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Original article

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EFFECTS OF THE IMIDAZOLINE-RECEPTOR-AGONIST MOXONIDINE ON HEMODYNAMICS, CORONARY FLOW, METABOLIC ISCHEMIC MARKERS AND THE NEUROHUMORAL SYSTEM IN PATIENTS WITH "MICROVASCULAR ANGINA"

SUMMARY

Moxonidine, a new centrally active imidazoline receptor–agonist, might represent a new clinically beneficial antihypertensive principle. This is the first investigation regarding the effects of moxonidine on coronary and systemic hemodynamics, metabolic markers of ischemia and neurohumoral parameters. We studied moxonidine (single dose of 0.4 mg p.o.) in 22 patients with hypertension (WHO I-II) and left ventricular (LV) hypertrophy, ST segment depressions during exercise, pectanginal complaints and negative coronarograms. Assessments included arterial blood pressure, cardiac output, pulmonary artery pressure mean (PAPm), pulmonary capillary wedge pressure (PCWP) and coronary sinus flow (CSF) by intravascular Doppler technique. The average moxonidine-induced parameter changes ($p<0.05$, at least), at about 2 hours later, were as follows: a decrease in systolic/diastolic pressure by 28/10 mmHg, and in heart rate by 5 bpm, associated with a decline of PAPm by 17% and of PCWP by 26%. LV-work was reduced by 26%, MVO_2 by 18% and CSF by 16%. Average peak velocity in CS fell by 18% and coronary flow reserve (with adenosine) increased by 12%. CS-0_2 saturation rose by 4%, accompanied by an increase in lactate extraction by 17%, a decrease in norepinephrine spillover by 30% and in arterial endothelin by 20%. Conclusion: moxonidine produces clinically relevant sympathicolysis with beneficial effects on hemodynamics, coronary circulation and neurohumoral parameters.

***Key words*: essential hypertension, coronary reserve, moxonidine, adenosine, hemodynamics, neurohormones**

INTRODUCTION

Approximately 50 – 70% of the patients showing essential hypertension, left ventricular hypertrophy and normal coronary angiogram may still suffer from anginal symptoms (1). Factors responsible for the pathogenesis of anginal symptoms are defined by reduced coronary reserve and increased myocardial oxygen consumption. Impaired coronary reserve in hypertensive disease is characterized clinically by angina pectoris, known as "microvascular angina", pathological ergometry results and a normal coronary angiogram (1).

Moxonidine, like rilmenidine, is a new centrally active antihypertensive drug with sympatholytic and neurohormonal effects (9–11). According to previous investigations (2,3) its pressure regulating properties are attributed to specific and selective affinities to imidazoline-1 (I_1)-receptors located in the medulla, kidneys and vessels which in

turn stimulate inhibitory systems by reducing central and peripheral sympathicotonus and the activity of the renin-angiotensin-aldosterone system (9,10). Recently, moxonidine's highly specific and selective affinity to I_1-receptors was found to be effective by the factor 300 as compared to alpha$_2$-receptor affinity (4–6). While classic centrally active alpha$_2$agonists (like clonidine) generate discomforting side effects, such as dry mouth and drowsiness by way of stimulating presynaptic alpha$_2$-receptors alone, the well tolerated moxonidine's lack of side effects may be due to its high selectivity for I_1-receptors (7,8).

The aim of the present study was to examine hemodynamics, coronary flow, neurohormonal activities, metabolic ischemia markers, and humoral parameters of endothelial function, both with and without moxonidine, in hypertensive patients with their coronary system intact. The same parameters were examined using adenosine as pharmacological stress test.

METHODS

Patients

Twenty-two patients with essential hypertension (WHO stage I-II) participated in the clinical investigation, 8 female and 14 male, with a mean age of 62.1±8.1 years. In all patients presenting with angina pectoris (CCS class II), coronarography had revealed the coronary system being intact and normal while ergometry testing showed ST segment depressions. Mean exercise tolerance amounted to 100±25 watt. Initial values for arterial pressures were 167±18/92±12 mmHg (mean±SD). Left ventricular hypertrophy was present both in the ECG and echocardiographic recordings in 14 patients, and in 8 patients in echocardiography only. Mean duration of hypertension was 8±3 years. No patient was reported to have diabetes mellitus, valvular diseases or hypertrophic cardiomyopathy. Hyperlipoproteinemia was found in 9 patients being treated with statins or fibrates. Of all patients included in the study, 10 had undergone treatment with ACE-inhibitors, 5 with Ca^{2+}-antagonists, 4 with betablockers and the remaining 3 with diuretics (5 – 11 years). Clinical and hemodynamic parameters are presented in table 1. Written informed consent was given by all patients; the study had been approved by the institutional committee on human research.

Design and course of the study

This was an open label, baseline controlled, monocentric study and all patients received a single oral dose of 0.4 mg moxonidine. After the screening visit, the accepted patients took part in a wash-out period for antihypertensive medication for 5-7 drug half lives at least. Only then were investigations carried out in all patients in fasting state at 8.30 a.m.

Table 1. Demographic and hemodynamic characteristics of the study group.

age	years	62,1 ± 8,1
sex	m/f	14 / 8
weight	kg	84,4 ± 15,9
height	m	1,71 ± 0,10
BMI		28,8 ± 3,5
heart rate	1/min	71 ± 11
blood pressure	mm Hg	167±18 / 92±12
CO	l/min	5,6 ± 1,4
PCWP	mmHg	8,9 ± 3,0
SVR	dyn·s·cm-5	1657 ± 387

BMI = Body Mass Index; CO = Cardiac Output; PCWP = Pulmonary Capillary Wedge Pressure; SVR = Systemic Vascular Resistance

Evaluation of hemodynamic parameters and Doppler flow measurements was performed by an experienced cardiologist knowing the measurement techniques, yet being uninformed about the patients and the order of examinations.

Hemodynamic measurements

Coronary sinus flow measurements were carried out via 7F-Elgamal catheter: the Doppler-tipped guidewire, the 0.018-in. Cardiometrix--Flow-Wire TM (AD Krauth, Hamburg), being advanced from the right V. femoralis into the right atrium, positioned into the coronary sinus under fluoroscopic control. Then adenosine was applied intravenously, 0.14 mg/kg/min, over 6 min, in order to achieve maximal coronary dilation for the assessment of coronary reserve. Coronary reserve was calculated as the relation of the maximal increase of the blood flow velocity over the flow velocity under resting conditions. Two hours after the oral administration of moxonidine 0.4mg, hemodynamic measurements as well as the assessment of the coronary reserve were repeated.

Pulsed-wave Doppler ultrasonography was used to assess the time-averaged peak coronary flow velocity calculated on-line over two cardiac cycles

through a 2-mm sample volume at a location approximately 5 mm distal of the tip of the guidewire. The information of the Doppler shift is assessed, transformed into a spectral image and then recorded. The flow-map system assesses the actual peak velocity of the curve (IPV). The basic measurements carried out by the flow-map system can be divided into four categories. The following measurements are based on the time-integrated peak mean velocity (IPV): APV (average peak velocity), MPV (maximum peak velocity), ADPV (average diastolic peak velocity), ASPV (average systolic peak velocity), DSVR (diastolic/systolic velocity ratio). An additional two measurements quantify the evolving signals as well as the coronary flow reserve. The coronary flow velocity reserve (CFR) is calculated by dividing APV adenosine by APV control ratio.

In 10 patients, assessment of the coronary sinus flow (CSF) was achieved according to the method as follows: radiologic measurement of the diameter (D) of the coronary sinus, to obtain the vessel's cross section: CSA (cm^2) = $(D/2)^2$. Calculation of stroke volume: SV (ml) = CSA x APV, of coronary sinus flow: CSF (l/min^{-1}) = SV x HF, of coronary vascular resistance: CVR (mmHg x ml^{-1}.x min) = AOPM/CSF x 80. For all assessments a 15 min resting period was allowed. Angiographic depiction of coronary sinus and diameter reference measurements were performed twice before adenosine application and were identical. Moxonidine measurements were done two hours after the first adenosine application, well after return to basic reference values.

Right heart catheterization used standard procedures. A 7F Swan-Ganz-Thermodilution Catheter was advanced via V. cubitalis into pulmonary capillary-wedge position. Evaluation of hemodynamic data, coronary flow and neurohumoral parameters was performed allowing 30 min rest following the insertion of all catheters and cannulae. Moxonidine was administered 10 min after the 1st adenosine test. Hemodynamic data were assessed: the resting control, during the 1st adenosine infusion, 2 hours after the application of moxonidine and finally after the 2nd adenosine infusion. Thermodilution cardiac output estimation used standard procedures. Myocardial oxygen consumption was calculated indirectly according to the formular of Rooke and Feigl (12). Arterial pressure was measured in the brachial artery.

Metabolic ischemia marker

Blood samples were taken from the coronary sinus via Elgamal catheter as well as arterially: at resting control, during adenosine application and 2 hours after moxonidine measurements of pH, pCO_2, pO_2 were taken pontiometrically and electrochemically using standard procedures; O_2 saturation was assessed photometrically (type Unistad, American Oxymeter). Lactate concentration was measured enzymatically (model Biosen 5020L). Potassium concentration was assessed flame photometrically (model 6341, Eppendorf). Extractions were calculated: lactate extraction = lactate (arterially) – lactate (coronary venously); oxygen extraction = $O_{2\ sat}$ (arterially) - $O_{2\ sat}$ (coronary venously).

Neurohumoral system

Blood samples (arterially and venously from the coronary sinus) were taken under resting conditions, after adenosine infusion and after the application of moxonidine. Plasma concentrations of noradrenaline and adrenaline were measured from 1 ml samples with use of HPLC with electrochemical detection after previous extraction. The lower limit of detection was 8 pg/ml. Transmyocardial noradrenaline spillover was calculated as aorto-coronary sinus difference. Plasma renin activity was measured in 1 ml samples with use of a competitive binding ^{125}I-radioimmunoassay of a commercially available angiotensin-I kit (Incstar, Stillwater, USA); the lower limit of detection was 0.02 ng/ml/h. Endothelin I concentration was assessed with the use a competitive binding ^{125}I-radioimmunoassay; the lower limit of detection for the commercial kit (Nichols Institute, Wijchen, The Netherlands) was 1,0 pg/ml.

Statistics

For hemodynamic parameters assessed, desciptive statistics (means and standard deviations) were calculated. For the neurohumoral parameters and the metabolic ischemia markers the median and the respective percentile (25% and 75%) were assessed. For the assessment of statistic significance, mean values and medians, respectively, were calculated by the t-test with Bonferoni's correction and a one-way ANOVA with repeated measurements, using Dunnett's post hoc test. For all comparisons, differences were considered to be statistically significant when $p<0.05$.

RESULTS

Heart rate and blood pressure

Adenosine-induced systemic vascular dilatation led to an increase in heart rate (HR) by 15 bpm (86 vs. 71 bpm; $p<0.01$). Moxonidine reduced HR by 5 bpm (66 vs.71 bpm; $p<0.05$). After another application of adenosine, the maximal decrease in HR

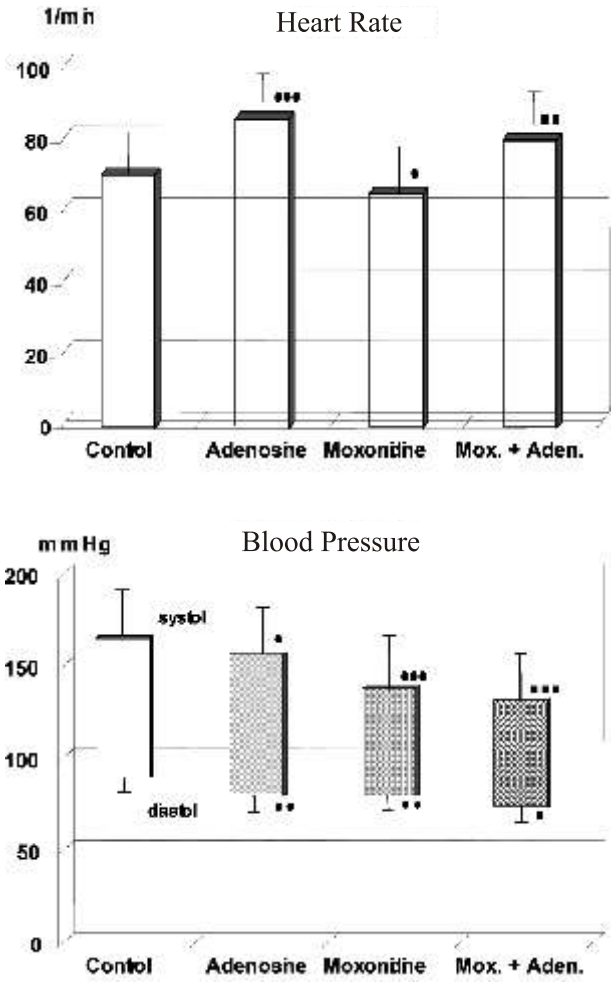

Figure 1. Changes in heart rate and blood pressure after adenosine, moxonidine and the combination of both (●=p<0.05; ●●=p<0.01; ●●●=p<0.001 vs. control; ■=p<0.05; ■■=p<0.01; ■■■=p<0.001 vs. adenosine).

was 5 bpm (p<0,01 vs the 1st adenosine infusion; fig. 1).

During the first application of adenosine, systolic blood pressure (BP) declined by 11 mmHg (p<0.05) and diastolic BP by 10 mmHg (p<0.01). After the application of moxonidine, systolic BP fell by 28 mmHg (p<0.001) and diastolic BP by 10 mmHg (p<0.001). After another application of adenosine, systolic BP was reduced additionally by 6 mmHg (p<0.01) and diastolic BP by 6 mmHg (p<0.05).

Right heart hemodynamics

Right atrial (RA) pressure did not change during any of the interventions (p>0.05).

Adenosine had no effect on pulmonary artery pressure mean (PAPm), but moxonidine induced PAPm to decrease by 3mmHg (p<0.001). After the 2nd adenosine infusion PAPm did not change (p>0.05; fig. 2).

With adenosine there was an increase in pulmonary capillary wedge pressure (PCWP) by 2.6 mmHg (11.5 vs 8.9 mmHg; p<0.01). Moxonidine induced a decrease of PCWP by 2.3 mmHg (6.6 vs 8.9 mmHg; p<0.001). The 2nd adenosine infusion promoted an increase of PCWP by 2.9 mmHg, less than control (p<0.01; fig. 2).

Cardiac output

The 1st adenosine infusion induced an increase of cardiac output (CO) by 2.4 l/min (8.0 vs. 5.6 l/min; p<0.001). Moxonidine reduced CO by 1,0 l/min (p<0.001). With the 2nd application of adenosine (vs.1st adenosine application), CO rather fell by 1.3 l/min (p<0.05; fig. 2).

With adenosine, stroke volume index rose by 6.4 ml/m^2 (p<0.05) and there was no change with moxonidine.

Systemic and pulmonary vascular resistance

The 1st adenosine-infusion induced SVR to decrease 520 dyne·s·cm^{-5} (1137 vs. 1657 dyne s cm^{-5}; p<0.001); moxonidine left it unchanged (p>0.05). The 2nd adenosine-infusion decreased SVR by 594 dyne s cm^{-5} (p>0.05) and thereby also failed to show relevant changes vs. the 1st adenosine application.

PVR-changes showed quite similar characteristics: PVR declined by 57.6 dyne s cm^{-5} (71.2 vs.128.8 dyne s cm; p<0.001) after adenosine. Moxonidine induced a slight increase to 143.4 dyne s cm^{-5}). With the 2nd adenosine-infusion, PVR was reduced by 47.9, i.e. an increase vs. the 1st adenosine-infusion by 24.3 dyne s cm^{-5} (p<0.01).

Coronary sinus flow, coronary flow velocity, coronary vascular resistance

Adenosine induced APV to increase by 8cm/s (19 vs.11 cm/s; p<0.001). The influence of moxonidine led to a decrease of APV by 2 cm/s; p<0.05. During the 2nd adenosine infusion, APV rose further, but was not significantly diminished as compared to control (fig. 3). Moxonidine induced an incease of CFR by 1.81 to 2.03 units. With the 1st adenosine infusion, CSF (n=10) rose by 194 ml/min (388 vs 194 ml/min; p<0.01), while the reduction with moxonidine was not significant after the 1st adenosine administration (by 31 ml/min; p>0.05). The 2nd adenosine infusion decreased CSF by 46 ml/min vs. the 1st adenosine infusion (p>0.05; fig. 3). While CVR (n=10) decreased by 35 mmHg/ml^{-1}/min (29.9 vs.64.9 mmHg/ml^{-1}/min; p<0.01), the moxonidine-induced decrease of CVR by 1.6 mmHg/ml^{-1}/min was insignificant (p>0.05).

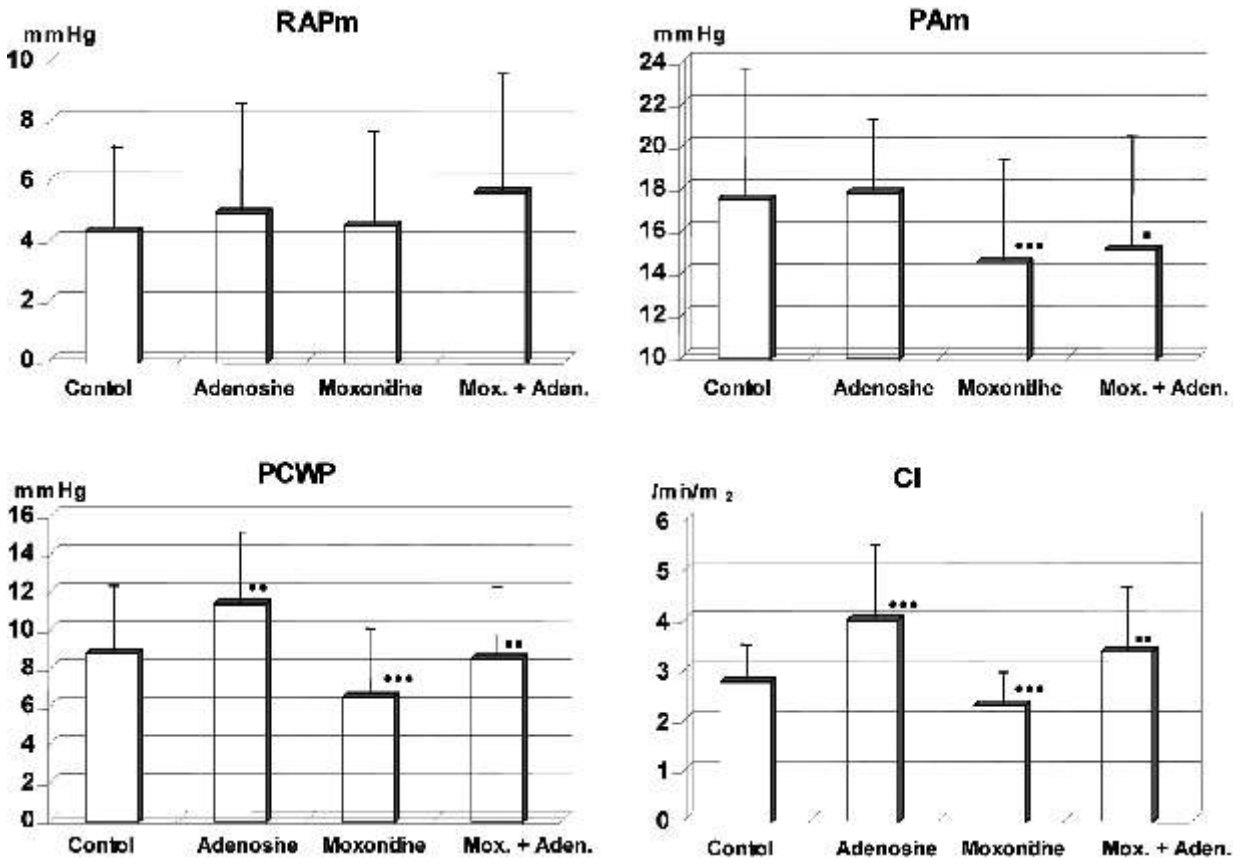

Figure 2. Hemodynamic changes of right atrial, pulmonary artery-, pulmonary capillary wedge pressure and cardiac index after adenosine, moxonidine and the combination of both (●=p<0.05; ●●=p<0.01; ●●●=p<0.001 vs. control; ■=p<0.05; ■■=p<0.01; ■■■=p<0.001 vs. adenosine).

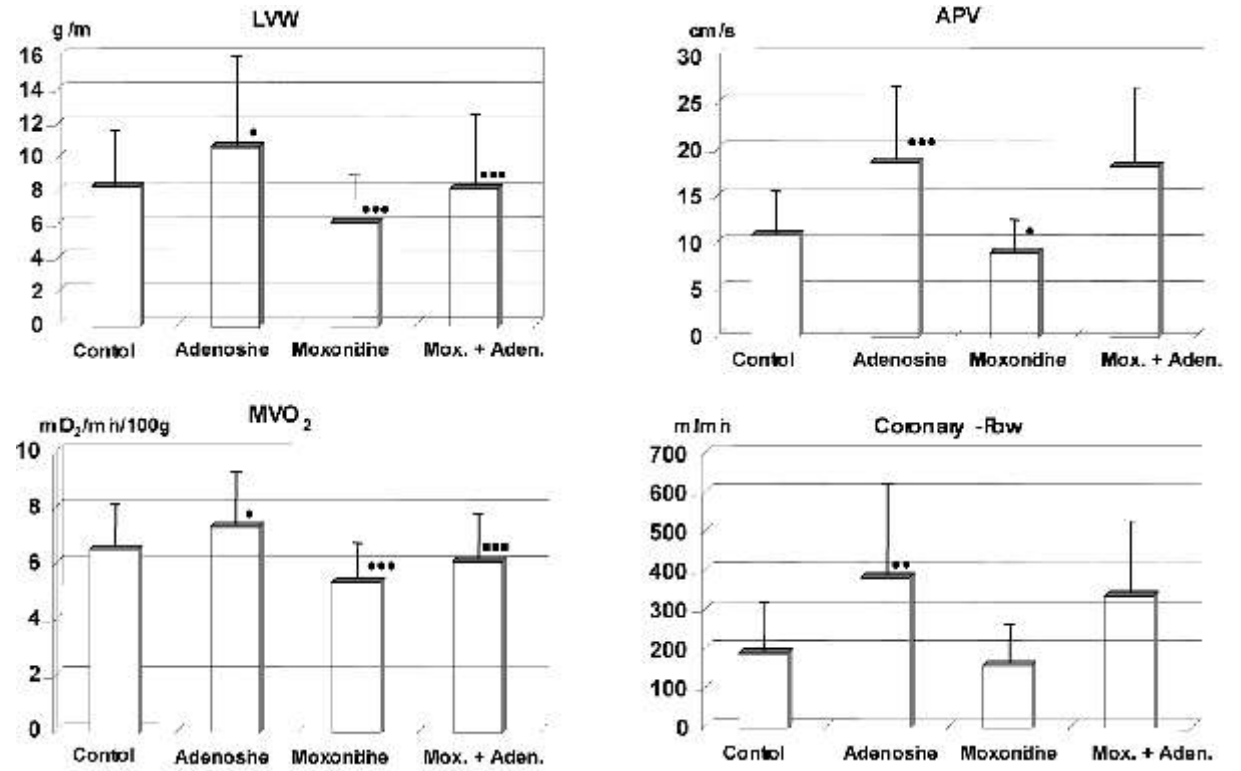

Figure 3. Changes of left ventricular work (LVW), average peak velocity (APV) in coronary sinus, myocardial oxygen consumption, and coronary flow (N=10) after adenosine, moxonidine and the combination of both (●=p<0.05; ●●=p<0.01; ●●●=p<0.001 vs. control; ■=p<0.05; ■■=p<0.01; ■■■=p<0.001 vs. adenosine).

With the 2nd adenosine infusion, CVR fell considerably and proved to be decreased by 4 mmHg/ml^{-1}/min vs. control.

Left ventricular stroke work index (LVSWI)

The 1st adenosine infusion induced an increase of LVSWI by 2.34 g/m (10.69 vs. 8.35 g/m; $p<0.05$). With moxonidine a decrease occurred by 2.15 g/m ($p<0.001$). The decrease of the LVSWI by 2.47 g/ml as induced by the 2nd adenosine infusion was significantly less as compared to the reduction during adenosine infusion alone ($p<0.001$; fig. 3).

Myocardial oxygen consumption (MVO_2)

During the 1st adenosine infusion, MVO_2 increased by 0.83 ml O_2/min/100g (7.39 vs. 6.57 ml O_2/min/100g; $p<0.05$). Moxonidine induced a decrease by 1.17 ml O_2/min/100g ($p<0.001$). During the 2nd adenosine infusion MVO_2 was diminished by 1.24 ml O_2/min/100g vs. the 1st adenosine infusion ($p<0.001$; fig. 3).

Metabolic ischemia marker

During the 1st adenosine-infusion, arterial O_2-saturation increased absolutely by 2.8% (96.8 vs. 94.0%; $p<0.05$) and O_2-saturation in the coronary sinus by 25.6% (74.6 vs. 49.0%; fig. 4; $p<0.001$). During control conditions, O_2-extraction was 45% and 22.2% after adenosine application, and after moxonidine it showed no difference ($p>0.05$): 94.2 vs. 94.0% as assessed in the arteries and 51.1 vs. 49.0% as collected in the coronary sinus.

During the 1st adenosine-infusion, arterial lactate decreased by 0.19 mmol/l (1.04 vs. 1.23 mmol/l; $p>0.05$), while in the coronary sinus lactate did not change ($p>0.05$). Lactate extraction was –0.06 mmol/l and with adenosine –0.27 mmol/l. With moxonidine there was a decrease of lactate, both arterially (1.03 vs. 1.23 mmol/l; $p<0.05$) and venously (1.08 vs. 1.29 mmol/l; $p<0.05$). Lactate extraction was –0.06 mmol in control and –0.05 mmol/l with moxonidine. With the 2nd adenosine infusion there was no change ($p>0.05$), while in the coronary sinus, lactate increased by 0.11 mmol/l (1.19 vs. 1.08 mmol/l). As compared to the 1st adenosine-infusion, this represented a decrease of 0.12 mmol/l ($p>0.05$). With moxonidine during the adenosine infusion there was an increase of lactate extraction (–0.27 vs. -0.21 mmol/l; fig. 4).

Concentration of hydrogen (pH) in arterial and venous blood samples increased further with adenosine ($p<0.01$), whereas with moxonidine no significant changes were found.

Neurohormones

With the 1st adenosine-infusion, arterial noradrenaline concentration rose by 23 pg/ml (248 vs. 225 pg/ml; $p<0.05$) while that in coronary sinus fell by 106 pg/ml (309 vs. 415 pg/ml; $p>0.05$; fig. 4). The noradrenaline spillover was 190 pg/ml (control) and 61 pg/ml after adenosine infusion. Moxonidine induced a decrease of noradrenaline arterially (148 pg/ml; $p>0.05$) and venously as well (281 pg/ml; $p>0.05$; fig. 4), while noradrenaline spillover fell from 190 to 133 pg/ml. With the 2nd adenosine-infusion, noradrenaline concentration again increased arterially 61 pg/ml less than with the 1st adenosine infusion ($p>0.05$) and decreased venously as well 46 pg/ml less than with the 1st adenosine infusion ($p>0.05$; fig. 4). Noradrenaline spillover decreased from 133 to 76 pg/ml, i.e. somewhat increased versus control.

During the 1st adenosine-infusion, no changes were observed in plasma renin activity or were induced by moxonidine (neither arterially nor venously). During the 2nd adenosine-infusion, plasma renin activity increased, but did not change venously compared to the 1st adenosine-infusion.

With the 1st adenosine-infusion, there was an insignificant increase in endothelin concentration, arterially (3.7 vs 3.0 pg/ml; $p>0.05$) as well as venously (3.43 vs. 3.3 pg/ml; $p>0.05$. A decrease was induced with moxonidine, arterially (2.4 vs. 3.0 pg/ml; $p>0.05$) as well as coronary-venously (3.1 vs 3.3 pg/ml; $p>0.05$. During the 2nd adenosine-infusion as well, endothelin concentration increased, both artertially (3.7 vs. 2.4 pg/ml; $p>0.05$) and venously (3.4 vs 3.1 pg/ml; $p>0.05$). Thus, the maximal endothelin concentration during adenosine-infusion plus moxonidine did not change ($p>0.05$).

Moxonidine was well tolerated by all patients with only one reporting a slight dryness of the mouth. Apart from this, no further side effects were observed.

DISCUSSION

Patients afflicted with arterial hypertension often present with upper thoracal pain sensations quite similar to those observed in angina pectoris vera. In addition they might show ergometer test results suggestive of myocardial ischemia. However, even though some of these patients in actual fact might suffer from coronary artery disease, most of them are found to present with normal coronary angiogram (13). Two main factors are involved in

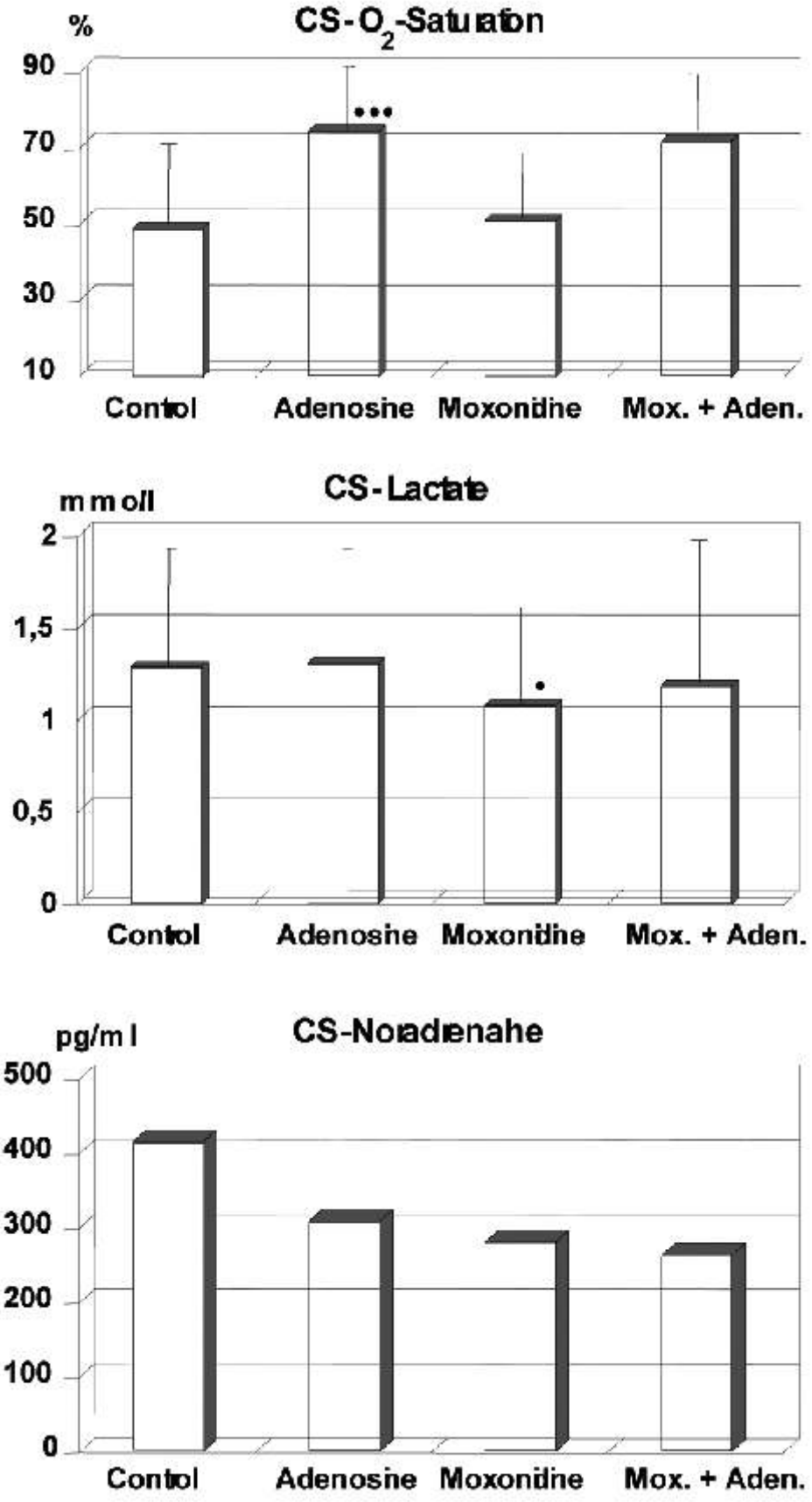

Figure 4. Changes of O2-saturation, lactate and noradrenaline in coronary sinus (CS) after adenosine, moxonidine and the combination of both (●=p<0.05; ●● =p<0.01 vs. control).

the pathogenesis of anginal symptomatology in these patients: reduced coronary reserve and increased myocardial energy demand (1). There are several potential factors responsible for a reduced coronary reserve, such as structural changes based on hypertension-induced left ventricular hypertrophy and there is wall thickening of the coronary microvascular tree (remodeling) and rarefication of the capillaries (reduced number of intramyocardial vessels) (14,15). In addition, there are functional mechanisms like endothelial dysfunction (16). Furthermore, extravascular effects, originating in the myocardium itself, might contribute to an increase of coronary vascular resistance in the hypertrophied heart. Although left ventricular hypertrophy obviously has its implications on ventricular diastolic function, its effects cannot be held responsible for the regression of coronary artery reserve under all circumstances (17,18).

All things considered, essential hypertension presents itself as a cardiac disease in which increased myocardial and coronary flow plus and augmented myocardial oxygen consumption are achieved even though coronary vascular resistance is elevated (19 – 21). For alterations of myocardial energy demand changes in coronary flow are the key issue since arteriocoronary-venous oxygen extraction is complete (maximal, submaximal, respectively) and cannot be augmented by additional oxygen extraction (22,23).

Hemodynamic changes

The patients investigated had elevated arterial pressures and mean systemic vascular resistance; heart rate, right ventricular pressure, cardiac output, stroke volume as well as pulmonary vascular resistance, all were within normal limits. Assessment of coronary reserve using adenosine infusion revealed an augmentation of the mean peak velocity of coronary sinus flow by 67%, while coronary vascular resistance was diminished by 54%. Coronary flow reserve averaged 1.81, which is indicative of a reduced coronary reserve. This correlates well with former investigators‘ results (24): During dipyridamol-infusion, flow velocity (Doppler Catheter) increased by the factor 2 and coronary flow reserve was markedly reduced in the presence of cardiac disease. In yet another investigation (25), using the Argon technique and dipyridamol, coronary vascular resistance correlated well with the left ventricular enddiastolic pressure, probably mainly on account of which a reduction of coronary reserve by 40% was appreciated.

In our own investigation, moxonidine, applied acutely, provoked a rather slight increase in coronary reserve, better results yet have been accomplished with chronic moxonidine-treatment (26). With moxonidine, a regression of left ventricular hypertrophy clearly has been achieved, which constitutes the most important single risk factor in hypertonics. Since moxonidine reduces left ventricular hypertrophy, coronary reserve improves. This effect is probably based on a regression of media hypertrophy of the myocardial arterioles, a decrease of the extracoronary resistance during the regression of left ventricular hypertrophy, and a reduction of intramural pressure. These microangiopathies cannot be appreciated by angiography, but they still may explain angina pectoris of hypertensive patients presenting with normal coronarograms.

With the application of moxonidine, beneficial effects on coronary flow reserve have been reproducibly achieved in hypertensive rats (26). Based on these results a clinical study was designed, involving hypertensive patients, who suffered from angina pectoris although coronarography had revealed normal coronaries. During their 9-12 months lasting moxonidine-treatment with a daily dosage of moxonidine 0.4-0.8 mg, coronary flow reserve doubled in all patients, and coronary resistance reduced about by one third. This indicates an improved coronary microcirculation which manifested itself clinically as well as an ergometrically raised anginal threshold (26).

Simultaneously, during adenosine application in this study, relevant hemodynamic alterations were ascertained: Stimulating the A2 receptors, peripheral vasodilation was registered, while systolic and diastolic pressures declined. This induced an increased sympathicus activity with an increment of heart rate by 21% and of cardiac output by 43%, while pulmonary capillary wedge pressure increased moderately.

Moxonidine reduced significantly systolic and diastolic pressures by 28 and 10 mmHg, respectively. With the repeat adenosine-infusion, an additive decrease of blood pressures ensued. Adenosine again induced an increase: maximal heart rate, however was found to be less by 5 bpm compared to control. PAPM (-17%) as well as PCWP (-26%) were significantly reduced with moxonidine. The increase of these adenosine-induced hemodynamic values was rather reduced with moxonidine. Due to sympathicolysis aside from a decrease in heart rate, cardiac output diminished by 18%.

Our present investigational results indicate moxonidine having induced clinically relevant sympatholysis as clinically reflected in a reduction of heart rate and arterial pressure. Diminished heart rate is accompanied by reduced cardiac output (27). With the reduction of cardiac output in the present

study peripheral and systemic vascular resistance rose even though arterial pressure had fallen.

The investigation of coronary hemodynamics under the influence of moxonidine produced a significant decline of the average peak velocity by 18%, of the average diastolic peak velocity by 20%. During repeat adenosine, stress average peak velocity rose nearly up to the values assessed during the 1st adenosine-infusion. Moxonidine induced an augmentation of coronary reserve by 12%, and a decrease of coronary sinus flow by 16%, while coronary resistance fell by only 3%.

Due to a decrease in blood pressure, moxonidine also produced beneficial work load conditions: left ventricular stroke work being reduced by 26% and myocardial oxygen consumption by 18% (correlating well with the fall of coronary flow). Simultaneously, there was a slight increase of O_2-saturation by 4% in the coronary sinus and an increase in lactate-extraction.

Influence on neurohumoral system

In the present study, noradrenaline plasma levels in the coronary sinus were elevated, arterially they were within normal limits. Moxonidine produced a decrease in the coronary sinus noradrenaline concentration by 31% and arterially by 33%. Furthermore, during moxonidine influence the increase of the noradrenaline level usually expected from adenosine stress was prevented. Noradrenaline concentration usually is found to be higher in the coronary venous system as compared to the arterial system: so noradrenaline is set free and produces a spillover being reduced by Moxonidine. Plasma renin activity in the coronary sinus diminishes somewhat, but does not change arterially. These decreases in plasma renin activity and noradrenaline plasma levels have been reported (10,27,28). The application of moxonidine led to a slight decrease of endothelin concentration, arterially by 20% and coronary venously by 6%, respectively.

Pathologically increased sympathotonus (may) lead to hypertension (29) and thereby is a precursor of left ventricular hypertrophy (30). In hypertonics, the renin-angiotensine system is activated by an increased sympathotonus, followed by rising arterial pressures, laying the ground for vascular hypertrophy, as well as for the development of myocardial hypertrophy (31). It is a new observation moxonidine to decrease plasma concentrations of endothelin. Although, obviously, there are interconnections of sympathotonus, plasma renin activities and endothelin levels, a clear cut pathophysiological explanation for this property of moxonidine is lacking. However, endothelin also has potent vasoconstrictor properties (32,33), and its diminution by moxonidine certainly can be considered as positive therapeutical aspect under hypertensive conditions.

LIMITATIONS OF THE STUDY

One of the major limitations of the present study is the absence of a control patient collective. For reason of the invasive character and the duration of the investigations, recruiting a control group and following a double blind study design was not justifiable from the investigators' point of view. The objectivity of the study was guaranteed by an independent evaluator unaware of the patients and the order of examinations. As to our knowledge, flow measurements in the coronary sinus by use of intravascular Doppler-technique are a novelty and therefore the present evaluation using this technique is to be regarded as pilot study. Although the position of the flow probe was constant at all times, proof for instability as induced by heart contractions cannot be established. In our view, the mistake induced thereby cannot be of relevance. The second venography of the coronary sinus performed two hours after administration of moxonidine demonstrated that the position of the Doppler flow wire was stable and flow signals were of good quality. Diameters of the coronary sinus did not change significantly after moxonidine compared to initial values. Corresponding measurements after administration of adenosine were not performed.

Measurements of changes in the coronary sinus flow reflect alterations found in left ventricular stroke work and MVO_2 confirming that the assessment of the coronary sinus flow by use of intravascular Doppler flow represents an accurate method as to scientific and diagnostic aspects. Nevertheless, further methodic investigations are required.

CONCLUSION

Summing up, there is evidence of moxonidine to generate eminent sympatholytic effects. This is born out by the moxonidine-induced depressions of heart rate and blood pressure, while left ventricular enddiastolic pressure is decreased improving left ventricular compliance. Thereby, stroke work and myocardial oxygen consumption are reduced and so is cardiac workload. Since coronary flow correlates directly with myocardial oxygen consumption, a reduction is imminent also in these parameters as also evidenced by the results of our study. These beneficial hemodynamics effects are active under

adenosine stress as well. In addition, moxonidine applied acutely, induces a slight increase of coronary flow reserve and a decrease of coronary vascular resistance. Generally, an improved coronary regulatory potential can be ascertained. While there is a decrease of myocardial oxygen consumption, coronary venous oxygen saturation rises at rest as well as during adenosine stress and lactate concentation decreases. At the same time lactate extraction rises. These findings document an improved balancing of myocardial oxygen consumption. Moxonidine induced sympathicolysis correlates well with decreased noradrenaline plasma levels at rest and during adenosine stress, as evidenced coronary venously as well as arterially, whereby the noradrenaline spillover has vanished 2 hours later already. From the results of the present investigation, moxonidine seems to generate beneficial therapeutic properties, such as in arterial hypertension, left ventricular hypertrophy and angina pectoris; the combination of arterial hypertension and ischemic coronary artery would probably benefit most from moxonidine-therapy. But further clinical studies are required to ascertain these theoretical assumptions.

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EFEKTI IMADAZOLIN -RECEPTOR-AGONISTA MONOXIDINA NA HEMODINAMIKU, KORONARNI PROTOK METABOLI^KE ISHEMIJSKE MARKERE I NEUROHUMORALNI SISTEM U BOLESNIKA SA “MIROVASKULARNOM ANGINOM”

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SA@ETAK

Moksonidin, novi centralno aktivni imidazolin-agonist, mo`e predstavljati nov, klini~ki upotrebljiv antihipertenzivni princip. Ovo je prvo istra`ivanje efekata moksonidina na koronarnu i sistemsku hemodinamiku, metaboli~ke markere ishemije i neurohumoralne parametre. Ispitivali smo moksonidin (pojedina~na doza od 0.4 mg p.o) na 22 pacijenta sa hipertenzijom (WHO I-II) i levom ventrikularnom (LV) hipertrofijom, depresijama ST segmenta tokom naprezanja, pektanginalnim tegobama i negativnim koronarogramima. Procene su uklju~ivale arterijski krvni pritisak, sr~ani autput (proizvod), prose~ni pritisak plu}ne arterije (PAPm), plu}ni kapilarni wedge-pritisak (PCWP) i koronarni sinusni protok (CSF) intravaskularnom Doppler tehnikom. Prose~ne moksonidinom indukovane promene parametara ($p<0.05$, najmanje) oko 2 sata kasnije bile su: smanjenje sistoli~nog/dijastoli~nog pritiska za 28/10 mmHg, pulsa za 5 bpm, uz smanjenje PAPm za 17% i PCWP za 26%. LV-rad bio je smanjen za 26%, MVO za 18% a CSF za 16%. Prose~an pik brzine u CS pao je za 18% a rezerva koronarnog protoka (sa adenozinom) porastao je za 12%. CS-O zasi}enje poraslo je za 4%, uz porast ekstrakcije laktata za 17%, smanjenje vi{ka norepinefrina za 30% i arterijskog endotelina za 20%. Zaklju~ak je da moksonidin proizvodi klini~ki relevantnu simpatikolizu sa pozitivnim efektima na hemodinamiku, koronarnu cirkulaciju i neurohumoralne parametre.

Klju~ne re~i: esencijalna hipertenzija, koronarna rezerva, moksonidin, adenozin, hemodinamika, neurohormoni