CHAPTER 1

INTRODUCTION

Disorders of the heart and blood vessels are together called as cardiovascular diseases (CVDs). It comprises of coronary heart disease (heart attacks), cerebrovascular disease (stroke), hypertension, peripheral artery disease, rheumatic heart disease, congenital heart disease and heart failure.

1.1 Myocardial infarction

Myocardial infarction is the abrupt ischemic death of the myocardial tissue. It is the foremost reason of global morbidity and mortality. The term "myocardial infarction" comes from two words, myocardium refers to muscular tissue of the heart and the word "infarction" comes from the Latin word "infarcire" meaning "to plug up or cram". It refers to the clogging of the artery. Myocardial infarction or heart attack is irreversible necrosis of cardiac muscle due to prolonged ischemia resulting in death of heart tissue. It is characterised by an acute imbalance between oxygen supply and demand. Diabetes, dyslipidaemia, hypertension, obesity, smoking and lack of exercise are predisposing factors for the myocardial infarction.
1.1.1 History of Myocardial Infarction

- In 1772, Heberden described the clinical features of angina [1].
- In the end of 19th century, occlusion of a coronary artery in the dog triggered “quivering” of the ventricles and was found to be serious as reported by cardiovascular physiologists [2, 3].
- In 1879, the pathologist Ludvig Hektoen established that myocardial infarction is produced by coronary thrombosis “secondary to sclerotic changes in the coronaries” [4].
- In 1910, two Russian clinicians defined five patients with the clinical features of acute myocardial infarction [5]
- In 1912-James B. Herrick advised total bed rest for myocardial infarction [6]
- In 1919 - electrocardiography was used for first time to diagnose MI [7]

1.1.2 Epidemiology of Myocardial Infarction

MI is the most important cause of mortality throughout the world [8]. In the year 2012, 17.5 million people died due to CVD representing 31% of all worldwide deaths [9]. It has a significant occurrence in both rural and urban population of India [10]. The prevalence of MI in India is 64.37/1000 people in men aged 29-69 years [11]. Mainly South Asians have greater risk of ischemic heart disease (IHD) compared with most other ethnic Groups [12, 13]. Various pre-existing reasons lead to prevalence of myocardial infarction. [14, 15]. Smoking is one of main cause for arterial thrombosis and MI, and is known to cause endothelial dysfunction [16].
1.1.3 Pathophysiology of Myocardial Infarction

![Pathophysiology diagram]

1.1.4 Signs and symptoms of Myocardial Infarction

In acute MI, chest pain or tightness in the chest starts just under the breast bone lasts for 10-20 minutes. It is a diffused kind of pain which gets radiated from left arm, neck or along the jaw line. It may be accompanied by dyspnoea, diaphoresis, dizziness, nausea, vomiting, muscle weakness, anxiety and syncope. Patient’s case history and ECG will give clear picture about the extent of ischemia. Definitive diagnosis of myocardial infarction is done with ECG, increased cardiac biomarkers like Troponin, CK-MB and myoglobin from damaged heart muscle into the bloodstream and Coronary angiography.
1.1.5 Clinical Diagnosis of Myocardial Infarction

Damaged myocytes releases proteins like myoglobin, cardiac troponin T and I, CK, LDH, as well as many others into the blood stream which marks the myocardial cell death [17]. Elevation in cardiac troponin or CKMB is the indicator of acute myocardial ischaemia [18] which reveals the myocardial necrosis [17, 19]. Cardiac troponin (I or T) indicates specificity and sensitivity to myocardial tissue, thereby reproducing microscopic areas of myocardial necrosis [17]. PR segment, the QRS complex, and the ST segment or T-waves in the ECG is an essential part of the diagnosis for patients with suspected myocardial infarction [20-23].

1.1.6 Drug treatment of Myocardial Infarction

1. Pain, anxiety and apprehension

Intravenous injection of morphine 10 mg/pethidine 50mg is given to combat pain. Anti-anxiety drug like Diazepam to overcome anxiety and to cause sedation.

2. Oxygenation

O2 inhalation, assisted respiration if needed

3. Thrombolytics

The primary goal of treatment with antiplatelet and antithrombin agents is to establish and retain the patency of the infarct-related artery. They can decrease the amount of damage and death, if started at the commencement of symptoms (within 6-12 hrs). Streptokinase 1.5 million unit’s infusion is given over 1 hour. Urokinase (15 mg bolus) or alteplase (0.5mg/kg) may be given as substitute over the next 90 minutes. Anistreplase is long acting, can be administered as single IV injection.

4. Antiplatelet drugs

To decrease mortality and to improve the effect of thrombolytics 300mg of aspirin given orally immediately at the beginning of symptoms. Oral clopidogrel is given to patients who cannot tolerate aspirin.
5. **Anticoagulants**

To inhibit the extension of thrombus and deep vein thrombosis, heparin is administered.

6. **Vasodilators**

Intra venous infusion of nitroglycerin or sodium nitroprusside may be used to decrease the cardiac workload and reduce mortality.

7. **Beta blockers**

Beta blockers are given to reduce the infarct size, occurrence of arrhythmias, improves the myocardial oxygen supply-demand relationship and to reduce mortality. To start with IV atenolol 5-10mg given over 5 minutes or metoprolol 5 mg administered over 2 minutes and then switching over to oral beta blockers.

8. **ACE inhibitors**

Within 24 hours, ACE inhibitors should be given. These drugs will prevent ventricular remodelling and decrease the progression of heart failure which adds to long term survival in these patients [24-27].

1.1.7 **Recent Advances in the treatment of Myocardial infarction**

Reperfusion therapy in the form of primary percutaneous coronary intervention is one of the recent advancements in the treatment of acute myocardial infarction. Protection against reperfusion injury and novel therapies like cardiac regeration and sonothrombolysis, where use of ultrasonic waves along with fibrinolytic agent shown to improve the outcomes of patients with stroke is few recent advancements being investigated. Use of GP IIb/ IIIa inhibitors by intracoronary has shown to be safe and advantage over intravenous route in selected patients were observed [28-30].
Stem cell therapy is being explored in patients with acute myocardial infarction (AMI) to possibly regenerate myocardium and limit myocardial damage. Several investigations reported that BMCs can significantly decrease patient mortality due to myocardial infarction, substantially reduce infarct size and increase LVEF [31, 32].

1.2 Endothelial dysfunction

1.2.1 Vascular Endothelium

It is a single layer of squamous cell epithelium which lines inner surface of blood vessels and lymphatic vessels. It makes a semi permeable membrane between circulating blood and vascular smooth muscle. Under normal condition, it plays a crucial paracrine, endocrine and autocrine role and maintains vascular homeostasis [33, 34].

1.2.2 Functions of vascular endothelium

It plays key role in the vascular permeability, maintaining vascular tone, angiogenesis, metabolism, vascular smooth muscle cell proliferation, fibrinolysis, platelet activation, thrombosis and white cell trafficking. It is also involved with vascular smooth muscle tone, blood flow to the various tissues, inflammation and conserving fluidity of blood.
1.2.3 Pathogenesis of endothelial dysfunction

Endothelium releases Nitric Oxide (NO) and prostacyclin as antithrombotic and von Willebrand factor (vWF) and plasminogen activator inhibitor-1 (PAI-1) as prothrombotic mediators. There is a strongly controlled balance between endothelium dependent vasodilator like endothelium-derived hyperpolarization factor (EDHF), NO [36,37], prostacyclin (PGI2) [38], endothelium derived vasoconstrictors like endothelin-1 (ET-1) [39], angiotensin II and reactive oxygen species (ROS) [40,41]. Vascular endothelium regulates well controlled equilibrium between different mechanisms like vasodilation, vasoconstriction, fibrinolysis, thrombogenesis, promotion or inhibition of platelet adhesion and aggregation [42].

Vascular endothelium is associated with the regulation of vascular tone and the maintenance of vascular homeostasis. It is a prognostic marker for future cardiovascular events. Endothelial dysfunction is the initial step in the atherosclerosis which includes development of plaque and associated complications [43, 44].

Figure 1.2.3. Pathogenesis of Endothelial dysfunction [35].
1.2.4 Progression of endothelial dysfunction and its risk factors

A proinflammatory and prothrombotic state associated with impaired endothelium dependent vasodilatation is collectively known as endothelial dysfunction. It is marked by imbalance between endothelium dependent contracting factors and vasodilators mainly, nitric oxide (NO) which ultimately causes interference with endothelium dependent vasodilatation [45].

![Diagram showing progression of oxidative stress and endothelial dysfunction]

Figure 1.2.4 Risk factors in the progression of oxidative stress and endothelial dysfunction [46]

Predisposing factors for the development of endothelial dysfunction are smoking, aging, hypercholesterolemia, hypertension, hyperglycaemia, a family history of premature atherosclerotic disease [47-49], obesity, elevated C-reactive protein, and chronic systemic infection [50-56].
1.2.5 Diagnostic markers of endothelial dysfunction

Under normal conditions, vascular endothelium is responsible for haemostasis, fibrinolysis, the synthesis of growth factors and regulation of vascular tone and permeability. It is well known from current literature that inflammatory mediators play an essential role in the atherosclerotic disease. Damage to vascular endothelium augments the synthesis of vWF, the tissue activator of plasminogen the inhibitor of plasminogen activator and C-reactive protein [57-65]. It is also linked with the enhanced levels of glycoprotein adhesion molecules of the selectin Group, such as E-selectin and V-CAM [66-68]. All these mediators of inflammation released from endothelium are the probable markers of endothelial dysfunction. Endothelial function may reveal the susceptibility of an individual towards atherosclerosis progression. Endothelial dysfunction is helpful in predicting, preventing, and treating cardiovascular diseases.

1.3 Crataegus oxyacantha L.

![Crataegus oxyacantha plant & its berries](image)

Figure 1.3 Crataegus oxyacantha plant & its berries

*Crataegus oxyacantha* is an Indian medicinal herb belongs to Rosaceae family. It is traditionally known as Hawthorn in the folklore medicine. In India, it is found widely in Himalayas, Kashmir and Himachal Pradesh [69].
The berries, fruits and leaves have been studied extensively for its medicinal properties throughout the world. Its cardio protective, antioxidant [70], hypolipidemic [71], hypotensive [72], antianxiety [73], diuretic [74], anti-inflammatory, gastro protective and anti-microbial activities [75] have been well documented in the literature by many researchers.

Till date, Studies related to the effect of ethanolic extract of *Crataegus oxycantha* on Isoproterenol induced myocardial infarction and endothelial dysfunction in rats have not been reported. In the current study, we have evaluated the effect of ethanolic extract of *Crataegus oxycantha* (COC) on myocardial infarction and endothelial dysfunction.