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Hemodynamic and Neurohumoral Effects of Moxonidine in Patients with Essential Hypertension

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Summary. **The hemodynamic and neurohumoral effects of a single oral dose (0.4 mg) of the novel centrally acting antihypertensive agent moxonidine were investigated over 4 hours in ten patients with essential hypertension (WHO I–II). Pulmonary pressure indices and cardiac output were determined both at rest and during ergometric exercise by means of Swan-Ganz catheterization. Blood pressure was measured by sphygmomanometry and in the brachial artery. Moxonidine induced a significant fall in blood pressure over the 4-hour observation period from 176/105 mmHg to 158/95 mmHg ($p < 0.01$), accompanied by a decrease in systemic vascular resistance from 1695 to 1427 dyn.sec/cm^5 ($p < 0.01$). Cardiac output remained unchanged, while heart rate increased slightly from 69 to 75 beats/min ($p < 0.01$). No significant changes were recorded for either pulmonary artery pressure or pulmonary vascular resistance. Plasma levels of noradrenaline (337 vs. 224 pg/ml) and renin (2.6 vs 2.0 ng/ml/hr) activity fell significantly after moxonidine ($p < 0.05$), both at rest and during exercise. Although aldosterone plasma levels fell slightly, levels of angiotensin II and ANF remained unchanged.**

Moxonidine has favorable effects on hemodynamics and the neurohumoral system in patients with essential hypertension and is well tolerated at the dose administered.

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Key Words. **moxonidine, hemodynamics, neurohumoral system, essential hypertension**

Moxonidine, 2-methyl-4-chloro-5(2-imidazoline-2-ylamino)-6-meth-oxy-pyrimidine, is a new antihypertensive agent that lowers elevated blood pressure by selective and specific stimulation of centrally located presynaptic α_2 receptors. This stimulation of presynaptic α_2 receptors leads to an inhibition of the vasomotor center in the brainstem and to a decrease in central and peripheral sympathetic activity [1,2].

Moxonidine differs from other α_2 agonists in the following properties: a high α_2/α_1 binding ratio, high selectivity for presynaptic α_2 receptors, and full intrinsic activity at the α_2 receptor site [3,4]. Furthermore, recent investigations have shown moxonidine to bind selectively to the imidazole receptor with about 100 times higher affinity at this than at α_2 sites [5]. It has been postulated that these differences may be responsible for the favorable hemodynamic profile of moxonidine observed in animal studies [2,6].

The antihypertensive effects of moxonidine following oral administration are well documented [7–9]. However, the hemodynamic mechanism by which this effect might be achieved in humans has not yet been investigated. The objective of this study was therefore to determine the effects of moxonidine on the hemodynamics and hormones involved in blood pressure regulation, both at rest and during exercise, in hypertensive patients.

Methods

Study population

Ten male hypertensive patients between 38 and 65 years of age (mean 52 years) took part in this study (Table 1). Prestudy blood pressure values varied between 150/95 mmHg and 230/115 mmHg, with an average of 176/105 mmHg; mean heart rate ranged from 58 to 76 beats/min, with a mean of 69 beats/min. Cardiac output and mean pulmonary artery pressures were normal. Four patients showed by ECG and ECHO evidence of left ventricular hypertrophy (Sokolow Lyon index > 3.5 mV; IVS > 12 mm; LVPW > 11 mm).

The study was approved by the Freiburger Ethik-Kommission in Germany, and all patients had given their informed consent prior to the beginning of the study and had been informed of the methods to be utilized and possible risks.

Study design

This study was designed as a single-center, open-labeled uncontrolled study of the hemodynamic effects

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Table 1. *Baseline clinical and hemodynamic characteristics of ten patients with mild to moderate hypertension*

Patient	Age (years)	Height (cm)	Weight (kg)	HR (min^{-1})	$BP_{syst/diast}$ (mmHg)	LV hypertrophy	Pap_m (mmHg)	CO (1/min)	SVR (dyn.sec cm^{-5})
1	56	183	93.0	75	230/115	Yes	18	5.9	2079
2	55	176	88.5	68	160/105	No	15	7.2	1333
3	46	172	82.2	58	190/110	No	16	8.0	1317
4	47	172	78.2	74	160/100	No	17	5.8	1632
5	60	180	106.7	75	150/95	No	22	6.8	1333
6	65	170	75.0	76	185/105	Yes	18	4.5	2400
7	38	174	86.3	68	155/100	No	17	5.6	1714
8	56	165	71.0	60	160/100	No	13	5.7	1661
9	54	175	95.5	64	180/115	Yes	15	7.3	1589
10	39	178	90.0	68	165/110	Yes	14	5.5	1891

HR = heart rate; PAP_m = mean pulmonary artery pressure; BP = blood pressure; CO = cardiac output; LV = left ventricular; SVR = systemic vascular resistance.

of moxonidine after single oral administration of a 0.4-mg tablet in patients with mild to moderate essential hypertension. All medication was withdrawn at least 7 days prior to the pretreatment assessment. The patients had been requested not to eat or drink anything before coming to the laboratory on the experimental day.

All hemodynamic variables were first recorded in resting patients. The patients then underwent supine bicycle ergometry starting at a load of 50 W, which could be increased to 100 W. Hemodynamic measurements were made at the fifth minute of each work level. Immediately after predrug assessments, a single 0.4-mg tablet of moxonidine was administered, after which hemodynamic recordings were repeated at 1, 2, 3, and 4 hours, both at rest and during exercise. Heparinized blood samples for the determination of moxonidine plasma concentrations were taken predrug and 1, 2, 3, and 4 hours after drug intake. Before and 4 hours postdrug following the hemodynamic recordings, blood samples were taken for the determination of noradrenaline, adrenaline, plasma renin activity, angiotensin II, aldosterone, and ANF.

Measurements

Blood pressure was measured in the supine patient by sphygmomanometry (triplicate) and intraarterially in the brachial artery. Pulmonary artery pressure was recorded by means of a 5F Swan-Ganz balloon catheter, which was inserted through the cubital vein and positioned in the pulmonary artery (PA-PCW-position), after measuring the right atrial and ventricular pressures. Cardiac output was determined according to the Fick principle. Both heart rate and the electrocardiogram were monitored constantly throughout the investigation.

Plasma catecholamines were assessed by means of HPLC [10]. Plasma renin activity (Travenol, I-125 kit), angiotensin II (Biermann, I-125 kit), aldosterone (Diagnostic Products Co., I-125 kit), and atrial natriuretic factor (ANF; IBL, I-125 kit) were determined by radioimmunoassay methods. Mean artery pressure, stroke volume, cardiac index, systemic vascular resistance, and pulmonary vascular resistance were calculated using standard formulae.

Analysis of moxonidine in plasma was performed using a validated gas chromatographic/mass spectrometric assay method [11].

Statistical methods

All values are expressed as mean ± standard deviation. The variables measured under exercise were evaluated at the highest workload, which was constant for each patient.

For the differences between postdrug and predrug values, two-sided p values of the Wilcoxon signed rank test were computed using the standard normal approximation without continuity correction. These p values are not based on statistical tests of the overall significance, but are rather descriptive measures for the change after drug administration.

Results

Heart rate

The mean heart rate at rest decreased slightly after the first hour. At all other times, heart rate was elevated: after 4 hours by approximately 6 beats/min ($p < 0.01$; Table 2, Figure 1). During exercise the mean heart rate was also increased by 4 (1 hour), 6 (2 hours), 8 (3 hours), and 12 beats/min (4 hours), respectively, compared to the predrug value of 110 beats/min ($p < 0.01$, at 4 hours).

Table 2. *Effects of 0.4 mg moxonidine on hemodynamic and neurohumoral parameters at rest and during ergometric exercise*

N × 10		HR (min-1)	BP syst/diast (mmHG)	PAP_m (mmHG)	CO (l/min)	SV (ml)	PVR (dyn.sec cm−5)	SVR	NA (pg/ml)	A (pg/ml)	PRA (ng/ml/h)	ANG II (pg/ml)	ALD (pg/ml)	ANF (pg/ml)
Control	E	110 ± 11	220/116 ± 32/10	33.2 ± 9.1	18.5 ± 3.1	170 ± 35	55 ± 23	674 ± 180	541 ± 220	110 ± 47	3.1 ± 2.4	13.8 ± 11.9	188 ± 148	258 ± 130
	R	69 ± 9	176/105 ± 25/8	16.5 ± 2.5	6.1 ± 1.1	93 ± 24	78 ± 21	1695 ± 350	337 ± 160	77 ± 31	2.6 ± 2.2	11.8 ± 8.8	171 ± 116	167 ± 79
1 hr	E	114 ± 10	211/114 ± 32/11	34.5 ± 9.5	19.2 ± 3.3	169 ± 32	57 ± 28	632 ± 177						
	R	67 ± 8	168/103 ± 30/13	14.8 ± 2.4	6.6 ± 1.2	100 ± 27	72 ± 20	1565 ± 381						
2 hr	E	116 ± 10	203/108 ± 22/12	32.6 ± 8.2	19.3 ± 3.6	166 ± 31	59 ± 24	601 ± 151						
	R	71 ± 11	159/99 ± 30/14	15.1 ± 2.8	6.2 ± 0.9	90 ± 25	77 ± 35	1567 ± 342						
3 hr	E	118 ± 11	202/107 ± 28/9	33.4 ± 7.7	18.7 ± 3.3	159 ± 27	53 ± 22	610 ± 135						
	R	72 ± 8	156/96 ± 23/9	15.9 ± 2.6	6.6 ± 0.9	92 ± 19	86 ± 28	1446 ± 300						
4 hr	E	122 ± 12	203/106 ± 26/9	31.1 ± 7.6	18.6 ± 3.9	154 ± 36	48 ± 16	619 ± 147	407 ± 146	81 ± 41	2.5 ± 1.8	13.2 ± 11.9	148 ± 11.9	198 ± 78
	R	75 ± 7	158/95 ± 28/14	16.1 ± 2.5	6.7 ± 1.1	91 ± 20	79 ± 28	1427 ± 341	224 ± 78	67 ± 23	2.0 ± 1.6	9.7 ± 9.4	124 ± 145	168 ± 66

Results are given as mean ± SD.
HR = heart rate; BP = blood pressure (by sphygmomanometry); PAP_m = mean pulmonary artery pressure; CO = cardiac output; SV = stroke volume; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance; NV = noradrenaline; A = adrenaline; PRA = plasma renin activity; ANG II = angiotensin II; ALD = aldosterone; ANF = atrial natriuretic factor; C = control; E = exercise; R = rest.

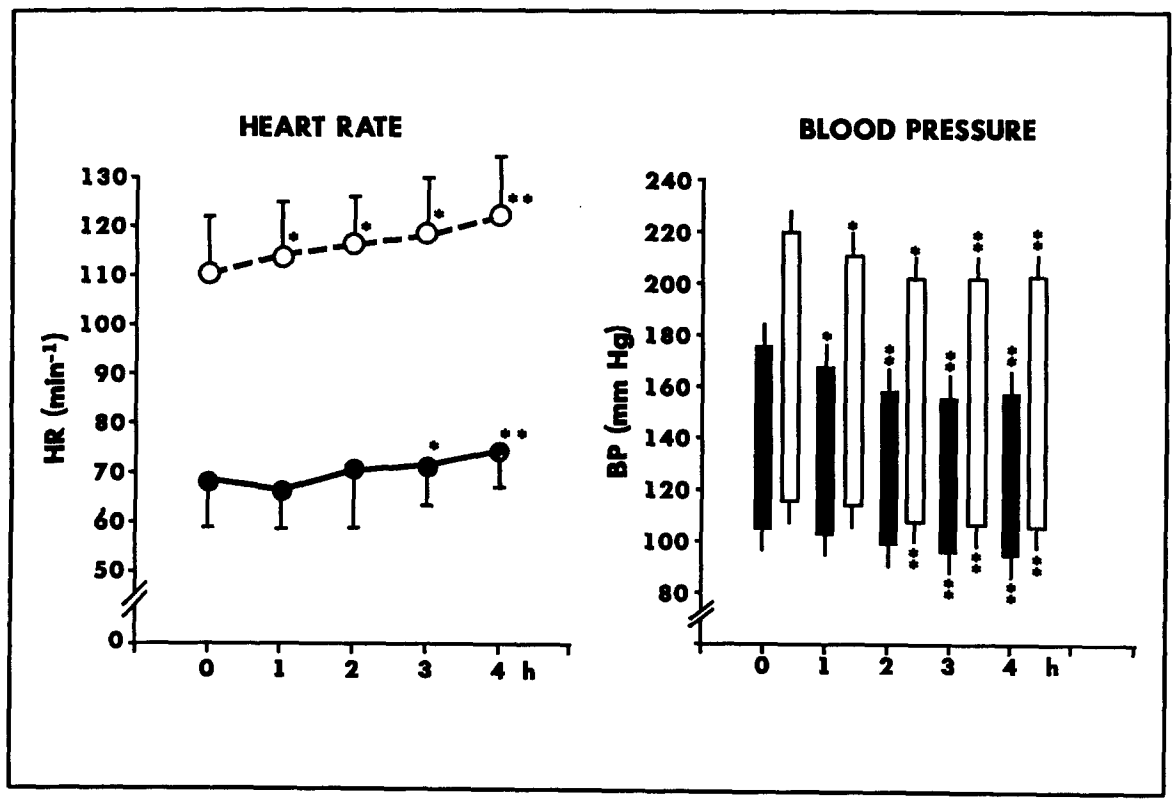

Fig. 1. *Influence of moxonidine on heart rate and blood pressure at rest and during ergometric exercise.* ●-● *= rest;* ○-○ *= exercise; *p ≤ 0.05; **; ≤ 0.01.*

Blood pressure

A significant reduction in systolic and diastolic blood pressure was observed both at rest and during exercise (Table 2, Figure 1) following moxonidine intake. Mean systolic and diastolic blood pressures at rest showed a time-dependent reduction 1, 2, 3, and 4 hours postadministration from 176/105 mmHg to 168/103, 159/99, 156/96, and 158/95 mmHg ($p < 0.01$ at 3 and 4 hours for both values). There was a similar reduction during exercise from a mean of 220/116 mmHg to 211/114, 203/108, 202/107, and 203/106 mmHg ($p < 0.01$ at 4 hours for both values). While there was no apparent correlation between the initial blood pressure and the extent of reduction following drug intake at rest, a correlation existed after 3 and 4 hours during exercise.

Figure 2 gives the values for systolic and diastolic blood pressure directly measured from the brachial

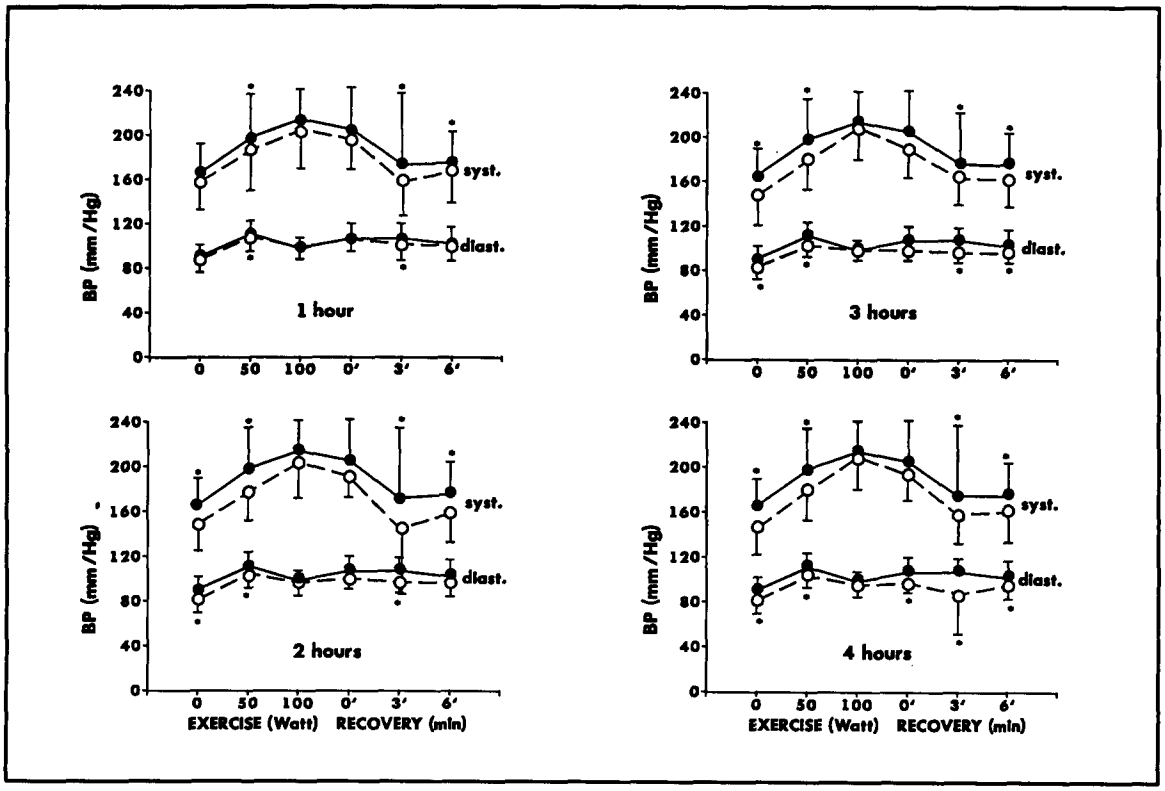

Fig. 2. Effects of exercise on arterial blood pressure 1, 2, 3, and 4 hours after moxonidine intake. ●-● = *control;* ○-○ = *moxonidine;* **p* ≤ *0.05.*

artery at rest and during exercise at 50 and 100 W, as well as during the recovery phases 1, 2, 3, and 4 hours following the administration of moxonidine. Compared to prestudy levels, blood pressure was lower at all time points, the slightest difference being found at 100 W. There was a good correlation between invasive measurement in the brachial artery and measurement by Riva Rocci for resting and exercise systolic blood pressure ($r = 0.91$ and 0.72, respectively; $p < 0.001$). A poor correlation was found for diastolic pressure at rest ($r = 0.59$; $p < 0.01$), and no significant correlation was found during exercise ($r = 0.39$; $p > 0.05$).

Hemodynamic parameters

Cardiac output, pulmonary artery pressure, and pulmonary vascular resistance showed no relevant changes after moxonidine either at rest or during exercise (Table 2). The stroke volume showed no clinically significant differences at rest, but demonstrated a downward trend during exercise after drug intake. The mean difference to the predrug value after 4 hours was −16 ml ($p < 0.01$). This slight decrease was compensated by a concomitant increase in heart rate.

A marked reduction in mean systemic vascular resistance at rest, from 1695 to 1565 dyn.sec/cm^5, was observed by the first hour, and was further reduced after 2, 3, and 4 hours postdrug to 1567, 1446, and 1427 dyn.sec/cm^5 ($p < 0.01$ at 2, 3, and 4 hours) (Figure 3). During exercise a slight decrease in the total resistance was seen as well: systemic vascular resistance fell from a mean of 674 to 632, 601, 610, and 619 dyn.sec/cm^5 after 1, 2, 3, and 4 hours, respectively (significant at the 5% level in each case).

Neurohumoral system (table 2)

At rest, three patients had elevated predrug plasma noradrenaline concentrations. A decrease in noradrenaline values was observed in nine patients. Four hours after moxonidine intake, noradrenaline fell from 337 to 224 pg/ml ($p < 0.03$) at rest and from 541 to 407 pg/ml during exercise ($p < 0.01$). Adrenaline showed no relevant changes (77 vs. 73 pg/ml at rest and 96 vs. 79 pg/ml during exercise) 4 hours postdrug.

Plasma renin activity (measured before as well as 4 hours after drug intake) decreased markedly from 2.6 to 2.0 ng/ml/hr at rest ($p < 0.01$) and from 3.1 to 2.5 mg/ml/hr during exercise ($p < 0.09$). The average angiotensin II concentrations at rest dropped from

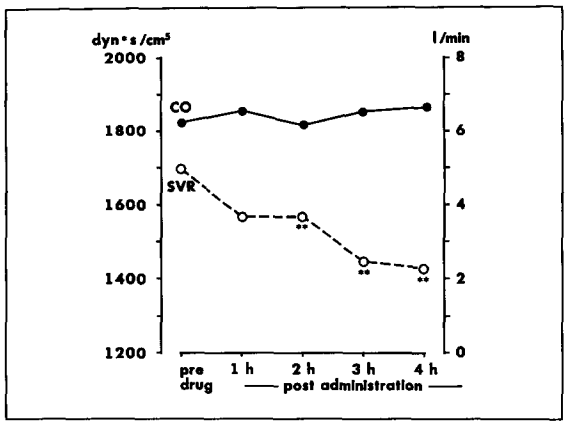

Fig. 3. *Effects of moxonidine on cardiac output (CO) and systemic vascular resistance (SVR) at rest. ○-○ = CO; ○-○ = SVR; *p = ≤ 0.05; **p = ≤ 0.01.*

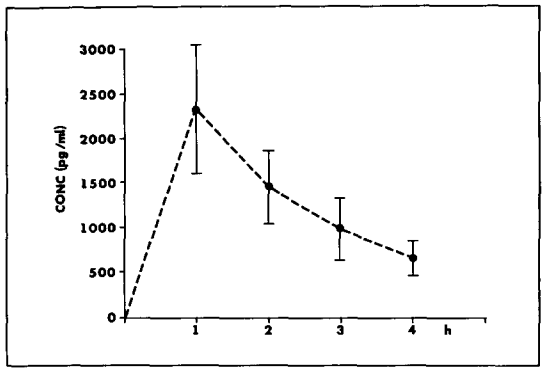

Fig. 4. *Moxonidine plasma concentrations following intake of a 0.4-mg tablet in ten patients.*

11.8 to 9.7 pg/ml (not significant). Aldosterone showed a mean decrease of 48 pg/ml at rest and 40 pg/ml during exercise (not significant). While there were no relevant changes in ANF at rest (167 vs. 168 pg/ml), the values fell during exercise from 258 to 198 pg/ml ($p < 0.04$).

Moxonidine plasma concentrations

The plasma levels of moxonidine 1, 2, 3, and 4 hours after drug administration are presented in Figure 4. The maximum plasma concentration of 2319 pg/ml was observed after the first hour, with a logarithmic decline during the next 3 hours. There was no obvious correlation between plasma concentrations and the degree of blood pressure reduction, with the exception of the diastolic value after the first hour.

Adverse events

Moxonidine was well tolerated. Adverse events were recorded in six patients during the study, but were only of short duration; five patients reported dry mouth, which was classified as mild in all cases. These adverse events occurred about 1 to 2 hours after intake of the drug and had a maximum duration of 6 hours. One patient suffered from hypotension and vertigo; his blood pressure was 100/70 mm Hg 4 hours after moxonidine. In no case was sedation observed.

Discussion

The results of this study indicate that moxonidine lowers blood pressure by reducing systemic vascular resistance while maintaining cardiac output and heart rate. At the same time, a suppression of both the sympathetic and renin-angiotensin-aldosterone systems could be recorded.

Thus, the mode of action exhibited by moxonidine differs from that of other centrally acting α-receptor agonists. Clonidine, for instance, is known to decrease blood pressure by reducing heart rate and cardiac output, while total peripheral resistance may even increase or remain unchanged [12,13]. This unfavorable hemodynamic response may be attributed to the marked agonistic effects of clonidine on postsynaptic α_1-receptors, thereby leading to peripheral vasoconstriction [14]. Moxonidine, in contrast, was shown to reduce both blood pressure and systemic vascular resistance at rest and also during exercise, with a concomitant slight increase in heart rate and cardiac output. However, since it is known that moxonidine has at least a tenfold higher specificity for α_2 receptors than clonidine [3], it may be reasonable to assume much weaker vasoconstrictive effects. Furthermore, moxonidine did not induce sedation, a typical side effect of centrally acting drugs.

Recent investigations into the mechanism of action of moxonidine have shown this to bind very selectively to the newly discovered imidazoline receptor in both the medulla oblongata and kidney [5]. In these tissues, the affinity of moxonidine to the imidazoline binding site was approximately 20 times greater than for clonidine [15].

Moxonidine was also devoid of the severe counterregulation that can sometimes be observed with calcium-channel antagonists or α_1 blockers, such as prazosine. These drugs induce direct vasodilation in the periphery, which may lead to reflex tachycardia and water retention [16–18]. Thus, the typical side effects can be explained: palpitation, flush, and edema.

Due to its sympatholytic mode of action, moxoni-

dine does not tend to induce counter-regulatory mechanisms, although a slight increase in heart rate could be observed in this study. Plasma levels of noradrenaline and renin activity were significantly reduced following moxonidine administration, which has also been shown previously [19]. These findings indicate that moxonidine may be useful in patients with congestive heart failure due to essential hypertension or even ischemic heart disease where afterload reduction, in the absence of adverse effects on contractility, is required.

Since activation of the sympathetic nervous system is being held responsible for the left ventricular hypertrophy observed in chronic hypertensive patients [20], one may expect moxonidine to exert a positive influence on this condition. Indeed, both clonidine and methyldopa have been shown to induce regression of left ventricular hypertrophy following long-term administration [21,22]. In any case, combined reduction of an abnormally augmented systemic vascular resistance, together with reductions in both renin activity and catecholamines, is likely to benefit patients with essential hypertension.

In conclusion, moxonidine appears to be a centrally acting drug that lowers systemic vascular resistance while preserving cardiac output with a concomitant hypotensive action in patients with mild to moderate hypertension. Whether the hemodynamic and neurohumoral effects observed in this single-dose study can be maintained during long-term administration must be clarified in future well-controlled trials.

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