrease in office systolic BPs observed in consecutive visits separated by 2 weeks. The BPs of both clinic-related components were significantly higher than those during the rest of the day. This indicates that cardiovascular responses are not only triggered by the encounter with the physician (white coat phenomenon) but that they occur as a consequence of unidentified stressors in anticipation of the medical visit.

We demonstrate a significant pressor response to the clinic with a single method of measurement. Its magnitude is less than that obtained by comparison of two methods or by use of an invasive device in hospitalized patients. We do not explore the mechanism of the response but offer indirect evidence suggesting autonomically mediated increases in ventricular stroke volume. The average response of our group of patients was not attenuated in a second study but that of individuals was not reproducible. Finally, we describe a new component in the pressor response to the clinic, which occurs in anticipation of the encounter with the physician and is therefore different from the white coat phenomenon.

Acknowledgments

We thank Alex Perez for his excellent technical assistance and the Faculty of the Division of General Internal Medicine for their recruitment efforts and criticism of the manuscript.

References


KEY WORDS • white coat phenomenon • ambulatory blood pressure • essential hypertension.
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Hypertension. 1990;15:I161
doi: 10.1161/01.HYP.15.2_Suppl.I161

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