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Effects of Moxonidine on the Sympathetic Nervous System, Blood Pressure, Plasma Renin Activity, Plasma Aldosterone, Leptin, and Metabolic Profile in Obese Hypertensive Patients

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Obesity accounts for around 70 % of the patients with primary hypertension. This association accentuates the risk of cardiovascular disease as it is frequently accompanied by the components of the metabolic syndrome. Clinical, epidemiological and experimental studies show an association between obesity-hypertension with insulin resistance and increased sympathetic nervous system activity. We conducted the present study to evaluate in forty obese hypertensives of both genders, aged 27 to 63 years old, the chronic effects of moxonidine – a selective imidazoline receptor agonist – on blood pressure, plasma catecholamines, leptin, renin-angiotensin aldosterone system and components of the metabolic syndrome. It was a randomized parallel open study, amlodipine was used as the control drug. Our results show that moxonidine and amlodipine significantly reduced blood pressure without affecting heart rate when measured by the oscillometric method and with twenty-four-hour blood pressure monitoring. Moxonidine therapy decreased systolic blood pressure from 160.4 ± 2.4 to 142.1 ± 3.3 mmHg ($p < 0.005$) and diastolic blood pressure from 102.4 ± 1.3 to 89.7 ± 1.6 mmHg ($p < 0.005$) after 24 weeks of treatment. Neither moxonidine nor amlodipine affected normal circadian variations on blood pressure. There was a reduction of the supine arterial plasma levels adrenaline from 63.2 ± 6.6 to 49.0 ± 6.7 pg/ml ($p < 0.005$), supine arterial levels noradrenaline from 187.9 ± 10.7 to 149.7 ± 13.2 pg/ml ($p < 0.01$) and orthostatic venous levels of noradrenaline from 258.6 ± 25.0 to 190.3 ± 16.4 pg/ml ($p = 0.03$) after moxonidine. These variables were not changed by amlodipine. Plasma leptin levels and plasma insulin after 120 min glucose load decreased after moxonidine from 27.2 ± 3.5 to 22.6 ± 2.9 pg/ml ($p < 0.05$) and from 139.7 ± 31.2 to 76.0 ± 15.2 U/ml ($p < 0.05$), respectively. However, amlodipine did not modify these variables. There were no alterations in plasma renin activity, and plasma aldosterone after moxonidine, although amlodipine significantly increased the plasma renin activity from 31.4 ± 4.6 to 47.7 ± 5.6 ng/ml/h ($p = 0.03$). Moxonidine and amlodipine had no significant effect on the other variables. This study shows a comparable reduction of blood pressure with both antihypertensive drugs. Moxonidine decreased sympathetic nervous activity, improved insulin resistance and reduced the plasma levels of leptin. *J Clin Basic Cardiol* 2004; 7: 19–25.

Key words: moxonidine, hypertension, plasma catecholamines, insulin, leptin, renin

Studies in populations throughout the world have shown that obesity is a major risk factor for development of hypertension [1, 2]. Obesity initiates a cluster of cardiovascular, renal, metabolic and neuroendocrine disorders that has been referred to as metabolic syndrome [3]. The root cause for these abnormalities seems to be the overactivity of sympathetic nervous system (SNS) [4, 5]. Insulin resistance and mild hyperinsulinemia, main features of the metabolic syndrome, may possibly be related to the reduced skeletal muscle blood flow resulting from neural vasoconstriction [6].

Abnormal kidney function, manifested as a shift of pressure natriuresis has a pivotal role in obesity hypertension [7]. Renal sympathetic nerves activation and stimulation of the renin-angiotensin system are mediating mechanisms in obesity renal sodium retention [7, 8]. Leptin, an adipocyte-derived hormone, is elevated in obese hypertensive patients [9], and its interactions with neurochemicals in hypothalamus may be another link between weight gain, increased sympathetic activity and hypertension [10].

Recently, imidazoline receptors in central nervous system have been identified; their stimulation predominantly located in the rostroventrolateral medulla leads to peripheral sympathoinhibition [11]. Moxonidine, an I₁-imidazoline receptor agonist, effectively reduces blood pressure; moreover side effects such as dizziness and dry mouth are much less than with older centrally acting antihypertensives, i.e., clonidine [12]. Given that sympathetic activation in obesity-related hypertension seems to contribute both to the blood pressure

elevation and to other adverse metabolic and cardiovascular effects, it might be appropriate to investigate therapies inhibiting the sympathetic nervous system under such conditions.

In order to test this possibility we performed the present study to evaluate in a multiethnic group of patients, whether antihypertensive treatment with moxonidine, with increasing therapeutic doses, reduces the sympathetic response, and also has favourable effects on insulin resistance, glucose intolerance, dyslipidemia, activity of renin-angiotensin aldosterone system and hyperleptinemia, which are frequently interassociated. The calcium channel blocker amlodipine was used as control drug.

Methods

Study Population

Forty patients (female and male) with diagnosis of hypertension and obesity, aged 27–65 years, were studied. All were screened by history, physical examination and laboratory evaluation. Patients with clinical or laboratory evidence of severe or secondary hypertension, diabetes mellitus, renal insufficiency, congestive heart failure, hepatic disease, arrhythmia, morbid obesity or chronic disease, that may influence the autonomic nervous system were excluded. Patients were eligible for inclusion whether sitting diastolic blood pressure (DBP) and systolic blood pressure (SBP) were in the range of 90–120 mmHg and 140–180 mmHg, and their body mass index (BMI) ≥ 30 kg/m². Baseline characteristics of the study appear in Table 1.

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Study Design and Conduct

The Ethics Committee of Rio de Janeiro State University approved the study protocol and informed written consent was required from all participants. The study was performed according to a randomized open parallel-group protocol. The calcium channel blocker amlodipine was used as control drug.

Following a two weeks washout period, patients were randomly assigned to treatment with either moxonidine 0.2 mg once daily or amlodipine 5 mg once daily. The total duration of active therapy was 24 weeks. Patients were reviewed at monthly intervals during the active treatment period. A complete physical examination including weight, height, blood pressure, and abdominal circumference was performed during each visit and at the end of the intervention period. For patients with blood pressure non-responding, DBP > 90 mmHg or SBP > 140 mmHg, dose adjustment was allowed from the V2 visit to moxonidine 0.4 mg or amlodipine 10 mg, once daily (Fig. 1). During the study, patients whose DBP or SBP exceeded 110 mmHg or 180 mmHg, respectively, on two consecutive visits, were excluded from the study. Compliance with study medication was monitored by

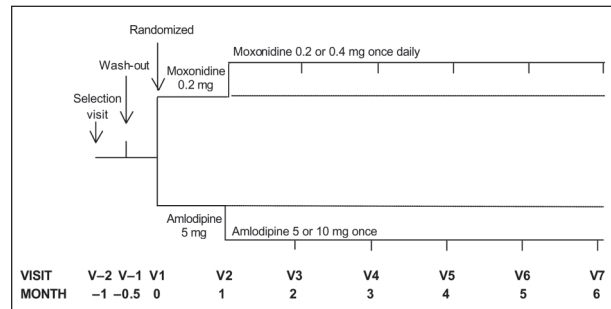


Figure 1. Study flow chart. Clinical evaluation: all visits; ambulatory blood pressure: visit 1 and 7; venous and arterial blood sample for assessment of catecholamines, insulin, glucose, leptin, plasma renin activity, plasma aldosterone, total cholesterol, triglycerides, HDL-C and LDL-C: visit 1, 4 and 7.

Table 1: Baseline characteristics of the intention-to-treat patient sample

	Moxonidine (n = 19)	Amlodipine (n = 21)	p
Age	48.7 ± 2.1	46.5 ± 1.8	0.42
Gender	15 ♀ / 4 ♂	18 ♀ / 3 ♂	0.88
BMI (kg/m ²)	35.4 ± 1.7	35.9 ± 1.4	0.82
Waist to hip ratio	0.95 ± 0.02	0.92 ± 0.02	0.29
HR (bpm)	79.5 ± 2.4	77.4 ± 1.7	0.47
SBP (mmHg)	160.4 ± 2.4	158.1 ± 3.1	0.56
DBP (mmHg)	102.4 ± 1.3	104.2 ± 1.3	0.30
SBP-ABP 24h (mmHg)	143.1 ± 4.2	143.3 ± 4.3	0.97
DBP-ABP 24h (mmHg)	86.1 ± 2.6	88.3 ± 2.7	0.56
Supine venous adrenaline (pg/ml)	53.6 ± 5.3	53.5 ± 5.5	0.99
Supine arterial adrenaline (pg/ml)	63.2 ± 6.6	60.3 ± 8.3	0.78
Orthostatic venous adrenaline (pg/ml)	50.4 ± 5.8	56.9 ± 5.7	0.44
Supine venous NA (pg/ml)	223.6 ± 24.9	186.5 ± 16.6	0.21
Supine arterial NA (pg/ml)	187.9 ± 10.7	193.4 ± 13.5	0.75
Orthostatic venous NA (pg/ml)	258.6 ± 25.0	216.3 ± 30.3	0.24
Leptin (pg/ml)	27.2 ± 3.5	32.3 ± 3.5	0.31
Fasting insulin (U/ml)	29.9 ± 5.7	23.5 ± 2.3	0.28
Insulin 120' after glucose load (U/ml)	139.7 ± 31.2	94.3 ± 19.2	< 0.0001
HOMA	7.2 ± 1.9	5.5 ± 0.6	0.37
Fasting glucose (mg/dl)	99.4 ± 3.4	99.0 ± 2.7	0.92
Glucose 120' after glucose load (mg/dl)	143.0 ± 10.9	149.7 ± 9.7	0.64
Aldosterone (pg/ml)	190.2 ± 28.8	198.2 ± 18.6	0.74
PRA (ng/ml/h)	42.6 ± 6.5	31.1 ± 4.6	0.45
Triglycerides (mg/dl)	175.0 ± 21.6	153.4 ± 16.1	0.42
Cholesterol (mg/dl)	225.2 ± 12.4	220.0 ± 8.6	0.72
HDL-cholesterol	47.4 ± 3.1	43.8 ± 2.7	0.38
LDL-cholesterol	144.9 ± 12.6	143.4 ± 16.1	0.96

Values are means ± SEM. BMI = body mass index; HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; ABP = ambulatory blood pressure; NA = noradrenaline; HOMA = homeostasis model assessment; PRA = plasma renin activity

counting returned capsules. A 24-hour ambulatory blood pressure monitoring was obtained at weeks 1 (V1) and 24 (V7).

All subjects were studied between 9:00 AM and 12:00 noon and were asked to avoid nicotine and caffeine products for 12 hours and alcohol and strenuous exercise for 24 hours before the investigation. Subjects maintained a usual intake of sodium, and they were not on calorie-restricted diet. They were requested to empty their bladders before beginning the study.

After the patients pre-fasted for 12 hours, a canula was inserted into an antecubital peripheral vein. After 30 min resting, venous blood samples were taken at baseline, 12th, and 24th weeks, to measure the following parameters: fasting insulin and glucose, insulin and glucose after 120 min glucose load (75 g of Dextrosol in 250 ml of water in less than 5 min), total cholesterol, HDL-cholesterol, triglycerides, and electrolytes. During the same visits (V1, V4, and V7) we obtained venous blood for plasma noradrenaline and adrenaline measurements (initially at rest and after orthostatic stimulation of sympathetic nervous activity where the patients stood for five minutes), and for determination of leptin, insulin, aldosterone and plasma renin activity (at supine rest). Arterial blood for noradrenaline and adrenaline was obtained with the subjects at supine rest, by introducing a 30 × 80 mm gauge needle percutaneously into the radial artery of either arm. Arterial specimen was taken only when painful stimulus of needle insertion was away.

Blood Pressure and Heart Rate

Blood pressure and heart rate were recorded by Dinamap 1846 Critikon automated sphygmomanometer, after 5 minutes rest in the sitting position. Measurements of blood pressure and heart rate were made each 3 min, during 15 min, in a darkened laboratory in which the temperature was constant at 22–24 °C. The first value was rejected and the mean of the last four readings was used in the efficacy analysis.

Ambulatory blood pressure was recorded using the SpaceLabs 90207 oscillometric BP monitors (SpaceLabs, Redmond, WA) calibrated against a mercury sphygmomanometer before use on each patient. Monitors were programmed to read blood pressure and heart rate every 20 minutes from 6:00 to 18:00 and every 30 minutes from 18:00 to 6:00. Mean daytime (6:00 to 18:00) and nighttime (18:00 to 6:00) BP and heart rate were calculated. The BP load was defined as the percentage of elevated BP reading while awake (> 140/90 mmHg) and while asleep (> 120/80 mmHg) in a 24 hours period.

Assay of Plasma Catecholamines

Sympathoadrenal activity was assessed from the assay of blood samples obtained at resting, in the supine position, and after orthostatic stimulation. Samples were transferred immediately to ice-chilled tubes containing ethylene guanine tetraacetic acid and reduced glutathione, centrifuged at 4 °C, and the plasma stored at -70 °C before assay. The plasma catecholamines were determined by high performance liquid chromatography as described [13]. Intra-assay variation was 6.5 % for plasma noradrenaline, and 4.4 % for plasma adrenaline.

Insulin Radioimmunoassay

Blood samples for insulin measurement were immediately centrifuged, and plasma samples were stored at -20 °C until assayed. A radioimmunoassay kit (Linco Research Inc., St. Charles, MO) was used with human insulin standard and antibodies directed against human insulin. Sensitivity of insulin radioimmunoassay was 1.1 mU/ml and the ultraassay and interassay coefficients of variation were 4.4 % and 6.0 %, respectively.

Plasma Renin Activity and Plasma Aldosterone

Plasma renin activity was measured by radioimmunoassay according with Haber method modified by Sealey and Laragh [14]. Plasma aldosterone was quantified by radioimmunoassay as described by Varsano and Ulick [15].

Plasma Leptin Assay

Plasma leptin was measured by radioimmunoassay (Linco Research Inc., St. Charles, MO), the intra-assay coefficient of variation was 6.2 % and the interassay coefficient of variation was 6.2 %.

Other Biochemical Analysis

Serum glucose, triglycerides, total cholesterol and HDL-cholesterol were measured enzymatically. The insulin resistance index was calculated by homeostasis model assessment (HOMA) [16].

Statistical Analysis

The values were expressed as mean $\pm$ SEM and $p < 0.05$ were considered significant for all statistic tests. Continuous data

were analyzed using Student's t-test for paired samples. When no normality evidence was available, nonparametric test, i.e., Wilcoxon's matched pairs signed rank test and Mann-Whitney U-test, were used for between and within-group comparisons. Chi-square or Fischer exact test was employed to compare categorical variables.

Results**Basal Values**

The general characteristics of the study population are given in Table 1. As shown in the table, the two groups were well matched for all variables studied, except for the plasma insulin 2 hours after oral glucose load which was significantly higher in the moxonidine group when compared with the amlodipine group ($p < 0.0001$).

Office Blood Pressure and Heart Rate Measurements

Table 2 summarizes the blood pressure and heart rate at baseline, after 12 and 24 weeks of treatment with moxonidine and amlodipine. Both moxonidine and amlodipine reduced blood pressure to a similar degree by Dinamap measurements. Moxonidine reduced sitting SBP and DBP from 160.4 ± 2.4 to 142.1 ± 3.3 mmHg and 102.4 ± 1.3 to 89.7 ± 1.6 mmHg, respectively; $p < 0.005$; and amlodipine from 158.1 ± 3.1 to 134.2 ± 1.7 mmHg and 104.2 ± 1.3 to 88.3 ± 1.0 mmHg, respectively; $p < 0.005$. The average reductions of office BP with both drugs were not statistically different. 58 % of 19 patients on moxonidine and 52 % of 21 patients on amlodipine had their blood pressure controlled (DBP < 90 mmHg) at V7. The required doses of the two study drugs are shown in Table 3.

Twenty-Four-Hour Blood Pressure Measurements

At week 24 moxonidine reduced 24-hour SBP, DBP and MBP from 143.1 ± 4.2 to 131.8 ± 4.0 ; 86.1 ± 2.6 to 79.7 ± 3.0 and 105.8 ± 3.1 to 98.3 ± 3.3 mmHg, respectively; $p < 0.005$; and amlodipine from 143.3 ± 4.3 to 127.2 ± 1.9 ; 88.3 ± 2.7 to 78.5 ± 1.6 and 107.3 ± 3.1 to 95.1 ± 1.4 mmHg, respectively; $p < 0.005$. At week 24 moxonidine reduced average day/night SBP, DBP and MBP from $144.1 \pm 4.2/140.3 \pm 4.8$ to $133.8 \pm 3.1/132.2 \pm 5.1$; $87.4 \pm 2.6/82.9 \pm 3.2$ to $80.9 \pm 3.0/78.6 \pm 3.2$

Table 2: Blood pressure and heart rate at baseline (V1) and after 12 (V4) and 24 (V7) weeks of treatment with moxonidine and amlodipine

	Moxonidine			Amlodipine		
	V ₁ (baseline)	V ₄	V ₇	V ₁ (baseline)	V ₄	V ₇
Office (mmHg)						
SBP	160.4 ± 2.4	$140.4 \pm 2.7^*$	$142.1 \pm 3.3^*$	158.1 ± 3.1	$137.5 \pm 2.2^*$	$134.2 \pm 1.7^*$
DBP	102.4 ± 1.3	$92.2 \pm 2.0^*$	$89.7 \pm 1.6^*$	104.2 ± 1.3	$89.5 \pm 1.6^*$	$88.3 \pm 1.0^*$
MBP	121.8 ± 1.3	$108.3 \pm 2.1^*$	$107.1 \pm 2.0^*$	121.7 ± 1.9	$105.5 \pm 1.7^*$	$103.2 \pm 1.2^*$
Average 24h BP (mmHg)						
SBP	143.1 ± 4.2		$131.8 \pm 4.0^*$	143.3 ± 4.3		$127.2 \pm 1.9^*$
DBP	86.1 ± 2.6		$79.7 \pm 3.0^*$	88.3 ± 2.7		$78.5 \pm 1.6^*$
MBP	105.8 ± 3.1		$98.3 \pm 3.3^*$	107.3 ± 3.1		$95.1 \pm 1.4^*$
Average day BP (mmHg)						
SBP	144.1 ± 4.2		$133.8 \pm 3.1^*$	145.4 ± 4.4		$129.0 \pm 1.9^*$
DBP	87.4 ± 2.6		$80.9 \pm 3.0^*$	90.8 ± 2.6		$80.6 \pm 1.7^*$
MBP	107.4 ± 3.0		$98.9 \pm 3.0^*$	109.8 ± 3.1		$97.1 \pm 1.5^*$
Average night BP (mmHg)						
SBP	140.3 ± 4.8		$132.2 \pm 5.1^*$	138.8 ± 4.3		$123.6 \pm 2.1^*$
DBP	82.9 ± 3.2		$78.6 \pm 3.2^*$	82.8 ± 3.2		$74.4 \pm 1.8^*$
MBP	103.1 ± 3.7		$97.8 \pm 3.8^*$	102.4 ± 3.4		$91.4 \pm 1.6^*$
Average 24h HR (beats/min)	79.5 ± 2.4		81.3 ± 2.0	77.4 ± 1.7		78.6 ± 1.8
Average day HR (beats/min)	85.0 ± 1.8		86.8 ± 2.6	86.2 ± 2.2		84.4 ± 2.2
Average night HR (beats/min)	73.6 ± 1.7		75.4 ± 1.9	76.4 ± 2.2		75.3 ± 1.7

Values are mean $\pm$ SEM; * $p < 0.005$ vs. baseline; BP = blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; MBP = mean blood pressure (DBP plus one third pulse pressure); HR = heart rate

and $107.4 \pm 3.0/103.1 \pm 3.7$ to $98.9 \pm 3.9/97.8 \pm 3.8$ mmHg, respectively; $p < 0.005$. At week 24 amlodipine reduced average day/night SBP; DBP and MBP from $145.4 \pm 4.4/138.8 \pm 4.3$ to $129.0 \pm 1.9/123.6 \pm 2.1$; $90.8 \pm 2.6/82.8 \pm 3.2$ to $80.6 \pm 1.7/74.4 \pm 1.8$ and $109.8 \pm 3.1/102.4 \pm 3.4$ to $97.1 \pm 1.5/91.4 \pm 1.6$ mmHg, respectively; $p < 0.005$. After 24 weeks (V7) moxonidine reduced 24-hour systolic, diastolic and mean blood pressure by 11.3 ± 4.0 , 6.4 ± 2.8 and 7.5 ± 3.2 mmHg, respectively compared with diminutions by 16.1 ± 3.2 , 9.8 ± 2.3 and 12.2 ± 2.2 mmHg, respectively in amlodipine treated patients (NS). No statistically difference in the achieved SPB on moxonidine and amlodipine was observed. Neither moxonidine nor amlodipine affected normal circadian variations in blood pressure. There was no change in heart rate measurement during daytime and overnight with either drugs (Tab. 2).

Arterial and Venous Plasma Catecholamines

After 12 weeks (V4) of moxonidine or amlodipine treatment, arterial or venous catecholamines were not significantly changed (Tab. 4). After 24 weeks (V7) of moxonidine, plasma arterial adrenaline and noradrenaline were significantly reduced with a reduction of 22.5 % and 20.4 % respectively. It was also observed a significantly reduction of 26.4 % of the venous standing noradrenaline after moxonidine. The venous supine and orthostatic adrenaline and venous supine noradrenaline did not change after 24 weeks treatment with

moxonidine. There were no significant changes of plasma catecholamines during amlodipine (Tab. 4).

Metabolic and Hormonal Parameters

At week 24, moxonidine reduced significantly plasma insulin after 120 min glucose load: -45.6 % reduction vs. V1, $p < 0.05$. There was also a 23 % reduction in fasting insulin and 18 % in HOMA model of insulin resistance index, although these changes were not statically significant. Serum fasting glucose and glucose after 120 min load were not changed throughout the study. Amlodipine was neutral concerning glucose metabolism (Tab. 5). Total cholesterol, triglycerides, HDL-C and LDL-C were not modified with moxonidine neither with amlodipine (Tab. 6).

After 24 weeks treatment, only moxonidine reduced significantly plasma leptin levels: -16.9 % reduction vs. V1, $p < 0.05$. Plasma renin activity and plasma aldosterone remained unchanged after 6 months treatment with moxonidine. Amlodipine significantly increased plasma renin activity (Tab. 6).

Adequate blood pressure response with moxonidine versus plasma levels catecholamines, insulin and leptin: When the subgroup of patients which had their blood pressure controlled (defined as office SPB < 140 mmHg and DBP < 90 mmHg) at week 24 by moxonidine was analysed separately, a significant greater reduction in standing catecholamines was observed in the subjects who succeeded blood pressure control, when compared with the subgroup which did not have their blood pressure controlled (-90.7 ± 40.4 pg/ml vs. -57.3 ± 33.9 pg/ml, $p < 0.003$, respectively). In the subjects with success in blood pressure control with moxonidine, plasma fasting insulin and leptin decreased significantly more, when compared with the same hormonal parameter of the subgroup of blood pressure non-responders (-5.5 ± 2.2 pg/ml vs. -4.3 ± 1.5 pg/ml for leptin, $p < 0.05$ and -9.6 ± 4.5 U/ml vs. -4.7 ± 3.3 U/ml, for insulin, $p < 0.05$) (Fig. 2).

Table 3: Dose required in intention-to-treat patient sample

	Moxonidine (n = 19)		Amlodipine (n = 21)	
	0.2 mg	0.4 mg	5 mg	10 mg
V1 (baseline)	100 %	0 %	100 %	0 %
V4	15.8 %	84.2 %	38 %	62 %
V7	15.8 %	84.2 %	28.6 %	71.4 %

Table 4: Supine and orthostatic plasma arterial and venous catecholamines at baseline (V1) and after 12 (V4) and 24 (V7) weeks of treatment with moxonidine and amlodipine

	Moxonidine			Amlodipine		
	V1 (baseline)	V4	V7	V1 (baseline)	V4	V7
Supine venous adrenaline (pg/ml)	53.6 ± 5.3	53.2 ± 5.6	50.2 ± 5.8	53.5 ± 5.5	53.0 ± 6.6	56.9 ± 5.3
Supine arterial adrenaline (pg/ml)	63.2 ± 6.6	61.4 ± 9.2	$49.0 \pm 6.7^*$	60.3 ± 8.3	49.8 ± 8.4	51.0 ± 8.4
Orthostatic venous adrenaline (pg/ml)	50.4 ± 5.8	52.9 ± 5.5	55.6 ± 5.1	56.9 ± 5.7	52.2 ± 4.6	71.1 ± 5.9
Supine venous NA (pg/ml)	223.6 ± 24.9	220.3 ± 19.0	188.0 ± 18.6	186.5 ± 16.6	191.9 ± 16.4	195.4 ± 17.4
Supine arterial NA (pg/ml)	187.9 ± 10.7	173.1 ± 17.5	$149.7 \pm 13.2^\dagger$	193.4 ± 13.5	158.4 ± 13.6	157.9 ± 16.3
Orthostatic venous NA (pg/ml)	258.6 ± 25.0	204.9 ± 16.2	$190.3 \pm 16.4^\ddagger$	216.3 ± 30.0	159.3 ± 18.0	168.7 ± 16.5

Values are mean $\pm$ SEM; * $p < 0.005$; $^\dagger p < 0.01$; $^\ddagger p = 0.03$ vs. baseline; NA = nordrenaline

Table 5: Fasting insulin and glucose concentrations, insulin and glucose after 120 min glucose load and HOMA at baseline (V1) and after 12 (V4) and 24 (V7) weeks of treatment with moxonidine and amlodipine

	Moxonidine			Amlodipine		
	V1 (baseline)	V4	V7	V1 (baseline)	V4	V7
Fasting insulin (U/ml)	29.9 ± 5.7	24.1 ± 1.9	23.1 ± 1.9	23.5 ± 2.3	26.4 ± 5.0	24.4 ± 2.6
Insulin after glucose load (U/ml)	139.7 ± 31.2	111.8 ± 29.6	$76.0 \pm 15.2^*$	94.3 ± 19.2	80.9 ± 10.6	88.5 ± 11.5
HOMA	7.2 ± 1.87	6.2 ± 0.66	5.8 ± 0.65	5.5 ± 0.6	7.0 ± 1.76	6.2 ± 0.73
Fasting glucose (mg/dl)	99.4 ± 3.4	105.5 ± 3.3	102.2 ± 4.6	99.0 ± 2.7	99.7 ± 3.8	101.7 ± 2.2
Glucose after dextrosol (mg/dl)	143.0 ± 10.9	141.2 ± 10.2	143.2 ± 9.0	149.7 ± 9.7	137.2 ± 10.2	142.1 ± 8.4

Values are mean $\pm$ SEM; * $p < 0.05$ vs. baseline

Table 6: Plasma leptin, plasma renin activity, plasma aldosterone, total cholesterol, HDL-C and LDL-C and triglycerides at baseline (V1) and after 12 (V4) and 24 (V7) weeks of treatment with moxonidine and amlodipine

	Moxonidine			Amlodipine		
	V ₁ (baseline)	V ₄	V ₇	V ₁ (baseline)	V ₄	V ₇
Leptin (pg/ml)	27.2 ± 3.5	27.2 ± 3.7	22.6 ± 2.9 *	32.3 ± 3.5	30.3 ± 3.7	29.6 ± 2.3
Plasma renin activity (ng/ml/h)	42.6 ± 6.5		43.6 ± 7.6	31.4 ± 4.6		47.7 ± 5.6†
Plasma aldosterone (pg/ml)	190.2 ± 28.8		200.7 ± 27.1	198.2 ± 18.6		214.7 ± 31.5
Cholesterol (mg/dl)	225.2 ± 12.4	230.4 ± 11.1	238.1 ± 10.2	220.0 ± 8.6	223.1 ± 10.8	223.3 ± 9.7
HDL cholesterol	47.4 ± 3.1	47.7 ± 3.1	48.3 ± 2.9	43.8 ± 2.7	41.0 ± 2.5	45.7 ± 2.5
LDL cholesterol	144.9 ± 12.6	152.5 ± 10.5	158.0 ± 9.9	145.5 ± 8.8	146.6 ± 11.9	156.7 ± 8.9
Triglycerides	175.0 ± 21.6	156.9 ± 15.6	158.6 ± 16.5	153.4 ± 16.1	162 ± 15.6	145.3 ± 16.6

Values are mean ± SEM; * p < 0.05 vs. baseline; † p = 0.03 vs. baseline

Discussion

Although the doses of moxonidine up to 0.4 mg used in this study were only up to mid range commonly employed in the treatment of hypertension, i.e. up to 0.6 mg/day, there were useful metabolic effects. This was in contrast to the absence of these actions with on amlodipine up to a dosage of 10 mg daily, the full dose used in the treatment of hypertension. There were no significant differences in the response of blood pressure; the trend in favor of amlodipine could be ascribed to the dosages employed in this study. After 24 weeks the overall response rate, i.e. an office diastolic blood pressure of less than 90 mmHg, was 58 % to moxonidine therapy, with 84 % of patients receiving 0.4 mg and 16 % with 0.2 mg, whereas this level of control was achieved by 52 % with amlodipine.

The antihypertensive efficacy of moxonidine and amlodipine was also confirmed by 24-hours ambulatory blood pressure monitoring. Moxonidine reduced systolic and diastolic blood pressure effectively during daytime activities (−10.3/−6.5 mmHg, respectively) and during nighttime (−8.1/−4.3 mmHg, respectively). Amlodipine also reduced SBP/DBP (daytime −16.9/−10.2 mmHg; nighttime −15.2/−8.4 mmHg). Neither moxonidine nor amlodipine affected the normal circadian variations in blood pressure.

The antihypertensive efficacy of moxonidine has been compared in double blind and placebo controlled clinical trials with other classes of antihypertensives such as diuretics [17], β-blockers [18], calcium antagonists [19] and ACE inhibi-

tors [20–22]. The overall level of blood pressure control in our obese hypertensives, i.e. the number of patients achieving a diastolic blood pressure of < 90 mmHg with moxonidine, was similar to the calcium antagonist amlodipine.

Landsberg [23] has constructed a hypothesis to explain the development of hypertension in obese individuals, suggesting that overeating activates the sympathetic nervous system in order to stabilize body weight, but at the price of sympathetic activation in the heart, kidneys and vasculature, elevating blood pressure. Overeating in humans does increase sympathetic nervous activity as expressed by an increase in whole body noradrenaline spillover rates [24], and potentiates the increment plasma levels of noradrenaline associated to SNS stimulation secondary to postural changing [25]. In obese hypertensive patients urinary norepinephrine levels increase with rising body mass index and also with increasing abdominal fat distribution [26]. Experimentally, in the spontaneously obese hypertensive rat with multiple metabolic abnormalities resembling human syndrome X, the reduction of blood pressure through activation of I₁-imidazoline receptors with moxonidine ameliorates glucose intolerance, reduces hyperinsulinemia and attenuates dyslipidemia. The possible mechanisms for these changes include a direct action on I₁-imidazoline receptors in the pancreas and the brainstem, and indirect effects through inhibition of sympathetic nervous system activity [27].

There are scarce human data on moxonidine effects on noradrenaline levels in obese hypertensive patients, usually restricted to data obtained from resting venous blood [28]. Our

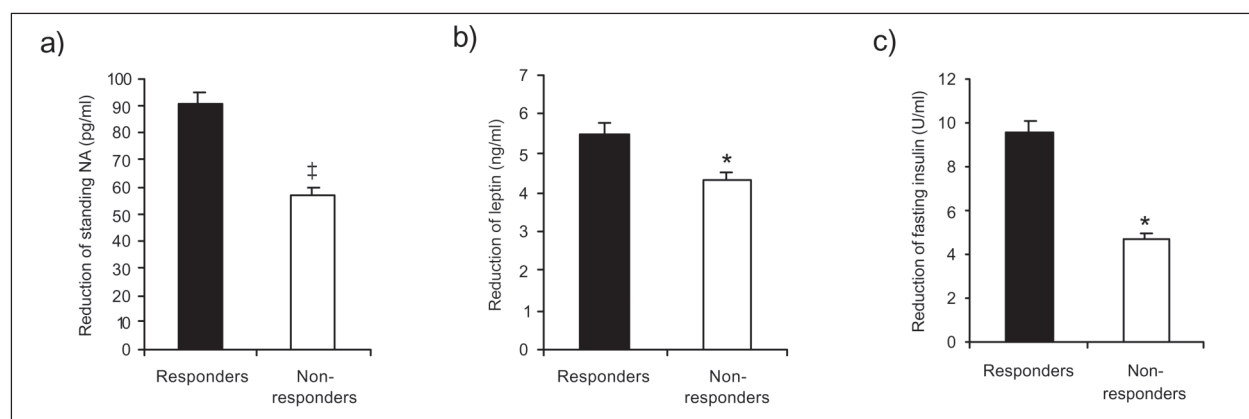


Figure 2. Effect of moxonidine at week 24 of on (a) standing plasma noradrenaline, (b) plasma leptin and (c) fasting plasma insulin interacting with blood pressure response responder and non-responder patients. NA: noradrenaline.

‡ p < 0.003 vs responders, * p < 0.05 vs responders.

study shows for the first time that chronic moxonidine administration to patients with obesity-hypertension significantly decreased the supine arterial plasma concentrations of noradrenaline and venous standing noradrenaline which suggests controlling the blood pressure levels through attenuation of sympathetic central nervous activity. Since moxonidine experimentally also stimulates presynaptic α_2 -receptors, decrease of plasma norepinephrine may also be due to this phenomenon in part [29]. There was also shown a fall in resting arterial adrenaline levels which is brought on by the high affinity moxonidine bound by I₁-imidazoline sites in membranes from adrenomedullary chromaffin cells [30].

The significant reduction of standing noradrenaline levels with moxonidine confirms the effectiveness of the drug in conditions of sympathetic overactivity. This effect was further confirmed by the findings of significant reduction of standing noradrenaline only in moxonidine-responders, when compared with the non-responders, in whom no adequate blood pressure control was observed. These differences probably represent the heterogeneity of sympathetic activity in obese hypertensive individuals. It is possible that significant effects on noradrenaline levels in non-responder groups may have been seen if a larger dose of moxonidine had been used. Amlodipine had no effect on resting and stimulated levels of catecholamines.

In the present study no significant changes in plasma renin activity and plasma aldosterone was observed with moxonidine. However, amlodipine significantly increased plasma renin activity. This is in contrast to other studies showing a decrease in plasma renin [31, 32] after single oral administration of moxonidine. Two possibilities could explain these findings. Firstly, our patients were in the supine position during sampling for renin activity. Therefore, plasma renin was not stimulated and could not be further suppressed by moxonidine. Secondly, it may be that in obese hypertensives more moxonidine is required to lower renin levels.

Reducing blood pressure is the main but not the only parameter that must be taken into account in the choice of therapeutic regimen in obesity hypertension. It has been reported that some antihypertensive drugs may exert a negative effect on glucose and lipid metabolism [33], while others have no effect on these parameters [34], or may improve insulin sensitivity [35].

Studies in animal models of insulin resistance, the fructose rat [36] and the spontaneously obese hypertensive rat [27], suggest that moxonidine might have favorable effects on features of the metabolic syndrome. Results of a double-blind placebo controlled study of moxonidine on whole-body insulin sensitivity, using glucose-clamp technique, showed that moxonidine improved insulin-mediated glucose disposal in obese patients with hypertension [37]. Our findings have shown that there was a statistically significant difference over the 6-month antihypertensive treatment in 120 min insulin after glucose load, 23 % reduction in fasting insulin and 18 % amelioration in HOMA insulin sensitivity. These effects on glucose metabolism were substantial considering that modifications on fasting and 120 min plasma glucose after glucose load were minor, which was accompanied by a decline in fasting plasma insulin, demonstrating an improvement in insulin sensitivity. Furthermore, patients who had their blood pressure controlled by moxonidine have shown a statistically greater reduction in fasting insulin concentration when compared with blood pressure non-responders on moxonidine. These evidences may support the conclusion

that moxonidine improves insulin sensitivity. This may be accounted for by its ability to reduce sympathetic activity [38] or by the capacity to increase the concentration of IRS-1, an intracellular factor essential for insulin-mediated activation of glucose disposal [39].

Several observations suggest that leptin and its multiple interactions with neurochemical pathways in the hypothalamus may be a partial link between excess weight increases, sympathetic overactivity and obesity hypertension [40, 41]. Most obese subjects and obese hypertensive patients have high circulatory leptin level, even when leptin is corrected for body mass index [9, 42]. This fact has been interpreted as resistance to the action of leptin as these subjects continue to overeat, despite leptin being an anorectic hormone by its interactions with an array of neurochemicals such as the melanin concentrating hormone [43].

In the present study plasma leptin levels had dropped at 24 weeks of treatment with moxonidine. Few clinical studies have examined the effect of moxonidine treatment on leptin levels [44]. Most of the data available are concerned with antihypertensive treatment concomitant with weight-loss and aerobic exercise, which may reduce adipose tissue, the main source of leptin [42]. However, our obese hypertensive patients maintained their weight practically unchanged throughout the intervention period, as they were not on calorie restriction diet.

It is not clear how moxonidine reduces plasma leptin. Moxonidine ability to improve insulin resistance and to suppress stimulated noradrenaline, confirmed in our study, could be a possibility. There is still ambiguity concerning the initiating event and which neuroendocrine changes are secondary in the evolution of obesity-related hypertension. On the other hand, our findings have shown that there was an interaction between plasma leptin level reduction and blood pressure response with moxonidine, since the subjects who had their blood pressure controlled had much greater decreases in fasting plasma leptin.

Blood pressure and neurohormonal changes were followed at 12-week intervals during moxonidine and amlodipine intervention. Decreases in standing venous noradrenaline, and insulin 120 min after glucose load were noted earlier, at 12-week visit, and with time there were further and significant declines in these parameters. Although plasma leptin levels did fall by 24-week, the reduction in plasma catecholamines and insulin level were noted prior to leptin decrease. These results suggest that moxonidine-induced blood pressure reduction is mainly related to suppression of SNS-overactivity, and improvement of insulin sensitivity.

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