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Pressor responses to hyperventilation in elderly subjects differentiate essential from secondary hypertension

Research Article

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Abstract: We evaluated pressor responses to the hyperventilation test in elderly normotensive (n=43, mean age 82 ± 5 years) and elderly hypertensive subjects (n=45 with essential hypertension, mean age 82 ± 2 years, and n=49 with secondary hypertension, mean age 82 ± 3 years). Hyperventilation did not change blood pressure (BP) in normotensive and secondary hypertensive subjects, whereas it decreased BP in essential hypertensives. Hierarchical cluster analysis based on BP responses to hyperventilation disclosed three groups of subjects in each population: group 1 exhibited a reduction in BP (essential hypertensives: 76%), group 2 no change (normotensives: 70%, secondary hypertensives: 76%), and group 3 an increase (normotensives: 19%, essential hypertensives: 13%, secondary hypertensives: 14%). Ambulatory BP monitoring found significant differences in pressor daytime profiles of hypertensive patients according to pressor responses to hyperventilation showing wide fluctuations in group 1 and 3 patients. Interestingly, the peak ambulatory SBP values correlated to the pre-hyperventilation SBP values in group 1, and to the hyperventilation peak SBP values in group 3. In conclusion: 1) Aging decreases reactivity to respiratory alkalosis in elderly normotensives; 2) hyperventilation induces significant pressor changes frequently in essential hypertension, but rarely in secondary hypertension; 3) the significant pressor responses to hyperventilation reflect the daytime pressor profiles predicting the highest daily fluctuations of BP values.

Keywords: *Hyperventilation • Respiratory alkalosis • Elderly hypertensive patients • Blood pressure ambulatory monitoring • White coat hypertension*

1. Introduction

Five minutes of forced hyperventilation test induces different blood pressure (BP) responses dividing young healthy subjects [1] and adult patients with mild or moderate essential hypertension [2] into three groups: the first responding with a decrease in BP, the second without any significant change in BP, and the third with an increase in BP. The different BP responses to hyperventilation seem to reflect the corresponding changes in sympatho-adrenergic tone [1,2]. This is supported by the correlations between the changes in pressor responses and plasma catecholamine levels [1]. Recently, we showed that in adult essential hypertensive patients, the pressor responses to hyperventilation reflect differences in pressor profiles assessed by daytime BP monitoring [3].

Increased sympatho-adrenergic activity and hemodynamic response to pressor stimuli are characteristic of elderly normotensive subjects [4], particularly elderly hypertensive patients [5], but data on hyperventilation response are lacking.

The present work evaluated whether BP responses to the test change with aging in elderly normotensive subjects and in patients with hypertension. We studied patients with essential and secondary hypertension to evaluate whether the different mechanisms inducing hypertension disclose distinct BP responses to hyperventilation. Moreover, to establish whether the test can yield information on the pressor daytime profile we

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Table 1. Clinical characteristics of elderly hypertensive patients.

Forms of hypertension	No	Sex, M/F	Age, y	SBP, mm Hg	DBP, mm Hg	HR, bpm	Cardiovascular involvement
Essential hypertension	45	27M/18F	82±2	178.0±5.5	97.0±5.8	72.0±3.1	LVH (n=12)
Secondary hypertension:							
-Isolated systolic hypertension	12	4M/8F	79±3	177.0±3.4	80.0±3.0	68.0±2.6	LVH (n=3), CIHD (n=1), CS (n=4), PVS (n=4), TIA (n=2)
-Bilateral chronic nephropathy	4	2M/2F	79±4	173.2±3.0	95.0±3.2	72.3±2.5	LVH (n=1), CIHD (n=2)
-Nephroangiosclerosis	18	8M/10F	85±1	174.2±3.4	96.0±4.1	78.2±3.3	LVH (n=5), CIHD (n=3), TIA (n=3)
-Diabetic nephropathy	11	5M/6F	84±2	169.0±2.1	98.0±3.0	74.3±3.0	LVH (n=3), CIHD (n=2), CS (n=2), PVS (n=2), TIA (n=2)
-Hyperparathyroidism	4	2M/2F	79±3	172.0±1.0	90.0±0.3	70.2±3.1	LVH (n=2)

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LVH, left ventricular hypertrophy; CIHD, chronic ischemic heart disease; CS, carotid stenosis ≤ 50%; PVS, peripheral vascular stenosis ≤ 50%; TIA, transient ischemic attack. Values are given as mean ± SD.

investigated the relation of the pressor responses to the hyperventilation test with particular pressor parameters recorded by ambulatory BP monitoring (daytime average ambulatory BP values, daytime peak BP values, average of the highest five BP values and daytime fluctuations of BP values).

2. Material and Methods

2.1. Patients characteristics

We enrolled 43 normotensive subjects (19 women and 24 men; mean age, 82 ± 5 years) without a family history of hypertension and 94 elderly drug-free patients (45 with essential hypertension of grades 1 and 2 according to the Sixth Report of the Joint National Committee and the World Health Organization, JNC VI/WHO [6], and 49 with secondary hypertension).

Patients were recruited from: [1] patients with a first diagnosis of hypertension, and [2] hypertensive patients after discontinuation of antihypertensive drugs during hospital admission for clinical and instrumental monitoring to adjust suboptimal antihypertensive therapy. Patients' clinical characteristics are summarised in Table 1. The patients with essential hypertension were included in the study only if they presented normal plasma creatinine values (≤ 1.2 mg/dl). Patients with nephroangiosclerosis were selected on the basis of plasma creatinine values > 1.7 mg/dl, abnormal renal echogenicity and vascular resistance index > 0.75.

The patients were enrolled only if they were free from acute cardiovascular disorders. The body mass index of normotensive subjects and patients was not ≥ 30. All subjects and patients refrained from tea, coffee and cigarettes for 36 hours before the study and none were under mental or physical stress.

Written informed consent was obtained from all participants, and the protocol was approved by the Research Committee of S. Orsola Hospital in accordance with the principles of the Declaration of Helsinki.

2.2. Experimental procedure

The study protocol included a hyperventilation test followed one or two days later by ambulatory BP monitoring throughout 12 hours (8 AM to 8 PM). Hyperventilation was performed between 8 and 12 AM, in a fasting state and in a supine position, after at least one hour of rest in a quiet room with BP values stable for at least 20 min. The subjects and patients were invited to breathe as deeply and rapidly as possible (at least 30 breaths/min) for five min. Only those who presented pH values > 7.60 in response to hyperventilation were included in the study. During hyperventilation, some patients presented dizziness, tingling, loss of concentration, dry mouth and hotness; others presented paraesthesias of the limbs or face. The electrocardiogram showed T wave inversion in leads V1-V4 during the hyperventilation test in 15 patients; the remainder did not present any electrocardiographic change indicating myocardial ischemia or arrhythmias. None complained of angina.

Arterial blood samples for evaluation of blood gas levels and pH were drawn from the radial or femoral artery. HR was monitored continuously by electrocardiogram, and BP determinations were made at one-minute intervals using a sphygmomanometer cuff placed on the right arm. The following parameters were investigated: clinic BP and HR values (*i.e.*, basal BP and HR values recorded immediately before the beginning of hyperventilation) and peak BP and HR changes during hyperventilation (detected in all subjects two minutes after the beginning of the test).

Daily ambulatory BP monitoring was performed one or two days after the hyperventilation test because the stress of the examination, the discomfort entailed and the arterial blood sampling to determine pH are all

Table 2. Hemodynamic parameters in elderly normotensive subjects and elderly hypertensive patients before (A) and after (B) hyperventilation.

	SBP (mm Hg)		DBP (mm Hg)		HR (beats/min)	
	A	B	A	B	A	B
Normotension	135.2 ± 5.2	136.2 ± 6.2	80.2 ± 3.8	82.2 ± 3.5	66.5 ± 7.0	83.1 ± 3.6*
Essential hypertension	178.0 ± 5.5	160.0 ± 5.8*	97.0 ± 5.8	84.5 ± 5.2*	82.0 ± 3.1	96.4 ± 3.9**
Secondary hypertension	175.4 ± 5.7	174.0 ± 6.5	92.0 ± 5.3	93.9 ± 5.0	73.5 ± 2.9	87.0 ± 3.1**

*SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate. Values are given as mean ± SD. *$p < 0.05$, **$p < 0.01$ versus respective values before hyperventilation.*

factors that could have an unexpected impact on BP values recorded in the hours following hyperventilation. BP monitoring was assessed every 20 min with a fully automatic recorder (Profilomat, Disetronic Medical Systems). During monitoring, no 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 BP and HR values obtained during the daytime. Average SD is a representative index of BP and HR variability [7]. The average of the five highest BP and HR values, excluding the peak value, was also calculated as an indicator of maximal values as previously done [3]. We considered five values because at least five BP and HR values above normal range over 12 hours of recording were found in all patients.

Elderly normotensive subjects only underwent the hyperventilation test. All procedures followed were in accordance with institutional guidelines.

2.3. Statistical analysis

ANOVA followed by Duncan's test was used to compare hemodynamic parameters recorded during the test in elderly normotensive subjects and elderly patients with essential and secondary hypertension studied as single groups. In normotensive subjects and elderly hypertensive patients, hierarchical cluster analyses [8] were then carried out using percent differences between basal values and successive values of BP, evaluated at time 0 and every minute during the five minutes of hyperventilation, as parameters. To verify that the three 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 three groups of normotensive subjects and hypertensive patients. Individual means were then compared using the post hoc Duncan test. The associations between BP and HR values obtained in basal conditions and during hyperventilation, and BP and HR values obtained during daytime ambulatory monitoring were analyzed by Pearson *r* correlation coefficient and regression analysis in hypertensive subjects. Values are expressed as mean ± SD; a value of $p < 0.05$ is considered statistically significant.

3. Results

3.1. Effects of hyperventilation on blood pressure and heart rate values in elderly normotensive subjects and elderly hypertensive patients

Hyperventilation significantly ($p < 0.05$) decreased BP in essential hypertensive patients, whereas it did not modify BP in normotensive subjects or in patients with secondary hypertension (Table 2). The test significantly ($p < 0.05$) increased HR in normotensive subjects and hypertensive patients (Table 2).

3.2. Identification of three different groups of elderly subjects discriminated according to distinct blood pressure responses to hyperventilation

As hyperventilation induced a wide range of BP responses in normotensive and hypertensive subjects, we used hierarchical cluster analyses to divide normotensive and hypertensive subjects, on the basis of their BP response to hyperventilation. Three groups (or clusters) of subjects were identified (Table 3).

3.2.1. Normotensive subjects

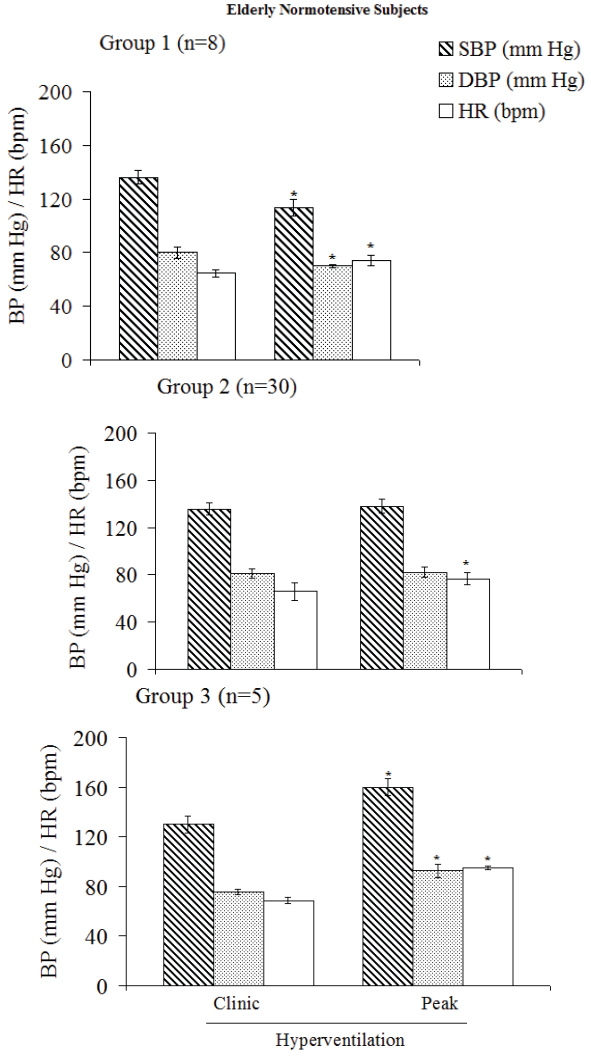
Group 1 (n=8) had a significant ($p < 0.05$) decrease in SBP (-17.2%) and DBP (-13.2%) two minutes after the onset of hyperventilation; group 2 (n=30) did not show any significant change in BP; and group 3 (n=5) had a significant ($p < 0.05$) increase in SBP (20.5%) and DBP (19.3%) two minutes after the onset of hyperventilation.

Clinic values of SBP, DBP and HR did not significantly differ among the three groups (Figure 1). In all groups, hyperventilation significantly ($p < 0.01$) increased HR values with respect to the respective clinic values (Figure 1).

Table 3. Elderly subjects distributed according to blood pressure response to hyperventilation.

Subjects	Blood pressure response to hyperventilation		
	Decrease (group 1)	No change (group 2)	Increase (group 3)
Normotensives, *n*	8	30	5
Essential hypertensives, *n*	34	5	6
Secondary hypertensives, *n*:	5	37	7
-Isolated systolic hypertension, *n*	2	6	4
-Bilateral chronic nephropathy, *n*	1	2	1
-Nephroangiosclerosis, *n*	1	16	1
-Diabetic nephropathy, *n*	1	9	1
-Hyperparathyroidism, *n*	-	4	-

Figure 1. SBP, DBP and HR before hyperventilation (Clinic) and 2 min after hyperventilation (Peak) in elderly normotensive subjects. The subjects were divided into 3 groups on the basis of the BP response to hyperventilation. Values are mean ± SD. *p < 0.05 versus respective clinic value.



3.2.2. Essential hypertension

Group 1 (n=34) showed a significant ($p < 0.05$) decrease in SBP (-15.0%) and DBP (-18.2%) two minutes after the onset of hyperventilation; group 2 (n=5) did not show any significant change; and group 3 (n=6) had a significant ($p < 0.05$) increase in SBP (10.8%) and DBP (14.3%) 2 minutes after the onset of hyperventilation.

Clinic values of BP and HR of group 1 were higher ($p < 0.05$) than the respective values of groups 2 and 3 (Figure 2). Hyperventilation significantly ($p < 0.05$) increased HR with respect to the clinic values in all three groups (Figure 2).

3.2.3. Secondary hypertension

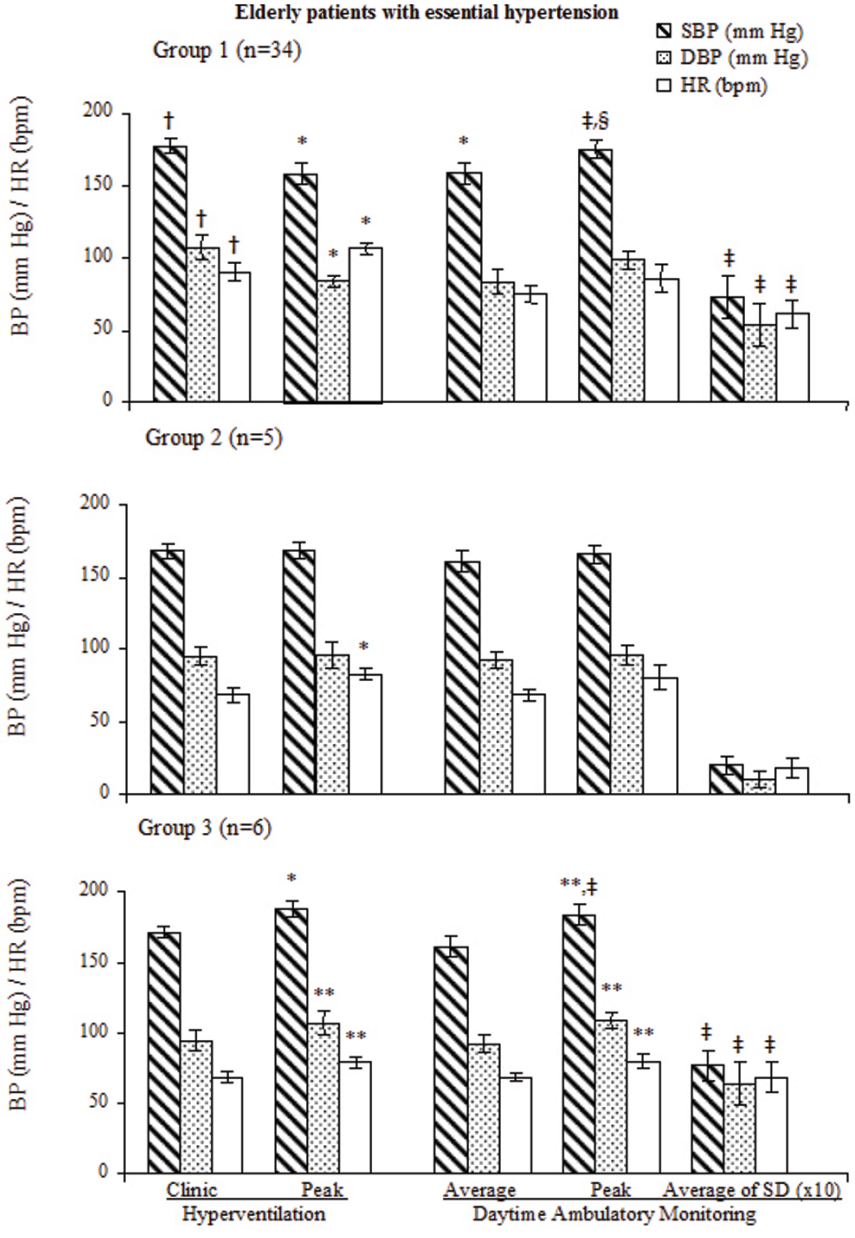
Group 1 (n=5) responded with a significant ($p < 0.05$) decrease in SBP (-12.2%) and DBP (-13.0%) two minutes after the onset of hyperventilation; group 2 (n=37) without any significant change in BP; and group 3 (n=7) with a significant ($p < 0.05$) increase in SBP (10.5%) and DBP (15.2 %) two minutes after the onset of hyperventilation.

Clinic values of SBP, DBP and HR did not significantly differ among the three groups (Figure 3). Hyperventilation significantly ($p < 0.01$) increased HR with respect to the clinic values in all three groups (Figure 3).

3.3. Blood pressure and heart rate values recorded during ambulatory monitoring in elderly hypertensive patients

In both hypertensive populations the daytime average ambulatory values of SBP, DBP and HR did not significantly differ among the three groups (Figures 2 and 3). However, peak SBP values of groups 1 and 3 were significantly ($p < 0.05$) higher than the respective values of group 2 (Figures 2 and 3). The variability of SBP, DBP and HR peaks of groups 1 and 3, expressed as average SD values, was significantly ($p < 0.05$) higher than the respective values of group 2 (Figures 2 and 3). The average of the highest five BP and HR values did not differ from the respective peak ambulatory values (not shown).

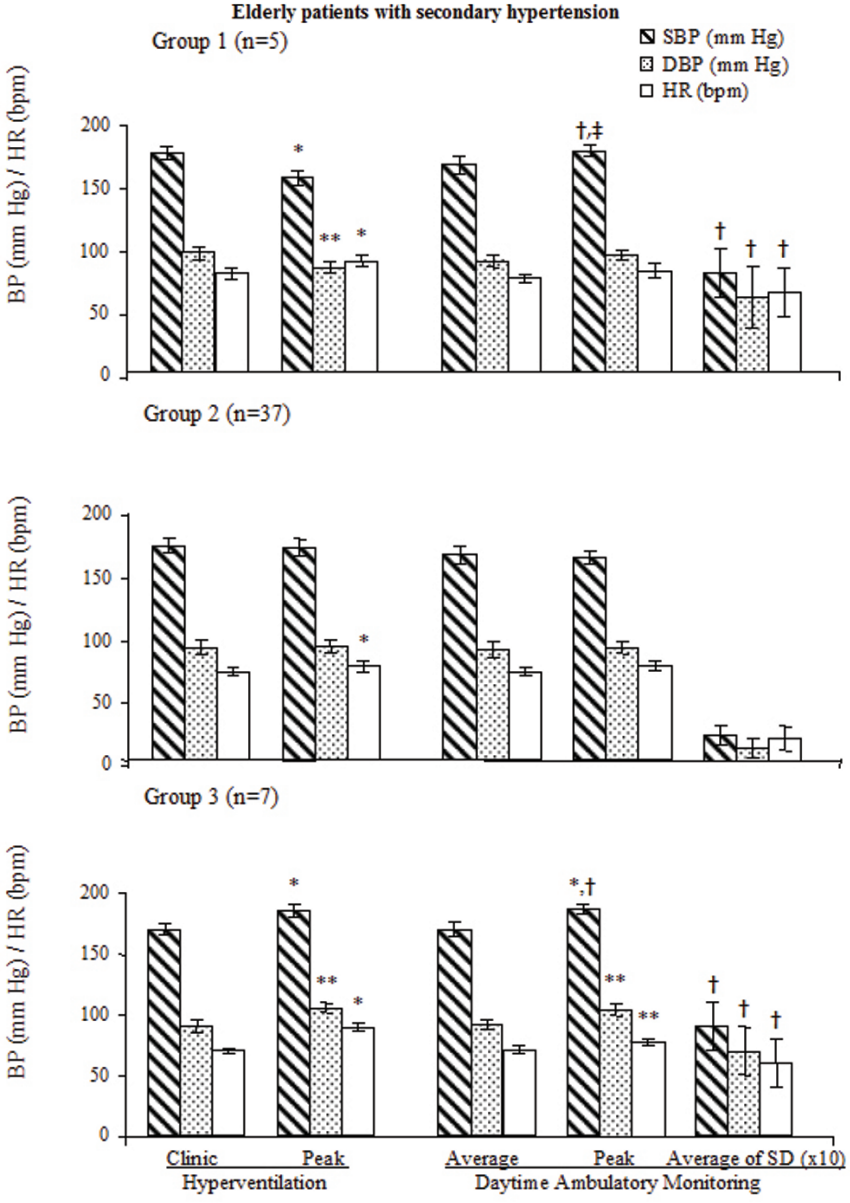
Figure 2. Relations between SBP, DBP and HR before hyperventilation (Clinic), 2 min after hyperventilation (Peak), and during ambulatory monitoring in elderly essential hypertensive patients. Values are mean ± SD. *$p < 0.01$; **$p < 0.05$ versus respective clinic value; †$p < 0.05$ versus respective values of groups 2 and 3; ‡$p < 0.05$ versus respective values of group 2; §$p < 0.05$ versus respective peak values of hyperventilation.



3.4. Relationship between blood pressure and heart rate values recorded during ambulatory monitoring and blood pressure and heart rate values observed during the hyperventilation test in elderly hypertensive patients

In group 1 essential hypertensive patients, the daytime average ambulatory values of SBP were significantly ($p < 0.01$) lower than the respective clinic values, whereas those of group 1 secondary hypertensive patients did not significantly differ from the respective clinic values (Figures 2 and 3). In both hypertensive populations: in group 1, peak ambulatory values of SBP were higher ($p < 0.05$) than the respective peak hyperventilation values, whereas they did not significantly differ from the respective clinic values (Figures 2 and 3); in group 3, peak ambulatory values of SBP, DBP and HR were higher ($p < 0.05$) than the respective clinic values and did not differ from the respective peak values during hyperventilation

Figure 3. Relations between SBP, DBP and HR before hyperventilation (Clinic), 2 min after hyperventilation (Peak), and during ambulatory monitoring in elderly secondary hypertensive patients. Values are mean ± SD. *$p < 0.01$; **$p < 0.05$ versus respective clinic value; †$p < 0.05$ versus respective values of group 2; ‡$p < 0.05$ versus respective peak values of hyperventilation.



(Figures 2 and 3); in group 2, peak ambulatory values of SBP, DBP and HR did not significantly differ from the respective clinic or hyperventilation peak values (Figures 2 and 3).

In both essential and secondary hypertensive patients, significant ($p < 0.01$) positive correlations were found between peak ambulatory SBP values and the respective clinic values in group 1 (r=0.60; r=0.56, respectively) and between peak ambulatory SBP values and the respective peak values during hyperventilation in group 3 (r=0.56; r=0.56, respectively).

4. Discussion

Our findings show that prolonged and vigorous hyperventilation produces a decrease in BP in elderly patients with essential hypertension, whereas it did not significantly change BP in elderly normotensive subjects and elderly patients with secondary hypertension. The high variability of BP values suggested different responses to hyperventilation among the subjects, prompting us to use hierarchical cluster analyses to identify sub-groups. We therefore identified three

groups of subjects in each studied population with homogeneous BP responses to hyperventilation: group 1 exhibited a reduction in BP values, group 2 no change, and group 3 an increase in BP values.

Cluster analysis indicates that most elderly normotensive subjects (70%) did not show any significant pressor response to hyperventilation, unlike healthy subjects (24%) previously assessed using the same methodology [1].

In elderly hypertensive patients the division into subgroups confirmed a distinct reactivity to hyperventilation between patients with essential hypertension and patients with secondary hypertension. Patients with essential hypertension had a significantly prevalent decrease in BP, whereas those with secondary hypertension had no change in BP response to hyperventilation. Interestingly, hemodynamic reactivity to hyperventilation in essential hypertension does not seem to change with aging. In fact, the results in elderly patients did not differ from those previously observed in adult patients, in whom BP decrease following hyperventilation was the most frequent response [2,3].

BP response to hyperventilation may be due to the effects of respiratory alkalosis on the chemoceptors and downstream mechanisms controlling the balance between sympathetic and parasympathetic systems [1,3,9]. Thus, the hemodynamic variability to hyperventilation may depend on the activation of either branch of the autonomic nervous system [1,2,9] that is inactive under basal pre-test conditions. The decrease in BP following hyperventilation is consistent with the activation of the parasympathetic nervous system during the test in subjects with a hyperactive sympatho-adrenergic tone in pre-test conditions [9].

The reduced occurrence of BP changes to hyperventilation in elderly normotensive subjects suggests a possible reduced sensitivity of the central pressor area regulating BP levels or less effective autonomic response associated with aging [10]. In fact, the regulatory function of sympathetic vasomotor activity is altered in elderly subjects [4,10]. For example, elevation of the plasma norepinephrine concentration, due to an increase in rates of spillover of norepinephrine to plasma and impairment of neuronal reuptake of the neurotransmitter by sympathetic nerves, has been observed in elderly subjects [4,11]. With increasing age reducing baroreflex sensitivity, an imbalance between decreased β- and increased α-adrenoreceptor sensitivity and/or reactivity [4,12,13] may maintain or further increase sympathetic peripheral effects independently of the impairment in the central sympatho-adrenergic activity [10,14]. A well-documented age-related reduction in vagal function [11,14,15] contributes to reduce the responsiveness of the autonomic nervous system, removing the normal opposing force for sympathetic activity and resulting in a pervasive mild hyperactivity of the sympatho-adrenergic system.

In contrast, respiratory alkalosis induces marked hemodynamic changes in elderly patients with essential hypertension as it is likely to act on the autonomic nervous central areas involved in the mechanisms determining hypertension. Clinically these patients often exhibit a spontaneous elevation of sympatho-adrenergic activity [16] that further increases when they are exposed to various stressors [17] including a medical visit, the so-called “white coat effect” [4,11]. In our elderly essential hypertensive patients, a large percentage responding with a decrease in BP to hyperventilation showed higher clinic BP values than average daytime ambulatory BP values, suggesting a major “white coat effect” due to their emotional reaction to the procedure.

The group of elderly essential hypertensive patients with an increase in BP during hyperventilation did not show a “white coat effect” since their clinic BP values were similar to the ambulatory daytime BP average. This suggests that the absence of autonomic nervous system activation in pre-hyperventilation condition will disclose the effects of respiratory alkalosis on the sympatho-adrenergic system.

The lack of pressor response to the test characterizing patients with secondary hypertension is consistent with the presence of hypertensive factors independent of autonomic nervous system function and hence is not sensitive to the effects of the emotional reaction or respiratory alkalosis.

The adrenergic hyperactivity in hypertension due to nephroangiosclerosis may depend on the activation of the renin-angiotensin system, whereas the sympatho-adrenergic function in isolated systolic hypertension and hyperparathyroidism has borderline hypertensive effects due to a reflected inhibition on sympathetic nervous control related to the increase in peripheral vascular resistance [18-21]. The absence of BP response to hyperventilation in diabetic patients confirms a major impairment of the autonomic reflexes controlling the vegetative functions [22].

Ambulatory BP monitoring showed significant differences in pressor daytime profiles of elderly hypertensive patients according to pressor responses to hyperventilation.

In patients who responded to hyperventilation with a decrease in BP, pressor daytime profile was characterized by wide BP fluctuations and the peak ambulatory SBP values were correlated to the clinic SBP values. Daytime BP profile also showed fluctuations in the hypertensive patients who responded to hyperventilation with a BP

increase, whereas the peak ambulatory SBP values were correlated to SBP peak values obtained during hyperventilation.

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 recorded by ambulatory monitoring.

In conclusion, the relatively low occurrence of significant BP response to the hyperventilation test in elderly normotensive subjects suggests that aging modifies the sensitivity and reactivity of the autonomic nervous system to the effects of respiratory alkalosis. Hyperventilation frequently induces significant pressor changes in elderly patients with essential hypertension, but rarely in elderly patients with secondary hypertension. This suggests that the simple hyperventilation test may provide useful diagnostic information. The decrease in BP identifies patients with essential hypertension whose clinic BP values are higher than the respective daytime average ambulatory BP values, suggesting that clinic pressure is affected by emotional response to the physician's visit. The pressor responses to the hyperventilation test reflect pressor daytime profile and will select both essential and secondary hypertension patients with daily unstable pressor control, predicting the highest daily fluctuations of BP values.

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