# SUMMARY AND CONCLUSION

Classic centrally acting antihypertensive drugs are assumed to induce peripheral sympathoinhibition and a reduction in blood pressure as a result of the stimulation of (X2-adrenoceptors. Their antihypertensive efficacy is beyond doubt, but their profile of adverse reactions is considered unfavourable. More recently, central imidazoline II-receptors have been recognized to be another target of centrally acting antihypertensive drugs.

Moxonidine is considered to be moderately selective II-receptor stimulant, it causes peripheral sympathoinhibition, triggered at the level of central nervous II-receptors. Moxonidine is effective antihypertensive with attractive mode of action and hemodynamic profile.

The aim of the present study was to characterize the cardiovascular effects of moxonidine both in-vivo and in-vitro as well as to investigate the possible analgesic effect of moxonidine.

Eighteen rats were used to demonstrate the effect of chronic moxonidine treatment on blood pressure, heart rat, renal and hepatic hemodynamic parameters, lipid profile, serum sodium, potassium and creatinine and histopathological changes in hypertensive hypercholesterolemic rats. Rats were divided into three equal groups: control group (group I), DOCA-salt hypertensive hypercholesterolemic group (group II) and DOCA-salt hypertensive hypercholesterolemic group treated with moxonidine (0.5 mg/kg I.P. for 2 weeks) (group III).

It was found that chronic moxonidine treatment significantly reduced arterial blood pressure and heart rate of hypertensive hypercholesterolemic rats, in addition it favourably affected renal and hepatic hemodynamic parameters.

Chronic moxonidine treatment induced significant increase in renal blood flow velocity, significant decrease in renal vascular resistance, pulsatility index and maximum and minimum systolic pressure in the renal artery in hypertensive hypercholesterolemic rats.

On the other hand, it produced insignificant increase of the hepatic blood flow velocity, while, the hepatic pulsaitility index was significantly decreased, with insignificant changes in other hepatic hemodynamic parameters.

However, in normotensive rats (n= 18), acute intravenous administration of various doses (0.1, OJ, 1.0 mg/kg) of moxonidine resulted in dose related increase in both renal and hepatic blood flow velocity, while, vascular resistance in both arteries was decreased. Other renal and hepatic hemodynamic parameters were not affected.

In our study, chronic moxonidine treatment produced beneficial effects on blood lipid profile as total cholesterol, triglycerides, LDL-cholesterol concentrations were significantly reduced while, serum HDL-cholesterol was insignificantly increased. In addition, moxonidine treatment resulted in a significant decrease in serum sodium with change in serum potassium and serum creatinine of hypertensive hypercholesterolemic rats.

Moreover, chronic moxonidine treatment of hypertensive hypercholesterolemic rats improved fatty degenerative changes and hydropic degeneration of the hepatocytes and reduced central vein congestion of the liver. It also reduced glomerulosclerosis in the kidney and decreased the size of fatty streaks appeared in the intima of the aorta with regeneration of endothelial cells.

As regard the prophylatic effect of moxonidine against drug-induced cardiac arrhythmia, our results showed that acute pretreatment of urethane-anaesthetized rats (n= 18) with moxonidine in different doses 15 minutes prior to intravenous injection of arrhythmogenic dose of adrenaline exhibited pronounced antiarrhythmic effects characterized by dose-dependent increase in adrenaline arrhythmogenic dose, significant decrease in the number of extrasystoles, significant delay of onset of arrhythmia with significant reduction of total duration of arrhythmia.

Furthermore, moxonidine in different doses, injected intravenously 15 minutes prior to intravenous administration of ouabain, increased both the arrhythmogenic and ventricular fibrillatory doses of ouabain in a dose-dependent manner in urethane-anaesthetized rats (n = 18). Therefore, it was concluded that moxonidine exhibits a significant protective effect against drug-induced cardiac arrhythmia, resulted from its ability to decrease the central sympathetic drive through stimulation of II-receptors.

Regarding the in-vitro results, moxonidine produced dose related inhibition of the force of contraction of the isolated perfused rabbit's heart. This inhibition was abolished by both muscarinic and nicotinic

receptors antagonist suggesting a vagal like action of moxonidine on isolated heart..

On the other hand, moxonidine produced dose-related contraction of the isolated rabbit's aortic strip. This effect is more likely to be through postsynaptic u2-adrenoceptor stimulation because yohimbine was more effective antagonist than prazosin indicating the higher selectivity of moxonidine for postsynaptic u2-adrenoceptor than ul-subtype.

Lastly, in the present study acute moxonidine administration was found to provide potent antinociceptive efficacy in control of acute pain in rats even in small dose and yohimbine, the selective U2-adrenoceptor antagonist, was able to antagonize moxonidine-induced antinociception suggesting that u2-adrenoceptor activation is involved in this effect.

In conclusion, moxonidine being an II-/U2-receptor agonist is an effective drug in lowering high blood pressure and heart rate. It offers other advantages including renoprotective effects, favourable effects on lipid profile, antiarrhythmic properties through its ability to reduce central sympathetic overactivity which is commonly considered a contributing factor in the development of hypertension and other associated disorders. Moxonidine also pocesses a powerful analgesic effect which may be of beneficial value in cases of diabetic peripheral neuritis. However, further investigations are needed to investigate other mechanisms by which moxonidine may produce its effects on cardiovascular system and other body systems.