1. Introduction

1.1 Cardiovascular system and the heart

The heart and the blood vessels (circulatory system) make up the cardiovascular system of the body. The heart is a hollow muscular organ that pumps blood through the blood vessels by repeated, rhythmic contractions throughout life (Leu et al., 2001). It contracts approximately 100,000 times each day, ejecting more than 7,200 L of blood that is carried through the vascular system to distribute oxygen and other nutrients to the body and collects CO₂ and metabolites for disposal (Ahumada, 1987).

The heart is composed of three major types of cardiac muscle: atrial muscle, ventricular muscle, and specialized excitatory and conductive muscle fibres. The atrial and ventricular muscle contracts similar to the skeletal muscle, except that the duration of contraction is much longer. The excitatory and conductive muscle fibres exhibit either automatic rhythmical electrical discharge in the form of action potentials or conduction of the action potentials through the heart, providing an excitatory system that controls the rhythmical beating of the heart (Guyton and Hall, 2006). The heart wall consists of three layers: a) Endocardium - the internal layer, b) Myocardium – the middle layer and c) Pericardium - the external layer. Among the three layers, myocardium is the thickest and consists of a diverse assemblage of cardiac muscle cells and cardiac fibroblasts and is responsible for the contraction – relaxation force generation (Junqueira et al., 1998).

‘Cardiovascular diseases’ (CVDs) is a generalized term referring to the diseases related to the heart and circulatory system. CVDs account for most number of deaths worldwide (WHO, 2015). At least three quarters of the world's deaths from CVDs occur in low- and middle-income countries, placing a heavy economic burden on the countries. According to World Health Organization (WHO, 2015), an estimated 17.5 million people died from CVDs in 2012, representing 31% of all global deaths. And the situation is only getting worse as by 2030, almost 23.6 million people are predicted to die from CVDs, mainly from heart failure. Heart failure is the condition where the heart is unable to pump sufficient oxygenated blood to the tissues to meet their metabolic needs (Ahumada, 1987). Many pathophysiological conditions can cause heart failure. The major ones have been elaborated below-

1.2 Types of cardiovascular diseases

A. Cardiomyopathy:

Cardiomyopathy ("heart muscle disease") refers to deterioration of the function of the myocardium (the heart muscle), usually leading to heart failure (Kasper et al., 2005). The
cardiomyopathies are classified by the dominant pathophysiology or by etiological/pathogenic factors into following subcategories (Richardson et al., 1996):

1. Dilated Cardiomyopathy (DCM): Dilated cardiomyopathy is characterized by dilatation and impaired contraction of the left ventricle or both ventricles. It may be ischemic, idiopathic, familial/genetic, viral, alcoholic/toxic, or associated with recognized cardiovascular disease in which the degree of myocardial dysfunction is not explained by the abnormal loading conditions or the extent of ischemic damage.

2. Hypertrophic Cardiomyopathy (HCM): Hypertrophic cardiomyopathy is characterized by left and/or right ventricular hypertrophy, which is usually asymmetric and often involves the interventricular septum. Typically, the left ventricular volume is normal or reduced.

3. Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC): Arrhythmogenic right ventricular cardiomyopathy is characterized by progressive fibro-fatty replacement of right ventricular myocardium, initially with typical regional and later global right and some left ventricular involvement, with relative sparing of the septum.

4. Restrictive Cardiomyopathy (RCM): Restrictive cardiomyopathy is characterized by restrictive filling and reduced diastolic volume of either or both ventricles with normal or near-normal systolic function and wall thickness. Increased interstitial fibrosis may be present. It may be idiopathic or associated with other disease (eg. amyloidosis; endomyocardial disease with or without hyper eosinophilia).

5. Non-compaction Cardiomyopathy (NCC): Non-compaction cardiomyopathy is also called spongiform cardiomyopathy which is a rare congenital cardiomyopathy that affects both children and adults. It results from the failure of myocardial development during embryogenesis.

B. Vascular Diseases:

Refers to a form of cardiovascular disease primarily affecting the blood vessels. Vascular disease is a pathological state of large and medium sized muscular arteries and is triggered by endothelial cell dysfunction. Following are the major types of vascular diseases:

1. Coronary Artery Disease (CAD): Refers to the condition where the arteries involved in coronary circulation of heart are blocked by cholesterol-laden plaque or blood clot and thereby cause oxygen and nutrient starvation in heart. It is one of the most common disease form, also termed myocardial infarction (MI) that cause sudden death in humans (Thomas et al., 1988).

2. Atherosclerosis: Atherosclerosis (also known as arteriosclerotic vascular disease) is a condition in which an artery wall thickens as a result of the accumulation of fatty materials such as cholesterol and triglyceride. It is a syndrome affecting arterial blood vessels in general, a
chronic inflammatory response in the walls of arteries, caused largely by the accumulation of macrophage, white blood cells and promoted by low-density lipoproteins (plasma proteins that carry cholesterol and triglycerides) without adequate removal of fats and cholesterol from the macrophages by functional high-density lipoproteins (Maton et al., 1993).

C. Inflammatory Heart Disease:

This disease form is caused by inflammatory changes in the endothelium, which begins to express several adhesion molecules like vascular cell adhesion molecule 1 that attracts monocytes, which then migrate through the endothelial layer under the influence of various proinflammatory chemoattractants. Once within the arterial intima, the monocytes continue to undergo inflammatory changes, transform into macrophages, engulf lipids, and become foam cells. T lymphocytes also migrate into the intima, where they release proinflammatory cytokines that amplify the inflammatory activity (Libby, 2006). Inflammatory heart disease can be further categorized into following subgroups:

1. Endocarditis: Refers to the condition where inflammation occurs in the endocardium i.e., the innermost layer of the heart wall.

2. Cardiomegaly: Refers to enlargement of heart which occurs due to inflammation.

3. Myocarditis: Refers to an inflammatory disease of the myocardium and is diagnosed by established histological, immunological, and immunohistochemical criteria. It often results in dilated cardiomyopathy. Several pathophysiological conditions may promote myocarditis, viz., Chagas’ disease, Human immunodeficiency virus (HIV), enterovirus, adenovirus, and cytomegalovirus infection (Richardson et al., 1996).

D. Hypertension:

Refers to a chronic medical condition in which the blood pressure in the arteries is elevated. This requires the heart to work harder than normal to circulate blood through the blood vessels. It is the most common disease in industrialized nations, with prevalence above 20% in the general population. It imparts an increased risk of stroke, myocardial infarction, heart failure, and renal failure (Nabel, 2003).

E. Valvular heart disease:

Refers to any disease process involving one or more of the valves of the heart- the aortic and mitral valves on the left and the pulmonary and tricuspid valves on the right. Valve problems may be congenital (inborn) or acquired (due to another cause later in life) (Bonow et al., 2006).

Of the various CVDs, myocardial infarction (MI) is the major cause of sudden cardiac arrest and heart failure (Thygesen et al., 2012).
In the following subsections MI and post MI remodeling has been discussed in brief.

1.3 Myocardial infarction and post MI remodeling

The term ‘myocardial infarction’ has been characterized by a loss of cardiac myocytes through necrosis as a result of prolonged ischemia, while ischemia is the condition of the heart tissue itself where an imbalance between blood supply and demand exists (Joint European Society of Cardiology/American College of Cardiology Committee, 2000). It refers to an acute loss in cardiomyocyte population caused by prolonged ischemia that occurs due to an imbalance between oxygenated blood supply and demand (Alpert et al., 2000). Complete necrosis of myocardial cells at risk requires at least 2–4 hours, or longer, depending on the presence of collateral circulation to the ischemic zone, persistent or intermittent coronary arterial occlusion, the sensitivity of the myocytes to ischemia, preconditioning, and individual demand for oxygen and nutrients (Thygesen et al., 2012). The entire process leads towards formation of an infarct patch which consists of dying cardiac cells.

There are a few studies dealing with the acute inflammatory response elicited by the cardiac cells immediately after MI. Several pro-inflammatory cytokines and chemokines have been reported to be involved in this process, viz., interleukin (IL)-1, IL-6, IL-8 and TNFα (Frangogiannis et al., 2002; Frangogiannis and Entman, 2005; van Nieuwenhoven and Turner, 2013). Rapid alterations in the redox balance and dynamics of Ca²⁺ transport in cardiomyocytes has also been attributed to be major features of MI (Swynghedauw, 1999). Epidemiological studies indicate that about 40% of patients have left ventricular diastolic dysfunction and 30%-45% of patients go on to develop heart failure after being diagnosed with MI as a result of post myocardial infarction remodeling of the cardiac tissue (Minicucci et al., 2011; Weir and McMurray, 2006). The nature of remodeling- adaptive or pathological- remains debatable, depending on the time lapsed after MI (Sutton and Sharpe, 2000; Cohn et al., 2000; Garza et al., 2015). Remodeling process after MI has been characterized by ventricular cavity increase, over a protracted time period, resulting in deterioration of heart function (Thygesen et al., 2012; Sutton and Sharpe, 2000). Various workers have characterized post MI cardiac remodeling as the driver of molecular, cellular and structural changes that lead to changes in heart size, mass, geometry and gives way to compromised cardiac function (Pfeffer and Braunwald, 1990, Cohn et al., 2000). The factors which lead to cardiac remodeling and compromised function are yet to be fully understood. Several workers have studied MI, its causes and consequences, to come up with a sizeable amount of diffused data, lacking a composite idea about the alteration of proteome and processes involved.
1.4 Cardiac Proteomics

With the emergence of high-throughput proteomic techniques, there have been several efforts to dissect out the cardiac proteome in various cardiovascular disorders in order to fish out markers specific for various types of pathological conditions (Arrell et al., 2001). MI has been traditionally studied by proteomic approaches for two main purposes. One purpose is to identify novel biomarkers to enhance diagnosis and treatment. Towards this end, several promising biomarkers, such as cardiac myosin binding protein (MybpC), Haptoglobin and Apolipoprotein J have been identified (Jacquet et al., 2009; Haas et al., 2011; Cubedo et al., 2011). The other purpose is to understand the molecular pathology behind myocardial death and damage occurring during MI. Toward this end, a study has elucidated endoplasmic stress mediated apoptosis to be the primary cell death process during MI (Mitra et al., 2013). Another study by the same group found that NRF2 played a protective role during the onset of MI via the heat shock protein alpha crystallin B (Mitra et al., 2014). They also found that glucose metabolism mediated by PDHE1β of the pyruvate dehydrogenase complex was severely hampered during MI (Mitra et al., 2015).

Few proteomic studies have probed the molecular events taking place after MI, a process that has been called post MI remodeling, which is at the core of poor long term prognosis after MI. After an event of acute MI, short term remodeling occurs with respect to necrotic tissue removal, scar formation, angiogenesis and wall thinning, some of them being instrumental for recovery of the myocardium (Cohn et al., 2000). A study of the infarct border zone during short term remodeling (10 days), found a profile of 69 proteins differing in expression during the given time interval (Xiang et al., 2011). Another study of the infarct border revealed the upregulation of cytoskeletal protein Nestin and stem cell markers c-kit, Sca-1, Mdr-1, and Abcg2 indicating that cardiac stem cells differentiated to cardiomyocytes during remodeling (Scobioala et al., 2008). Another remodeling study of the infarct border over a period of 4-45 days revealed 13 proteins belonging to functional groups oxidative stress, ion channels, metabolism and cytoskeleton, to be altered during remodeling (Li et al., 2014). Another aspect of remodeling addressed by proteomics is the alteration in extracellular matrix of cardiomyocytes. Studies have reported that matrix metalloproteinases (MMPs) 7 and 9 were key players in the remodeling process (Chiao et al., 2010; Zampila et al., 2010; Yabluchanskiy et al., 2013).

Proteomic studies have thus focussed mostly on short term remodeling post MI and on the infarct border zone. This does not take into consideration the fact that remodeling is essentially a time dependent process and involves the cardiac tissue as a whole, both the infarct and non-infarct regions. This study has been undertaken to determine the major proteins and functional