Introduction
Among the many health predictions for the new millennium, the most alarming is cardiovascular disease (CVD) - heart disease and stroke, topping the list for death and disability (Padmavathi, 2002; Manson et al., 1993). It kills victims faster than most malignant neoplasm's (Siltanen, 1990). Among the cardiovascular diseases, coronary heart disease (CHD) appears to be the most prominent one.

Demographic shift in population age-increase profile combined with lifestyle related increase in cardiovascular risk factors are accelerating CHD epidemic in India (Reddy and Yusuf, 1998) and the social economic indices of epidemiological transition explain the increasing CHD prevalence (Gupta and Singhal, 1997). In urban population, it is increased from 3.5% in 1960's to 9.5% in 1990's. In rural areas, it is increased from 2% in 1970's to 4% (Gupta and Gupta, 1996). Population based surveys pointed out that there are great regional variations (Padmavathi, 2002) while there are undoubted regional differences between the developed countries and other economies, the predictions for India by 2015 show a steady increase since 1985. The projected rate is higher than that for other causes such as cancer (Padmavathi, 2002). The Framingham study also showed that myocardial infarction (MI), sudden ischemic cardiac deaths or acute coronary insufficiency were the first manifestations of 70% of men and 50% of women (Mascri, 1995).
Ischemic heart disease is the generic designation for a group of closely related syndromes resulting from an imbalance between the supply and demand of the heart for oxygenated blood. It is a condition in which an imbalance between myocardial oxygen supply and demand results in myocardial hypoxia and accumulation of waste metabolites most often due to atherosclerotic disease of the coronary arteries ("coronary artery disease").

 Depending on the rate of development of the arterial narrowing and its ultimate severity the following conditions might result.

- Angina pectoris
- Myocardial infarction the most important of ischemic heart disease.
- Chronic ischemic heart disease
- Sudden cardiac death

**MYOCARDIAL INFARCTION**

Infarction is defined as tissue necrosis resulting from inadequate blood supply following occlusion of an end artery. When this process occur in the heart it is called myocardial infarction (Gregory, 1991) (Or) Myocardial infarction (MI) is the acute condition of necrosis of the myocardium that occurs as a result of imbalance between coronary blood supply and myocardial demand (Nageswari et al, 1999). The lack of blood supply is caused by closure of the artery (coronary artery) that supplies that particular part of the heart muscle with blood. The artery is closed or narrowed by a plaque that usually occurs in a coronary artery by atherosclerosis.
AETIOLOGY

- The most common cause of myocardial infarction is narrowing or occlusion of a major coronary artery or one or more of its branches, usually as a result of atherosclerotic disease (William et al, 1965).

- Pre-existing coronary artery disease with narrowing of the lumen is often a predisposing factor in situations in which there is a reduction in coronary artery blood flow as in shock, hemorrhage or prolonged tachycardia associated with marked hypotension and temporary increase in demand for coronary blood flow as in prolonged or unusual effort. Disproportion between muscle mass and vascular supply, as in hypertension with marked left ventricular hypertrophy and coronary artery spasm as in association with pulmonary embolism (William et al, 1965).

- Rare causes of coronary occlusion include aortic dissection, embolism as in bacterial endocarditis, collagen diseases such as polyarteritis nodosa, lupus erythematosus and scleroderma, infections such as syphilis and rheumatic fever, amyloidosis and trauma (William et al, 1965).
• Contributing factors include those, which predispose to coronary arteriosclerosis such as hypertension, diabetes mellitus, hypothyroidism, and hypercholesterolemic states. The middle-aged man is particularly susceptible to the disease (William et al., 1965).

• Genetic factors and environmental stress have also been emphasized in studies relating to the etiology of the disease (William et al., 1965).

PATHOLOGY

Under normal conditions, the blood flow in coronary arteries is closely matched to the metabolic demands of cardiac muscle. Ischemic heart disease results when the blood supply becomes insufficient, because 1. either the blood supply itself is impaired or 2. the myocardium becomes hypertrophic and makes a greater demand on the blood supply.

Myocardial infarction is the result of an imbalance between the available blood supply and the simultaneous need of the myocardium. The available blood supply will depend upon intercoronary collateral channels from adjacent vessels in addition to branches from the occluded artery. In most instances of myocardial infarction, a major coronary artery or one of its branches is gradually or rapidly occluded by degenerative and proliferative alterations in an atherosclerotic plaque (William et al., 1965).
The pathological process may be caused by lesions varying in extent between thrombosis of a small segmental branch of one coronary artery and multiple thromboses in all of the major branches of the coronary arteries. The corresponding areas of infarction from focal, microscopic necrosis to diffuse, grossly visible lesions (William et al, 1965).

- The most common site of occlusion is the anterior descending branch of the left coronary artery, 2-3 cm from its origin. Infarction correspondingly occurs in the anterior wall of the left ventricle and includes the apical region and the contiguous portion of the interventricular septum (William et al, 1965).

- The left ventricle is particularly vulnerable because its oxygen requirements is greater than that of any other cardiac chambers refluxing its muscle mass and wall tension, both of which are major determinants of oxygen demand. Thus, while coronary artery disease may affect oxygen delivery to any part of the heart, the left ventricle is worst affected (Bateman, 1996).

- Myocardial infarction may affect the entire thickness of the wall-transmural infarction, or it may involve only a part of the thickness of the wall-intramural infarction (William et al, 1965).

- Pathological studies of regional transmural infarctions have revealed that the supplying artery is totally occluded in over
90% of cases, suggesting that persistent occlusions is related to greater risk of fatal out come possibly because of larger infarct size (Kim and Braunwald, 1993).

- Necrosis limited to the subendocardial portion of the wall (subendocardial infarction) is more frequent than involvement limited to the subepicardial portion of the wall (subepicardial, non transmural infarction), because of differences in available blood supply (William et al, 1965).

However, the two types (transmural, non transmural) are closely interrelated because in experimental models and likely in humans the transmural infarct may begin with subendocardial necrosis that extends in a wave front across the full thickness of the ventricular wall (Goldberger, 1982).

- The sub-endocardial layers of the myocardium are at particular risk from ischemia. In the subendocardial infarction, there is a recent plaque disruption in the supplying artery but there is far lower incidence of total arterial occlusion (Dewood et al, 1981). Blood vessels are collapsible tubes and are susceptible to compression when tension within the myocardial wall increases. This tension is greatest when the ventricles are dilated, especially in the subendocardial layer. Subendocardial infarcts have a good initial prognosis and the incidence of cardiac failure and death is less than with transmural infarcts.
PATHOPHYSIOLOGY

- Coronary thrombosis and occlusion initiate MI (Buja et al., 1981)
- Neutrophil infiltration at infarct periphery (Vinten Johansen, 2004)
- Interstitial edema and (or) focal hemorrhage (Deray, 2004)
- PMN infiltration at maximum at 3-5 days
- Fibroblast appear at the end of 1st week
- Granulation tissue by mid 2nd week
- Collagenization of infarct by 6th week

RISK FACTORS FOR MYOCARDIAL INFARCTION

Increasing age

The incidence of death from ischemic heart disease increases by decade up to the age of about 85 years. The risk of heart disease increases with age, 4 out of 5 people who die of heart disease are 65 or older (Schaeffer et al, 1995).

Sex

Prior to the menopause, clinical ischemic heart disease is rare in women, and until aged about 70 is commoner in males than females. Men and women are both at risk but men are generally affected a decade earlier than women, which is due to protective action of female sex hormone, estrogen (American and Canadian Paper, 1995).
Figure 1: Pathophysiology of acute myocardial infarction
Preexisting evidence of ischemic heart disease

This factor results from the familial tendency to hyperlipidemia, hypertension, diabetes and obesity.

Hyperlipidemia

Many studies comparing populations in different countries have led to the appreciation of a direct relationship between the mean serum cholesterol of a population, low density lipoproteins and the incidence of death from ischemic heart disease. By contrast, the role of plasma triglycerides and very low density lipoproteins in the pathogenesis of ischemic heart disease is unclear. Elevated LDL-cholesterol is considered as a major cause of CHD (Stanler et al, 1986). High intake of saturated fats and cholesterol leads to myocardial infarction (Shkella et al, 1981).

Hypercholesterolemia is a risk factor for arteriosclerosis (Buring et al, 1992) and it is responsible for coronary artery occlusion (Kriesberg, 1983). Reducing dietary intake of cholesterol and saturated fats reduce plasma lipids by about 10-20% on an average, and although unproven in a large population, hopefully reduces mortality from ischemic heart disease. The oxidation of HDL protein could contribute to the atherogenetic process by limiting their capacity to accept cholesterol from cell membranes (Delattitre et al, 1993).

Hypertension

In men aged less than 45 years, the risk of death from ischemic heart disease is related more to elevation of diastolic than systolic blood
pressure, and in men aged 45-60 years, the risk is approximately the same for
elevation of either pressure. Treatment of hypertension provides some
protection against cardiovascular disease but significantly greater protection
against stroke and heart failure (Collins and MacMahon, 1994). Hypertension
becomes a risk factor of greater clinical significance when it is associated
with elevated plasma lipid levels (Levy and Leren, 1986)

**Diabetes**

Due to the micro and macro vascular disease with which diabetes is
associated, the occurrence and mortality of ischemic heart disease among
diabetics is more than twice that of non-diabetics. Recent data suggest that
increased insulin resistance and hyperinsulinemia in diabetics may be
associated both with their abnormal cardiovascular disease risk profile and
with their increased risk of coronary heart disease (Manolio et al, 1991).

**Obesity**

Because of confounding factors such as hyperlipidemia and
hypertension, both of which are associated with obesity, opinion is divided
about the contribution of obesity that makes to the incidence of death from
ischemic heart disease. Obesity promotes insulin resistance, hyperinsulinemia,
hypertension, hypertriglyceridemia and high blood cholesterol (Eckel and
Krauss, 1998; Kannel et al, 1996). Obesity increases the amount of work
required by heart affects the blood cholesterol levels and increases the risk of
diabetes (Stern, 1995).
Personality

It has been suggested, but is disputed that on the basis of their personalities the population can be divided into two groups at differing risk of death from ischemic heart disease. Cohort studies have shown that persons who are more physically active have a lower risk of subsequent coronary heart disease than do those who are not physically active (Pomrehn et al., 1982).

Smoking and alcholism

There is a linear relationship between the number of cigarettes smoked per day and the risk of dying of ischemic heart disease. This is associated with accelerated arteriosclerosis and increased mortality from ischemic heart disease, particularly of sudden death. Smokers have increased levels of oxidation products including oxidized low-density lipoproteins (Ferri et al., 1991). Passive smoking also increases coronary heart disease (Glantz and Parmely, 1995). Cigarette smoking also lowers the cardio protective levels of HDL protein. Their effects along with direct effects of carbon monoxide and nicotine produce endothelial damage. Possibly through these mechanisms, smokers have increased vascular reactivity (Cellermajer et al., 1993). Smoking causes an increase in resting heart rate and an increase in resting systolic and diastolic blood pressure there by increasing the myocardial oxygen demand (Aronow et al., 1974). Excessive intake of alcoholic beverages can contribute to ischemic heart disease (Gould and Gomprecht, 1970).
Above average levels of blood clotting factors

Recently, attention has been focused on hypercoagulability of the blood as an important risk factor. Raised levels of fibrinogen, in part due to smoking, raised levels of factor VII, due mainly to dietary fat, and of factor VIII and an inhibitor of plasminogen activity are now each recognized as risk factors for intra-arterial thrombosis and death from ischemic heart disease (Meade et al, 1986; Kennel et al, 1987).

COMPLICATIONS (William et al, 1965)

Early complications

Shock, acute pulmonary edema, congestive heart failure, arrhythmias, thromboembolism and myocardial rupture

Late complications

Ventricular aneurysm, post myocardial infarction syndromes, shoulder hand syndromes and cardiac necrosis.

MECHANISM OF MYOCARDIAL DAMAGE

Role of Free Radicals

Free radicals can be defined as molecular or molecular fragments with an unpaired electron. Examples of free radicals are ground state O₂, singlet O₂, super oxide anion radical, hydroxyl, carbon centered radical, alkoxy, peroxy, thyl, and nitroxyl free radicals. Among these super oxide
Figure 2: The proposed cellular and subcellular effects of the oxygen free radical system as a result of ischemia or reperfusion. (Hammond and Hess, 1985).
Figure 3: Free radicals and active O₂ species derived molecular oxygen (SOD, H₂O₂, OH⁻ radical) contribute to tissue injury (Mccord JM. 1998)
anion and hydroxyl radical are the common radicals in living systems and have been implicated as cause or contributing factor in a variety of types of cell injury and ischemia (Slater, 1984; Hess et al, 1982). Free radicals are continuously produced in the body mostly by biochemical redox reactions involving oxygen which occur as part of normal cell metabolism, by phagocytes, as part of an uncontrolled inflammatory reaction, occasionally in response to exposure to ionizing radiation, UV light, environmental pollution, cigarette smoke, hyperoxia, excess exercise and ischaemia.

Majid Ali and Omar Ali propose that ischemic heart disease (IHD) is caused by "AA oxidopathy"-a state of accelerated oxidative molecular injury to blood corpuscles and plasma components (Ali and Ali, 1997) There is substantial evidence that ischemic tissue generates oxygen-derived free radicals (oxygen radicals), i.e., oxygen molecules containing an odd number of electrons, making them chemically reactive, and often leading to chain reactions (Hammond and Hess, 1985; Ambrosio et al, 1987).

The oxygen radicals, in turn, can contribute to ischemic damage. These moieties react with almost any biological molecule in their vicinity. It has been proposed (Hammond and Hess, 1985) that by causing peroxidation of cell membranes, oxygen radicals damage cell membranes and contribute to cell death.

Role of Metal Catalyst

Iron is usually sequestered in proteins like transferin and heme protein (Halliwell and Gutteridge, 1986). Once released, iron in its free form
accelerates lipid peroxidation induced by free radicals (Biemond et al, 1984). Iron can also generate O$_2^\cdot$ and H$_2$O$_2$ by accelerating the non-enzymatic oxidation of several molecules like adrenaline and glutathione (Poliodoro et al, 1984).

**Role of LPO**

Lipid peroxidation is often a late event, mediated by free radicals accompanying cell death (Halliwell and Gutteridge, 1984). It can be broadly defined as oxidative deterioration of polyunsaturated lipids (Tappel, 1973). These oxidative reactions are the pathogenic processes associated with cell break down, ageing, ischemia and injury (Tappel, 1973; Machlief and Bendich, 1987). Biological membranes are rich in unsaturated fatty acids and are easily susceptible to peroxidative attack. Malondialdehyde is the breakdown product of the unsaturated fatty acids and is a measure of the peroxidation event. The membranes surrounding the cells and cell organelles contain large amounts of polyunsaturated fatty acid side chains. Production of highly reactive free radicals lead to damage of cells through a pathway dependent essentially on membrane damage.

Gudjarnason et al (1983) have postulated that lipid peroxidation may be associated with MI. Burton (1985) has also reported that the superoxide anions and the hydroxyl radicals have been implicated in the development of myocardial damage induced by ischemia. Increased level of myocardial lipid peroxides can result in the structural changes and cause myocardial necrosis (Singal et al, 1983).
Necrosis of myocardial tissue is followed by the infiltration of a large number of neutrophils into the localized site followed by activation of these cells to generate oxygen and \( \text{H}_2\text{O}_2 \) (Halliwell and Gutteridge, 1989). Oxygen free radicals and their metabolites play an important role in the myocardial ischemia (Manning et al, 1984; Woodwar and Zakaria, 1984). Lipid peroxidation is increased within the atherosclerotic lesion and lead to form cell generation, lesion growth, stenoses and hence myocardial infarction (Steinberg et al, 1989).
(Steinberg, 1989).

Role of Thrombosis

It is generally accepted that the final common pathway to coronary artery occlusion represents an interaction between atheromatous plaque and thrombus formation (Antman and Braunwald, 1997). Following occlusion of the lumen of the vessel, loss of blood supply to the myocardium results in ischemia and then necrosis (infarction). Contributing factors include deposition of fibrin with organization, necrosis with ulceration, hemorrhage, and thrombosis (William et al, 1965).

Research has shown that most myocardial infarctions are caused by rupture of the plaque, and that small plaques are often responsible. All plaques have a fatty core covered with a top composed of a meshwork of fibers. If the top covering of the plaque is thick and the core is small, dry and hard, the plaque is stable and is unlikely to rupture. Big plaques are often stable.
However, if the top covering of the plaque is thin and if the core is filled with soft, fatty material, the plaque is unstable and can rupture and break (Richardson et al., 1989).

When the top ruptures, the blood in the artery comes in contact with the fatty material in the core of the plaque. As blood hits a plaque during each heartbeat, the plaque may crack open and expose the inner cholesterol. The fatty build up or plaque can break open and lead to the formation of a big clot that seals the break. The clot reduces blood flow. The cycle of fatty buildup, plaque rupture and blood clot formation causes the coronary arteries to narrow, reducing blood flow. When a plaque fissure or ruptures, collagen and other connective tissue elements come in contact with circulatory blood platelets. Platelet aggregation occurs leading to thrombus formation.
This process appears to be important in the genesis of unstable angina (Ambrose et al., 1986) and myocardial infarction (Ambrose et al., 1988).

**Role of neutrophils**

Neutrophils are important for the development of reperfusion injury by releasing oxygen free radicals, proteases and pro-inflammatory mediators that further amplify the infiltration of neutrophils into the jeopardized myocardium (Jordan et al., 1999; Hansen, 1995). Depletion by administration of antibodies directed against neutrophils or neutrophil clearing filters attenuates the 'no reflow' area and reduces infarct size (Romson et al., 1983; Litt et al., 1989) Several studies have evaluated the effect of blocking adhesion molecules as a tool to inhibit neutrophil-mediated injury and thereby reducing reperfusion injury. Administration of a monoclonal antibody to dogs following coronary artery ligation and reperfusion resulted in significant reductions in infarct size (Simpson et al., 1990) and was associated with reduced neutrophil accumulation in the jeopardized myocardium. In addition, intravenous administration of antibodies before reperfusion to cats significantly reduced neutrophil adhesion or transmigration and attenuated infarct size by more than 50%. Conversely, addition of neutrophils to buffer-perfused hearts at the onset of reperfusion significantly aggravates myocardial dysfunction (Shandelya et al., 1993). These studies support the notion that infiltrating neutrophils play an important role in the development of the reperfusion injury.
Role of calcium

Myocardial injury induced by ischemia is associated with complexes of calcium in the tissue detectable by electron microscopy (Reimer and Jennings, 1986). The reintroduction of Ca$^{++}$ and/or of oxygen to hearts previously perfused with Ca$^{++}$ free hypoxic media causes marked damage to the sarcolemma and entry of large quantities of Ca$^{++}$ into the ischemic cells. These phenomenon has been termed the Calcium paradox (Hearse, 1977) and the oxygen paradox respectively (Hess and Manson, 1984).

The free radicals are involved in the mechanism that may cause an increase in the calcium permeability and reduction of calcium accumulation of cardiac sarcoplasmic reticulum vesicles. Free radicals also stimulate the sodium-calcium exchange activity in cardiac sarcolemma. The break down of sarcoplasmic reticulum and sarcolemma function may serve as the source of intracellular calcium overload (Eichiré Okabe and Haruo Ital, 1988). Calcium overload may contribute to ischemia or reperfusion injury in several ways. It may for instance induce excessive myofilament activation at the moment of reoxygenation and in addition, the rise in intracellular calcium causes an increase in mitochondrial calcium. This leads to decreased mitochondrial ability to generate ATP limiting metabolic recovery of the myocyte (Qing Dong Wang et al, 2002).

The hypothesis that the entry of Ca$^{++}$ into ischemic cells may be harmful and is based on the observation that after a period of myocardial ischemia and subsequent reperfusion the accumulation of excess Ca$^{++}$ in the
mitochondria may interfere with their capacity to generate ATP. The destructive chain of metabolic events provoked by increased intracellular Ca\(^{2+}\) appears to be responsible, at least in part, for the death of cells in the ischemic myocardium (Eugene Braunwald et al, 1988).

**Role of Lysosomes** (Eugene Braunwald et al, 1988).

Most tissues contain latent lysosomal hydrolases capable of mediating proteolysis under certain conditions. Lysosomal hydrolases are activated by an acid pH, although mammalian cells contain neutral proteases as well. Relatively, late reparative processes in myocardium undergoing infarction are accompanied by consistent increases in lysosomal hydrolase activity in tissue extracts as well as in the circulation suggesting that activation of proteases with dissolution of cellular debris is a component to the response to irreversible injury. However, the extent to which activation of lysosomal hydrolase contributes to early manifestations of ischemia or irreversibility remains controversial. What is clear is that much of the lysosomal activity in the heart undergoing infarction comes from cells participating in response to inflammation such as polymorphonuclear leucocytes than myocardial cells per second.

**METABOLIC ALTERATIONS** (Maximilan and Willerson, 1991)

Ischemia induces profound metabolic changes in the myocardium. Oxygen deficiency induces metabolic changes including decreased ATP, decreased pH and lactate accumulation in ischemic myocytes. The altered metabolic milieu leads to impaired membrane transport, with resultant
Figure 4: The postulated sequences of alterations involved in the pathogenesis of irreversible myocardial injury (Reimer and Jennings, 1986).
derangements in intracellular electrolytes. An increase in cytosolic Ca\(^{2+}\) might trigger the activation of proteases and phospholipases with resultant cytoskeletal damage and impaired membrane phospholipid balance. Lipid alterations include increased phospholipid degradation with release of Free Fatty Acids and lysophospholipids and decreased phospholipid synthesis. Lipid peroxidation occurs as a result of attack by free radicals which are produced at least in part by the generation of excess electrons in oxygen deprived mitochondria. Free radicals might also be derived from metabolism of arachidonic acid, metabolism of adenine nucleotides by xanthine oxidase and activation of neutrophils. Irreversible phase of injury appears to be mediated by severe membrane damage produced by phospholipid loss, lipid peroxidation and cytoskeletal damage.

**BIOCHEMICAL ALTERATIONS**

The biochemical alterations leading to myocyte necrosis involve cellular processes. At the cellular level, several structural alterations in cardiocytes and interstitium occur in the failing heart which upon acting individually or in concert can adversely influence global left ventricular contractile performance. Such alterations include hypertrophy of residual myocytes, abnormalities of mitochondrial and myocyte contractile structures and progressive accumulation of collagen in the interstitial space.

**BIOCHEMICAL MARKERS FOR THE DETECTION OF MI**

Myocardial necrosis results in and can be recognized by the appearance in the blood of different proteins released into the circulation due
to the damaged myocytes (Albert et al, 2000). These biomarkers reflect myocardial damage but do not indicate its mechanism (Albert et al, 2000). The diagnostic markers for acute myocardial infarction are creatine kinase, lactate dehydrogenase, aspartate amino transferase and alanine amino transferase (Ruzich, 1992). These enzymes serve as sensitive index to assess the severity of myocardial infarction (Suchalatha and Devi, 2004).

Each enzyme shows a different time course for release into the plasma and subsequent disappearance. These differences depend on the concentration of each present in cardiac tissue, their subsequent rate of release and clearance (Horder and Wilkinson, 1979).

CK is released within few hours of muscle damage, and usually reaches a peak within 12-24 hours (Sharkey et al, 1991). There is only one form of CK-MB₂ but this is converted in the blood to CK-MB, which is detected within 6 hrs of the onset of symptoms (Puleo et al, 1994).

High molecular weight (1, 35,000 Dalton) markers such as LDH are released more slowly. Because serum levels remain elevated for 2 weeks, this is useful for patients who present late symptoms (Vasudevan et al, 1978). LDH isoenzyme fractions are distributed differently in tissue. LDH 1 is in highest concentration in the heart, renal cortex, and RBCs. However in an acute MI, the greater concentration of LDH₁ than LDH₂ in cardiac muscle results in a great increase in LDH₁ than LDH₂ in the serum (Edward and Goljan, 1998).
Figure 5: Typical plasma profiles for creatine kinase (CPK), Glutamate oxaloacetate transaminase (GOT) and Lactate Dehydrogenase (LDH) activities following the onset of acute myocardial infarction.
Aspartate aminotransferase (AST, formerly termed serum glutamic oxaloacetic transaminase or SGOT) is less frequently used in documenting myocardial injury owing to its lack of specificity for cardiac muscle. It first appears in 6-12 hours, peaks in 1-2 days, and returns to normal in 5-9 days. But AST level rises less rapidly than that of CK after myocardial infarction, although minor increases in AST may be detected after 9 hrs (Kathleen Dracup, 1994)

ALT or SGPT levels are within normal limits or are only marginally elevated in uncomplicated myocardial infarction (Moss and Henderson, 1999)

**ELECTROCARDIOGRAPHY**

Myocardial necrosis or clinically established MI may be defined from 12 lead ECG criteria. Several combinations of changes may occur in the QRS complex, the ST segment or the T wave, but the typical sequence of changes is as follows. ST segment elevation is a sign of acute myocardial infarction (Albert and Braunwald, 1984). Epicardial ST segment elevation correlates both with regional myocardial blood flow and myocardial lactate concentrations and inversely with high-energy phosphate concentrations (Gefti et al, 1984, Harken et al, 1978). Small changes in the ratio of intracellular to extracellular potassium have a marked effect on the polarity of cellular membranes and the alterations in this ratio induced by ischemia appears to play a critical role in generating ST segment elevation (Johnson, 1976)
Figure 6: A typical elevation of ST segment during myocardial infarction.
Gradual reduction of ST elevation occurs with the development of a rounded symmetrical T wave inversion due to abnormalities of repolarisation. Reciprocal ST depression may occur in the leads opposite an infarct.

SYNTHETIC DRUG THERAPY FOR ACUTE MYOCARDIAL INFARCTION

World Health Organization (WHO) has defined primary prevention of coronary heart disease as prevention of its first events, beginning early in childhood and continuing throughout childhood, youth and adult life. Primordial prevention is defined as prevention of risk factors themselves beginning with change in social and environmental conditions in which these factors are observed to develop and continuing for high-risk children, adolescents and young adults (WHO Study Group, 1985). Drug therapy is another option for myocardial infarction.

Thrombolytic agents

Streptokinase activates the fibrinolytic system by combining with plasminogen to form a plasminogen activator complex that is rapidly converted to a streptokinase plasmin complex capable of converting plasminogen to plasmin. Insoluble fibrin within the thrombus is lysed by plasmin, resulting in dissolution of the thrombus (Goa et al, 1990).
Tissue plasminogen activator has significant plasminogen activator activity. It binds to fibrin and directly activates fibrin bound plasminogen leading to the formation of plasmin and ultimate lysis (Majerus et al., 1990).

In contrast, urokinase has intrinsic proteolytic activity and can activate plasminogen directly. Urokinase is a fibrinolytic drug, which reestablishes blood flow by cleavage of the fibrin strands (Ohmae, 1982).

**Antifibrinolytic drugs**

The role of fibrinolytic therapy in unstable angina remains to be more accurately defined as to which patient will benefit from this therapy, though it is found useful in successful treatment of some patients (Nicklas et al., 1987).

**Antiplatelet drugs and vasodilators**

Aspirin can reduce the incidence of acute myocardial infarction and mortality in patients with unstable angina (Lewis et al., 1983, Cairns et al., 1985, Theroux et al., 1988). It protects against myocardial infarction by reducing platelet aggregation. Its mechanism of action seems to be inhibition of arachidonic acid metabolism.

Ticlopidine is another antiplatelet agent, which has shown similar benefit in patients with unstable angina (Balsano et al., 1990). Prostacyclin, a vasodilator, is also being used clinically as an antiplatelet agent (Ribeiro et al., 1981). Vasodilators are useful in reducing excessive preload and after load. Sodium nitroprusside and nitrates are best vasodilators.
Anticoagulants

The coumarin anticoagulant that includes warfarin and dicoumarol lower thrombin generation and clot formation by impairing the biological activity of the prothrombin complex proteins (Handin, 1994)

The usefulness of heparin has also been documented in the acute phase of unstable angina. Heparin can control severe recurrent ischemia (Nerismeri et al, 1990)

Betablockers

Beta-adrenoreceptor blockers appear to prolong the survival of several ischemic tissue judging from changes in ST segments, QRS complexes, myocardial creatine kinase activity and electron microscopic, histochemical and histological criteria (Braunwald et al, 1983). In addition, these drugs appear to improve the ratio of subendocardial to subepicardial blood flow in both ischemic and normal areas of myocardium in dogs with coronary occlusion.

Beta adreno receptor blockade appears to be more useful in delaying than preventing cell death and is especially effective in limiting infarct size in animals subjected to coronary occlusion and reperfusion (Hammerman et al, 1984, Miyazawa et al, 1986).

Betablockers further have antiarrhythmic properties and appears to increase threshold for ventricular fibrillation (Stone and Sacks, 1996)
Over view analysis indicates that therapy with betablockers reduces mortality approximately 20% compared to placebo (Yusuf et al, 1985, Lau et al, 1992)

**Calcium - channel blocking agents**

Calcium antagonists are cardio protective in the setting of myocardial ischemia/reperfusion when administered prior to the induction of ischemia. It was suggested that the beneficial effects of calcium antagonists were related to the negative inotropic and/or chronotropic, the energy saving effect of these compounds. In addition, some calcium antagonists are antioxidants or nitric oxide synthase regulators (Qing-Dong Wang et al, 2002)

More recent studies have, however, revealed that calcium antagonists do not only have an anti-ischemic effect, they are also protective against myocardial injury caused by reperfusion in itself. A number of reports showed that calcium antagonists given immediately before or at the onset of reperfusion were protective suggesting an effect against reperfusion injury (Herzog et al, 1997)

Calcium antagonists have also been shown to reduce reperfusion arrhythmias and attenuate myocardial stunning. Verapamil decreased reperfusion arrhythmias in isolated rat hearts as well as in pigs (Opie et al, 1988, Muller et al, 1998). Calcium antagonists are particularly helpful when they are administered prophylactically i.e., before the development of ischemia or early in the course of ischemia (Lo et al, 1985, Campbell et al, 1986, Nayler et al, 1987)
Diltiazem and nifedipine are also reported as calcium antagonists (Purell and Mulcahy, 1997). Nifedipine has been shown to have antiarrhythmic activity in an isolated rat heart model but has minimal electrophysiological effects in man (Singh, 1983).

**Angiotensin converting enzyme inhibitors**

Angiotensin converting enzyme (ACE) inhibitors reduce reperfusion arrhythmia and infarct size and results in improved functional recovery. Captopril exerts a protective role against ischemia/reperfusion injury, which might relate to free radical scavenging activity (Westlin and Mullane, 1988, Chorpa et al, 1992).

In anesthetized pigs, the AT₁ receptor blockers candesartan (Shimizu et al, 1998) and EXP3174 (Schwarz et al, 1997) protect the heart through inhibition of local cardiac angiotensin II. Short episodes of exposure to angiotensin II prior to ischemia mimic ischemic preconditioning, rendering the myocardium resistant to ischemic damage (Liu et al, 1995) Angiotensin II subsequently activates the AT₂ receptor in endothelial cells, resulting in enhanced formation of bradykinin (Liu et al, 1997) and may contribute to cardio protection. Activation of bradykinin B₂ receptors result in stimulation of cyclooxygenase and nitric oxide synthase with subsequent increase in the synthesis/release of prostacyclin (Revtyak, et al, 1990) and nitric oxide (Liu et al, 1999), which are possibly responsible for the cardio protective effects obtained with AT₁ receptor blockers
Nitric oxide

Preliminary work is now being done to investigate that inhaled nitric oxide, a vasodilator substance produced by the endothelium, as a possible treatment for chronic heart failure (Hare et al, 1997, Matsumoto et al, 1997).

Nitric oxide donor substances are also being evaluated (Heilsch et al, 1997). Accordingly, administration of nitric oxide dissolved in aqueous medium or nitric oxide donors reduce infarct size in various experimental models of ischemia and reperfusion in the cat and dog (Siegfried et al, 1992; Lefer et al, 1993).

Cardio protective effects determined as reduction in infarct size in vivo and enhanced recovery of myocardial function in vitro have in addition been obtained with the nitric oxide precursor-arginine (Pernow et al, 1994, Li et al, 1996)

There are also studies indicating that NO may exert anti-arrhythmic actions during ischemia/reperfusion. A NO donor was shown to suppress arrhythmias in pigs subjected to coronary artery occlusion (Wainwright and Martorana, 1993)

Intravenous nitroglycerin has been reported to affect infarct size in patients. Derrida et al (1978) have reported that this drug causes a greater reduction in ST segment elevations and less R wave fall at initially ischemic
sites. Furthermore, in patients with heart failure, mortality and serious ventricular arrhythmias appeared to be reduced in the nitroglycerin treated group (Derrida et al, 1978).

**Glucose potassium insulin**

In the ischemic dog heart, oxidative phosphorylation and cardiac function are enhanced by the infusion of glucose-insulin-potassium (GIK) (Calva et al, 1965). In the anoxic isolated heart, both electrical and mechanical functions improve and recovery occurs more rapidly when glucose is added to the perfusate (Henry et al, 1974).

**Lipid lowering agents**

Antilipolytic agents such as beta-pyridyl carbinol and lipid free albumin infusion reduces myocardial ischemic injury that inhibit myocardial extraction of free fatty acids thus indirectly favoring glucose metabolism (Kjekshus, 1976)

Injury is also reduced by sodium dichloroacetate which enhances the utilization of glucose relative to that of free fatty acids and by L-carnitine, which by reversing the inhibition of adenine nucleotide translocase prevents the depletion of cytoplasmic high energy phosphate stores (Folts et al, 1976).

**Glucocorticoids**

Large doses of glucocorticosteroids reduce myocardial infarct size in the dog with coronary occlusion (Libby et al, 1973; Masters et al, 1976).
These compounds limit myocardial necrosis through mechanisms that are not clearly defined. They may also increase blood flow to the ischemic myocardium. Regardless of the effect of corticosteroids on the extent of myocardial ischemic injury, there is also evidence that when multiple doses are employed they may inhibit healing of the infarct, increasing the risk of ventricular rupture or aneurysm formation (Hammerman et al, 1983).

**Potassium channel openers**

It has a mechanism of action that involves dilating both the arteries and veins allowing blood to flow more easily, thus allowing the heart to do less work while allowing more oxygen to reach the heart muscle. Nicorandil is a best potassium channel opener (Garlid et al, 2003)

**Cardiac glycosides**

Digoxin, digitonin and lanatoside C are cardio glycosides. They are group of chemically similar compounds that can increase the contractility of the heart muscle and are therefore widely used in treating heart failure. (Kontoyannis et al, 2001)

**Diuretics**

They relieve pulmonary congestion and peripheral oedema. It decreases plasma volume and subsequently decreases venous return to the heart. Diuretics also decrease after load by decreasing blood pressure.
DISADVANTAGE OF SYNTHETIC DRUG THERAPY

In the practice of modern medicine, it is recognized that high blood pressure, atherosclerosis, easy blood clotting, and heart enlargement can lead to catastrophic events such as heart attack and stroke, which are the principal causes of death in persons over 40 years of age. As a result, millions of adults are taking one or more of the drugs to lower blood pressure, lower cholesterol, and/or to reduce platelet aggregation and the prescribed regimen must be adjusted for individual needs by modulating the drug dosage and selecting from a collection of possible drugs to yield the desired response while keeping serious side effects to a minimum. Among the side effects commonly reported are fatigue and lowered libido from some anti hypertensive drugs and liver damage from cholesterol reducers.

Anticoagulant therapies carry the risk of bleeding episodes and cause considerable worry about interactions with drugs, herbs, vitamins and even ordinary foods.

In addition to regular use of the drugs, patients with elevated risk are also asked to participate in a program of cardiovascular preventive health care including a lower fat diet and increased exercise.

PLANT DERIVED PHYTOCHEMICALS AS THERAPEUTIC AGENTS

Presently, the medical fraternity and the patients have increasingly started using plants to overcome various illnesses and sufferings mainly to
obviate the profound side effects encountered in usage of modern drugs (Bhavapriya et al., 2001; Subhuti Dharmananda, 2002). The various indigenous systems such as siddha, ayurveda, unani and sometimes allopathy use several plant species for degenerative diseases (Rabe and staden, 1997). Several compounds from spicy and aromatic plants are confirmed to possess strong antioxidant activity. Thus, phenolic diterpenoids: carnosol, rosmanol, carnosolic acid from sage (Salvia officinalis L), rosemary (Rosmarinus officinalis L) in thyme (Thymus vulgars L), dimers of thymol and flavonoids, flavonoids in oregano (Origanum vulgare L), pepper (Piper nigrum L) and trilololein from plant panax pseudoginseng, essential oils such as volatile compounds of many aromatic plants, monoterpene ketones (thujone, menthone, carvone) and hydrocarbons possess significant antioxidant properties and as a strong free radical scavenger are confirmed (Mimica-Dukic, 2001, Mimica-Dukic and Bozin, 2002; Bozin et al., 2002) Polyphenols probably protect LDL oxidation in vivo with significant consequences in arteriosclerosis (Halliwell, 1999). Xanthones are found in a selected number of rain forest plants, widely distributed in higher plants reported to have anti platelet action (Teng et al, 1989). It is likely that the cardio protective effect of xanthones is related to inhibition of peroxide generation (Librowski et al, 1999).

ADVANTAGE OF PLANTS DERIVED ANTIOXIDANT THERAPY

The natural compounds protect plants from free radicals which are generated by sunlight, pollutants and weather-related stresses. When people
eat or administered the plant foods, they acquire the protective benefits of these antioxidants. These substances can be ingested or administered in quantities of several hundred milligrams per day and appear to be safe for long-term administration and they are considered non-toxic.

Many aromatic and spicy plants as well as their essential oils could serve not only as a flavoring agent but also as a safe food antioxidant and supplement in preventing deterioration of foodstuffs. Consumption of food produced with natural essential oil or aromatic plant extracts are expecting to prevent the risk of many free radical mediated diseases including cardiovascular diseases. They safely interact with free radicals and terminate the chain reaction before vital molecules are damaged (Chitra and Pillai et al, 2002)

Most drugs are based on single, or "mono," compounds. Even when these compounds are derived from herbs, they have a singular action in the body. In contrast, "herbs seem to work in many different ways." and generally have a low risk of side effects

With technological advancement of science, the isolation, identification and elucidation of chemical principles from natural sources have become much simpler and have contributed significantly to the development of new drugs from medicinal plants (Cox, 1990; Cox and Balick, 1994)
Figure 7: *Mangifera indica* Linn plant
PLANT DERIVED ANTIOXIDANTS IN CVD

The prophylactic and therapeutic effect of many plant foods and extracts in reducing cardiovascular disease has been reviewed (Walker, 1996). Prominent herbs identified for cardiovascular diseases were Achillea millefolium (yarrow), Allium sativum (garlic), Convallaria majalis (lily of the valley), Crataegus laevigata (hawthorn), Cynara scolymus (globe artichoke), Gingko biloba (gingko) and Viburnum opulus (cramp bark) (Walker, 1996). Epidemiological studies have shown that a higher intake of these compounds is associated with lower risk of mortality from coronary heart disease. Like dietary antioxidants some non-nutrient based antioxidants from plants such as sulphur containing compounds in garlic, phyto-estrogens in soy, green tea, anthocyanins in red berries, lycopene in tomatoes, red wine and white wine from grape seeds are increasingly being recognised as potential health promoters in reducing the risk of cardiovascular disease and atherosclerosis.

MANGIFERA INDICA Linn (Scarazzini and Speroni, 2002)

It belongs to the family of anacardiacae, mangifera genus and indica species. The parts used are fruits, leaves, bark, latex, flowers, seed kernel, stems and roots. The common names are mango, manga, mangga, mangot, mamuang, merpelam, pelem, anbah, manguier, manga agaci, mangot fil, and anlo kuo. The general properties of this plant are astringent and useful in haemoptysis, haemorrhage, nasal catarrh, diarrhea, ulcers and diphtheria. It accelerates the rate of wound healing stops dysentery and corrects the blood born disorders. It is useful in uterotonic, cardiotonic and aphrodisiac and it is
also used in menorrhagia, bleeding piles and gonorrhea. The major and important phytochemical in *Mangifera indica* is mangiferin (Ansari *et al.*, 1967).

**ACTIVE PRINCIPLE - MANGIFERIN**

Mangiferin has been reported to be present in various parts of *Mangifera indica* viz. leaves (Desai *et al.*, 1966), fruits (Ansari *et al.*, 1971), stem bark (Ansari *et al.*, 1967; Bhatia *et al.*, 1967), heartwood (Ramanathan and Seshadri, 1960) and roots (Nigam and Mitra, 1964).

**Structure of mangiferin**

Its chemical name is 2-C-beta-D-glucopyranosyl-1, 3, 6, 7-tetrahydroxy xanthone, generally called as C-glucosyl xanthone. Molecular formula: C_{19}H_{18}O_{11}. Molecular weight: 422.35. Melting point-anhydrous-271°C (Muruganandan *et al.*, 2002).

**Mangiferin from various sources of plants**

It is a pharmacologically active phytochemical and natural polyphenolic antioxidant and glucosyl xanthone derivative present in different plants such as in the bark, and leaves of *Mangifera Indica* Linn (Aritomi and Kawasaki, 1969), in the root of *Anemarrhena asphodeloides* Bung (Aritomi and Kawasaki, 1969), the leaf of *Hibiscus liliastrum* (Cafferty *et al.*, 1996), *Urena lobata* (Srinivasan and Sankara Subramanian, 1981), *Salacia reticulata*, *Swertia chirata* BuchHam and *Canscora Decussata* Schultz (Masayuki Yoshikawa *et al.*, 2002).
Figure 8: Structure of mangiferin (1,3,6,7 tetra hydroxy xanthone 2-glucopyranoside) (Sato et al, 1992)
Figure 9: Mangiferin Powder from *Mangifera indica* Linn.
Antioxidant properties of mangiferin

Recently, pharmacological functions of mangiferin in altering the oxidative mechanisms have received much attention (Sanchez et al, 2000). The bioactivities of mangiferin are seemed to be mediated by systemic antioxidant / antiradical functions and immunomodulation (Ghosal et al, 1996).

Vimang, an extract obtained from the stem bark of selected varieties of Mangifera indica Linn contains a defined mixture of components which includes mangiferin and shows a very potent activity against hydroxyl radicals and hypochlorous acid, a significant inhibitory effect on the lipid peroxide of rat brain phospholipids and a protective effect against DNA damage induced by Iron or Cu²⁺ (Sanchez et al, 2000).

Mangiferin has been reported to show antioxidant properties in some invitro models (Cholbi et al, 1991; Sato et al, 1992; Hsu et al, 1997).

Mangiferin have a strong antioxidant activity in the biological peroxidation system and their capacities might result from their action of scavenging free radicals e.g. OH⁻ and O₂⁻ associated with initiation of lipid peroxidation rather than terminating radical chain reaction in lipid peroxidation (Sato et al, 1992).

Mangiferin, the poly phenol of vimang, has been tested invitro for its antioxidant (Sato et al, 1992, Rouillard et al, 1998; Markus, 1996) immunostimulatory and antiviral properties (Ritchey et al, 1981).
Mangiferin and cardioprotection

Mangiferin has cardiotonic activity (Srinivasan and Sankara Subramanian, 1981; Rastogi, 1968) and diuretic properties. Mangiferin rich plants are reputed medicinal plants recommended in the Indian systems of medicine (Ghosal et al, 1996) for the treatment of immuno-deficiency diseases such as arthritis, diabetes, hepatitis and in cardiac and mental disorders. The finding that mangiferin enhances TGF-beta gene expression suggests that this polyphenol might also be of value in the prevention of cancer, autoimmune disorders, arteriosclerosis and coronary heart disease (Leiro et al, 2003).

Pharmacological and other properties of mangiferin

Mangiferin from the leaves of Mangifera indica linn. has been reported to possess anti-inflammatory and displays a high antibacterial activity against grampositive bacteria (Chattopadhyay et al, 1986; Chattopadhyay et al, 1987). Diuretic, choleric and cardiotonic effects are also attributed to it (Srinivasan and Sankara Subramanian, 1981).

Mangiferin acts as an inducer of extensive proliferation of splenic lymphocytes and lectin unresponsive splenocytes of tumor-bearing mice (Bhattacharya et al 1976). Mangiferin with exercise reduces blood cholesterol and triglyceride levels in mice (Miura et al, 2001). Recent studies have indicated that mangiferin has wide range of pharmacological activities including antioxidant (Sato et al, 1992), antidiabetic (Ichiki et al, 1998),

Mangiferin shows antiviral effect against type 1 herpes simplex virus (HSV-1). It has been recommended as a drug in preventing dental plaques, and displays a high antibacterial activity against gram-positive bacteria. Mangiferin has also been used for nervous debility by providing monoamine oxidative inhibition in traditional Indian medicine (Bhattacharya et al, 1972). The free form of a drug is considered the pharmacologically active portion because it can diffuse out of the vascular compartment through cell membranes to reach target tissues (Ling Lai et al 2003).

It has also been found to be effective in non-insulin dependent diabetes mellitus (Ichiki et al, 1998). Mangiferin has been shown to have \textit{in-vivo} growth inhibitory activity against ascitic fibrosarcoma in mice (Ichiki et al, 1998). Mangiferin possesses antidiabetic activity (Guha et al, 1996). The bioactivities of mangiferin are seemed to be mediated by its systemic antioxidant / anti radical functions and immunomodulation (Ghosal et al, 1996).

**Mechanism and action of mangiferin** (Ghosal et al, 1996)

Mangiferin is an important antioxidant at different levels of oxidation sequence able to
- Prevent the lipid peroxidation by decreasing the $O_2$ concentration and generating mangiferin phenoxy radicals
- Bind metal ions like $Fe^{3+}$, $Fe^{2+}$ preventing the generation of hydroxyl radicals and/or oxoferryl groups.
- Regulate the polymer chain initiation by interaction with ROS and to produce feebly reactive oxo-radical.
- Act like a scavenger to lipid peroxy and alkoxy radicals and prevent the abstraction of hydrogen ion from cellular lipids and
- Maintain the balance of cellular oxidant and antioxidant.

**EXPERIMENTAL INDUCTION OF MYOCARDIAL INFARCTION IN ANIMALS**

Patients who have survived previous heart attacks and those would have subjected to the subsequent acute myocardial infarction is readily understood by little experimental research in myocardial infarction studies in animals. By studying the biochemical changes that takes place in the animal model, it is possible to gain more insight into the mechanism leading to the altered metabolic processes in human myocardial infarction (Ravichandran and Puvanakrishnan, 1993)

Several methods have been used to induce experimental myocardial infarction in different animals. Ligation of either of the two major branches of the left coronary artery has been one of the most popular techniques for this purpose in large animals like dogs, monkeys and pigs etc (Moore and Spear,
1984). However, in smaller animals like rats this method is inconvenient because of the relatively smaller size of the coronary arteries. Methods like coronary ligation and feeding of infarct producing diet are commonly employed to produce myocardial infarction in animals. Such animal models are utilized for experimental studies although these procedures differ from the varied conditions and factors that are attributed to favor MI in man (Kela et al, 1980).

Isoproterenol

Isoproterenol induced myocardial infarction serves as a well standardized model to study the beneficial effects of many drugs and cardiac function (Partha and Devi, 1997).

Isoproterenol structure and properties

Isoproterenol, (1-(-3, 4) dihydroxy phenyl-2-isopropyl amino ethanol hydrochloride) a synthetic catecholamine and beta-adrenergic agonist, has been found to cause a severe stress in the myocardium resulting in infarct like necrosis of the heart muscle.

Administration of isoproterenol is known to produce electrocardiography and enzymatic changes suggestive of myocardial ischemia in experimental animals (Dwivedi et al, 1987).

The use of isoproterenol a sympatho mimetic amine has during the recent decade heralded useful informations on experimental myocardial metabolic changes (Wexler, 1975; Bora et al, 1984).
Figure 10: Structure of Isoproterenol (1-(3,4) - dihydroxy phenyl-2- isoprophyl amino ethanol hydrochloride
Isoproterenol is capable of producing gross and microscopic myocardial necrosis, when administered subcutaneously. Wexler and Kittinger (1968) have described a close correlation between the dose of the drug injected and the degree of severity of necrosis—which makes possible the production of standardized myocardial lesions.

The myocardial infarction produced by high doses of isoprenaline has certain advantages that it does not require any expertise or extensive equipment and is less time consuming coupled with low mortality (Rona et al., 1959).

Isoproterenol administration is an important experimental tool to produce consistent myocardial infarction in animals (Rona et al., 1959) as surgical methods are found to be disappointing because of the difficulty in achieving standard myocardial infarcts (Norman et al., 1961) and pharmacological induction of myocardial infarction by subcutaneous administration of isoproterenol in smaller animals like rats has been found to be convenient.

Oxygen free radical is implicated as a mediator of tissue injury in cardiovascular pathology (Kakreja and Hess, 1992). It is also well known to generate free radicals and to stimulate lipid peroxidation, which may be a causative factor for irreversible damage to the myocardial membrane (Sushamakumari et al., 1989; Chein et al., 1978).
Mechanism of action

Catecholamines are important regulators of myocardial contractility and metabolism. However, it has been known for a long time, that less catecholamines are responsible for cellular damage, observed in clinical conditions such as transient myocardial hypoxia, angina, acute coronary insufficiency and subendocardial infarct. Catecholamine induced myocardial injury is a classical example of stress cardiomyopathy. This term is also used to denote the cause of sudden unexplained death, elicited by extreme stressful like circumstances (Cibils and Hirstat, 1980).

Catecholamine markedly enhanced the workload of the heart resulting in relative ischemia of the heart and its subsequent necrosis. The cardiac stimulation by catecholamine is through the activation of beta adrenoreceptors (Saxena et al, 1977). It appears that although the pathogenesis of catecholamine induced myocardial necrosis is multifactorial, oxidative stress plays a major role in it. Since, catecholamine rapidly undergo oxidation, it has been suggested that the oxidative products of catecholamines are also responsible for myocardial changes (Yates and Dhall, 1975).

Though the mechanism by which isoproterenol acts and induces myocardial infarction is still not clear, studies have shown that the pathophysiological changes that take place following myocardial infarction induced by isoproterenol administration are comparable to the changes taking place after myocardial infarction (Wexler, 1978). The mechanism of isoproterenol induced myocardial lesion is probably by myocardial calcium
Figure 11: \( \beta \)-adreno messenger system mechanism
(Wollen Berger, 1975)
overload and consequent high-energy phosphate depletion. The high-energy phosphate depletion is directly proportional to the degree of myocardial damage induced by isoproterenol (Fleckenstein, 1983). Tachycardia which ensures after isoproterenol treatment not only increases oxygen demand but it also decreases myocardial O₂ supply because of diastolic filling time of the coronary circulation. Thus, it lowers the end diastolic coronary perfusion pressure. The intensity of tachycardia outstrips the ability of coronary arteries to provide adequate blood supply to the myocardium. Thus, a stage of relative myocardial ischemia develops which results in a necrosis (Opie, 1975; Maroko and Braunwald, 1976).

Isoproterenol induced cardiac necrosis include increased myocardial contractility, increased oxygen consumption, alterations of membrane permeability, increased calcium overload and accumulations, increased intracellular acidity and free fatty acids, increased myocardial cAMP concentration, changes in intermediate cardiac cell metabolism, deranged electrolytes milieu and mechanical or dynamic hindrance of coronary circulation. Isoproterenol, being a beta-adrenergic agonist, increases the heart rate, force of myocardial contraction, atrial and ventricular conduction It also causes decreased peripheral resistance and increased cardiac output. The increase in heart rate usually accompanies an increase in myocardial oxygen consumption (Wexler, 1973).