THE ROLE OF RENAL HEMODYNAMICS IN THE ANTIHYPERTENSIVE ACTION OF MEPIRODIPINE, A NEW CALCIUM ANTAGONIST

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To evaluate the role of regional hemodynamics in the anti-hypertensive effect of mepirodipine, a new dihydropyridine-derivative calcium antagonist, we measured systemic, renal, hepatic, and forearm hemodynamics in 10 patients with essential hypertension treated with mepirodipine (15 mg/day) for 4 weeks. After the administration of mepirodipine, a significant decline in mean blood pressure ($-13.8 \pm 2.3\%$, $p < 0.01$) accompanied by a decrease in systemic vascular resistance ($-21.1 \pm 2.6\%$, $p < 0.01$) was observed. Although forearm vascular resistance did not change significantly, both renal ($-19.2 \pm 6.7\%$, $p < 0.01$) and hepatic vascular resistance ($-17.6 \pm 3.8\%$, $p < 0.01$) decreased considerably. The decrements of mean blood pressure with mepirodipine did not correlate with those of hepatic or forearm vascular resistance but correlated positively with those of renal vascular resistance ($r = 0.699$, $p < 0.05$). Moreover, the increment of renal blood flow with mepirodipine was negatively correlated with the pretreatment level of renal blood flow ($r = -0.670$, $p < 0.05$); renal blood flow increased to a greater extent in patients with lower pretreatment renal blood flow. These findings suggest that the oral administration of mepirodipine in patients with essential hypertension can produce selective vasodilation in the renal vasculature, which may play an important role in the relatively long-term antihypertensive effect of this drug. (*Jpn Circ J* 1992; 56: 21–26)

AN increase in total peripheral vascular resistance is a well-documented feature in established essential hypertension! The vasodilators decrease blood pressure associated with decreased total peripheral vascular resistance. However, the decrease in vascular resistance is not homogeneous among individual vascular beds; renal vascular resistance decreases but forearm vascular resistance does not. Therefore, the measurement of overall peripheral vascular resistance alone is not enough to estimate the con-

tribution of regional hemodynamics to the control of systemic blood pressure and the hemodynamic action of antihypertensive drugs?

In general, the kidneys are engaged in the long-term regulation of arterial blood pressure, and renal hemodynamics play an important role in the development and maintenance of high blood pressure^{3–5}. Since renal vasoconstriction is often seen in patients with essential hypertension, it could be expected that vasodilators such as calcium channel blockers, which decrease renal vascular resistance, might be beneficial in the treatment of essential hypertension.

Recently, a novel dihydropyridine calcium

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TABLE I CLINICAL AND LABORATORY FINDINGS

	Before*	After	P Value
Body weight (kg)	63±6	63±7	NS
Mean BP (mmHg)	119±10	102±7	<0.01
Systolic BP (mmHg)	160±11	137±13	<0.01
Diastolic BP (mmHg)	106±4	88±6	<0.01
CI (l/min/m ²)	2.35±0.38	2.56±0.38	<0.01
HR (bpm)	61±7	61±3	NS
SI (ml/m ²)	39.0±9.0	42.0±6.3	NS
SVR (dynes·sec·cm ⁻⁵ ·m ²)	4098±576	3213±452	<0.01
FBF (ml/100 ml/min)	3.69±1.31	3.80±1.62	NS
FVR (units)	41.6±35.3	32.9±17.6	NS
RPF (ml/min)	624.6±126.3	648±99.4	NS
RBF (ml/min)	1074.1±232.5	1120.6±184.0	NS
RVR (units)	11.7±3.0	9.4±2.3	<0.01
HBf (ml/min)	1565±600	1828±1147	NS
HVR (units)	8.4±2.4	6.8±2.4	<0.01
PRA (ng/ml/hr)	1.01±0.73	1.17±0.68	NS
Plasma aldosterone (pg/ml)	83±32	78±31	NS
Plasma norepinephrine (pg/ml)	170±83	241±114	<0.05
Plasma epinephrine (pg/ml)	34±14	24±16	NS

Values are given as mean ± SD.

* Before=before treatment with mepirodipine, After=4 weeks after mepirodipine administration. P, blood pressure; CI, cardiac index; HR, heart rate; SI, stroke index; SVR, systemic vascular resistance; FBF, forearm blood flow; FVR, forearm blood flow; FVR, forearm vascular resistance; RPF, renal plasma flow; RBF, renal blood flow; RVR, renal vascular resistance; HBf, hepatic blood flow; HVR, hepatic vascular resistance; PRA, plasma renin activity. P value was analyzed by paired t-test

antagonist, mepirodipine hydrochloride, which is a derivative of nicardipine and a single stereoisomer (+)-(S)-(S) conformation, has been developed⁶ It showed a potent long-lasting vasodilator effect in the canine isolated, blood-perfused heart preparation in comparison with nifedipine and nicardipine⁷

In the present study we have investigated the effect of mepirodipine on not only central hemodynamics but also renal, hepatic and forearm hemodynamics. Moreover, we studied the relationship between the changes in renal hemodynamics and the other hemodynamic changes and decrease in blood pressure.

MATERIALS AND METHODS

Patients: Ten patients (all men) with mild to moderate essential hypertension were included in the study. All patients had a supine diastolic pressure consistently above 90 mmHg but under 120 mmHg. Detailed clinical evaluation did not show a secondary

cause of hypertension. Each subject provided informed consent to a protocol that had been approved by our institution's review committee.

Protocol: All antihypertensive medication was discontinued for at least 2 weeks prior to the study. Systemic and forearm hemodynamic measurements were repeated until 3 similar determinations, 15 min apart, demonstrated stability. The mean of these determinations of both systemic and forearm hemodynamics was calculated. Patients received 15 mg/day of mepirodipine on an out-patient basis, for 4 weeks. On day 29 of mepirodipine treatment, the patients were given 15 mg of mepirodipine in the morning in the laboratory, and their hemodynamic data were obtained approximately 60 to 75 min later.

Systemic hemodynamics: Systemic blood pressure was measured by sphygmomanometer. Cardiac output was determined by a dye dilution method (indocyanine green)⁸ Measurements were made after the patients had rested in the supine position for at least

Fig.1. Changes in cardiovascular hemodynamics with mepirodipine in 10 hypertensive patients. Mean blood pressure (MBP), heart rate (HR), cardiac index (CI) and systemic vascular resistance (SVR) before and after 4 weeks of mepirodipine administration.

Fig.2. Changes in renal hemodynamics with mepirodipine in 10 hypertensive patients. Renal blood flow (RBF) and renal vascular resistance (RVR) before and after 4 weeks of mepirodipine administration.

30 min. Systemic vascular resistance (SVR) was calculated as the ratio of mean blood pressure to cardiac output and corrected for body surface area, expressed in dynes·sec·cm⁻⁵·m².

Forearm hemodynamics: Forearm blood flow (FBF) was measured by plethysmogra-

Fig.3. Relationship between changes in renal vascular resistance (% RVR) and those in mean blood pressure (% MBP) with mepirodipine in 10 hypertensive patients.

Fig.4. Relationship between pretreatment levels of renal blood flow (RBF) and changes in renal blood flow (% RBF) with mepirodipine

phy, as previously described⁸. FBF was calculated from the change in forearm circumference during acute venous occlusion with 40 mmHg pressure and was expressed as milliliters per 100 ml forearm volume per min. Forearm vascular resistance (FVR) was calculated as the ratio of mean blood pressure to FBF, expressed in units of mmHg/ml/100 ml/min.

Renal hemodynamics: Renal blood flow was determined by PAH (para-aminohippuric acid) clearance without urine collection⁹. Patients were given a bolus injection of 8 mg/kg of PAH, and subsequently received an intravenous infusion (12 mg/min) with a constant infusion pump. Zero time for blood samples started at the end of the bolus injection. Blood samples were obtained at 30, 45, and 60 min for plasma PAH determinations. Analytical errors did not exceed 3%. Renal

plasma flow was calculated as proposed by Sapirstein et al.¹⁰ Renal vascular resistance (RVR) was calculated as the ratio of mean blood pressure to renal blood flow, expressed in units of $\text{dynes}\cdot\text{sec}\cdot\text{cm}^{-5}\cdot\text{m}^2$.

Hepatic hemodynamics: Hepatic blood flow was estimated by injection of 50 mg of indocyanine green into the venous line and drawing blood at 4, 6, 8, 10, 12, 14, 16, 18 and 20 min after the injection. Fractional clearance was calculated using the method of the least squares for the natural logarithmic values of the serum concentration.¹¹ Subsequently, the fractional clearance was multiplied by the plasma volume to obtain plasma clearance of indocyanine green. This value was corrected for the body surface area and hematocrit to obtain the total blood clearance.

Hormonal factors: Before and after mepirodipine treatment, blood for hormonal determinations was drawn from the patients in the supine position, and the plasma was frozen at -40°C . Plasma renin activity (PRA) was determined by radioimmunoassay of angiotensin I.¹² Plasma aldosterone concentration was measured by radioimmunoassay, with the use of a commercial kit (CEA-IRE-SORIN).⁸ Plasma norepinephrine and epinephrine were measured by the method of Schwedt,¹³ using high-pressure liquid chromatography combined with an automatic fluorimetric detector.

Statistics: Numerical results are expressed as mean $\pm$ standard error of the mean. Statistical analysis of the data was performed by means of paired and unpaired t-tests and regression analysis according to standard procedures. Difference at a 5% level ($p < 0.05$) was considered significant.

RESULTS

The patients recruited were 44 ± 9 years of age (Range 26 to 57 years). Mean blood pressure decreased significantly ($-13.8 \pm 2.3\%$, $p < 0.01$), from 119 ± 10 to 102 ± 7 mmHg with mepirodipine (Table I & Fig. 1). Declines in both systolic ($-22.6 \pm 4.2\%$, $p < 0.01$) and diastolic ($-17.4 \pm 4.8\%$, $p < 0.01$) blood pressure were statistically significant. Body weight remained unchanged (Table I). SVR fell substantially ($p < 0.01$), from 4098 ± 576 to 3213 ± 452 $\text{dynes}\cdot\text{sec}\cdot\text{cm}^{-5}\cdot\text{m}^2$ (Table I & Fig. 1).

cardiac output increased significantly ($9.6 \pm 2.6\%$, $p < 0.05$); Stroke index was slightly increased (42.0 ± 6.3 vs 39.0 ± 0.9 ml/m^2 , $0.05 < p < 0.1$), but heart rate was not significantly changed. There was a significant ($r = 0.724$, $p < 0.05$) relationship between changes in mean blood pressure and those in SVR. Neither FBF nor FVR changed with the administration of mepirodipine (Table I). Hepatic vascular resistance (HVR) decreased significantly ($p < 0.01$), from 8.4 ± 2.4 to 6.8 ± 2.4 units (Table I). RVR decreased significantly ($p < 0.01$), from 11.7 ± 9.4 to 9.4 ± 2.3 units (Table I & Fig. 2). There were no significant differences between the percent age decrements of RVR ($-17.6 \pm 3.8\%$, $p < 0.01$) and those of HVR ($-19.2 \pm 6.7\%$, $p < 0.01$). However the decline in RVR correlated significantly ($r = 0.699$, $p < 0.05$) with that in mean blood pressure (Fig. 3), although the change in HVR did not significantly correlate with that in mean blood pressure ($r = 0.495$, NS). Moreover, the pretreatment levels of renal blood flow correlated negatively ($r = -0.670$, $p < 0.05$) with the changes in renal blood flow (Fig. 4).

With the mepirodipine treatment plasma norepinephrine was significantly ($p < 0.05$) elevated, but plasma epinephrine was unchanged.

DISCUSSION

Our first relevant observation was that the 4-week-treatment with mepirodipine, decreased blood pressure consistently with a fall in SVR in patients with mild to moderate hypertension. It suggests that mepirodipine, which acts as a vasodilator, is an efficacious therapy for hypertension. The main aim of the present study was to clarify the role of regional hemodynamics in the antihypertensive effect of calcium antagonist. Mepirodipine treatment caused a heterogeneous pattern of vasodilation; substantial reduction of RVR and HVR but no vasodilation in the forearm vascular beds. Several investigators have noted the occurrence of this peculiar pattern of vasodilation with the other calcium antagonists in hypertensive man and rats.¹⁴⁻¹⁹ It suggests that calcium antagonists produce vasodilation on a selective basis.

FVR did not decrease with mepirodipine. Similarly, some investigators reported that the changes in limb vascular resistances with calcium antagonists did not parallel those in SVR.²⁰ It is well known that the sympathetic nervous system plays an important role in the control of limb vascular tone. Therefore, unchanged FVR observed in the mepirodipine-treated patients could be attributable to the enhanced sympathetic activity, which might result from reflex neurogenic stimulation by the fall in blood pressure, since plasma norepinephrine increased significantly after the administration of mepirodipine.

Several investigators have demonstrated that renal hemodynamics may play an important role in the antihypertensive effect of vasodilators such as angiotensin converting enzyme inhibitors, α_1 -blockers and calcium antagonists. In contrast to FVR, in the present study RVR and HVR decreased markedly with mepirodipine. Of course, reduction of RVR and HVR might contribute partly to the reduction of SVR. However, it should be noted that there was a significant correlation of the decrease in mean blood pressure to that in RVR but not to that in HVR; patients with lower RBF had a greater incremental response of RBF to mepirodipine. It suggests that mepirodipine-induced increases in renal blood flow, which largely depend upon the preexisting vascular tone, may play a role in its hypotensive action.

Indeed, vasodilators are ideal drugs for the treatment of hypertension, since hypertension is usually associated with increased peripheral vascular resistance. However, conventional antihypertensive drugs such as alpha-methyl dopa, diazoxide and hydralazine often cause sodium retention, leading to the attenuation of the hypotensive effect of these drugs. In contrast, extracellular fluid volume and plasma volume did not increase after the long-term treatment of calcium antagonists.²¹ In fact, in the present study the mepirodipine-treated patients had no significant increase in body weight, suggesting no apparent fluid retention. It was supported by the experiments showing that the injection of mepirodipine into the renal artery in dogs caused marked diuresis and natriuresis associated with selective arteriolar dilatation in the kidneys.^{22,23} Thus, there

is some possibility that the absence of sodium retention, which might be due partly to selective renal vasodilation, could contribute to a potent and long-lasting reduction in blood pressure with mepirodipine therapy.

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