Spontaneous Fall in Blood Pressure and Reactivity of Sympathetic Nervous System in Hospitalized Patients with Essential Hypertension

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We evaluated whether reduction in sympathetic reactivity plays a major role in the spontaneous falls in blood pressure (BP) experienced during hospitalization by patients with essential hypertension. In the present case BP fell on the 2nd day of hospitalization. The responses of plasma catecholamines (CA) and BP to both handgrip and tilting were not altered during either the first 24 hours or the entire 7 days of hospitalization. The effect of phentolamine on BP was similar on the 1st, 2nd and 7th days. However, the resting levels of plasma norepinephrine before handgrip, tilting and phentolamine were significantly diminished on the 7th day, but not on the 2nd day. In conclusion, the diminution of sympathetic activity may be partly responsible for the hospitalization-induced fall in BP in the late stages.

Key words: Spontaneous blood pressure fall, Hospitalization, Sympathetic nervous system, Essential hypertension

Hypertensive patients often exhibit a spontaneous fall in blood pressure (BP) during hospitalization (1-4). Although the mechanisms responsible for this spontaneous reduction should provide considerable insight into the pathophysiology of essential hypertension, only a few investigations have been carried out to elucidate this phenomenon. On the basis of the findings that the resting levels of plasma and urinary catecholamines (CA) decrease in relation to the decrease in BP during hospitalization, diminished sympathetic nervous function in the course of hospitalization has been demonstrated to play a major role in the spontaneous BP fall (1, 3-7). However, only the measurement of resting levels of plasma CA and urinary excretion of CA, as an index of sympathetic activity, have a well-known limitation (8-12). Therefore, many physiological maneuvers, including the isometric handgrip exercise (13, 14) and upright tilting (15, 16), have been used to elucidate the function of the sympathetic nervous system. Additionally, the application of specific antagonist of alpha-adrenoceptors may be useful in directly determining the influence of the sympathetic nervous system on BP.

In the present study, BP and plasma CA responses to handgrip and tilting as well as the hypotensive effects of phentolamine were examined sequentially on the 1st, 2nd and 7th day of hospitalization. The possible contribution of the sympathetic nervous system to the spontaneous fall in BP during hospitalization in essential hypertensive subjects (EHT) was evaluated.

MATERIALS AND METHODS

Twelve untreated EHT (seven men, five women) whose mean age was 46.7 ± 3.0 (range, 23-64 years) participated in this study. They had no
symptoms or signs of major target organ damage due to the hypertension, and there were no major disorders besides the hypertension. The diagnosis of EHT was made for cases of hypertension who were not associated with any abnormal renal, endocrinologic or metabolic findings. Precordial voltage (SV$_1$ + RV$_5$) and ST-T change were evaluated on electrocardiograms (ECG) and the cardiothoracic ratio (CTR) was measured on chest X-rays. The optic fundi were graded according to Keith-Wagener’s classification. No patients had received antihypertensive medication for at least 14 days before or during the hospitalization. All patients gave free consent to the study after having had the objectives and purpose fully explained. This study was performed after approval by the Institutional Human Investigations Committee.

After admission they were placed on a diet containing 102–136mmol of sodium per day. The BP measurements were obtained every morning (10:00 AM) with a standard sphygmomanometer after they had been sitting or lying for 5 minutes or longer. The level at which the Korotkoff sounds disappeared was taken as the diastolic blood pressure (DBP). Pulse rate (PR) was also recorded at the same time. Twenty-four hour urine collection for determination of CA (norepinephrine, epinephrine), sodium, potassium and creatinine was started from 8:00 AM on the 2nd day and continued for 1 week. The accuracy of collection was assessed by creatinine excretion according to the methods of Kawasaki et al (17). Body weight was also recorded everyday at 8:00 AM. Venous blood was drawn for measuring serum electrolytes (Na, K, Cl), total protein, creatinine and blood urea nitrogen (BUN) on the 2nd and 7th days of hospitalization. BP, PR as well as plasma CA (norepinephrine, epinephrine) and plasma renin activity (PRA) responses to both isometric handgrip and upright tilting were determined on the 1st, 2nd and 7th days in the afternoon between 1:00 PM and 4:00 PM. Changes in BP and PR, following the intravenous administration of phentolamine, were also determined at the same time, on the 1st, 2nd and 7th days. The handgrip test was performed first, the upright tilting second, and the phentolamine last of all. The interval between each test was at least 30 minutes.

The handgrip test was performed in the supine position at least 30 minutes after the insertion of a venous line to allow for stabilization of BP, PR and plasma level of CA. All subjects were instructed to exert a maximum brief compressive force with their right hand to determine the maximum voluntary contraction. They were requested to hold 30% of the force level of the maximum voluntary contraction for 3 minutes. BP and PR were recorded by an automatic monitor (BP-203X model, Nihon-Kohlin, Japan) before and during each minute of the 3-minutes static muscle test. Ten ml blood samples were removed from an indwelling venous catheter before and 3 minutes after the start of the handgrip test for determination of plasma norepinephrine (NE), epinephrine (E) and PRA. Plasma aldosterone concentration (PAC) and hematocrit were also measured from the blood taken before the test.

Before the tilting test, all subjects rested initially for at least 30 minutes on the table in the horizontal position to establish a steady state of BP and PR. Thereafter, tilting was made by passively raising the subjects from the supine to a 60° head-up position. The change from the lying to the tilting position was accomplished within 5–10 seconds, and was maintained for 15 minutes. BP and PR were measured before and during the tilting test using an automatic sphygmomanometer with digital display. Venous blood samples of 10 ml were taken for CA and PRA before and 5 and 15 minutes after the start of the postural change.

After another 30 minutes for stabilization of BP and PR, phentolamine (0.1 mg/kg) was intravenously administered. Patient were in the recumbent position during administration. BP and PR were similarly monitored before and after the administration of the blocking agent. Blood for CA and PRA was drawn immediately before the injection from the venous catheter.

Based on changes in BP after admission, the patients were divided into two groups. Group 1 (n = 6) consisted of those patients, whose SBP (systolic BP) fell spontaneously by more than 20% within 1 week of hospitalization; group 2 (n = 6) was comprised of the other subjects. The changes after hospital admission in resting plasma CA, BP, PRA, urinary sodium excretion, urinary CA excretion and the hypotensive effect of phentolamine were compared between the groups.
Plasma NE and plasma E kept at -80°C were measured by the diphenyl ethylenediamine method with high performance liquid chromatography (Otsuka Laboratories, Japan). PRA and PAC were determined by radioimmunoassay technique.

All data are presented as means±SEM. Differences were examined with the two-tailed Student’s t-test for paired comparison. Linear correlation and regression coefficients were also calculated. Results were considered to be significant when the p value was less than 0.05.

**RESULTS**

Systolic blood pressure (SBP) in the supine position fell significantly during hospitalization as shown in Fig. 1. The degree of fall in SBP was similar in the supine and sitting positions. Supine and sitting diastolic blood pressures (DBP) also tended to decrease, although the magnitude was not so significant as in the findings of SBP. The levels of SBP and DBP on the 2nd hospitalization day were similar to those on the 7th day. PR was not altered over the entire 7 days of hospitalization.

Urinary volume did not change during hospitalization. Similarly, urinary excretion of NE and E was not altered with time after admission as indicated in Fig. 1. The level of 24 hour urinary excretion of sodium was lowered significantly only on the 5th and 6th days after admission compared to the findings on the 2nd day, although the degree of reduction of urinary sodium excretion did not correlate with that of SBP reduction. Urinary potassium and creatinine excretions were also not influenced by the hospitalization. Body weight on admission was 63.9±3.9kg, and had not significantly changed by the 2nd day. However, on the 7th day, a slight reduction of body weight was observed (62.4±4.0kg, p <0.05). The body weight decrease on either the 2nd or 7th day did not correlate with the fall in BP.

Isometric handgrip loading markedly raised SBP, DBP and PR, to a similar degree on the 1st, 2nd and 7th days of hospitalization (Fig. 2). The increase in SBP by handgrip was 45.2mmHg on the 1st day, 46.2 on the 2nd day, and 49.2 on the 7th day. The amplitude of rises in DBP was approximately 20mmHg on any day. The resting level of SBP before handgrip tended to decrease with time, there being a significant difference between the values on the 1st and 7th days of hospitalization (p <0.01). However, resting DBP and PR were not significantly altered during the course of hospitalization.

NE and E responses to isometric handgrip are shown in Fig. 3. The degree of increases in the level of plasma NE was similar for the different days, although the resting level of plasma NE tended to fall with time. A significant reduction in resting plasma NE was observed on the 7th day as compared to the findings on the day of admission (p <0.05). Plasma NE concentration before phentolamine administration, which was obtained at least 30 minutes after completion of the tilting test, also tended to decrease during the course of hospitalization (188 ±41 pg/ml on the 1st day, 141 ±24 on the 2nd day, 111 ±15 on the 7th day; p <0.05, 1st vs
Fig. 2. Changes in SBP, DBP and PR during isometric handgrip test on the 1st, 2nd and 7th day of hospitalization.
* p<0.05, † p<0.01 in comparison with the value immediately before the test. n=12. BP, blood pressure; PR, pulse rate.

7th day). The elevation of NE by handgrip correlated significantly with the handgrip induced-increased in SBP on either experimental day (p<0.05) (Fig. 4). The level of plasma NE after 3 minutes of handgrip did not change significantly during hospitalization. Plasma E was not altered by isometric muscle contraction.

Upright tilting did not influence SBP for the 15 minutes of the test, but slightly raised DBP a few minutes after the initiation of tilting on the 1st and 2nd days (Fig. 5). PR was increased to a similar degree on the 3 different days. Resting SBP and PR on admission were significantly higher than the findings on the 2nd and 7th days (p<0.05), while DBP was not altered during the 1-week period of hospitalization.

Figure 6 shows the changes in plasma NE and E during the tilting test on the 1st, 2nd and 7th days of hospitalization. Tilting increased NE on each of the 3 days to a similar degree. In contrast, the upright postural change did not increase plasma E levels on the 1st or the 2nd day. Plasma concentra-
Fig. 4. Relationships between increases in systolic blood pressure and those in plasma norepinephrine induced by handgrip loading on the 1st, 2nd and 7th days of hospitalization. 
\( \Delta \text{SBP} \), increases in systolic blood pressure; NE, increase in plasma norepinephrine.

Fig. 5. Changes in SBP, DBP and PR during upright tilting on the 1st, 2nd and 7th days of hospitalization. Arrow shows the time of the start of tilting. 
* \( p<0.05 \), † \( p<0.01 \) in comparison with the findings immediately before tilting. \( n=10 \). 
BP, blood pressure; PR, pulse rate.
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Figure 6. Changes in plasma NE and plasma E before and, 5 and 15 minutes after, the start of upright tilting.
* p<0.05, † p<0.01 in comparison with the value before the tilting. n=10.
NE, plasma norepinephrine; E, plasma epinephrine.

Figure 7. Changes in BP, DBP and PR following intravenous administrations of phentolamine (0.1mg/kg) on the 1st, 2nd and 7th days of hospitalization. Arrow shows the time of phentolamine administration.
* p<0.05, † p<0.01 in comparison with the value immediately before administration. n=12.
BP, blood pressure; PR, pulse rate.

NE, plasma norepinephrine before the tilting test on the day of admission were significantly higher than those on the 2nd and 7th days (p<0.05), while the elevated level of plasma NE induced by upright tilting was not altered by the hospitalization.

Figure 7 indicates changes in BP and PR following the intravenous administration of phentolamine on 3 different days. The fall in SBP and DBP was induced immediately after the administration, then diminished with time. The amplitude of the fall in SBP and DBP was within the range of 10–15 mmHg on either day, with little difference between the 3 days. The increase in PR induced by phentolamine was also essentially identical for all 3 days.

Handgrip did not raise PRA on any day in spite of a marked elevation in BP (Fig. 8). In contrast, PRA was raised by upright tilting to a similar extent on the different days. The resting level of PRA did not change during the time course of hospitalization. PAC taken before the handgrip test was also not influenced by 7 days of hospitalization.
Fall in BP during Hospitalization

Similarly, hospitalization did not effect the hematocrit or serum total protein until the 7th day of hospitalization.

After hospital admission there were no significant differences between group 1 and group 2 in the alteration of resting plasma CA, BP, PRA, urinary sodium excretion, urinary CA excretion and the hypotensive effect of phentolamine. Similarly, BP and CA responses to handgrip and tilting did not differ between the groups. Hypertensive complications represented by precordial voltage on ECG, CTR on chest X-ray, Keith-Wagener's grading in optic fundi and creatinine clearance also showed similarity between the two groups.

**DISCUSSION**

The present findings that the BP decreased spontaneously during hospitalization were in agreement with those in other investigations (1-7, 18-20). The degree of fall in BP was greater in SBP than in DBP. The spontaneous blood pressure fall was observed on the 2nd day of hospitalization before body weight had declined, thereby suggesting that reduction in body weight had not contribute significantly to the decrease.

A reduction in sympathetic activity may be responsible for the early phase (2nd day of hospitalization) of spontaneous blood pressure fall after admission (1, 3-7, 20). The resting level of plasma CA was not consistently altered until the 2nd day, providing evidence against the concept that the early reduction of BP may be induced by diminished function of the sympathetic nervous system, although a significant reduction of resting plasma norepinephrine before tilting test might indicate some contribution of sympathetic activity to the initial blood pressure fall induced by hospitalization. Since there are problems using the resting levels of plasma and urinary CA as an indicator of sympathetic function (8-12), we examined the reactivity to two different sympathetic stimuli and also to an alpha-adrenergic blocker. However, the responsiveness of BP and CA to the handgrip and tilting tests, and phentolamine was not altered by hospitalization, indicating little change in sympathetic function reactivity. Lack of changes in
responses of not only plasma CA but also BP and PR to these maneuvers confirm the evidence against the contribution of the sympathetic nervous system to the spontaneous fall in BP during early hospitalization. When the changes in plasma NE from the 1st to the 2nd day were compared between those patients whose SBP decreased by more than 20% and the other subjects, there was no difference between the two groups. This result is also in disagreement with the concept that reduction of sympathetic activity may explain the hypotensive response to the early stage of hospitalization.

Similarly, the late fall in BP (on the 7th day) may not have resulted mainly from a reduction in the activity of the sympathetic system. The reactivity of plasma CA, BP and PR did not differ between the 1st and 7th days. Moreover, the hypotensive effect of phentolamine did not decline on the 7th day. However, the significant fall in plasma NE in the resting condition on the 7th day, as compared to the findings on the 1st day, indicates that a part of the spontaneous fall in BP at the late stage may be induced by a diminution in sympathetic activity during the course of hospitalization. In addition, decreases in both body weight and sodium intake after admission may be partly responsible for the gradual decrease in BP. However, lack of correlation between changes in both body weight and urinary sodium excretion with the alteration of BP on the 7th day indicates that neither body weight reduction nor sodium restriction are primarily responsible for the spontaneous fall in BP on the 7th day of hospitalization.

PRA and PAC, both resting and stimulated values, did not change during hospitalization, suggesting that the renin-angiotensin-aldosterone system may not be related to the fall in BP after admission. Similarly, the hypotensive effects of hospitalization may not result from the decrease in plasma volume, since hematocrit and serum total protein were not altered during the time course of hospitalization. Other investigators (19) have reported that BP in EHT with severe hypertensive complications decreases less as a result of hospitalization than in those without complications. However, in the present study, there was no difference in the findings on ECG, chest X-ray and ocular fundi between patients with and without a spontaneous blood pressure fall during hospitalization. Older patients with EHT were also reported to have less significant decreases in BP than younger subjects following admission (7), although we failed to find any difference in age between the responding and non-responding patients.

In conclusion, in the early phase of hospitalization, none of the changes in sympathetic activity, the renin-angiotensin-aldosterone system, body weight, sodium intake and plasma volume could be demonstrated to contribute to the spontaneous fall in BP. In contrast, the hypotensive effects of hospitalization for 7 days may be related in part to the diminution of sympathetic function and also to reduction of both body weight and salt intake.

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