INTRODUCTION

ANGINA PECTORIS

Angina pectoris is the principal manifestation of myocardial ischemia, a disease caused by an imbalance between myocardial oxygen supply and myocardial oxygen demand. Myocardial oxygen supply is primarily dependent on coronary blood flow. This imbalance between myocardial oxygen supply and demand can occur either from a primary decrease in coronary blood flow, without an increase in myocardial oxygen demand, or from a disproportionate increase in myocardial oxygen demand in relation to the capacity to increase coronary blood-flow **(Hoffman, 1987).** In patient with variant (Prinzmetal's) angina a primary decrease in coronary blood flow is the principal mechanism. Effort angina (classic angina) is most frequently precipitated by an insufficient increase in coronary blood flow in response to an increase in myocardial oxygen demand **(Quyyumi et al., 1987).**

The myocardial oxygen requirement increases when there is an increase in heart rate, contractility, arterial pressure or ventricular volume **(Klocke et al., 1985).** These hemodynamic alteration frequently occur during physical exercise, which often precipitates angina in patients with obstructive coronary artery disease **(Hoffman and Buckberg, 1978).**

Oxygen supply in a function of myocardial delivery and extraction, since myocardial oxygen extraction is nearly maximal at rest, there is little reserve to meet increased demand, furthermore, the oxygen content of the blood can not be significantly increased under normal atmospheric conditions. Thus increased myocardial demands for oxygen in the normal heart are met by augmenting coronary blood flow **(Wyatt, 1975)**. Coronary blood flow is directly related to the perfusion pressure (aortic diastolic pressure) and the duration of diastole. Because coronary flow drops to negligible values during systole, the duration of diastole becomes a limiting factor for myocardial perfusion during tachycardia **(Wyatt, 1975)**.

Types of Angina Pectoris:

A- Angina of Effort (Classic Angina):

In this type of angina, resting coronary blood flow is adequate and proportionate to myocardial oxygen demand at rest. During exercise, as a result of autoregulatory vasodilatation, there is a 2 to 4 fold decrease in the resistance of the distal coronary vascular bed. Although such vasodilatation always increases flow, the increase in flow required for a given increase in demand becomes progressively curtailed as the degree of stenosis increases. Thus despite an absolute increase in flow, relative myocardial ischemia develops and angina is experienced because the

increase in flow or the oxygen supply to the myocardium is disproportionate to the increase in oxygen requirement **(Hoffman, 1987).**

B- Variant Angina (Prinzmetal's Angina, Vasospastic Angina) :

It is characterized by cyclic recurrent chest pain at rest that is unrelated to effort but is associated with ST segment elevation on the ECG **(Prinzmetal et al., 1959).** In this type of angina, coronary blood flow decreases during rest, thus it seems highly possible that myocardial ischemia is precipitated in variant angina by spontaneous decrease in coronary blood flow unrelated to changes in myocardial oxygen demand. The primary decrease in coronary blood flow during variant angina appears to be caused by coronary artery spasm **(Klocke et al., 1985).**

C- Unstable Angina :

The term unstable angina applies to angina of changing intensity. The patients with unstable angina have prolonged angina at rest and they do not have evidence of myocardial necrosis at the time of initial presentation. Both coronary artery spasm and increased myocardial oxygen demand may be implicated in the pathogenesis of unstable angina **(Braunwald, 1983).**

D- **Mixed Angina :**

In patients with mixed angina, attacks occur at variable levels of exercise. Patients may also experience rest angina with a symptom profile typical of variant angina. Symptoms may be precipitated by emotional stress and exposure to cold. Both increased coronary vascular tone and increased myocardial oxygen requirement have been suggested as underlying mechanisms for mixed angina **(Hoffman, 1987).**

Main Lines of Treatment of Angina Pectoris:

In addition to modification of the risk factors for coronary atherosclerosis (smoking, hypertension and hyperlipidemia), the treatment of angina is based on reduction of myocardial oxygen demand and increase of coronary blood flow to the potentially ischemic myocardium to restore the balance between myocardial oxygen supply and demand **(Oram, 1981).** In classic angina, pharmacologic agents are effective mainly in reducing myocardial oxygen demand. However, in variant angina, some drugs are effective in preventing and reversing coronary spasm and therefore can increase oxygen supply to the myocardium **(Katzung and Chatterjee, 1987).**

Medical treatment of patients with ischemic heart disease has improved greatly during the past two decades. Nitrates continue to play a vital role in therapy. The introduction of beta-blockers provided a second highly

effective and extremely safe therapeutic modality for relieving angina, reducing blood pressure and antagonizing certain cardiac arrhythmias **(Chamberlain, 1987)**. Recently, calcium slow-channel blockers are used extensively in treatment of various forms of angina **(Godfraind, 1987)**.

Nitrates:

Nitroglycerine and other organic nitrates are direct smooth muscle relaxants and cause vasodilatation of the peripheral vascular bed **(Abrams, 1978)**. Nitrates are active after being converted to nitric acid or nitric oxide which is then converted to nitrosothiols by reacting with the sulphydryl compounds in vascular smooth muscle **(Ignarro et al., 1981)**. These nitrosothiols in turn stimulate guanylate cyclase and increase production of guanosine 3,5-monophosphate (cyclic GMP) which reduces calcium entery into the muscle cell **(Mittal and Murad, 1982)**. It should be noted too that nitric oxide has recently been identified as endothelium derived relaxing factor **(Palmer et al., 1987)**. This factor is present in intact endothelium and it is believed to mediate some physiological vasodilatation and there is some evidence that defects in this mechanism may have a role in vascular disease **(Palmer et al., 1987)**.

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Nitrates can be used in various forms of angina. In angina of effort, nitrates decrease the venous return to the heart, as a result of peripheral venous pooling with subsequent reduction of intracardiac volume which is the principal hemodynamic effect. At the same time, arterial pressure decreases because of modest reduction of systemic vascular resistance and lowered or unchanged cardiac output **(Abrams, 1978)**. Decreased intraventricular pressure and left ventricular volume are associated with decreased wall tension and lead to decreased myocardial oxygen requirement **(Chamberlain, 1987)**. At the same time nitrates relax the smooth muscle of large conductance arteries such as epicardial coronary arteries, so that they increased collateral blood flow **(Ignarro et al., 1981)**. However, when administered by the usual systemic routes, nitrates consistently decrease overall coronary blood flow and myocardial oxygen consumption **(Ignarro et al., 1981)**.

Intracoronary injection of small dose of nitroglycerine, which increases total coronary blood flow but does not produce systemic hemodynamic effects, does not relieve angina. Yet systemic administration of nitroglycerine, which decreases arterial pressure and left ventricular volume, does relieve angina despite decrease coronary blood flow **(Parker et al., 1987)**. These finding indicate that the relief of effort angina with nitrates is due primarily to

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decreased myocardial oxygen demand and not increased coronary blood flow **(Chamberlain, 1987).**

The principal mechanism by which, nitrates exert their beneficial effects in vasospastic angina is relaxation of smooth muscles of the epicardial coronary arteries and relief of coronary artery spasm with subsequent increase in coronary blood flow **(Hiller and Braunwald, 1978).** In unstable angina, nitrates may induce their therapeutic effects both dy dilating the epicardial coronary arteries and simultaneously reducing myocardial oxygen demand **(Hoffman and Buckberg, 1978).**

The most potential deleterious effects of nitrates in angina are reflex tachycardia and reflex increase in myocardial contractility which decrease the diastolic perfusion time and increase myocardial oxygen requirement. However, these effects can be overcommed by concomitant use of beta-adrenergic blockers **(Macleen and Feely, 1983).**

BETA-ADRENOCEPTOR BLOCKING DRUGS

Adrenergic receptors which recognize the endogenous catecholamines, adrenaline and noradrenaline can be divided into four subtyps: $alpha_1$, $alpha_2$, $beta_1$, $beta_2$ based on agonsit and antagonist potencies for a variety of physiological responses **(Ahlquist, 1948; Lands et al., 1967; Starke, 1981).** Whereas $beta_1$ and $beta_2$- adrenergic receptors both activate adenylate cyclase and stimulate generation of the second messenger cyclic AMP, signal transduction by $alpha_1$ and $alpha_2$ adrenergic receptors may occur through a variety of effector systems. These includs inhibition of adenylate cyclase ($Alpha_2$), Ca^{++} mobilization ($Alpha_1$ and $Alpha_2$), phosphatidyl -inositol hydrolysis ($Alpha_1$), enhancement of Na^+ or K^+ flux ($Alpha_1$ and $Alpha_2$) and arachidonic acid release ($Alpha_1$ and $Alpha_2$) **(Exon, 1985; Limibird and Sweatt, 1985).**

Despite functional heterogencity all adrenergic receptors are thought to act via interaction with one on more transduction proteins (the guanine-nucleotide binding (G or N) proteins), which couple the receptors to their respective effector mechanisms. These proteins interact with the receptor-ligand complex, bind GTP, and become activated. They then interact with adenylate cyclase to alter the rate of c-AMP synthesis, finally, they terminate their effect on adenylate cyclase and

return to the basal state by hydrolyzing GTP to GDP. Three G proteins have been recognized, namely: G_s, G_i, and G_o **(Casperson and Bourne, 1987).**

Lands and Coworkers (1967) Categorized beta receptors as either $beta_1$ or $beta_2$: $beta_1$ adrenergic receptors predominate in cardiac tissues, while $beta_2$ receptors are present primarily in smooth muscle. However, different tissues may possess both $beta_1$ and $beta_2$ receptors in varying proportion **(Minneman et al., 1979).** Among responses presumed to be mediated by $beta_1$ receptors are cardiac stimulation, intestinal relaxation, lipolysis, and renin release, where as $beta_2$ receptor stimulation mediates broncho dilatation, relaxation of vascular and uterine smooth muscle, glycogenolysis, and insulin secretion **(Weiner and Taylor, 1985).** In addition, presynaptic beta receptors on the nerve terminals are believed to enhance transmitter release **(Dixon et al., 1979).**

Beta adrenergic receptors have been identified in many tissues with the use of highly selective potent radio labeled beta adrenergic blockers such as [^{125}I]iodopindolol or [^{125}I] iodocyanopindolol **(Barowsky and Brooker, 1980; Engel et al., 1981).**

Historical Review:

The introduction of drugs with beta-blocking activity was started by **Powell and slater (1958)** who described a compound, dichloroisoproterenol (DCI), which specifically blocked beta-adrenergic receptor sites. At that time, the full therapeutic implications of these advances in knowlege were not immediately realized. Few years following the introduction of DCI, **Black and Stephenson in 1962** introduced a second beta-adrenergic antagonist, pronethalol (Nethalide, Alderlin) which was structurally releated to both isoproterenol and dichloro-isoproterenol. From the experiments conducted in animals and man, pronethalol had much weaker intrinsic sympathom-imetic activity than DCI **(Black and Stephenson, 1962).** However, studies of its actions in man were curtailed because it produced malignant tumours of the thymus gland in mice **(Paget, 1963).**

However, **Black and his colleagues** had by this time prepared a non-carcinogenic beta -adrenoceptor blocker more potent than pronethalol and virtually devoid of intrinsic sympathomimetic activity, this substance was called propranolol and was first described by **Black et al., (1965).** Since then a large number of beta-adrenergic

blocking agents were introduced e.g. sotalol **(Lish et al., 1965)**, alprenolol **(Johnsson et al., 1966)**, butoxamine **(Levy, 1966)**, pindolol **(Saameli, 1967)**, oxprenolol **(Brunner et al., 1968)**, practolol **(Dunlop and Shanks, 1968)**, metoprolol **(Ablad et al., 1973)**, timolol **(Scriabine et al., 1973)**, atenolol **(Robertson et al., 1983)** and esmolol **(Gorczynski et al., 1983)**.

Classification:

Beta-adrenergic blocking drugs may be classified as nonselective and cardioselective on the basis of their relative abilities to block beta receptors in different tissues in the same range of doses. The non selective beta blockers can block $beta_1$ and $beta_2$ adrenergic receptors and include: propranolol, timolol, nadolol pindolol, sotalol, oxprenolol and alprenolol. The cardioselective beta blockers block only $beta_1$ adrenergic receptors and include: atenolol, metoprolol and acebutolol **(Robertson et al., 1983)**.

Butoxamine is a somewhat selective $beta_2$ adrenergic receptor antagonist which blocks $beta_2$- Vasodilator and other smooth mucle inhibitory effects of isoproterenol **(Levy 1966)**.

Beta-adrenoceptors blocking drugs can also be classified according to their relative solubility in lipids and in water into lipid soluble and water soluble agents: Lipid soluble agents include: propranolol , alprenolol, oxprenolol,metoprolol, tiomolol and labetalol. They are more rapidly absorbed and are extensively metabolized to water soluble substances that can be eliminated by the kidney; they readily enter the CNS; they have shorter t1/2 than do water soluble members. Water soluble agents include: atenolol, practolol, sotalol and nadolol. They are less subject to liver metabolism being excreted unchanged by the kidney, thus their half lives are much prolonged in renal failure. Water soluble agents may also have a lower incidence of some effects attributed to penetration of CNS e.g. night mares**(Laurence and Bennett, 1987).**

some beta blockers have agonistic action, i.e. they are partial agonists. This is sometimes described as having intrinsic sympathomimetic activity. Partial agonistic activity is an important pharmacological property of certain beta-adrenergic antagonists, such as practolol, pindolol, acebutolol, alprenolol and oxprenolol **(Prichard, 1978).** The clinical significance of this partial agonistic activity is uncertain, although drugs

with this activity do not elicit significant bradycardia or negative intotropic effect at rest(**Prichard et al., 1980, McDevit , 1983**).

Some beta-blockers also have direct actions on cell membranes which are described as membrane stabilizing, local anaesthetic or quinidine-like. The local anaesthetic potency of propranolol is about equal to that of Lidocaine, while oxprenolol is about half as potent (**Moralez Aguilera and Vaughan Williams, 1965; Jaju et al., 1966, Sinha and Jaju , 1967**).

Uses of Beta-Adrenergic Receptor BlockingDrugs:-

1- **Angina pectoris and myocardial infarction**:-

Beta-blcoking drugs are extremely useful in the management of stable and unstable angina pectoris (**Oram, 1981**). Such beneficial effects of beta-blockers in angina of effort and ubstable angina are related primarily to the decrease in the rate pressure product (Heart rate X systolic blood pressure) at rest and on exercise. On the other hand, beta blockers decrease myocardial contractility. These hemodynamic effects lead to decreased myocardial oxygen requirements and the cardiac work at rest and on exercise (**Breckenridge, 1983**). In the same time, decreasing the heart rate is also associated with an

increase in diastolic perfusion time that may increase myocardial perfusion **(Chamberlain, 1987).** It has been suggested that the beta-blocking agents can cause a favorable redistribution of coronary blood flow to the ishemic myocardium based on different effects on the coronary vascular resistance in the relatively ischemic and non-ischemic myocardial segments **(Pitt and Carven, 1970; Gross and Winbury, 1973).** However, reduction of heart rate and blood pressure and consequently decreased myocardial oxygen consumption appear to be the most important mechanisms for relief of angina and improved exercise tolerance **(Breckenridge, 1983).**

The therapeutic response to beta-blockers does not correlate in a linear fashion with the oral dose or plasmalevel. Differences in thedegree of absorption and variation in hepatic metabolism give rise to unpredictable plasma levels.However, the same blood level may elicit a different cardiovascular response in patients depending on the individul variations in sympathetic and vagal tone, and the population of beta receptors **(Pratt and Roberts, 1983).** The dose is usually adjusted to achieve a heart rate of 50-60/min at rest, and <110/min on exercise **(Pratt and Roberts, 1983).** The effective

cardioprotective dose (i.e. the dose shown to reduce the incidence of reinfarction and death in post myocardial infarction patient) may be different from the dose necessary to achieve control of angina. When possible the dosage of beta-blocker should be kept within the cardio protective range **(Khan, 1984)**. An increase in the dose beyond the cardioprotective dosage in order to have better control of angina, hypertension or arrhythmia may have a poor reward. That is these could be an increase in side effects especially heart failure and distressing fatigue. In some patients, satisfaction should be accepted with 75% control of symptoms and if necessary , the addition of another therapeutic agent **(Chamberlain, 1987)**.

Undesirable effects of beta-blockers in angina include an increase in end-diastolic volume that accompanies slowing of the heart rate and an increase in ejection time with resulting increased myocardial oxygen requirement which partially effset the beneficial effects of beta-blocking agents. These potentially deleterious effects of beta-blocking agents can be balanced by the concomitant use of nitrates. Combined therapy reduces myocardial oxygen demand at rest and during exercise. The rate pressure product remains consistently lower

during exercise with nitrate or beta-blocker therapy, and combination therapy produces synergistic effects **(Katzung and Chatterjee, 1987).**

The cardioprotective effect of beta-blockers in acute myocardial infarction is related mainly to reducion of cardiac work and myocardial oxygen consumption and thus they may minimize the extent of the infarct **(Braunwald,, 1983).** In addition, decreasing the heart rate that is associated with improved ventricular diastolic relaxation and an increase in diastolic perfusion time may increase myocardial perfusion **(Chamberlain, 1987).** Whilst, there is an overall depression of contractility, there is in contrast an improved contraction of ischemic myocardium after administration of beta-blockers. This has been shown with ventriculo-graphic studies with propranolol **(Ludbrook et al., 1973),** echocardiographic studies with pindolol and practolol **(Heikkila and Nieminen, 1978)** and radionuclide angiographic studies with propranolol **(Battler et al.,1979),** which seems to be a good evidence of improved oxygenation of ischemic myocardium **(Risoe et al, 1987).** Studies in dogs have indicated that internal shunting occurs in the coronary circulation after beta-adrenoceptor blockade, so that flow to an ischemic area is maintained or improved even if there is an overall

fall in coronary flow **(Vatner et al., 1977)** Also, beta-blockers can counteract the early increase in sympathetic tone associated mainly with anterior infarction, mainfested in form of tachycardia and a rise in blood pressure **(Khan, 1984).** Similarly, beta-blockers can prevent serious ventricular arrhythmias including venticular fibrillation which are probably induced by increased levelsof catecholamines commonly present during the early phase of infarction **(Braunwald , 1983).** At the same time, beta-blockers prevent the release of free fatty acids so they prevent their adverse effects on ventricular arrhythmias and on the increase in the oxygen consumption **(Opie and Thomas, 1976).**

Under normal circumstances, the main sympathetic stimulator is probably noradrenaline acting on $beta_1$ receptors in the heart. During acute stress, however, huge amounts of adrenaline are released in the circulation from the adrenal medulla. Adrenaline in addition to its direct stimulatory effect, also, has indirect effect by increasing noradrenaline release from sympathetic nerves via presynaptic $beta_2$ receptors **(Vincent et al., 1983).** A selective $beta_1$ blockade will thus not abolish all sympathetic effects in the human heart during stress reactions.

Beta-blockers also can relieve chest pain in acute myocardial infarction by improving myocardial ischemia, which may be another foctor in limiting infarct size **(Herlitz et al., 1986).** However the main risk of using beta-blockers in acute myocardial infarction is the production of left ventricular failure in response to withdrawal of sympathetic drive from the damaged ventricle **(Oram, 1981).**

Theoretically, in order to achieve a favorable effect on infart size, beta-blockers must be intiated prior to or within the first 4 hours of infarction and certainly not later than 5 hours from the onset of symptoms. patients on beta-blockers prior to infarction appear to benefit **(Risoe et al, 1987).** The evidence for the early use of beta-blockers in patients with anterior infarction associated with sinus tachycardia > 100/min. and systolic blood pressure > 100 mm/Hg in the absence of heart failure or other contraindications is compelling if not definitive **(Khan, 1984).**

A reduction of infarct size with the early use of timolol in acute myocardial infarction has been documented in a randomized clinical trials **(Roque et al, 1987; Risoe et al., 1986, 1987, and Sederoholm, 1984, 1986).** propranolol also reduced the size of experimental myocar-

dial infarction induced by coronary artery ligation in dogs, as measured by changes in E.C.C. and CPK enzyme level **(Maroko et al., 1971).**

Studies by **cairns** and **Klassen (1975)** and **Gold et al (1976)** indicate that propranolol administered early to patients with uncomplicated acute myocardial infarction reduces the evidence of myocardial ischemia. In other studies,propranolol given to patients within 5 hours of onset of acute myocardial infarction reduces the final size of the infract as measured by peak creatine kinase release **(Peter, et al., 1978)**, and also when administered earlier to those patients with threatened acute myocardial infarction, it prevented the development of an infarct in some and siginficantly reduced the size of the infarct in others **(Norris et al., 1978).**Further, **sloman and Colleagues (1981)** emphasised that, there was no rebound of enzyme rise and of chest pain when propranolol was gradually withdrawn. At the same time, the sympathetic hyperactivity, reflected by plasma catecholamine level is acutely reduced by propranolol in patients during evolution of myocardial infraction **(Muller and Ayres, 1980).**

The effects of the beta-adrenoceptors antagonists exerted on the myocardium, however, can not be explained

simply in terms of establishment of beta-adrenoceptor blockade and the associated withdrawal of sympathetic support. Probably, it may result from or reflect a complex interaction of those drugs with the cardiac plasma membrane or intracellular calcium regulating structures **(Kloner et al., 1978 and Nayler et al., 1978).**

2- **Arrhythmias**:-

Beta-blcokers are effective in abolishing arrhythmias produced by increased catecholamines. The main effect of beta-blockers is the depression of phase 4 diastolic depolarization **(Walden and Hernandz, 1982).** Maximum impulse traffic through the atrioventricular (AV) node is reduced and the rate of conduction is slowed; **(Ranganathan, et al., 1988).** Paroxysmal supraventricular tachycardia due to AV nodal reentery is often abolished by beta-blockers, which also slow the ventricular rate in atrial flutter and atrial fibrillation. There is a variable effect on ventricular arrhythmias which may be abolished if induced by increased sympathetic activity as in case of myocardial ischemia and infarction **(Ranganathan, et al., 1988).**

3- Hypertension:-

Chronic administration of beta blockers to hypertensive patients leads to gradual fall of blood pressure. The possible mechanisms of this action include: reduction of cardiac output, **(Helfant et al., 1971)**, reduction in plasma renin activity by inhibition of secretion of renin by the kidney **(Buhler et al., 1972)**, inhibition of release of norepinephrine from adrenergie nerve terminals by blocking the presynaptic $beta_2$ adrenergic receptors **(Langer, 1981)**, resetting of baroreceptors leading to peripheral vasodilatation **(Prichard and Gillam, 1969)** and a central nervous system sympatholytic action **(Scraibine et al., 1979).**

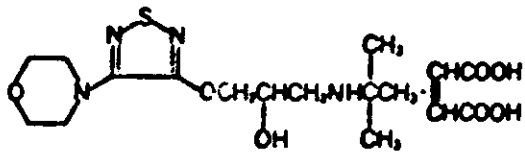
Other uses of beta-adrenergic blockers:-

Beta adrenergic receptor blocking agents are also used in hypertophic obstructive cardiomyopathies **(Shand et al., 1971)**; hyperthyroidism **(Ingbar, 1981)**; glaucoma **(Boger et al., 1978)**; Portal hypertension **(Lebrec et al., 1981)**; anxiety **(Bonn et al., 1972)**; and prophylaxis of migraine **(Peat field, 1983).**

TIMOLOL MALEATE

Timolol maleate is a nonselective beta-adrenergic receptor blocking agent . It dose not have significant sympathomimetic, direct myocardial depressent, or local anaesthetic activity **(Daley, et al., 1984)**. On a weight to weight basis, it is 5 to 10 times as potent as propranolol **(Scriabine et al., 1973)**.

Timolol maleate is chemically, (S)-1-[(1,1 dimethylethyl) amino]-3-[[4- (4-morpholinyl)-1,2,5-thiadiazol-3- YL]Oxy]-2-propanol, (Z)-butenedioate (1:1) salt. It possesses an asymmetric carbon atom in its structre and is provided as the levoisomer. It has the following structural formula **(Hall et al, 1975)**.



Timolol maleate is a white crystaline compound(molecular weight 432.49) which melts with decomposition at approximately 198-199^{o}C. It is soluble in water, ethanol, and methanol. It is sparingly soluble in chloroform, very slightly solbule in cyclohexane and practically insoluble in isooctane.It

is stable in aqueous solutions in the full range of physiologic pH. The solid is stable when exposed to air at 150°c for at least one month **(Hall et al, 1975).**

Timolol maleate is rapidly and nearly completely absorbed (about 90%) following oral ingestion. Detectable plasma levels of timolol occur within half an hour and peak plasma level occur in about one-two hours. The drug plasma half-life is approximately 4 hours and this is essentially unchanged in patients with moderate renal insufficiency as timolol is pratially metabolized by the liver and the drug and its metabolities are excreted by the kidney. Timolol is not bound extensively to plasma proteins, i.e. < 10% by equilibrium dialysis and appoximately 60% by ultra-filteration **(Scriabine et al., 1973).**

Plasma levels following oral administration are about half those following intravenous administration indicating approximately 50% first pass metabolism. The level of beta-sympathetic activity varies widely among individuals, and no simple correlation exists between the dose or plasma level of timolol maleate and its therapeutic activity. Therefore, objective clinical measurements such as reduction of heart rate and/or blood pressure should be used as guides in determining the optimal dosage for each patient **(Daley et al., 1984).**

Timolol as other beta-blockers is used in angina of effort and unstable angina **(Given wilson and Jay, 1985)**. Therapy should be initiated with 5 mg orally two or three times aday and the usual dosage range is 15 to 45 mg per day **(Daley et al., 1984)**.

Timolol is also used to reduce infarct size in patients with early acute myocardial infarction especially in the first 5 hours from occurrence of infarction **(Rogue et al., 1987; Risoe et al, 1987 and Sederoholm, 1984, 1986)**. The recommended initial dose is 1 mg intravenously followed 10 minute later by another intravenous dose of 1 mg. Therapy should be continued for 24 hours with an intravenous infusion at the rate of 0.6 mg/hour. After the first 24 hours,treatment may be continued with oral dose of 10 mg twice daily to reduce the risk of cardiac death, including sudden death, and reinfarction in those who have survived the acute phase of myocardial infarction **(Khan, 1984; Gunderson et al., 1986)**.

A norwegain multi-centre, double-blind study (1981) compared the effects of timolol maleate with placebo in 1884 patients who had survived the acute phase of a myocardial infarction. Timolol therapy following infarction was shown to reduce overall mortality,

which was primarily attributable to a reduction in cardiovascular fatality. The protective effect of timolol was consistent regardless of age, sex or site of infarction and was clearest in patients with a first attack who were considered at a high risk of dying.

Timolol maleate can be used also in supraventricular arrhythmias as paroxysmal atrial tachycardia and atrial fibrillation. Also it can be used in ventricular extrasystoles due to excessive catecholamine production as in emotionally induced ventricular arrhythmias **(Simon et al., 1978)**, or those following acute myocardial infarction **(Ranganathan et al., 1988)**.

Timolol maleate is also used in essential hypertension (including the hyper kinetic heart syndrome), the intial dosage is10 mg/day given orally in a single or divided dose. Depending on the response of the patient, the increase in dose can be made to a maximum of 60 mg daily. The drug can be used with thiazides, hydralazine or methyldopa **(Simon et al., 1978)**.

Unlike the majority of the available beta-blockers, timolol has no membrane stabilizing effect, and because of its high potency and lack of local anaesthetic effect, the drug is the only beta-blocker which was proven to be

safe and effective in the treatment of glaucoma when used topically. The mechanism by which, timolol reduces intraocular pressure is unclear, but it may be related to decreased production of aqueous humor **(Watanabe and Chiou, 1983).**

CALCIUM ANTAGONISTS

Historically, the development of calcium antagonists dates back to the early 1960s, at which time, it was observed that prenylamine, a newly developed coronary dilator (at that time), and verapamil, another phenylalkylamine with coronary dilating properties, exerted negative intoropic effects on isolated cat and rabbit myocardium and also depressed cardiac performance in the canine heart-lung preparation. This potent cardiodepressent effect of these two agents appeared to distinguish them from the classic vasodilators,because drugs such as nitroglycerine and papaverine with potent smooth-muscle relaxing properties could depress cariac muscle only at high concentration. As the inotropic and chronotropic effects of prenylamine and verapamil were quite opposite to those elicited by catecholamines, the new drugs were first believed to be adrenergic blocking agents **(Melville and Benfey, 1965)**. However, **Fleckenstein et al (1968)** were the first to report that the effects of both prenylamine and verapamil differed from beta-adrenergic receptor antagonist. They observed that both agents depressed cardiac contractility without altering the height of the contour of the monophasic action potential, and they concluded that, thses drugs act as uncouplers of excita-

tion-contraction coupling. The action of these drugs was attributed to inhibition of the influx of calcium into the myocardial cells, consequently,these agents were called calcium antagonists.

Calcium ion concentration is responsible for the control of many intra and extra- cellular physiological processes. It is important for blood clotting, bone metabolism, stimulus secretion coupling in the endocrine system, enzymatic reaction, electrical activation of various excitable cells and muscular contraction **(Merin, 1982).**

It is now well recognized that activation of cardiac contraction results from elevalion of the intracellular concentration of calcium above 10^{-7}M. This in turn,removes the inhibitory influence of the troponin-tropomyosin protein complex on the interaction between actin and myosin, actin filaments are displaced relative to myosin filaments, and contraction ensues **(Church and Zsoter, 1980).** Thus calcium that enters the cell during the plateau of the action potential plays an essential role in coupling myocardial excitation to contraction, although there is some evidence that transmembrane flux of calcium may merely trigger the release of larger

quantities of the ion from intracellular store and that is the latter that actually activates the contractile mechanism **(Fleckenstein , 1981).**

Extracellular calcium is bound to the cell surface coat, and intracellular calcium is sequestered in the sacroplasmic reticulum. In skeletal muscle, the calcium that triggers contraction comes maily from internal stores in the plentiful sacroplasmic reticulum. In cardiac muscle, the sacroplasmic reticulum is not so plentiful, and the calcium current that flows from the cell surface to the interior during the action potential plateau plays a more important role than in skeletal muscle **(Church and Zsoter, 1980).** In vascular smooth muscle, membrane calcium may play an even more important role in contraction and maintenance of tone. The lumina of coronary and systemic arteries may be altered by changes in smooth muscle tone induced by the movement of calcium across the membranes of smooth muscle cells. Recent evidence indicates that vascular smooth muscle tone can be increased either by increasing cytoplasmic calcium ion (Ca^{++}) levels or by increasing the sensitivity of the contractile apparatus to calcium. Therapeutic agents designed to decrease intrinsic myogenic tone directly could be designed to either decrease Ca^{++} or to

decrease the sensitivity of the contractile apparatus to calcium **(Morgan, 1987)**. If extracellular calcium is prevented from penetrating the cell membrane, muscular contraction will be prevented. In addition vascular smooth muscle will relax, producing vasodilation and cardiac muscle will contract less powerfully **(Johns et al., 1987)**.

In addition to its role in contraction of heart muscle, calcium is important for the generation and conduction of the cardiac impulse. Reduction of clacium ions results in atrioventricular block. In reentrant supraventricular tachyarrhythmias, the A-V node is considered to be the site of the recurrent pathway. Agents that inhibit calcium flux tend to block conduction within the A-V node and depress reentrant circuits, thereby preventing or arresting supraventricular tachycardia. After depolorizations are also inhibited by these agents. Thus, the genesis of extrasystoles is depressed **(Antman and Smith, 1985)**.

Overwhelming evidence has accumulated in the last two decades indicating that calcium ions are required during excitation in order to activate the biochemical processes that utilize adenosine triphosphate (ATP) for

contraction. Thus, calcium ions not only trigger the contractile process but also control quantitavely the output of mechanical tension by regulating the amount of ATP that is metabolized during activity **(Johns et al., 1987).**

Classification and Mechanism of Action:-

Calcium antagonists a class of drugs that includes two groups of drugs. The first group includes drugs which are selective for slow Ca^{++} channels as nifedipine, verapamil and diltiazem The other group of drugs are nonselective for slow Ca^{++} channels, have predominant inhibitory effect on Ca^{++} entry in addition to other effects not related to blockade of Ca^{++} entry, inculde prenylamine, Cinnarizine and perhexiline **(Vanhoutte, 1987).** Entry of extracellular Ca^{++} occurs by a number of routes, only one of which is through channels sensitive to the calcium antagonsits. These channels are closed in an unstimulated cell but open during excitation. In cardiac tissue, Ca^{++} entry carries charges responsible for the plateau of the action potential and is recognized as slow inward current, in voltage- clamp studies, the channels are termed slow Ca^{++} channels. In smooth muscles Ca^{++} channels can be opened by depolarization, in which case they are termed potential-operated channels. Altern-

atively, other channels may be opened during activation of cell membrane receptors without a change in membrane potential and are termed "receptor operated channels". Slow Ca^{++} channels of the heart, receptor-operated channels and potential operated channels do not open in the presence of calcium antagonists as shown by electrophysiological studies **(Vanhoutte, 1987).**

Calcium channel blockers bind to specific receptor sites that are associated with a voltage dependent calcium channel. As a result of drug binding to the receptors, the amount of Ca^{++} flowing through the channel is decreased which in turn changes the intracellular Ca^{++} concentration and several cellular function **(Vaghy et al., 1987).** It is important to note that not all voltage dependent calcium channels are susceptible to the action of calcium channel modulators. Recent electrophysiological studies show that subtypes of calcium channels which are insensitive to organic calcium channel modulators exist in cardiac,smooth and skeletal muscle and in neuronal tissue **(Friedman et al., 1986).** It is not known however, if the lack of response of certain calcium channel subtypes to drugs is due to the lack of binding or if binding occurs but does not produce the desired signal that is directly responsible for the

channel activation and/or inactivation **(Vaghy, et al., 1987).** It has been suggested recently that calcium antagonists may bind to the calcium-dependent regulatory protein or calmodulin. Because this protein may serve as the calcium-binding protein of the smooth-muscle contractile machinery, this may represent their site of action as calcium antagonists in vascular smooth muscles **(Freidman et al., 1986).**

Cardiovascular Actions and Uses:-

The predominant pharmacologic effects of calcium channel inhibitors are: coronary, peripheral and cerebral vasodilation, a negative inotropic effect and an inhibition of excitation of sinoatrial and atrioventricular nodes. These effects explain their remarkable therapeutic value in angina pectoris, hypertension,post hemorrhagic cerebral vasopasm and supraventricular tachycardia **(Snyder and Reynolds, 1985).** Other effects have also been reported such as inhibition of platelet aggregation, relif of migraine and bronchial asthma and protection of ischemic myocardium **(Vaghy et al., 1987).**

Calcium entry - blocking agents constitute an important family of drugs for treatment of angina pectoris. These drugs decrease myocardial contractile force,

which in turn reduces myocardial oxygen requirement. Inhibition of calcium entry into arterial smooth muscle is associated with decreased arteriolar tone and systemic vascular resistance, resulting in decreased arterial and intraventricular pressure thus left ventricular wall stress declines, which also reduces the myocardial oxygen requirement **(Church and Zsoter, 1980)**. Decreased heart rate with the use of some calcium entry blocking agents (Verapamil, diltiazem and prenylamine) causes a further decrease in myocardial oxygen demand **(Zelis and Flaim, 1981)**. Calcium channel blockers also relieve and prevent focal coronary artery spasm, the primary mechanism of vasospastic (Variant) angina, besides they decreas the Ca^{++} content of the red blood cells. This combination of effects decreases the resistance to flow through the coronary arteries and allows an improved supply of blood to the myocardial tissues **(Saini, 1984)**. In addition, the available red blood cells can fulfill their function at the microcirculatory level because they regain their normal flexibility. Thus the use of these agents has emerged as the most effective treatment for the vasospastic form of angina pectoris **(Findlay et al, 1986)**.

Verapamil, nifedipine and diltiazem have all been shown to be strikingly effective in controlling frequent

attacks of variant angina resistant to beta blockers with or without nitrates **(Antman et al., 1980).** Repeated attacks of ventricular fibrillation complicating attacks of variant angina have also been shown to respond to calcium antagonists. Also, such agents have been shown to consistently block the coronary spasm and ST elevation provoked, by ergonovine in patients with variant angina **(Saini, 1984).**Although, nifedipine was the most efficacious in preventing coronary spasm, yet the combination of long acting nitrate and a calcium antagonist may be more effective than either agent alone in preventing attacks of variant angina **(Antman et al., 1980).** This in contrast to the combination a calcium antagonist with a beta-blocker where the recurrent episodes of variant angina might be aggravated **(Zelis and Flaim, 1981).**

In angina of effort, calcium antagonists by their potent coronary vasodilator property, by decreasing peripheral vascular resistance, and reducing myocardial contractility, these agents may decrease myocardial oxygen consumption and thereby improve the relation between myocardial oxygen supply and demand **(Brunwald , 1982).**

In patients with unstable angina with recurrent ischemic episodes at rest, the addition of nifedipine to

beta-blocker and nitrate therapy can decrease the frequency of rest angina, the incidence of myocardial infarction and the necessity for emergency myocardial revascularization **(Khan, 1984).**

In addition to their beneficial effects in various froms of angina pectoris, calcium antagonist drugs may be used to protect ischemic myocardium and may limit infarct size **(Crottogini, 1985).** Numerous studies in experimental animals have indicated the beneficial potential of calcium antagonists in salvaging ischemic myocardium. However, it is unkown whether or not such salutary effects result in lowering morbidity and mortality from acute myocardial infarction if the intervention is applied in early phases of coronary occlusion in humans **(Vaghy et al., 1987).** There are several ways by which calcium antagonists could protect the ischemic myocardium. BY inhibiting slow-channel transport, such agents produce negative inotropic effects, under these conditions, myocardial ATP consumption is reduced, leaving ATP available for maintaining intracellular homeostasis, particularly with respect to calcium and sodium. This in turn, prevents mitochondrial calcium overloading, thereby possibly ensuring their functional survival **(Yellon et al., 1983).** The hemodynamic properties

of reducing myocardial contractility and reducing afterload would tend to reduce myocardial oxygen requirements. Their potent coronary vasodilator action could enhance collateral blood flow, even in the presence of a fixed coronary occlusion, thereby ensuring tissue viability **(Crottogini, 1985).** In addition slow channel blockade has been shown to prevent the reduction of ventericular fibrillation threshold induced by adrenergic stimulation which in turn is strikingly increased within 2 minuts after coronary ligation **(Brooks et al, 1980).** It also shortens post repolarization refractoriness in ischemic myocardium, thus exerting an antiarrhythmic effect on ischemia related reentrant ventricular tachycardia. **(El sherif and Lazzara, 1979).** Finally, by preventing the development of coronary spasm, these agents may prevent the occurrence of or may relieve myocardial ischemia **(Findlay et al., 1986)** Nifedipine, verapamil and diltiazem have been shown to alter regional myocardial blood flow after coronary occlusion in the dog and to exert variable effects on the size and manifestions of myocardial infarction **(Crottogini, 1985).**

Prenylamine was shown to have a protective effect against myocardial ischemia **(Manning et al., 1981).** Also administration of prenylamine to rats was found to cause

an enhancement of post-ischemic functional recovery, reduction of enzyme leakage during reperfusion, reduction of post-ischemic arrhythmias and the total abolition of reperfusion-induced ventricular fibrillation **(Manning et al., 1982)**. In addition, prenylamine was found to inhibit isoprenaline-induced myocardial lesions **(Milei et al., 1982)**.

The antiarrhythmic effects of calcium antagonists are due to their direct electrophysiological actions. The experimental data indicate that the depression of the slow response by calcium antagonists in pathologic tissues may abolish arrhythmias due to reentry as well as automaticity **(Fleckenstein, 1977)**. Verapamil is the drug of choice for treatment of reentrant supraventricular tachycardia, irrespective of whether reentry is intranodal or occurs in association with an accessory pathway. Verapamil probably acts by lengthening the effective and functional refractory period of the A-V node and prolonging the A-V nodal conduction time **(Singh, 1980)**. At the cellular level, it may be counteracting the increase in intracellular calcium concentration induced by decreased mitochondrial calcium-binding activity **(Fleckenstein, 1977)**. Verapamial does not appear to be a very effective drug for treatment of

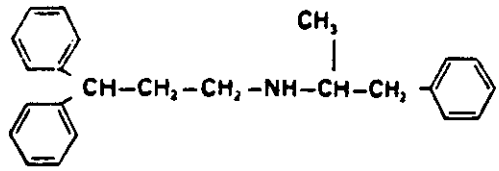
ventricular arrhythmias except in instances in which such arrhythmia arise because of coronary vasospasm with transmural myocardial ischemia **(Church and Zsoter, 1980). Brooks et al (1980) and El Sherif and Lazzara (1979)** had shown that calcium antagonsits were effective in elevation of ventricular fibrillation threshold in acute myocardial infarction and in abolishing ischemia-related reentrant ventricular tachycardia.

All calcium antagonists are arterial vasodilators therefore they are potentilly useful in treating systemic arterial hypertension. Nifedipine in this respect exerts the most potent vasodilatory effect, with the least adverse electro-physiologic effects. Nifedipine administration orally or sublingually promptly reduced systolic and diastolic pressures in patients with severe hypertension, therefore in hypertensive emergencies, oral nifedipine may be a valuble alternative to intravenous diazoxide or nitroprusside **(Findlay et al., 1986)**. Verapamil and diltiazem have been found to produce only small decrease in blood pressure without affecting the plasma renin concentration **(Fleckenstein, 1977)**. However, both nifedipine and verapamil were found to be effective in patients with chronic hypertension. Thus calcium antago-

nists may be useful for the treatment of mild hypertension complicated by coronary disease or impaired ventricular perforemance or both. The mechanism of antihypertensive effect is not clear, but it may involve diminution of vascular tone **(Saini, 1984).**

PRENYLAMINE LACTATE

Prenylamine lactate is a fine white powder slowly soluble in water and freely soluble in organic solvents. Its chemical structure is:



The molecular formula is N-(3,3-diphenylpropyl)-1-Methyl-2-phenylethylamine. The molecular weight is 419.57. The melting point is about 140°c **(Lindner, 1971).**

Prenylamine is rapidly and almost completely absorbed after oral administration **(Dengler et al., 1970).** It is excreted in the bile and undergoes enterohepatic circulation, metabolism occuring partly in the liver **(Schmidt et al., 1963).** In humans, maximum serum concentration is achieved after 60-90 minutes, the serum half life of prenylamine is approximately 14 hours (iv.) or 7 hours (oral) **(Dengler et al., 1970).** About 41.3% of

prenylamine dose is excreted in the urine and 37.4% in the faeces during the first tendays after intravenous administration. The majority have been excreted within five days **(Dengler et al., 1970).**

There are two major ways by which prenylamine acts; namely: antagonizing calcium by blockode of slow calcium channels and slowing of calcium transport through the endoplasmic reticulum of the myocardium, thereby reducing myocardial metabolism during work **(Nayler, 1968).** The other mechanism of prenylamine is on catecholamine uptake and release, particularly in storage sites in the myocardial and certain other tissues thus modifying the results of sympathetic stimulation **(Iversen, 1967; Manning et al., 1982).**

During electromechanical coupling energy is provided by breakdown of adenosine triphosphate (ATP), an effect which is calcium dependent **(Johns et al., 1987).** Prenylamine could delay calcium transport by binding to phospholipids in the membrane of the endoplasmic reticulum **(Hasselbach et al., 1968).** At the same time, it inhibits the magnesium dependent calcium transport ATP-ase in the granules of the endoplasmic reticulum of the heart muscle **(Lindner, 1971). Moreover Saini(1984)**

and Fagbemi (1984) had shown that prenylamine as other calcium antagonists can inhibit the influx of Ca^{++} into the myocardial cells by slow-channel blocking effect.

Since schoene and Lindner (1960) had described the decrease of catecholamine content of sympathetically innervated organs by prenylamine, numerous investigators had demonstrated the catecholamine depletion induced by prenylamine using chemical, fluorescent, microscopic and radio chemical methods **(Lindner, 1971).**

In sympathetic nerves, catecholamines are present in bound form in intracellular granules. The most important action of prenylamine is the competitive inhibition of the uptake of catecholamine by these storage granules (Uptake III) **(Lindner, 1971).** Even at concentrations as low as 10^{-6}M., **Carlsson and waldeck (1968)** were able to demonstrate 50% inhibition of adrenaline uptake in isolated adrenal medullary-granules. Normally, active amine uptake into the catecholamine granules and passive diffusion into the intracellular space are in equilibrium. Thus, when the uptake of catecholamine is inhibited, continued spontaneous release leads inevitably to depletion of granules. Since pre-treatment with prenylamine attenuates the effect of reserpine, it is assumed that

both drugs compete for a common site on the catecholamine granules **(Lindner, 1971)**. However, cardiac tissue is more sensitive than brain tissue to depletion of catecholamine by prenylamine, whilst the reverse is true for reserpine **(Obianwu, 1965)**.

Prenylamine induced depletion of noradrenaline from the granules can be demonstrated by an initial increase in catecholamine excretion, both in healthy subjects and in patients with coronary artery insufficiency **(Bauminger et al., 1970; Schmidt et al., 1968)**. However after prolonged treatment with prenylamine, the excretion of the major catecholamine metabolite vanil-mandelic acid (VMA) decreases and in addition, it has been shown that emotion and exercise-induced elevation of VMA excretion are reduced by prenylamine pre-treatment **(Lindner, 1971)**.

It is important to note that, even in maximal doses (80-100 mg/kg), prenylamine does not produce complete depletion of noradrenaline in the myocardial cells. Thus, the physiological transmitter substance is not completely eleminated, leaving a sympathetic reserve for response to stress **(Nielson and Owman, 1967)**.

Although, like propranolol, prenylamine has some negative inotropic effects, it is relevant that the

decrease in heart rate and peripheral resistance is not due to specific beta-adrenergic receptor blocking effects **(Fleckenstein et al., 1968).** It does not inhibit the relaxing effect of isoprenaline on the tracheal muscle , nor does it block the action of isoprenaline on cardiac beta-receptors in normal subjects when given intravenously **(Hodge, 1969).**

Prenylamine is a potent coronary vasoditator and has been shown to increase coronary blood flow **(Bauminger et al., 1970)** and this effect was confirmed experimently by **Lindner (1968)** who showed that there was a dose related increase in coronary blood flow in isolated perfused guinea pig heart and intact dogs after injection of prenylamine. Also **Starey (1972)** was able to demonstrate the development of collaterals of coronary vessels in dogs on oral administration of prenylamine for 14 weeks.

prenylamine reduces heart rate by a direct inhibition of the sinoatrial node. This effect was particularly marked on administration of large doses of prenylamine **(Lindner, 1969).** while an intravenous injection of 1 mg/Kg of prenylamine in humans was found to decrease blood pressure, yet its oral administration even when continued for

days did not affect the blood pressure although the heart rate was lowered. **(Stauch and Harich, 1972).** Prenylamine has an antiarrhythmic action. It lengthens the relative refractory period of an electrically irritated, isolated left guinea pig atrium **(Lindner, 1963).** It could protect isolated guinea pig heart against ventricular fibrillation induced by digitoxin and aconitine **(Lindner, 1963).** It could protect cats against ventricular fibrillation induced by hypothermia **(Nielsen, and owman, 1967).** It also can antagonize the lethal ventricular fibrillation provoked by calcium chloride in mice **(Ferrini and Miragoli, 1979).**

Prenylamine is used mainly in angina pectoris, as it has coronary dilator effect leading to increase in coronary blood flow. Moreover it leads to decrease in cardiac work through its bradycardia and mild negative inotropic effects **(Lindner 1971).** Extensive clinical investigation showed prenylamine to have beneficial effects in angina within a narrow dosage range and without frequent or troublesome side effects **(Murphy, 1973). Batson et al., (1971)** had shown that both prenylamine and a standard beta-adrenergie blocking agent significantly reduced post-exercise tachycardia. Between **1964 and 1971,** ten double blind controlled clinical

trials have demonstrated that prenylamine is significantly superior to placebo in angina pectoris **(Cardoe, 1968, 1970; Winsor, 1971).** The majority of patients respond to high dosage range (180-300 mg daily), with significant decrease in attacks of angina pectoris and with good tolerance of the drug **(Murphy, 1973). Slegers et al (1985)** had shown that prenylamine has a place in the therapeutic management of angina pectoris especially in patients in whom beta-blockers are contraindicated or in patients who have side effects of beta-blockers or other calcium channel blockers.

CARDIAC ARRHYTHMIAS

Ischemic heart disease is one of the important factors which can precipitate or exacerbate cardiac arrhythmias and these occur commonly in patients with acute myocardial infarction and vasospastic angina **(Braunwald, 1983).**

Many factors can precipitate arrhythmias as ischemia, hypoxia, acidosis or alkalosis, electrolyte abnormalities, excess catecholamines, drug toxicity (e.g. digitalis), over stretching of cardiac fibres and presence of scarred or otherwise diseased tissue **(Hondeghem and Mason, 1987).**

Post-Ischemic (Infarction) Arrhythmias:-

When patients with acute myocardial infarction are continuously monitored in a ccu, 75% to 95% will show some arrhythmias. Many factors contribute to the development of these arrhythmias e.g., the location and size of the infarct which may determine whether the AV Junction or the bundle of His or its branches are involved. Pain, anxiety , hypoxia, acidosis, electrolyte disturbances (Particularly hypokalemia), congestive heart failure, shock and straining at stool may also induce arrhythmias **(Goldberger, 1982).** In addition, pericarditis associated

with acute myocardial infarction which involves the SA node and drugs such as morphine, digitalis , antiarrhythmic drugs and sympathomimetic drugs can cause different arrhythmias **(Alexander, 1976).**

Cardiogenic shock is usually associated with serious arrhythmias. Life theatening arrhythmias occur in more than 90% of patients with acute myocardial infarction and cardiogenic shock, and in only about 50% of patients without shock. Similarly, AV block is three times more frequent and ventricular fibrillation is twice as frequent after acute myocardial infarction, if shock is present. However, ventricular tachycardia occurs equally in patients with myocardial infarction with or without shock **(Crottogini et al., 1985).**

The cardiac arrhythmias usually appear within the first hours after the acute myocardial infarction. The heart is then particularly susceptible to ventricular fibrillation for about one week therafter. The ventricular fibrillation threshold in acute myocardial infarction is decreased by factors as ischaemia and catecholamine release in the area of infarction. Catecholamines increase the level of cyclic AMP, which is an important facilitating factor in the development of ventricular

fibrillation **(Nanas and Kralios, 1986).** Similarly, tachycardia, hypoxemia, alkalosis or acidosis and hypokalemia all might lower the ventricular fibrillation threshold **(Khan, 1984).**

Adrenaline Induced Arrhythmia:

Adrenaline in toxic doses, can cause various forms of arrhythmias as ventricular extrasystoles, ventricular tachycardia and ventricular fibrillation. All these arrhythmias originate mainly from icreased abnormal automaticity of the ventricular tissues **(Hondeghem and Mason, 1987).**

The interval between depolarizations of a pacemaker cell is the sum of the duration of the action potential and the duration of the diastolic interval, thus shortening of either duration results in an increase in pacemaker rate. The more important of the two is the diastolic interval which is dependent on 3 Factors: maximum diastolic potential, solpe of phase 4 depolarization, and threshold potential **(Hoffman and Rosen, 1981).** Acclerat-ion of pacemaker discharge is often brought about by increased phase 4 depolarization slope, caused by beta-adrenoceptor stimulation, catecholamines, hypokalemia, fibre stretch, acidosis and partial depolarization by

currents of injury. Vagal discharge slows normal pacemaker rate by making the maximum diastolic potential more negative and reducing the phase 4 slope. On the other hand, beta-adrenergic receptor blocking drugs markedly reduce phase 4 slope. **(Hoffman and Rosen, 1981).**

All cardiac cells, including normally quiescent atrial and ventricular cells, may show repititive pacemaker activity when depolarized under appropriate conditions especially hypokalemia and catecholamine toxicity. $Beta_1$- receptor activation in the heart results in increased calcium influx in cardiac cells with consequent electrical and mechanical effects. For example, the pacemaker activity, both normal (sinoatrial node) and abnormal (Purkinje Fibres) is increased (Positive chronotopic effect). Conduction velocity in the atrioventricular node is also increased (Positive dromotropic effect) and the refractory period is decreased. In the same time, the intrinsic contractility is increased (Positive inotropic effect) and relaxation is accelerated **(Hondeghem and Mason, 1987).**

Several recent radioligand binding studies have indicated a relatively high proportion of (B_2) $Beta_2$ receptors in the human heart, up to 50% **(Brodde et al.,**

1982; Heitz et al., 1983 and Stiles et al., 1983). It has been shown that myocardial $beta_2$ receptors can induce chronotropic changes in man (Brown et al., 1986), and it has been assumed that $beta_2$ receptors are linked with chronotropic effect while $beta_1$ (B_1) receptors account for both inotropic and chronotropic responses (Stene Larsen, et al., 1986).

Digitalis Induced Arrhythmia:

The effect of digitalis on the electrical properities of the heart in the intact organism are a complex mixture of direct and indirect actions. Direct actions on the membranes of the cardiac cells follow a well defined progression, an early brief prolongation of the action potential with an increase in membrane resistance, followed by a protracted period of shortening of the action potential (especially the plateau phase) associa - ted with a decrease in membrane resistance. This decrease in membrane resistance is probably the result of increased intracellular calcium, which is known to increase membrane potassium conductance. The latter change would result in action potential shortening (Katzung and parmley, 1987). All of these effects can be observed in the absence of overt toxicity. With more toxic concentration, resting membrane potential is reduced as a result

of inhibition of the sodium pump and reduced intracellular potassium. As toxicity progresses, oscillatory depolarizing after potentials appear following normally evoked action potentials **(Antman and Smith, 1985).** The after potentials (also known as delayed after depolarization) are associated with overloading of the intracellular calcium stores and oscillations in the free intracellular calcium ion concentration. When these after potentials reach threshold, they elicit an action potential (Premature ventricular depolarization or ectopic beat), that is coupled to the proceeding normal one. If after potentials in purkinje conducting system regularly reach threshold, bigeminy will be recorded on the E.C.G. with further toxic deterioration, each after potential-evoked action potential will itself elicit a sizable after potential, and a self sustained arrhythmia (ventricular tachycardia) will be established if allowed to progress, such a tachycardia may deteriorate into ventricular fibrillation **(Antman and Smith, 1985).**

Indirect actions of cardiac glycosides on the heart involve the autonomic nervous system and occur through the therapeutic and toxic dose ranges. In the lower doses cardioselective parasympathomimetic effects

predominate. While at toxic doses sympathetic outflow is increased by digitalis **(Lathers, 1980)**. This effect is not essential for typical cardenolide toxicity but sensitizes the myocardium and exaggerates all of the toxic effects of the drug **(Katzung and Parmley, 1987)**.

LIMITATION OF INFARCT SIZE

Coronary heart disease is a common cause of sudden death. In about 25 perecent of those who develop the features of ischemic heart disease, sudden death is its first manifestation. It also complicates the early hours of acute myocardial infarction, but can occur at a later stage of this disorder, or unexpectedly in a patient with apparently stable angina pectoris **(Jullian and Campbell, 1981)**. However, despite the advance in management of patients with acute myocardial infarction, mortality from power failure following acute myocardial infarction has been altered very little **(Hood, 1975)**.

It has been reasonably established that power failure in the absence of complicating lesions such as ventricular septal defect or mitral regurgitation, occur strictly in proportion to the amount of myocardium which is damaged i.e. in proportion to infarct size **(Page et al., 1971; Shell and Sobel, 1973, and Norris et al., 1975)**.

According to **Maroko and his colleagues (1971) and Braunwald and Maroko (1974)**, it has become apparent that infarction is not a discrete event, but rather a dynamically evolving process. The Morphological observa-

tions of infarct lesions in heart have allowed to consider the existence of a reactive area surrounding the necrotic zone. This area is not primarily caused by the arterial occlusion responsible for the heart attack, but is due to reaction secondary to the initial necrosis. **Braunwald (1976)** pointed out that this ischaemic "twilight zone"may increase in size for some time, while the necrotic zone remains relatively small. This increase in size occurs during the 18 hours following the occlusion when the necrotic zone remains unchanged. Thereafter, the central necrosis progress out-wards as a "wave front" at the expense of this ischaemic tissue **(Melon and Marrelli, 1978; and sloman et al., 1981).** It has been suggested that following permanant coronary artery occlusion, there are at least two zones of myocardial within the ischaemic tissue, a zone with severe ischemia destined to become necrotic irrespective of any intervention and a border zone of less severe ischaemia with damaged viable myocardium that can be salvaged by the appropriate intervention. If so, the progression of biochemical abnormalities in the ischaemic myocardium should be non-uniform, that is, the salvageable cells should exhibit either qualitatively diffecent biochemical changes or the same changes proceeding more slowly than those in the non-salvageable cells **(Michael et al.1980).**

The prognosis for patients with chronic ischaemic heart disease suffering acute myocardial infarction is dependent on the amount of necrotic tissue involved **(Sloman et al., 1981)**. Tachycardia, hypertension, hypotension in particular hypovolemic hypotension which may be induced by diuretics or nitrates, arrhythmias and hypoxemia, all these factors can increase the infarct size **(Henry, 1979)**. Increased sympathetic activity associated with pain, anxiety and apprehension during the early phase of infarction lead to increase in cardiac work and increase in circulating free fatty acids, which lead to accelerated oxygen consumption with consequent depletion of ATP and creatine phosphate which contribute to further damage and/or dysrhythmias **(Strubett and Siegers, 1975)**.

Another factor which may increase the myocardial infarct size is that myocardial cells injured by ischemic conditions show an acute myocardial increase in cytosolic calcium **(Hearse et al., 1977)** such an uncontrolled rise in calcium is known to activate a number of energy consuming reactions, thus accentuating the ischemia induced decrease in cellular adenosine triphosphate (ATP) content, which further depletes cellular energy stores making the heart even more susceptible to ischemic damage and irreversible cell injury **(Katz and Reuter, 1979)**.

Increase in cellular calcium may result from impairment of the mechanism that pumps calcium out of the myocardium against a very large electrochemical gradient and/or from damage to the membrane system that regulates calcium entry into the cell (Zamanis et al., 1982). It has been proposed that reduction of calcium entry and/or accumulation into the ischemic myocardial cell could be beneficial to the ischemic myocardium (Reimer et al., 1977).

The prognosis after acute myocardial infarction depends directly on the quantity of remaining viable, normally functioning myocardium (Page et al., 1971). Similarly, the incidence of sudden death due to early ventricular fibrillalion following acute myocardial infarction increases proportionally with the size of the infarct (Endo et al., 1983). If myocardial cell death after acute coronary occlusion could be reduced,a greater guantity of viable myocardium would remain and this might be expected to reduce the incidence of cardiogenic shock and pulmonary oedema and therby immediate mortality and chronic heart failure would be less likely (Maclean et al., 1978; Crottogini et al., 1985). Therefore, salvage of ischemic myocardium by different pharmacologic interventions in an attempt to reduce infarct size is a matter of permanent interest.

The balance between myocardial perfusion and metabolic requirements must not be adversely affected by therapy. It is thus of paramount importance to avoid and /or correct measures that may increase infarct size **(Endo et al., 1983).**

The therapeutic strategies to limit infarct size include (1) Decreased myocardial oxygen demand by the use of beta-blocking agents, decreasing afterload in hypertensive patients and circulatory support with counter pulsation. (2) Reduction of myocardial ischemia by restoring perfusion or augmentation of flow through collaterals, thus increasing myocardial oxygen supply by the use of calcium antagonists, thrombolytic therapy and elevation of coronary perfusion pressure by intraa - ortic ballon counterpulsation and/or norepinephrine in patients with cardiogenic shock. (3) Protection against infarction intiated autolytic and heterolytic processes by the use of experimental agents such as cobra venom factor **(Khan, 1984; Herlitz et al., 1986).**

Another foctor which may limit infarct size is intravenous nitroglycerine which experimentally appears to reduce infarct size **(Derrido et al., 1978).** However, at this stage, the use of intravenous nitrate to limit

infarct size must be considered experimental and controversial and thus can not be recommended for general use **(Davies and Thomas, 1984).**

Thrombolytic therapy is another important factor in limiting infract size in acute myocardial infarction, when intracoronary or intravenous streptokinase is given in the first 4 hours of the onset of chest pain and other symptoms and signs of acute myocardial infarction **(Anderson, 1983).** Several non-randomized clinical studies claim benefit from the use of thrombolytic therapy. In a randomized study, mortality appears to have been significanlty reduced in patients followed up to 6 months post intracoronary streptokinase therapy **(Kennedy et al., 1983).**