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Clonidine Induced Variations of Plasma Norepinephrine and Blood Pressure in Essential Hypertension

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To assess the contribution of sympathetic outflow to blood pressure in patients with essential hypertension, clonidine induced variations of plasma norepinephrine, mean arterial pressure and the pulse rate three hours after a 300 μg dose of oral clonidine, an antihypertensive agent that decreases central sympathetic outflow, were studied.

Baseline and clonidine suppressed plasma norepinephrine levels were not significantly different between the normal controls and patients with essential hypertension. The average plasma norepinephrine level, mean arterial pressure and pulse rate were significantly decreased from the baseline value in both normal control and essential hypertension ($p<.005$). The depressor response to sympathetic inhibition after clonidine were exaggerated in significant proportion in patients with essential hypertension compared to normal control group.

Our study suggests that the pressor sensitivity to norepinephrine plays more important role than sympathetic overactivity in some patients with essential hypertension.

Key Words: *Hypertension, Clonidine, Norepinephrine*

INTRODUCTION

The role of the sympathetic nervous system in essential hypertension is still poorly understood. Slightly to moderately increased levels of circulating catecholamines were thought to reflect the increased sympathetic tone in patients with essential hypertension[1~6]. Louis et. al[3]. described a direct relationship between plasma norepinephrine levels and diastolic blood pressure, and others[5,6] also reported that increased levels of the sympathetic neurotransmitter (norepinephrine) in the plasma of some patients with essential hypertension, suggesting that sympathetic overactivity involved in the pathogenesis of the blood pressure elevation, although disputed[7~10].

Clonidine lowers blood pressure in animals by decreasing the efferent cardiovascular outflow of the sympathetic neuron. This action mediated by the clonidine activation of postsynaptic α-adrenergic receptors in the cardiovascular control center to the medulla oblongata[11,12]. Clonidine, although it is not a purely sympatholytic drug, appears to exert its hypotensive effect in human at least partly by acting on the central nervous system to inhibit sympathetic outflow. Thus when administered to tetraplegic patient[13] or patients

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with orthostatic hypotension associated with degeneration of sympathetic nerve[14], clonidine has no hypotensive effect, and even raises blood pressure. Clonidine, therefore, seemed to be a reasonable choice as a drug that inhibits central sympathetic outflow.

To assess the contribution of sympatheteic outflow to blood pressure in patients with essential hypertension, we measured blood pressure and plasma norepinephrine responses to clonidine in 19 patients with essential hypertension and in 8 normotensive control subjects.

MATERIAL AND METHOD

1. Patients

We studied 19 patients with essential hypertension (mean age 53.5±7.4) and 8 normal subjects (mean age 51.9±3.6) who were admitted to Koryo General Hospital from June 1985 to December 1986.

All patients with essential hypertension were free of medications at least a month. They were recently detected patients whose blood pressure were over 140/90 mmHg and patients with previous diagnosis of essential hypertension.

A complete medical history, physical examination, blood chemistry, complete blood count, urinalysis, electrocardiogram and chest x-ray were performed. We excluded those patients with secondary hypertension, heart failure, diabetes mellitus, cardiac arrhythmia, renal failure, myocardial infarction, angina pectoris and cerebral vascular accident in this study.

2. Methods

After a light breakfast at 7:30 AM, all subjects underwent clonidine suppression testing from 9:00 AM to 12:30 PM. They remained supine for at least 10 minutes, and then blood pressure and heart rate were measured manually. 10 ml of blood was sampled through antecubital vein and collected into glass tube with 0.5 ml of sodium citrate. Twenty minutes later, the subjects took 300 μg of clonidine with water, and were remained in bed for 3 hours. Exactly 3 hours after taking the clonidine, a second blood sample was taken and blood presure and heart rate were measured again. The blood samples were spun in a refrigerated centrifuge, and the plama was transferred to glass tube containing 10 mg of cystein. The tube was stored at -4℃ until plasma norepinephrine test upto a week. Plasma was assayed for norepinephrine content using HPLC (high performance liquid chromatography)[15].

RESULTS

1. Baseline

The baseline plasma norepinephrine levels averaged 0.386±0.174 ng/ml in the normal control group, and 0.419±0.257 ng/ml in the essential hypertensive group. The distribution of values for plasma norepinephrine level in the hypertensive patients was displaced toward higher values than that of the normal control subjects, but this was considered to be not significance (Table 1).

The baseline mean arterial pressure averaged 91.2±10.2 mmHg in the normal control, and 122.5±9.9 mmHg in the essential hypertensive group. The hypertensive group had a significantly higher mean arterial pressure than the normal control group ($p<.005$) (Table 1).

The baseline mean arterial pressure was unrelated to baseline plasma norepinephrine in both groups ($r=0.09$ among the control and $r=-0.06$ among the hypertensive subjects).

The baseline pulse rate averaged 73.4±10.0 beats/min in the normal control group, and 72.5±6.9 beats/min in the essential hypertensive group. The baseline pulse rates were similar in both groups (Table 1).

2. Effects of Clonidine on Plasma Norepinephrine

Three hours after the 300 μg dose of oral clonidine, the levels of plasma norepinephrine in the normal control and essential hypertension averaged 0.179±0.155 ng/ml and 0.211±0.150 ng/ml, repectively (Table 1). Both normal control and essential hypertension had significantly decreased values of plasma norepinephrine level from the baseline ($p<.005$) (Fig. 1). The average plasma norepinephrine level after clonidine in the hypertensive group was higher than that of the control, but there was no significance.

The percent changes of the decrease in plasma norepinephrine level after clonidine from baseline (Δ%NE) averaged 59.0±29.0%(ΔNE 0.27±0.13 ng/ml) in normal control group and 45.6±23.4% (ΔNE 0.208±0.161 ng/ml) in the essential hypertensive group (Table 1). The normal control group had higher Δ%NE than the essential hypertension group, but this was no significance.

3. Effects of Clonidine on Mean Arterial Pressure

After clonidine suppression, the mean arterial

pressure averaged 80.8±10.0 mmHg in the normal control, and 104.3±13.2 mmHg in the essential hypertensive group (Table 1). Both the control and hypertenisve groups and significantly decreased values of the mean arterial pressure from the baseline ($p<.01$, $p<.005$, respectively) (Fig. 2).

Table 1. Circulatory Variables and Plasma Norepinephrine Before and 3 Hours After Clonidine Treatment in Patients with Essential Hypertension and in the Normal Control Group

	Normal control (n=8)	Hypertensive group (n=19)	P values *
Age yrs,	51.9 ± 3.6†	53.5 ± 7.4	NS
Mean aterial pressure, mmHg			
Before	91.2 ± 10.2	122.5 ± 9.9	<0.005
After	80.8 ± 10.0	104.3 ± 13.2	<0.005
Change	10.4 ± 7.9	18.2 ± 12.0	NS
% change	11.2 ± 8.6	14.4 ± 9.3	NS
Heart rate, beats/min			
Before	73.4 ± 10.0	72.5 ± 6.9	NS
After	63.3 ± 8.2	64.1 ± 5.1	NS
Change	10.1 ± 4.2	8.4 ± 4.5	NS
% change	13.5 ± 4.2	11.3 ± 5.7	NS
Norepinephrine, ng/ml			
Before	0.386 ± 0.174	0.419 ± 0.257	NS
After	0.179 ± 0.155	0.211 ± 0.150	NS
Change	0.207 ± 0.130	0.209 ± 0.161	NS
% change	56.0 ± 29.0	45.6 ± 23.4	NS

* P values are for the difference between the hypertensive and normal control groups.
NS = non-significant difference
† All mean values expressed ± 1SD.

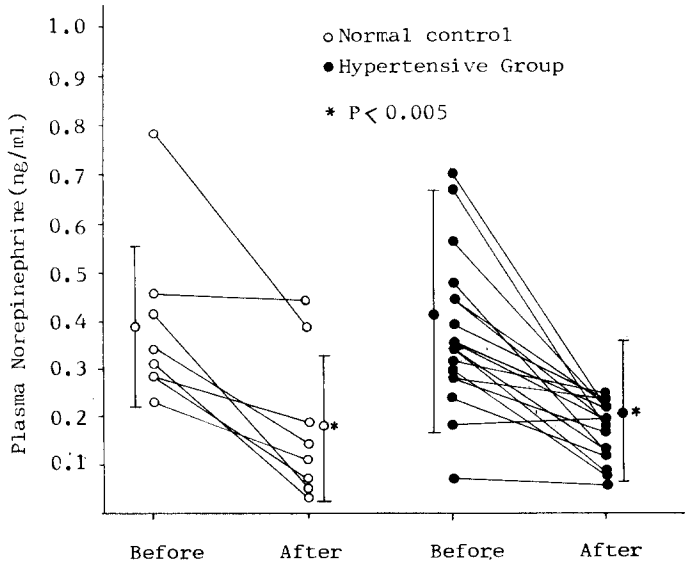

Fig. 1. *Plasma norepinephrine variations in normal control and essential hypertension subjects, before and after clonidine.*

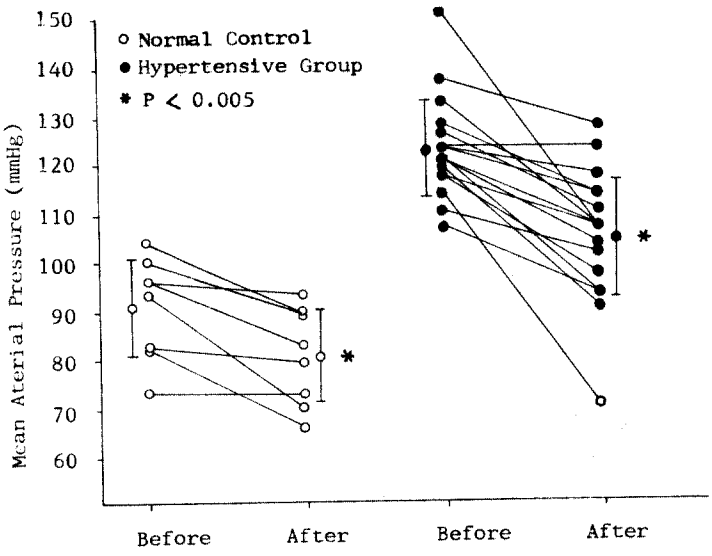

Fig. 2. *Mean aterial pressure in normal control and essential hypertension subjects, before and after clonidien.*

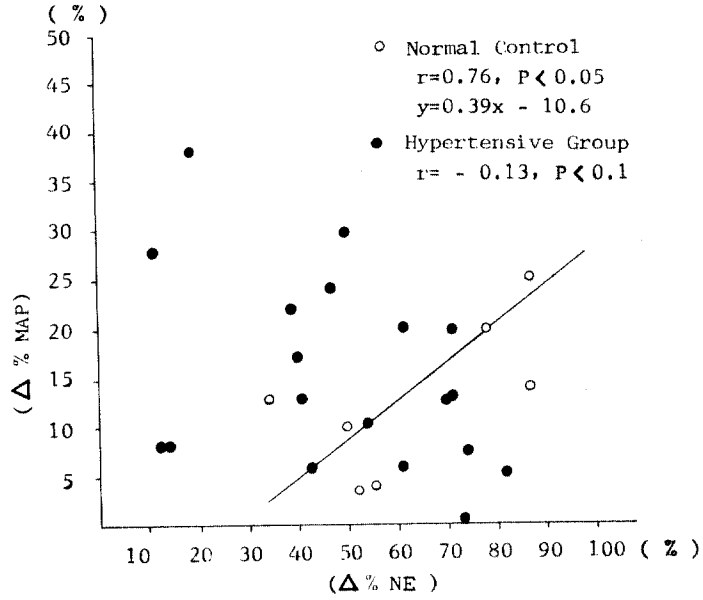

Fig. 3. *Decreased percentage in mean aterial pressure (Δ % MAP) as a function of decreased percentage in plasma norepinephrine (Δ %NE). The line is the linear regression line for normal control group.*

There was significant difference in mean arterial pressure after clonidine between normal control and hypertensive group ($p < .005$).

The percent changes of the decrease in the mean arterial pressure from the baseline (Δ% MAP) averaged 11.2±8.6% (ΔMAP 10.4±7.9 mmHg) in normal control, and 14.4±9.3% (ΔMAP 18.2±12.0 mmHg) in hypertensive group (Table 1). The hypertensive group tended to have a higher Δ %MAP than the normal control group, but there

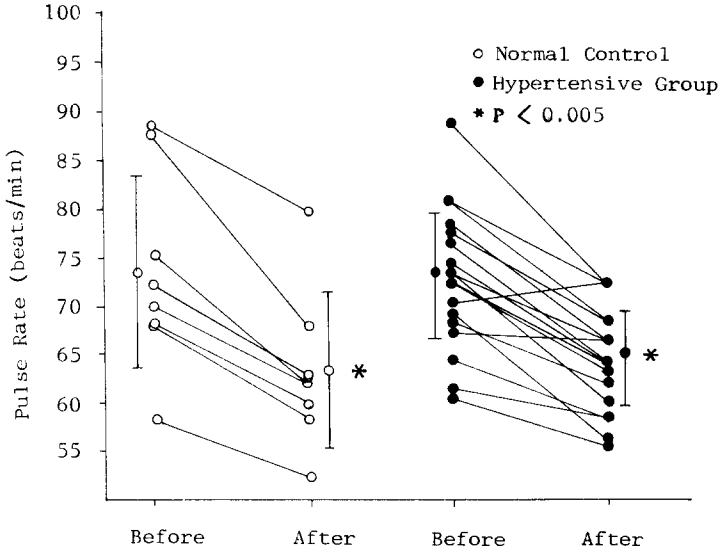

Fig. 4. *Pulse rate in normal control and essential hypertension subjects, before and after clonidine.*

was no significance. The Δ%MAP were closely related to Δ%NE in normal control group ($r=0.76$, $p<.05$), but not in the hyperensive group ($r=-0.13$, $p>0.1$) (Fig. 3).

4. Effects of Clonidine on Pulse Rate

The average pulse rate after clonidine was 63.3±8.2 beats/min in the normal control, and 64.1±5.1 beats/min in the essential hypertension (Table 1). These pulse rate were significanlty decreased from baseline in both group ($p<.005$) (Fig. 4).

The percent changes of pulse rate after clonidine (Δ%PR) averaged 13.5±4.2% (ΔPR 10.1±4.2 beats/min) in normal control, and 11.3±5.7% (ΔPR 8.4±4.5 beats/min) in the essential hypertension (Table 1). These changes were similar in each group.

5. %MAP: %NE Ratio

The Δ%MAP:%NE ratio in normal control averaged 0.18±0.12 (ΔMAP:ΔNE ratio 41±42), and 0.32±0.58 (ΔMAP:ΔNE ratio 164±123) in hypertensive group. The Δ%MAP: Δ%NE ratio of the hypertensive group tended to be higher than that ratio of the normal control, but there was no statistical significance. 7 of 19 (36.8%) patients with essential hypertension had a ratio of Δ%MAP: Δ%NE exceeding 2SD. Their baseline plasma norepinephrine levels averaged 0.320±0.007 ng/ml, which was similar to the value of normal control group.

DISCUSION

The sympathetic nervous system plays an important role in the body's sodium state, the renin-angiotensin-aldosterone system, and some other components in the regulation of blood pressure. Whether and to what extent this complex neurohumoral axis plays a role in the pathogenesis of essential hypertension is still unclear. Several authors reported increased plasma or urinary norepinephrine[1~6] or epinephrine[16] levels in some patients with essential hypertension, but others found mostly normal values[7~10].

We observed that the average baseline values for plasma norepinephrine level tended to be higher in the essential hypertenison than that of the normal control group. However, the average mean arterial pressure was significantly higher in the essential hypertension than that of the normal control group. These findings agree with the findings of others[7~10,20]. But Goldstein et al[17]. reported that both the mean arterial pressure and plasma norepinephrine levels were significantly higher in the hypertensive group than those of the control group. The baseline mean arterial pressure were unrelated to the baseline level of plasma norepinephrine in both the control and hypertensive groups in this study. Our findings agree with the findings of Goldstein et al[17]. and Philipp et al[18].

Three hours after the 300 μg dose of oral

clonidine, we observed that the average value of plasma norepinephrine, mean arterial pressure and pulse rate were significantly decreased from those of baseline in both the hypertensive and control group, as reported by Goldstein et al[17], and Campese et al[19].

This study showed significant clonidine induced decreases in plasma norepinphrine level and corresponding changes in the mean arterial pressure and the pulse rate of both the control and hypertensive group, suggesting that the mechanism of sympathetic outflow inhibition after clonidine administration.

But catecholamine measurement alone may not allow us to understand of sympathetic role on the mechanism of hypertension, since there are several other vasoactive factors such as renin-angiotensin-aldosterone system[21], the body sodium volume state[22], humoral depressor agent (prostaglnadin, bradykinin)[23], and intrinsic alteration of the blood vessel wall[24,25]. Campese et al[19], reported that inhibition of the sympathetic nervous system by clonidine changed significantly in exchangable body sodium and blood volume, which was associated with plasma renin activity, However, findings of Weidmann et al[20], were contradictory to the above findings. We did not evaluate those factors in our study.

To analyze the relationship between plasma norepinephrine and mean arterial pressure more quantitavely, we calculated the ratio between the clonidine induced variations in plasma norepinephrine (ΔNE ng/ml) and corresponding changes in mean arterial pressure (ΔMAP mmHg) and percentage variations (Δ%MAP/Δ%NE). We observed that Δ%MAP: Δ%NE ratio was prone to be higher in hypertensive group than that of normal control group. Since Δ%MAP: Δ%NE ratio may reflect the vascular sensitivity to endogenous norepinephrine, the presenting findings suggest that the depressor response to sympathetic inhibition by clonidine (the pressor sensitivity to norepinephrine) has tendency to be exaggerated in the essential hypertension group.

The individual Δ%MAP was closely related to Δ%NE in the normal control group, but not in the essential hypertension group. We believe these results may be due to altering the pressure sensitivity to norepinephrine in some patients with essential hypertension. We found that 7 of 19 patients with essential hypertension had a ratio of Δ%MAP: Δ%NE exceeding 2 SD from the normal subject, but none of normal subject had that ratio exceeding 2 SD. Their baseline plasma norepinephrine level was similar to that the normal control group. These findings suggest that a significant proportion in the essential hypertension group had exaggerated response to clonidine induced plasma norepinephrine variation when compared to normal control group. This results are similar to the results of Goldstein et al[17], and Weidmann et al[20].

Summarizing this study, first, both the normal control and essential hypertension groups had significant decreases in plasma norepinephrine and a corresponding decrease in mean arterial pressure and pulse rate due to a decreased sympathetic outflow after clonidine. Second, the average of the mean arterial pressure was significantly different between the normal control and essential hypertension groups, before and after clonidine, but the plasma norepinephrine level was not. Third, the depressor responses to sympathetic inhibition by clonidine were exaggerated in the significant proportion of patients with essential hypertension compared to normal control group.

Thus our study suggests that an increased pressure sensitivity to norepinephrine plays a pathophysiologic role in some patients with essenetial hypertension rather than sympathectic overactivity.

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