SUMMARY AND CONCLUSION

The present study was performed to evaluate some cardiovascular effects of two antianginal drugs namely, timolol and prenylamine. The effects investigated were: their action on acute myocardial ischemia, their effect on certain forms of arrhythmias and their action on coronary spasm and hypertension induced by ergotamine. All studies were made in chlorolose-anaesthetized cats.

In the first part of this work, cats were subjected to coronary artery ligation for 5 hours. They were divided into: Control group which were given saline only before ligation of left anterior descending coronary artery (LAD), timolol treated group which were injected with timolol (25 ug/kg), 15 min. prior to ligation of LAD and prenylamine treated group which received prenylamine (3 mg/kg), 15 min. prior to ligation of LAD. Each group consisted of 5 cats. Three parameters were studied namely, electrophysiological parameter (ST segment elevation, heart rate and mean arterial blood pressure), biochemical parameter (Serum CPK before and 5 hours after ligation of LAD) and histochemical parameter (Staining heart sections with triphenyl-tetrazolium, 5 hours after ligation of LAD and the infarct area was computed).

In this study, timolol had cardioprotective effect in acute myocardial ischemia in cats as it decreased significantly ST segment elevation 30 min. ($P < 0.05$) and 300 min ($P < 0.01$) after ligation of LAD compared to control group. The mean ST segment level at 300 min. after LAD occlusion was 0.13 ± 0.04 MV in the timolol treated group compared to 0.67 ± 0.07 MV in the control group at the same time interval. Also, timolol significantly decreased the rise in CPK level 5 hours after ligation of LAD compared to control group ($P < 0.01$). The mean CPK level at 300 min. after LAD ligation in timolol treated group was 195 ± 17 U/L compared to 724 ± 60 U/L in the control group at the same time interval. At the same time, timolol decreased infarct size significantly compared to control group ($P < 0.01$). The mean surface area of infarcted heart at 300 min. after LAD ligation in timolol treated group was 83.4 ± 22 mm^2 compared to 315.4 ± 34 mm^2 in the control group at the same time interval. Timolol decreased the myocardial damage and infarct size mainly through its beta-blockade. Timolol had decreased the heart rate significantly ($P < 0.01$) from 195 ± 17 beats/min at o time to 102 ± 12 beats/min. at 300 min. after LAD ligation, while in control group, heart rate had been decreased insignificantly from 167 ± 11 beats/min. at o time to 144 ± 13 beats/min. at 300

min. after LAD ligation ($P > 0.05$). At the same time, timolol had decreased the mean arterial blood pressure significantly ($P < 0.05$) from 202±18 mm/Hg at o time to 172±15 mm/Hg at 300 min. after ligation of LAD, while in control group, the mean arterial blood pressure had been decreased insignificantly from 155±13 mm/Hg at O time to 140±9 mm/Hg at 300 min. after LAD ligation ($P > 0.05$). This effect led to decrease in cardiac work and myocardial damage. Also this cardioprotective effect of timolol might be attributed to better diastolic filling induced by timolol, decreasing the level of free fatty acids after acute myocardial infarction, opposing the action of high level of catecholamines commonly present during acute myocardial infarction and may be through the decrease in the level of intracellular calcium through an action on receptor operated channels or an action on the mitochondria.

Prenylamine also was found to have cardioprotective effect in acute myocardial ischemia in cats as it decreased significantly ST segment elevation 30 min.($P<0.05$) and 300 min. ($P<0.01$) after ligation of LAD compared to control group. The mean ST segment level at 300 min. after ligation of LAD in prenylamine treated group was 0.15±0.04 MV compared to 0.67±0.07 MV in the control

group at the same time interval. Also, it significantly decreased the rise in CPK level 5 hours after ligation of LAD compared to control group ($P < 0.01$). The mean CPK level at 300 min. after ligation of LAD in prenylamine treated group was 193 ± 25 U/L compared to 724 ± 60U/L in the control group at the same time interval. At the same time, prenylamine significantly decreased infarct size compared to control group ($P < 0.01$). The mean surface area of infarcted heart in prenylamine treated group at 300 min. after LAD ligation was 119.2 ± 25 mm^2 compared to 315.4 ± 34 mm^2 in the control group at the same time interval. Prenylamine had decreased the myocardial damage and infarct size through decreasing the cardiac work. Prenylamine had decreased heart rate significantly ($P < 0.01$) from 172 ± 25 beats/min. at O time to 92 ± 17 beats/min. at 300 min. after ligation of LAD., while in control group, heart rate had been decreased insignificantly ($P > 0.05$) from 167 ± 11 beats/min. at O time to 144 ± 13 beats/min at 300 min. after ligation of LAD. At the same time prenylamine had decreased the mean arterial blood pressure significantly ($P < 0.01$) from 205 ± 14 mm/Hg at O time to 165 ± 11 mm/Hg at 300 min. after ligation of LAD., while in control group, blood pressure had been decreased insignificantly from 155 ± 13 mm/Hg at

O time to 140±9 mm/Hg at 300 min. after LAD ligation ($P > 0.05$). This effect of prenylamine may be attributed to calcium channel blockade and depletion of catecholamine stores. Also prenylamine has a potent coronary vasodilator effect that increased blood flow to ischemic areas. In addition, prenylamine decreased markedly the level of intracellular calcium with consequent decrease in myocardial damage.

In the second part of this work, timolol and prenylamine were tested against certain forms of cardiac arrhythmias in chlorolose anaesthetized cats. In ouabain induced arrhythmia, cats were divided into 3 groups: a control group which were given ouabain (20 ug/kg) every 15 min. until death and the mean time to occurrence of arrhythmia and to death was recoreded. In timolol treated group , timolol (3 mg/kg) was given 15 min. prior to injection of ouabain. In prenylamine treated group, prenylamine (3 mg/kg) was injected 15 min. prior to injection of ouabain. In this work, timolol increased significantly the mean time to onset of arrhythmia and to death compared to control group ($P < 0.01$). The mean time to arrhythmia and to death in timolol treated group were 71±7 min. and 93±5 min. respectively compared

to 19±5 min. and 31±5 min. in the control group. Timolol was used in this high dose (3 mg/kg) as the beta blocking dose (25 ug/kg) was ineffective in this type of arrhythmia. Timolol was seemed to exert its beneficial action in this high dose level against ouabain induced arrhythmia partly through beta blockade and partly through the decrease of post-ganglionic cardiac sympathetic neural discharge.

Prenylamine was found to increase significantly the mean time to arrhythmia and to death compared to control group ($P < 0.01$). The mean time to arrhythmia and to death were 60±4 min. and 92±4 min respectively in prenylamine group, compared to 19±5 min. and 31±5 min. in the control group. Prenylamine seemed to exert its beneficial action in ouabain induced arrhythmia through its ability to block calcium channels and its ability to deplete catecholamine stores as digitalis toxicity is mainly due to increased intracellular level of calcium and increased central sympathetic flow.

Moreover, timolol and prenylamine were tested against adrenaline induced arrhythmia in chlorolose anaesthetized cats. In this study, animals were divided into: adrenaline / timolol treated group in which the

minimal arrhythmogenic dose of adrenaline before and after injection of timolol (25 ug/kg) was determined, and adrenaline/prenylamine group in which the minimal arrhythmogenic dose of adrenaline before and after injection of prenylamine (5 mg/kg) was determined. In this study, timolol increased significantly ($P < 0.01$) the dose of adrenaline that could Produce arrhythmia. Timolol increased the arrhythmogenic dose of adrenaline from 26 ± 2 ug/kg to 800 ug/kg. This effect of timolol could be attributed to beta blockade. On the other hand, prenylamine had insignificant effect ($P > 0.05$) aganist this form of arrhythmia. It increased the arrhythmogenic dose of adrenaline from 12 ± 3 ug/kg to 19 ± 8 ug/kg. Prenylamine has no beta blocking effect, so it was ineffective against adrenaline induced arrhythmia.

Moreover, the effect of both timolol and prenylamine was tested against post-myocardial infarction arrhythmia in cats subjected to LAD ligation. Both drugs increased the number of animals surviving the period of the experiment (5 hours) and they decreased the incidence of ventricular arrhythmias. Timolol exerted its benificial action in post ischemic arrhythmia via beta blockade and may be through the decrease of

the level of free fatty acids, and the reduction of infarct size which decreased the incidence of arrhythmia. On the other hand, prenylamine seemed to be beneficial in this type of arrhythmia through calcium-channel blockade and depletion of catecholamine stores. These actions led to decrease in infarct size and consequently reduction of post-myocardial infarction arrhythmia.

In the third part of this work, the effect of both timolol and prenylamine was tested against ergotamine-induced coronary spasm and hypertension in anaesthetized cats. In this study, prenylamine was highly effective in preventing and reversing the coronary spasm as well as the hypertension induced by ergotamine and this effect is due to the potent coronary as well as peripheral vasodilator effect of the drug which is attributed to its calcium-channel blockade. On the other hand, timolol was completely ineffective in preventing or reversing coronary spasm or hypertension induced by ergotamine .

From all results of this study, it can be concluded that both timolol and prenylamine beside being antianginal drugs, can be used in acute myocardial infarction to limit infarct size. At the same time,

both drugs are effective in preventing post-myocardial infarction and ouabain-induced arrhythmia. But, while timolol is highly effective in adrenaline induced arrhythmia, prenylamine is completely ineffective in this respect. And , while prenylamine is highly effective coronary and peripheral vasodilator and could block the vasoconstrictor effect of ergotamine, timolol is completely ineffective in this respect.

Anginal patients are subjected to many complications including myocardial infarction and various types of cardiac arrhythmias, so the use of timolol or prenylamine in these patients may be of great value in decreasing the incidence of myocardial infarction or decreasing the infarct size, if acute myocardial infarction develops. Also, these drugs can antagonize various types of arrhythmias in these patients. In addition, prenylamine is of great value in patients with vasospastic angina as it has potent coronary vasodilator effect where timolol (a non-selective beta-blocker) is contraindicated in this type of angina.