Effect of Clonidine on Blood Pressure in Chronic One-Kidney, One-Clip and Two-Kidney, One-Clip Hypertensive Rats*

Tatsuo Kokubu, M.D.; Haruhisa Hashimoto, M.D.; and Kunio Hitooda, M.D.

Oral administration of clonidine lowered the high blood pressure in two-kidney, one-clip hypertensive rats in chronic stage (three to four months), but not in one-kidney, one-clip hypertensive rats. This reduction of blood pressure was well correlated with decrease in plasma renin concentration, but not with decrease in urinary noradrenaline excretion. These results suggest that the reduction of blood pressure in two-kidney, one-clip hypertensive rats may be due to reduced renin release through the action of clonidine, while in one-kidney, one-clip hypertensive rats the sympathetic nervous activity may play little or no role in the maintenance of high blood pressure.

The blood pressure-regulating mechanisms of one-kidney, one-clip and two-kidney, one-clip hypertensive animals are considered to be different. Gavras and Liang have shown that stimulated sympathetic nervous system due to increase in plasma angiotensin II level contributes to the high blood pressure in acute two-kidney, one-clip hypertensive dogs. However, the role of sympathetic nervous system in chronic one-kidney, one-clip and two-kidney, one-clip hypertensive animals is unknown. The hypotensive action of clonidine is generally considered to be a stimulation of central α-adrenergic receptors, causing a reduction in peripheral sympathetic outflow. We investigated the role of sympathetic nervous system in chronic one-kidney, one-clip and two-kidney, one-clip hypertensive rats utilizing clonidine.

Materials and Methods

Six normal, 12 one-kidney, one-clip, and 12 two-kidney, one-clip hypertensive rats (female Wistar strain, weighing 220 to 270 g) were used in this study. One-kidney, one-clip and two-kidney, one-clip hypertensive rats were prepared by the method described previously. All rats were maintained on regular rat chow (Oriental Yeast Co.), and water ad libitum. Twelve to 16 weeks after the operation, clonidine (50 µg/kg/day for seven days) was orally administered to

*From the 2nd Department of Internal Medicine, Ehime University School of Medicine, Ehime, Japan.
Reprint requests: Dr. Kokubu, 2nd Department of Internal Medicine, Ehime University School of Medicine, Onsen-gun, Ehime 791-02, Japan
Results were expressed as mean ± SEM. Statistical analysis was performed with an analysis of variance or paired t test for comparison within groups and Student’s t test for comparison between groups.

RESULTS AND DISCUSSION

Figure 1 shows the change in systolic blood pressure. Clonidine lowered systolic blood pressure in chronic two-kidney, one-clip hypertensive rats, but did not lower systolic blood pressure in chronic one-kidney, one-clip hypertensive rats or in normotensive rats. Pretreatment values of heart rate were not significantly different in three groups (two-kidney, one-clip hypertensive rats, 389.3 ± 12.1; one-kidney, one-clip hypertensive rats, 394.9 ± 8.0; normotensive rats, 382.0 ± 9.6 beats/min), and similar bradycardia was observed after clonidine administration. The mean reduction of heart rate in each group was about 40 to 65 beats/min, being not significant between groups. Clonidine sharply decreased urinary noradrenaline excretion in three groups, and the significant reduction was observed throughout the experimental period in each group (Fig 2). Urinary noradrenaline excretion decreased by 45 percent in two-kidney, one-clip hypertensive rats, by 65 percent in one-kidney, one-clip hypertensive rats, and by 48 percent in normotensive rats on the first day compared with the pretreatment values. Pretreatment values of urinary adrenaline excretion were not significantly different (two-kidney, one-clip hypertensive rats, 15.2 ± 2.0; one-kidney, one-clip hypertensive rats, 13.7 ± 1.3; normotensive rats, 14.1 ± 1.4 ng/mg Cr), and no significant change was observed after clonidine in three groups. Plasma renin concentration significantly decreased after clonidine in chronic two-kidney, one-clip hypertensive rats (52.3 ± 7.3 before and 22.6 ± 3.6 ng Al/mI/hr after) and in normotensive rats (36.8 ± 5.5 before and 28.0 ± 2.4 ng Al/mI/hr after). In contrast, in chronic one-kidney, one-clip hypertensive rats, plasma renin concentration was essentially unchanged (21.7 ± 3.4 before and 23.2 ± 4.4 ng Al/mI/hr after). In chronic two-kidney, one-clip hypertensive rats, fall in systolic blood pressure was well correlated (Fig 3) with decrease in plasma renin concentration (r = 0.78, n = 12; p < 0.01), but not with decrease in urinary noradrenaline excretion (r = 0.12, n = 12; NS).

These results suggest that decreases in plasma renin concentration mediated by reduced sympathetic outflow mainly relate to the hypotensive action of clonidine in chronic two-kidney, one-clip hypertensive rats. Contrary, in chronic one-kidney, one-clip hypertensive rats, clonidine produced no depressor effect, suggesting that the sympathetic nervous system in this model plays little or no role in the maintenance of high blood pressure.

REFERENCES


Cardiovascular Hemodynamic Interactions between Clonidine and Minoxidil in Hypertensive Patients*

Manuel Velasco, M.D.; Honorio Silva, M.D.; Julio Morillo, M.D.; Adalberto Urbina-Quintana, M.D.; Otto Hernandez-Pieretti, M.D.; and Miriam Angeli-Greaves, M.D., Ph.D.

The systemic, cardiovascular hemodynamic and biochemical interactions between clonidine and minoxidil were studied in ten patients with refractory and/or accelerated hypertension. Clonidine in oral doses of 150 to 900 μg/day decreased mean blood pressure (MAP) 18.6 mm Hg (p < 0.01), average heart rate (HR) 16.4 bpm (p < 0.01), limb blood flow 1.63 ml/100 g min (p < 0.05), plasma renin activity (PRA) 1.13 ng/ml/hr (p < 0.025), and urinary excretion 16.45 mg/hr (p < 0.05). Clonidine increased the prejection period index (PEPI) 12.4 msec (p < 0.01), but did not alter cardiac index (CI), total peripheral resistance index (TPRI), limb vascular resistance nor dopamine β-hydroxylase activity. When minoxidil in oral doses of 5 to 22.5 mg was added, a further decrease in MAP of 24.2 mm Hg (p < 0.01) was observed; PEPI decreased 20.6 msec (p < 0.01), limb blood flow decreased 13.2 mm Hg/min 100

*From the Clinical Pharmacology Section, Department of Pharmacology and Division of Cardiology, Vargas Medical School, Central University of Venezuela, Caracas, Venezuela.

Reprint requests: Dr. Velasco, Apartado Postal 76333, Caracas 1070A, Venezuela