Blood Pressure Response to Hyperventilation Test Reflects Daytime Pressor Profile

Fiorella Fontana, Pasquale Bernardi, Giuseppina Lanfranchi, Maria Sole Pisati, Emilio Merlo Pich

Abstract—Recent studies show that healthy subjects and patients with moderate hypertension have different pressor responses to hyperventilation, depending on their sympathoadrenergic reactivity. In the present study, we investigated whether a different response to the hyperventilation test is related to differences in the daily blood pressure profiles recorded with noninvasive ambulatory monitoring. Forty-five healthy subjects and 67 patients with essential hypertension of grades 1 and 2 (Joint National Committee VI and World Health Organization) were investigated. Healthy subjects and hypertensive patients responding to hyperventilation with an increase in systolic blood pressure had, during daytime ambulatory blood pressure assessment, peak systolic blood pressure values (146.0±5.0 mm Hg, 182.2±9.0 mm Hg, respectively) similar to the hyperventilation peak systolic blood pressure values (147.2±3.5 mm Hg, 183.0±4.7 mm Hg, respectively). Hypertensive patients responding to hyperventilation with a decrease in blood pressure showed clinic systolic blood pressure values (178.4±3.2 mm Hg) higher than daytime average ambulatory systolic blood pressure (155.2±7.1 mm Hg; P<0.01). Our results indicate that a hyperventilation test yields information on daily peak blood pressure values in healthy subjects and hypertensive patients when it induces a pressor increase and can identify hypertensive patients with the so-called “white coat effect” when it induces a pressor decrease. (Hypertension. 2003;41:244-248.)

Key Words: hypertension, essential ■ blood pressure determination ■ blood pressure monitoring, ambulatory ■ hypertension, white-coat

Blood pressure (BP) fluctuates over time. 1 Because of their high and spontaneous variability, BP measurements performed in the clinic or physician’s office cannot predict hypertensive fluctuations occurring during everyday life. 2,3 Although BP values measured during the doctor’s visit may be affected by the patient’s emotional reaction, 4 ambulatory BP monitoring provides more reliable measurements of BP values for better assessment of hypertensive patients. 2,5-7

Previously, we showed that in healthy subjects 8 and in patients with mild or moderate hypertension, 9 a prolonged and forced hyperventilation induced different BP responses, dividing the subjects into 3 groups: the first responding with a decrease in BP, the second without any significant change, and the third with an increase. The changes in BP response to the hyperventilation test were associated with corresponding changes in sympathoadrenergic tone. There is also evidence that the daily pressor spontaneous fluctuations of hypertensive patients are due to changes in sympathoadrenergic activity. 10,11 Moreover, in these patients, daily BP elevations recorded during ambulatory monitoring are closely related to the increase in BP found during standardized psychophysiological stress tests. 12

To establish whether hyperventilation can yield useful information on daytime pressor profiles, we evaluated the association of pressor responses to hyperventilation with particular pressor parameters recorded by ambulatory BP monitoring (daytime average ambulatory BP values, daytime peak BP values, average of the highest 5 BP values, and daytime fluctuations of BP values).

Methods

Patients

We enrolled young healthy subjects (n=45, 21 women and 24 men; mean age, 30±6 years) and subjects with essential hypertension (n=67, 30 women and 37 men; mean age, 62±5 years) of grades 1 and 2 according to the Sixth Report of the Joint National Committee and the World Health Organization (JNC VI/WHO). 13 Healthy subjects were selected among young physicians and medical students at our university. No subject had a personal or family history of hypertension. All had resting systolic blood pressure (SBP) values <135 mm Hg and diastolic blood pressure (DBP) values <85 mm Hg.

Hypertensive patients were recruited from 3 cohorts: (1) patients who underwent medical examination, (2) patients admitted to the hospital for other diseases in whom hypertension was found for the first time, (3) patients attending the hypertension clinic at our institution during a period of discontinuation of antihypertensive drugs. Patients were asymptomatic and had SBP within 158 and 190 mm Hg and DBP within 85 and 110 mm Hg. Routine laboratory
tests were normal, and secondary causes of hypertension were excluded.

Written informed consent was obtained from all patients, and the protocol was approved by the Research Committee of S. Orsola Hospital.

Experimental Procedure
The study protocol included a hyperventilation test and daily ambulatory BP monitoring throughout 12 hours (8 AM to 8 PM). The hyperventilation test was performed between 8 and 12 AM, in a fasting state and a supine position, after at least 1 hour of rest in a quiet room. During this period, BP and heart rate (HR) were recorded every 5 minutes. The test was performed when BP values were stable for at least 20 minutes. The hyperventilation test was performed by asking the patients to breathe as deeply and rapidly as possible (at least 30 breaths/min) for 5 minutes. ECG leads were placed on the chest, and a sphygmomanometer cuff was placed on the right arm. HR was monitored continuously by ECG, and BP determinations were made at 1-minute intervals throughout the study. Arterial blood samples for evaluation of blood gas levels and pH were drawn from the radial or femoral artery. Only subjects and patients who presented pH values >7.60 in response to hyperventilation were included in the study. The following parameters were investigated: clinic BP and HR values (ie, basal BP and HR values recorded immediately before the beginning of hyperventilation) and peak BP and HR changes during hyperventilation, appearing in healthy subjects 4 minutes after the beginning of the test, and in hypertensive patients after 2 minutes.

Daily BP monitoring was assessed every 20 minutes during daytime with a fully automatic recorder set (Profilomat, Disetronic Medical Systems). During monitoring, no subject or patient was exposed to unusual physical or psychological stressors such as excessive food intake, exaggerated physical exercise, work overload, or anxiety. The following parameters were investigated: average, peak, and average of SD of SBP, DBP, and HR values obtained during the daytime. Average SD is a representative index of BP and HR variability.14 The average of the 5 highest BP and HR values, excluding the peak value, was also calculated as an indicator of maximal values. We considered 5 values because at least 5 BP and HR values above normal range over 12 hours of recording were found in all subjects or patients.

To avoid confounding order effects, 22 healthy subjects and 30 hypertensive patients underwent first the hyperventilation test and, 1 or 2 days later, ambulatory BP monitoring, whereas in the remaining 23 healthy subjects and 37 hypertensive patients, the order of the tests was reversed.

Statistical Analysis
Both in healthy subjects and in hypertensive patients, hierarchical cluster analyses were carried out by using percent differences between basal values and successive values of SBP (healthy subjects) or SBP and DBP (hypertensive patients), evaluated at time 0 and every minute during the 5 minutes of hyperventilation. To verify that the 3 identified clusters corresponded to distinct populations, we adopted the distribution-free Wilcoxon rank-sum test. Two-way ANOVA was used to compare hemodynamic values in each of the 3 groups of healthy subjects and hypertensive patients. Individual means were then compared by means of post hoc Duncan test. Both in healthy subjects and in hypertensive patients, the associations between BP and HR values obtained in basal condition and during hyperventilation, and BP and HR values obtained during daytime ambulatory monitoring were analyzed by Pearson r correlation coefficient and regression analysis. Values are expressed as mean±SD; a value of \( P<0.05 \) was considered statistically significant.

Results

Hemodynamic Responses to the Hyperventilation Test
Hierarchical cluster analysis was used to divide healthy subjects into 3 groups on the basis of SBP response to hyperventilation: Group 1 (n=15) had a significant \( (P<0.05) \) decrease in SBP (−17.8%) 4 minutes after the onset of hyperventilation; group 2 (n=15) did not show any significant change in SBP, and group 3 (n=15) had a significant \( (P<0.05) \) increase in SBP (14.2%) 4 minutes after the onset of hyperventilation. The clinic values of SBP, DBP, and HR did not significantly differ among the 3 groups (Figure 1). In all groups, hyperventilation significantly \( (P<0.01) \) increased DBP and HR values with respect to the respective clinic values (Figure 1). Arterial blood pH did not differ significantly among the 3 groups either under basal conditions (group 1: 7.38±0.004; group 2: 7.39±0.005; group 3: 7.38±0.003) or in response to hyperventilation (group 1: 7.63±0.003; group 2: 7.62±0.004; group 3: 7.62±0.003).

On the basis of the SBP and DBP responses to hyperventilation, hypertensive patients were also divided into 3 groups by a hierarchical cluster analysis: group 1 (n=25) had a significant \( (P<0.05) \) decrease in SBP (−15.2%) and DBP (−13.5%) 2 minutes after the onset of hyperventilation; group 2 (n=22) did not show any significant change, and group 3 (n=20) had a significant \( (P<0.05) \) increase in SBP (12.5%) and in DBP (16.2%) 2 minutes after the onset of hyperventilation. Clinic values of SBP, DBP, and HR of group 1 were higher \( (P<0.01) \) than those in groups 2 and 3 (Figure 2). Hyperventilation significantly \( (P<0.01) \) increased HR with respect to the clinic values in all 3 groups (Figure 2). Arterial blood pH did not differ significantly among the 3 groups either under basal conditions (group 1: 7.39±0.003; group 2: 7.39±0.001; group 3: 7.38±0.002) or in response to hyperventilation (group 1: 7.62±0.002; group 2: 7.62±0.003; group 3: 7.63±0.004).

Hemodynamic Profiles Obtained During Daytime Ambulatory Monitoring
In healthy subjects of groups 1 and 2, the daytime average ambulatory values and peak ambulatory values of SBP, DBP, and HR did not significantly differ from respective clinic values (Figure 1). In the subjects of group 3, the average of SBP, DBP, and HR did not differ from respective clinic values, but their peak ambulatory values of SBP, DBP, and HR were significantly \( (P<0.01) \) higher than respective clinic values and not significantly different from the respective hyperventilation values. In group 3, the average of SD of SBP, DBP, and HR was significantly \( (P<0.01) \) higher than the respective values of groups 1 and 2 (Figure 1).

In hypertensive patients, daytime average ambulatory values of SBP, DBP, and HR did not significantly differ among the 3 groups (Figure 2). Interestingly, in group 1, daytime average ambulatory values of SBP were significantly \( (P<0.01) \) lower than the respective clinic values. In group 1, SBP, DBP, and HR peak ambulatory values did not significantly differ from the respective clinic values, whereas in group 3, SBP, DBP, and HR peak ambulatory values were significantly \( (P<0.01) \) higher than respective clinic values and did not differ from the respective peak values during hyperventilation (Figure 2). In group 2 SBP, DBP, and HR average and peak values did not significantly differ from the respective clinic values. The average of SD of SBP, DBP, and
HR of group 2 was significantly \( (P<0.01) \) lower than the respective values of groups 1 and 3 (Figure 2).

In all groups of both healthy subjects and hypertensive patients, the average of the highest 5 BP and HR values did not differ from the respective peak ambulatory values.

Significant positive correlations were found between clinic SBP values and the respective peak ambulatory values in group 1 \( (r=0.70, \ P<0.001) \) and between peak SBP during hyperventilation and the respective peak ambulatory SBP values in group 3 \( (r=0.65, \ P<0.001) \).

**Discussion**

We previously reported that healthy subjects and hypertensive patients can be divided into 3 groups on the basis of their pressor response to prolonged and vigorous hyperventilation (group 1 with a decrease in BP, group 2 without changes, and group 3 with an increase).\(^8,9\) In this report we show that the responses to hyperventilation reflect differences in pressor profiles assessed by daytime BP monitoring.

In healthy subjects, daytime average ambulatory BP values were similar to clinic BP values independent of the BP response to hyperventilation. In the hypertensive patients who responded to hyperventilation with a decrease in BP, daytime average ambulatory BP values were lower than the respective clinical BP values, whereas in the hypertensive patients who responded to hyperventilation with an increase or no change in BP, daytime average ambulatory BP values were similar to clinic BP values.

It is known that when ambulatory BP monitoring shows daytime average BP lower than clinic BP, it suggests that clinic pressure is affected by the emotional response to the physician’s visit, a phenomenon called the “white coat effect.”\(^4,15\) This mechanism may also explain so-called “white coat hypertension,” a condition characterized by high clinic BP values but normal BP values recorded during daytime ambulatory BP assessment.\(^18,19\)

The data suggest that the patients responding to hyperventilation with a decrease in BP have clinic BP values affected by the “white coat effect.” As the decrease in clinic SBP in response to hyperventilation was above 10%, this threshold in the SBP response to hyperventilation may be a useful marker to identify patients affected by an emotional reaction. It may be speculated that hyperventilation reveals the presence of “white coat hypertension” when it normalizes abnormal clinic BP values. In our study, the hyperventilation test did not reveal “white coat hypertension” in any subject because the study population included true hypertensive patients or healthy subjects selected among medical students or staff already exposed to a hospital environment, with clinic BP values within a limited normal range.

The response to hyperventilation may also provide useful information on the daytime pressor profile. In healthy subjects, the increase in BP in response to hyperventilation characterizes subjects with wide daily pressor fluctuations and peak ambulatory BP values similar to those observed during hyperventilation, thus revealing an unstable daily pressor control. In the patients in whom hyperventilation decreased BP levels, the peak ambulatory BP values recorded during the day were correlated to the clinic BP values. This suggests that in these patients the simple clinic BP measure-
ment predicts the highest daily fluctuations of BP values. Conversely, in patients with a net increase in BP in response to hyperventilation, the hyperventilation peak values were informative of the values reached by the spontaneous hypertensive fluctuations as assessed by the peak ambulatory BP values correlated to hyperventilation peak BP values. Finally, the lack of hemodynamic response to the hyperventilation test was in line with the lack of major BP fluctuations during the day, as corroborated by the significantly lower variability of the hemodynamic parameters.

We previously reported that hypertensive patients who respond to hyperventilation with a decrease in BP have high BP and HR values and plasma catecholamine levels above the normal range, suggesting a basal sympathoadrenergic hyperactivity, whereas patients who respond to hyperventilation with an increase in BP have normal plasma catecholamine levels associated with lower levels of BP and HR.9 These different phenotypes, characterizing hypertensive patients with a similar pressor daytime profile but different BP response to hyperventilation, are probably attributable to a different genetic background, as previously described for the responses to mental stress in normotensive offspring of hypertensive parents.20

Our findings in hypertensive patients are in agreement with previously reported data showing a direct correlation between the increase in BP in response to standardized psychological tests and daytime peak ambulatory BP values, suggesting that mental stress-induced BP increases can be useful to predict daily BP variations.12

Hyperventilation may be even more useful than psychological tests because it may disclose a “white coat effect” and provide information on the daytime ambulatory BP profile and the presence and extent of daily BP fluctuations. A strong pressor response to hyperventilation in healthy subjects is associated with an unexpected pressor instability during daily ambulatory assessment which may unmask an otherwise undetected hypertension risk.

**Perspectives**

A number of tests have been proposed to disclose a predisposition to hypertension in normotensive subjects and in normotensive offspring of hypertensive patients. Our findings suggest that the hyperventilation test can be adopted in routine clinical practice in normotensive subjects and, particularly, in normotensive offspring of hypertensive patients to unmask an unstable pressor control. The test may also be useful to identify hypertensive patients whose blood pressure values during the physician’s visit are affected by an emotional reaction. Systemic injury is common in patients with fluctuating arterial pressure changes. By identifying hypertensive patients with pressure fluctuations, the hyperventilation test may serve to disclose the risk or the presence of systemic lesions in asymptomatic subjects.
References


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