CHAPTER II

General review of Literature, Digitalis and Calcium Channel Blockers
2.1 History: The digitalis was first mentioned in 1250 in the writings of Welsh physician. It was described botanically 300 years later by Fuchsius who gave it the name Digitalis purpura. It was first published by William in 1785 in his famous book "An Account of Foxglove and some its Medical Uses with Practical Remarks on Dropy and other diseases (Withering, W. 1937). In 1799 John Ferriar first described the action of Digitalis in heart and diuretics effects are the secondary importance.

Cushny, Mackenzie, Lewis and other described its specific action in the treatment of atrial fibrillation. During last 60 years it has been established that the main value of Digitalis is in the therapy of congestive heart failure.

2.1.1 Mechanism of Action of Digitalis:

2.1.2 Pharmacodynamics: Digitalis is used in congestive heart failure to increase the circulation and to slow down the ventricular rate in the presence of atrial fibrillation and atrial flutter. The main property of Digitalis is to increase the force of contraction of the myocardium. The main effects observed in congestive heart failure include:

i) Increased cardiac output
ii) Decreased heart size
iii) Decreased venous pressure
iv) Decreased blood volume
v) Diuresis
vi) Relief of oedema
These effects are due to the positive inotropic effect of digitalis. The second important effect is slowing of ventricular rate in atrial fibrillation and flutter. In 1938, Cattell and Gold first showed direct inotropic action of digitalis in cardiac muscle. The biochemical, pharmacological and the physiological studies have been done by different authors (Akera, T. and Brody, T.M., 1978, Akera, T., 1981, Glynn, J.M., 1979, Lee, K.S. and Klaus, W., 1971, Nable, D., 1980, Schwartz, A. et al, 1975, Smith, T.W. and Haber, E., 1973) to study the mechanism of inotropic effect of digitalis. It acts directly on smooth muscle of ventricular system and also exerts some effects on the neural tissue and this indirectly influences the mechanical and electrical activity of the heart and modifies vascular resistance and capacitance. The change in the circulation brought about by digitalis after results in reflex alteration in autonomic activity and hormonal balance that indirectly influences the cardiovascular action. So, digitalis has two types of actions - direct and indirect.

2.1.3 Direct action:

1) Myocardial contractility: Positive inotropic effect of Digitalis is a dose dependent factor. The effects are similar on the atrial and the ventricular muscles and in the normal as well as the failing heart. The contraction is isotonic and isometric which is clearly demonstrated in the figure (Goodman and Gilman 731 30 1).

2.1.4 Mechanism of action: The manner of inotropic action of digitalis has been studied by a variety of techniques. It has been seen that digitalis in therapeutic concentration exerts no
direct effect on the contractile proteins or on the interaction between them. The most probable explanation for this action is the ability to inhibit the membrane bound Na\(^+\)K\(^+\) activated adenosine triphosphatase (Na\(^+\)K\(^+\)ATP\(_\text{ase}\)). The hydrolysis of ATP by enzyme provides the energy for the so called potassium pump – the system in the sarcolemma of cardiac muscle fibres that actively extrudes sodium and also transports sodium into the fibres. The digitalis glycosides bind specially to the Na\(^+\)K\(^+\) ATP\(_\text{ase}\), inhibit its enzymatic activity and inspire the active transport of the two monovalent cations. As a result there is increase of intracellular sodium and gradual but small decrease of Potassium. These changes are small at therapeutic concentrations of the drug.

The cardiac muscles possess a unique property for exchange of intracellular Sodium with extracellular calcium ion. When inhibition of the pump by digitalis causes (Na\(^+\)) extracellular calcium with intracellular sodium. This causes an increase in the net influx of Ca\(^{++}\) and an increase in the concentration of Calcium ion in the sarcolemma.

Fig. 9 clearly demonstrates the flows of Na\(^+\), K\(^+\) and Ca\(^{++}\) across the cardiac muscle membrane and the effect of digitalis.

2.1.5 Electrical activity: The therapeutic and the toxic effects of digitalis can be related to the actions upon the electrophysiological properties of the heart.

Purkinji fibres: The direct effect of digitalis on the electrical activity of the cardiac fibres has been demonstrated on the transmembrane potentials of mammalian cardiac Purkinje fibres. The action potential (AP) and the resting potential (RP) of the cardiac Purkinje fibres are dependent on both lines of exposure

If the preparation is stimulated at low rates, there is small increase in action potential duration (APD). This is not seen if the rate of stimulation is high; subsequently there is decreased APD followed by plateau (phase 2) and again there is increase in the slope in phase 4 due to depolarisation.

When the toxic effect is fully developed, the RP is markedly decreased and conduction velocity is reduced and ultimately the fibres become unexcitable. The effect of digitalis on phase 4 varies as function of \((K^+)_o\) and other factors at low values of \((K^+)_o\) the most consistent effect is an increase in the slope of phase 4. This results in automaticity which can be demonstrated if the driving stimulus is terminated. At higher levels of \((K^+)_o\) (4 mM) a different change in the membrane potential can be seen in phase 4. This is called delayed after depolarisation (Doors 1973, Furrier et al 1973, Rosen et al, 1973(b), Ledever and Jäsien, 1976) have called this transient depolarisation. As toxicity progresses, the after depolarisation increases in amplitude until it attains the threshold for initiation of an action potential.

The digitalis can initiate ectopic impulse by two different means:

1) Enhancement of normal phase 4 depolarisation
2) Development of delayed after depolarisation

But it is not possible clinically to differentiate between the two conditions.
2.1.6 Other Specialised Fibres: Digitalis exerts direct effects on the fibres of SA node, AV node and on the specialised atrial fibres system. The effect on SA node is mediated through the sympathetic and parasympathetic nervous system.

Net results are -

i) decrease in conduction velocity

ii) increase the effective refractory period (ERP)

2.1.7 Atrial and ventricular muscle fibres: The direct effect of the Digitalis is on the transmembrane potentials of ventricular muscle. It causes decrease of after potential in Purkinje fibres. In E.C.G. it is documented by decrease in QT interval. The alteration of transmembrane potential is evident by ST segment and T wave changes. It does not cause phase 4 depolarisation in atrial and ventricular muscle fibres (Furrier, C.R., 1976).

2.1.8 Indirect effect:

Electrical Activity: It is mediated through autonomic neural activity and neurotransmitters. To decrease in sinus heart rate are acting through the vagus nerve. The improvement of circulation is due to decrease of sympathetic tone. The vagal activity is the results from the action of different sites like -

i) arterial baroreceptors, Gaffney et al (1958)

ii) afferent nerve terminals, Saum et al (1976)

iii) afferent nerve impulse in carotid sinus, Pace & Gilbs, 1976

iv) Vagus nerves and nodose ganglion, Chai et al, 1967

v) Autonomic nerve ganglion, Perry and Reintert, 1954.
2.1.9 **Atrial fibres**: Digitalis causes prominent changes in electrical activity of the atrium. The indirect effect is more dominating than direct effect. The most significant effects in therapeutic concentration are decrease in atrial APD and EHP.

2.1.10 **A.V. Node**: It is strongly influenced by the indirect action of digitalis. It enhances the vagal activity and decrease in sensitivity to catecholamine. The ultimate effect is prolongation of ERP and the conduction is slow. Thus, in atrial, atrial flutter, atrial fibrillation, administration of digitalis will decrease the ventricular rate because of block of an increased fraction of atrial impulse in A.V. junction.

2.1.11 **His - Purkinje system**: It is strongly influenced by sympathetic nervous system but ordinarily is thought not to be particularly sensitive to changes in vagal activity. Thus in contrast to SA node and AV node the indirect effect of Digitalis mediated through the sympathetic nervous system most likely influences the electrical activity of the specialised ventricular system.

2.1.11 **Mechanism of Congestive Heart failure**:

A Congestive heart failure is a syndrome of inadequate cardiac output in relation to the bodily needs (at rest and during exercise) caused by myocardial dysfunction (Dev. V. & Tendon, R., 1988). The myocardial dysfunction may be related to -

i) a primary heart muscle disease

ii) infiltrative disease of the myocardium

iii) after loading condition of the heart pressure and volume overload

iv) Coronary artery disease.
Inadequate cardiac output is associated with peripheral and pulmonary venous congestion and a host of compensatory systemic neurohormonal responses which include marked increase in the activities of sympatho-adrenal system (SAS), renin angiotensin-aldosterone system (RRAS) and the secretion of antidiuretic hormone (Francis, G.S., 1985). The net effect of neurohormonal activation is a pronounced increase in the heart rate, relation of sodium and water, increase in peripheral vascular resistance (PVR) and a marked increase in the myocardial oxygen and energy requirement (Mancini et al, 1986). Though these responses are essential for survival during acute haemodynamic burden in chronic CCF they seem to perpetuate the myocardial damage and worsen the symptoms.

2.1.12 Pathophysiology of CCF:

It is clearly known that function of intact heart is determined by -

i) heart rate
ii) myocardial contractility
iii) Preload
iv) After load

2.1.13 Heart rate (HR): It is directly related to cardiac output and is utilized as a compensatory mechanism for increasing or decreasing the cardiac output. It can be expressed by the equation

\[ C.O. = SV \times HR. \]

SV represents the stroke volume per minute. If the stroke volume falls the heart rate increases secondary to increased catecholamine secretion to compensate the fall of cardiac output.
2.1.14 **Myocardial contractility**: Represents the inherent capacity of the heart muscle to increase the force and magnitude of contractions independent of loading condition (Tendon, R., 1986). It is dependent to a large extent on the availability of calcium ions to the contractile proteins of the heart muscle. Myocardial contractility (MC) can be increased or decreased by hormonal stimuli, drugs, autonomic stimuli and myocardial disease. The clinical assessment of MC is not possible but can be deduced approximately from the parameters of cardiac function such as -(i) ejection fraction (ii) velocity of circumferential fibres shortening (iii) end systolic force and volume relationship (iv) ratio of wall thickness to chamber radius in relation to ventricular systolic pressure. Many of these parameters can be obtained by utilizing non-invasive techniques like echocardiography and radionucleide method. Long term prognosis is also a good criteria of MC.

2.1.15 **Pre-load**: Is the diastolic loading or filling of ventricle dependent on the venous return and capacity of the ventricles to dilate and accommodate the venous return i.e. compliance of the ventricle. The ventricular end diastolic volume and pressure are dependent on the pre-load according to starling's law, in normal heart, increased venous return by increasing diastolic stretch causes an increase in force and extent of myocardial contraction. Thus pre-load will increase the stroke output. Clinically pre-load is measured as the left or right atrial pressure and represents the left or right ventricular end diastolic pressure. It is found that cardiac output occurs at left atrial pressure in the range of 14-18 mm Hg. Above the level at 25 mm Hg, there is pulmonary oedema. Low
cardiac output with elevated left atrial pressure indicates failing of left ventricle. Increased preload in CCF results in pulmonary congestion and dyspnoea.

2.1.16 After Load: Represents the resistance of ventricular emptying. In normal heart, resistance to ventricular emptying is not an important determinant of cardiac output. The ventricles by increasing the preload increases the cardiac output. The damaged heart, however, losses the reserve capacity. The increased preload associated with CCF is not able to increase the cardiac output. The pressure (P) dependent on flow (C.O.) and resistance (SVR)

\[ P = C.O \times SVR \]

The increased cardiac output in CCF is accompanied by increase in systemic vascular resistance brought about by catecholamine to maintain adequate perfusion pressure for the coronary, cerebral and renal vessels. Unfortunately in the presence of CCF the resistance increases inappropriately. The reason for this is not clear. If the left ventricle is normal, increase in resistance can be tolerated but for the diseased left ventricle, this represents further increase of work and decrease output. Thus a vicious cycle is established and results in progressive pump failure. The increased after load reduces the stroke volume or the cardiac output and increases the ventricular end diastolic pressure and the filling pressure (Pre-load) of a failing heart: Reduction in after load would result in an increase in cardiac output.

2.1.17 Physiological effects of heart failure:

Myocardial performance decreases when 20% of the contractile units are impaired. Further impairment causes rapid decompensation. Renal blood flow is decreased in proportion to reduction of cardiac
output. This leads to activation of Renin-angiotensin activity which causes increased tubular reabsorption of sodium and water. This causes increased blood volume which increases venous pressure and causes oedema formation. There is increased sodium content of extracellular and intracellular fluids. The reduced cardiac output is associated with increased ventricular diastolic pressure, atrial pressure as well as systemic resistance. This increased systemic resistance is related to increased catecholamine outflow, renin angiotensin system as well as an increased vascular stiffness.

2.1.18 Management: The management of CCF involves a series of steps which are intended to reverse one or more of the events starting from a poor myocardial contractility. The atrial natriuretic hormone secreted by cardiac endocrine system produces natriuresis, vasodilatation and inhibition of angiotensin II aldosterone and ADH secretion. Thus there is reversal of some of the harmful effects (Needleman, P. et al 1986). Despite increased levels of AVF the haemodynamic changes in CCF are characterized by the dominant effects of the powerful RAAS and SAS (Raine,A.E.G. et al 1980). The availability of synthetic ANF or its analogues in failure may open a new approach to the management of CCF (Needleman, P. et al 1986). Since the congestive cardiac failure means inadequate cardiac output the management consists of a "four pronged attack" for the correction or inadequate output.

i) Augmenting myocardial contractility and then increasing the cardiac output

ii) Improving myocardial performance by reducing the heart size by inotropic agents

iii) Reducing cardiac work to make the cardiac output adequate

iv) Correcting the underlying cause
2.1.19 **Inotropic agents**: The poor myocardial contractility is the basic abnormality. The logic for inotropic agents therapy is obvious (Cullucci TH and Sonnenblock, E.H., 1984). Digitalis has been used for the last 2 centuries as an inotropic agent in CCF. Positive inotropy is finally mediated by an increase in myoplasmic calcium available for actinomysin coupling (Collucci, W.S. et al, 1986).


i) The failing heart is already exposed to high concentration of potent inotropic agents (epinephrine, norepinephrine and angiotensin).

ii) Further administration of positive inotropic agents may just be flogging a tired horse.

iii) Agents which act by stimulating β - receptors show significant degree of tolerance in CCF because of down regulation of β - receptors and delinking of β - receptors from adenylate cyclase complex.

iv) Ruffolo, R.R., J.R., Kapea, G.A.(1986) have described that C.P2 and H2 receptors do not show tolerance and may open new avenues for inotropic therapy in CCF.

v) Increase the myoplasmic concentrations of C-AMP and Ca++ is potentially arrhythmogenic and hence all positive inotropic agents may produce arrhythmias. Increased myoplasmic calcium is known to perpetuate myocardial damage.
iii) Reducing the cardiac work to make the cardiac output adequate.

This can be achieved by decreasing the venous return. The venous return can be decreased by decreasing the circulatory over-load by using diuretics. The commonly used diuretics are -- Thiazide, Loop diuretics, potassium sparing diuretics. These can be used either alone or in combination.

iv) The specific therapy depends on the etiology of congestive heart failure.
2.2 CALCIUM CHANNEL BLOCKERS

2.2.1 Nifedipine:

It is 4 Aryl 1, 4 dihydroxypridine 3,5 dicarboxylates.

The effect of Nifedipine is mediated by -


ii) Decrease myocardial oxygen demand and also myocardial work:

Early administration of Nifedipine does not affect global or regional left ventricular function or myocardial infarct size proved by Thallium Scintigraphy. But early administration of Nifedipine decrease the mortality and reinfarction (Muller et al 1974, Sirne's et al 1984, Wilcox et al 1980).

iii) Reduction of after load by peripheral vasodilation

iv) Direct protective effect on myocardium.

v) The animal experiment shows the reduction of infarct size with nifedipine before and after coronary infusion (Mullan et al 1984, Salwyan et al 1979, Nayler et al 1970). Nifedipine limits the infarct expansion, because the left ventricular wall tension is an important determinant of expansion when the infarction is transmural.

2.2.2 Calcium in Ishaemic and Reperfusion Injury:

Sarcolammal damage is associated with depletion of high energy phosphate compound. It is found that Ca\(^{++}\) ion entry preceds the development of irreversible ischaemic injury. Next
follows Ca\textsuperscript{++} ion deposition in mitochondria and clinically it can be detected by myocardial sc\textsuperscript{a}ntigrams with technetium 99 m. In damaged cell there is severe uptake of calcium during reperfusion with contraction band necrosis and mitochondrial over loading of Ca\textsuperscript{++}. It is a matter of conjecture whether Ca\textsuperscript{++} plays role in Ischaemic Injury or a result. Poole & Wilson (1984) have described that entry of Ca\textsuperscript{++} due to activation of enzyme like Phospholi-
pases and protease.

2.2.3 Calcium Antagonist on Experimental Ischaemia & Infarction:

There are many conflicting results about the use of Calcium antagonist in experimental ischaemia or infarction. Willerson, J. et al (1984) has found that favourable effects are found when the drug is given before the onset of ischaemia. It is due to increased coronary blood flow or decreased myocardial oxygen demand. Hygenhaltz et al (1984) proposed a direct antischaeamic effect to maintain high energy phosphate level. He-use (1984) points out that most interventions designed to decrease ischaemic injury or the size of the infarction is due to reperfusion by the cardioprotection in the injured site.

2.2.4 Pharmacology of Calcium Antagonist Sarcolemmal Binding Sites:

Ca\textsuperscript{++} antagonist first developed by Fleckenstein (1984). Potentially Ca\textsuperscript{++} ions play the most fundamental role in regulation of CVS. An influx of Ca\textsuperscript{++} ion into the cytosol is required for myocardial contraction. Myocardial relaxation induced by Ca\textsuperscript{++} ions by Sarcoplasmic, Ca\textsuperscript{++} antagonist agents, by modifying these Ca\textsuperscript{++} induced effects.

Calcium ion Fluids: The major site of Ca\textsuperscript{++} antagonist is the influx of Ca\textsuperscript{++} across the Sarcolemma. Ca\textsuperscript{++} ions enter the
heart muscle through the voltage controlled Ca++ channel. The density of Ca++ channel is about 0.1 Ca++ channel per m² in the surface of cardiac cell culture compound with Na+ 16 per m². There is difference of Ca++ in different tissues like myocardium (Class I), Vasculature (Class II), Nodal tissue (Class III). The different Calcium antagonist acts differently. Verapamil and deltaxem inhibit supraventricular arrhythmia, whereas nifedipine acts on peripheral vasculature. Ca++ channel are controlled by Catecholamine stimulation which is activated by phosphorylation. The rhythmical contraction and relaxation of myocardium depends on the Ca++ concentration in cytosol. Theoretically the Ca++ channel inhibitors are specifies subtypes of Ca++ antagonists whose major site of action is to decrease Ca++ influx through the slow Calcium channel. This inhibition of the Ca++ has been well recognised as the major site of action of Ca++ antagonists (Fleckenstein, 1984).

Two types of Sarcolemmal binding site have been identified:
1st -- Dihydropyridine site should bind the Nifedipine.
2nd -- Other Ca++ channel antagonist such as verapamil and diltaiazem site to modify the dihydropyridine site. This dihydropyridine binding site may be near the Ca++ channel or a part of it. The different effects of different Ca++ antagonists are due to the effects of different sites i.e. myocardial contractile tissues, vascular bed or nodal tissues. The Verapamil group of Ca++ antagonists is structurally characterised by an aryl ring connected to an alkylamino or aralkylamino group. This group includes Verapamil, diltiazam, cinnarizine and tipamil (Major 1984). This
group probably binds to one site which is identified as 3H Cinnanizine. Both Verapamil and diltiazem have stereoselectivity. A second group (Nifedipine) group of Ca\(^{++}\) antagonists includes the 1,4 dihydropyridines which probably binds to another site, identified by 3H Nitrendipine. The second group is completely different in structure from the verapamil group and includes Nicardipine, Nitrandipine, Nimo dipine, Nisoldipine and Felodipine. A third and very new group of Ca\(^{++}\) antagonist KB-944 resembles diltiazam from the pharmacological point of view but has an aralkyl phosphonate group (Meyer, H., 1984).

2.2.5 Calcium Antagonists versus \(\beta\) Blockade:

In cellular level, there are marked differences between the effects of \(\beta\) adrenergic blockade and Ca\(^{++}\) antagonists on the vascular smooth muscle, where \(\beta\) blockade tends to vasoconstrict and Ca\(^{++}\) antagonist to relax. In the case of myocardium, a common property is shared i.e. reducing Ca\(^{++}\) influx by slow channel (Nayler et al 1984). The Ca\(^{++}\) antagonists do directly by closing the number of slow channels (Reuter, H., 1980) and the antagonists act indirectly by decreasing the phosphorylation of a protein which is hypothetically involved with slow channel control. Ca\(^{++}\) antagonist drugs have their therapeutic effect without a negative inotropic effect whereas in case of \(\beta\) blockade the negative inotropic effect is an integrated part of the anti-anginal mechanism. (Jee & Opie, 1984).
2.2.6 Adrenoceptors and Calcium:

Alpha one receptors are increased in density in Ischaemia and they enhance calcium ion entry into the Ischaemic cells. This may lead to Malignant arrhythmias. Experimentally it has been proved that blockers such as prazosin or labetalon prevent this arrhythmias. Verapamil has alpha antagonistic activity thereby it has some role in ventricular arrhythmias.

2.2.7 Calcium Antagonist for Ischaemic heart disease:

Verapamil has been used for the treatment of Angina Pectoris. It has a very powerful inhibitory effect on supraventricular Tachycardia due to inhibitory action on calcium dependent conduction through A.V. Node.

Nifedipine was originally used for Angina Pectoris due to it's powerful antihypertensive effects (Rosendroff, 1984).

Diltiazem more closely resembles verapamil than Nifedipine. All the three agents (Verapamil, Nifedipine and Diltiazem) improve myocardial infarction.

2.2.8 Coronary Artery Spasm:

Prinzmetal have described that angina occur at the side of atheromatous lesion of a large coronary artery, Yasue, H. (1984) shows there is marked circadian rhythm in the susceptibility to coronary artery spasm. Most of the attacks occurring at night or in the early morning possibly as result of high blood pH at night which in turn may induce an increase in the ionised serum Ca++ to provoke attacks. Ca++ antagonist (Diltiazem, Nifedipine, Verapamil) all inhibit these attacks, Hugenholty et al (1984) have described that B Blockade i.e. propranolol is ineffective.
and may be harmful. According to Opie et al (1984) the present concept of management of Angina pectoris is the combination of isosorbide dinitrate and nifedipine.

2.2.9 Angina at rest:
Hugennoltz et al (1984) have described that Ca\(^{++}\) antagonist are better therapy in Angina at rest. Maseri, A. & Gear P. A. (1984) have shown that B Blockade is ineffective and Ca\(^{++}\) antagonist is very effective in angina at rest. Yasue, H. (1984) has the opinion that spasm is responsible for development of angina at rest Ca\(^{++}\) antagonist relieves the Spasm.

2.2.10 Stable Angina of Effect:
Initially it was thought that Ca\(^{++}\) antagonist acts by unloading the heart as a result of peripheraly Vasodilatation. Lichtlen et al (1984) has shown two further important effects of Ca\(^{++}\) antagonist. These are -

i) Increased poststenotic coronary flow

ii) Action to relieve the previous coronary obstruction by vasodilatation. Thereby Ca\(^{++}\) antagonists are effective in most of the patients with stable angina.

2.2.11 Calcium antagonist and Atheroma:
A logical proposition has been made that Ca\(^{++}\) deposition is an important aspect of severe atherosclerosis. It is expected that Ca\(^{++}\) antagonist can be antiatherogenic.

2.2.12 Arrhythmias:

Sperelakis, N. (1984) has shown that slow response action potential are Ca++ dependent and this is responsible for ventricular arrhythmias in ischaemic tissue.

Cyclic AMP may phosphorylate a membrane protein constituent of slow channel to make it available for voltage activation. The voltage required for slow channel activation is above -35 MV compared with -55 MV for Na+ fast channel. Slow responses may be inhibited in severely ischaemic tissue by marked acidosis. According to Opie et al (1984) slow response play a role in ischaemic ventricular fibrillation and it may be expected that Ca++ would not be active against ventricular arrhythmias arising in severely ischaemic heart disease. Another opinion for ineffectiveness of Ca++ in some model may be that the slow action potential in ischaemic tissue are not a pure slow action potential but rather a fast Na++ whose activity is depressed. Clusin et al (1984) proposed that ischaemic induced intracellular Ca++ overload causes arrhythmogenic effects by shortening the action potential and ischaemic depolarisation.

2.2.13 Hemodynamics:

It was documented that pressure decrease from 102±18 to 96±14 mm Hg (P 0.05) after mifedipine and continued to decrease to a slow rate upto 85±15 mm Hg (P 0.05) following sublingual administration. Heart rate rises form 66±9 to 70±6 (P 0.05) after buccal nifedipine. In the present study the assessment was done by relief of chest pain sense of well being along with E.C.G. changes.
Richard et al (1984) have done a study to see the effects of coronary dilatation by using Nifedipine alone or combination of nifedipine and Nitroglycerine in 96 patients. They have assessed the size of coronary artery dilatation by doing coronary angiography. They have documented the increase in size by 28.2% after Nifedipine. 82% of the patients showed coronary dilatation with Nifedipine and Nitroglycerine combination. But the most interesting facts noted by them that there was decreased in coronary size in 6 patients with Nifedipine and no patient with combination of therapy. In the present study the patients were given only Nifedipine.

Antman et al (1984) have documented the beneficial results (87%) with Nifedipine therapy in coronary artery spasm. Richard et al (1984) have documented that such promising results are not found in those patients who have received prior Nitrates.

Thus the present study was conducted only with Nifedipine. Those who have received prior Nitrates were excluded from the study.
The table showing the action of different Calcium Channel Blockers and β Blockers and Nitrates (Richard et al. 1984)

<table>
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<tr>
<th>Points</th>
<th>Nitrate</th>
<th>Blockers</th>
<th>Ca(^{++}) antagonist</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Diltiazem</td>
<td>Verapamil</td>
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<tr>
<td>Myocardial Oxygen uptake</td>
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<td>Heart rate</td>
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<td>L.V. Wall tension volume</td>
<td>↓↓↓</td>
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<td>Systolic Pressure</td>
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<td>Diastolic Pressure</td>
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<tr>
<td>Coronary Blood flow</td>
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<td>Aortic pressure</td>
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<td>Coronary Resistance</td>
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<td>Epicardial artery size</td>
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→ = Mild effect
⇒ = Moderate effect
⇒⇒ = Marked effect
n.c. = No command
Thus beneficial effects of Nifedipine are --

1). Dilate the coronary arteries to maintain coronary blood flow.

2). To decrease the systemic arterial pressure and decrease the peripheral vascular resistance.

3). Dilate the peripheral vein and thus decrease the ventricular volume and pressure.

2.2.14 Protocol of the Study:

Myocardial infarction was defined as -- typical chest pain which lasted for 30 minutes with associated Electrocardiographic changes of ST Segment elevation. 1 mm, new Q wave, persistent T wave inversion in at least two leads. Enrolment did not require enzymatic confirmation which was done subsequently. The treatment was started as early as possible. Patients were excluded if they systolic pressure is 100 mm of Hg., symptomatic Thrombovascular disease, P-R interval 0.245, higher degree of A - V Block without a pace maker, Pulmonary oedema cardiogenic shock.

2.2.15 Study Design:

The patient admitted in R.G.Kar Medical Intensive Care Unit of Cardiology Department from 1986-1988 were included in the study. In all the cases detailed history was taken and thorough clinical examination was done. The criteria of inclusion of the cases is already mentioned in the protocol of the study. All the cases E.C.G. were taken at the time of admission and subsequently Serum Na, K⁺, Ca++, Aldolase, C.P.K., S.G.P.T., S.G.O.T., Blood Urea, Creatine and Blood were done and repeated accordingly.