Abstract

Cardiovascular complications account for significant morbidity and mortality worldwide. In spite of several developments with respect to the medications, devices and stem cell therapy, assessment, treatment and management of heart failure are still challenging for the physician. With the advent of research, several humoral, cellular and sub-cellular targets have been identified, with a hope to get novel drug for the prevention and treatment of heart failure especially the stage of congestive heart failure. A number of molecules acting on specific targets are known and drugs are being developed but, even today, one has to rely on the currently available anti-hypertensives, lipid lowering, anti-diabetic, diuretics and antithrombotic drugs for heart failure. In the early stages we carried out animal and clinical studies on proper selection of anti-diabetics and anti-hypertensives related to cardioprotection, justifying use of selective ACE inhibitors and calcium channel blockers in NYHA class 1 cardiac failure. Similarly metformin was reported to be relatively cardio protective as compared to sulfonylureas, giving rise to a new era for insulin sensitizers. Further, clinical studies in patients undergoing coronary artery bypass surgery in NYHA Class-2 and Class-3 heart failure, suggested suitability of perindopril and ramipril over other ACE inhibitors. We also reported that adenosine and sodium nitroprusside administered sequentially as intracoronary boluses are effective in establishing TIMI and TMP flow grade-3 in most of the patients. Monitoring of pulmonary artery pressure in NYHA Class 3 and Class 4 heart failure patients showed that while metoprolol was effective in most of these patients, some patients did not show improvement possibly because of gene polymorphism. However, in general there is need to revisit currently used drugs in different stages of heart failure and suggest development of Drug Directed Targets rather than Target Directed Drugs.

Introduction:

Heart failure, often termed as congestive heart failure, is a condition when cardiac muscles fail to pump the blood efficiently or within physiological limits. In 2010, more than 41 million patients were living with heart failure, an increase by 14% from 1990. Globally, 38% of heart failure cases were caused by coronary heart disease (CHD) and 34% by the next three largest causes, hypertension, rheumatic heart disease and cardiopulmonary disease. Thus, congestive heart failure is the tip of the iceberg resulting from these conditions. In the USA, over one million hospitalizations occur each year for HF, an increase of over 175% in the last 25 years. These hospitalizations mark a substantial crossroad for patients, as greater than one-third will be re-hospitalized or dead within 90 days post-discharge. Studies of Indian immigrants and cross sectional studies in India, have demonstrated that CHD is rampant in Indians and that its prevalence is several folds higher than in industrialized nations. A conservative estimate indicates that there could be 30 million CAD patients in India of which 14 million are in urban and 16 million in rural areas. In spite of several developments with respect to the medications, devices and stem cell therapy, assessment, treatment and management of heart failure
are still challenging for the physician. In order to determine the best course of therapy, physicians often assess the stage of heart failure according to the New York Heart Association (NYHA) functional classification system (Table 1). This system relates symptoms to everyday activities and the patient’s quality of life.

**Table 1: New York Heart Association (NYHA) functional classification of Heart Failure**

<table>
<thead>
<tr>
<th>Class</th>
<th>Patient Symptoms</th>
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<tr>
<td>Class I (Mild)</td>
<td>No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).</td>
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<tr>
<td>Class II (Mild)</td>
<td>Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.</td>
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<tr>
<td>Class III (Moderate)</td>
<td>Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.</td>
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| Class IV (Severe)  | Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased. |}

**Pathophysiology of heart failure:**

The basic underlying physiologic mechanisms in the development and progression of chronic heart failure are an initial insult followed by ventricular remodeling. The initial insult sets into motion a destructive cycle in which the remaining normal myocardium undergoes changes in cell metabolism and morphology, leading to hypertrophy and fibrosis. These cellular changes gradually lead to alterations in the ultrastructural properties of the ventricle through a process called remodeling. Although remodeling initially occurs as an adaptive response to improve cardiac performance, over time, the response becomes counterproductive and maladaptive leading to the progression of heart failure.

The process of myocardial remodeling consists of a number of molecular and cellular changes. In general, pathologic myocardial remodeling involves an increase in myocardial mass associated with hypertrophy of individual myocytes, alterations in gene expression, and changes in both the quantity and quality of the extracellular matrix. The contractile unit of myocardium consists of three integrated components: myocytes, extracellular matrix, and the capillary microcirculation. The extracellular matrix provides a stress-tolerant, viscoelastic scaffold consisting of type I and type III collagen that couples myocytes and maintains the spatial relations between the myofilaments and their capillary microcirculation. Myocardial infarction results in the migration of macrophages, monocytes, and neutrophils into the infarct zone; this initiates intracellular signaling and neurohormonal activation, which localizes the inflammatory response. Post infarction remodeling can be divided into an early phase (within 72 hours) and a late phase (beyond 72 hours). In the early phase there occurs expansion of the infarct zone resulting into ventricular rupture or aneurysm formation whereas the late phase is associated with increased wall stresses, formation of collagen scar by extracellular matrix, a time-dependent dilatation, distortion of ventricular shape, and mural hypertrophy.
A number of inflammatory cytokines (e.g., interleukin-1b) have been identified to be involved in heart failure. Although the central feature of remodeling is an increase in myocardial mass associated with myocyte hypertrophy, there is evidence that pathologic remodeling also involves the death of myocytes by apoptosis, or programmed cell death. Many factors are known or suspected to be involved in heart failure include catecholamines, angiotensin, inflammatory cytokines, reactive oxygen species, nitric oxide, hypoxia, peptide growth factors, and mechanical stretch have been shown to cause apoptosis of cardiac myocytes in vitro. Conversely, some factors that can cause myocyte hypertrophy have not been shown to cause apoptosis. Thus, although there appears to be a relation between stimulation of myocyte growth and apoptosis, the two events may not be linked for all stimuli.

The heart is an omnivorous organ whose metabolic machinery is exquisitely atuned both to its metabolic needs and to the available energy substrates in its local environment. The diabetic metabolic milieu is another factor that creates an environment taking the heart into a progressively maladaptive state from which it cannot escape by its own devices. Thus diabetic cardiomyopathy is one of the most common causes of heart failure that exists independent of atherosclerosis. The heart as such is normally adapted to both to its metabolic needs and to the available energy substrates in its local environment. However, in the diabetic metabolic milieu it progressively gets into a maladaptive state and there occurs cardiac dysfunction. Various studies indicate that the diabetic environment can signal changes in gene expression via epigenetic mechanisms in heart and vasculature. In the diabetic heart mode of delivery and utilization of metabolic substrates gets altered. There occurs a shift from glucose utilization to fatty acid metabolism. Simultaneously, cardiac fatty acid oxidation is increased and becomes the heart’s only fuel. The fatty acid delivery to the heart from the coronary lumen by the enzyme lipoprotein lipase and its uptake by fatty acid transporters to myocardium increases beyond the capacity of the heart to utilize fatty acids resulting in accumulation of lipids in cytoplasm in the form of long-chain acyl-CoA’s which are converted into the toxic substance ceramide and in turn, induces reactive oxygen species and cardiomyocyte apoptosis. Fatty acids bind and activate peroxisome proliferator-activated receptors (PPAR’s) of which PPAR-α is the key isoform in the heart. This induces genes involved in fatty acid metabolism leading to the development of diabetic cardiomyopathy.

In parallel with this metabolic remodeling, there is contractile remodeling. There are some similarities and differences between remodeling after CAD and diabetes. In diabetes there occurs re-expression of genes like skeletal muscle actin, beta myosin heavy chain, atrial natriuretic peptide within the ventricle, along with blunting of the expression of genes like alpha-myosin heavy chain, cardiac actin, sarcoplasmic reticulum calcium ATPase-2 (SERCA-2). These result in a shift from the fast V1 isomyosin pattern seen in the normal heart to a predominantly V3 pattern in the diabetic heart. There also occurs cardiac hypertrophy and fibrosis, causes worsening of the diastolic dysfunction and the appearance of a mild systolic dysfunction sufficient to activate the renin-angiotensin system and the sympathetic nervous system.

**Pharmacological Treatment of Heart Failure:**
Heart failure patients need multiple medications. The elucidation of the fundamental mechanisms involved in progressive congestive heart failure has led to the development of a number of new pharmacological agents. Among these are inhibitors of the mediators that contribute to vasoconstriction and to the maladaptive processes in heart failure. The renin-angiotensin-aldosterone system may be inhibited at different levels by ACE inhibitors and by angiotensin-II receptor antagonists. The use of ACE inhibitors has revolutionized the treatment of patients with chronic heart failure during the last 2 decades and has led to improvement in both symptoms and survival rates. In fact, studies have shown that even patients with asymptomatic systolic dysfunction benefit from ACE-I therapy. Newer angiotensin-II receptor antagonists are also being considered. These agents not only improve hemodynamics, but they also slow the progression of myocardial damage at the tissue level and favorably alter remodeling. The effects of neuroendocrine inhibition are also evident from the results of large clinical trials in which selective β-blockers have been used to treat heart failure. In particular, the nonselective β-blocker carvedilol appears to improve the symptoms and the systolic function of the heart and to prolong life, again by altering abnormal hemodynamics and by protecting the heart at the tissue and cellular level. The newest area of interest with regard to the pharmacologic treatment of heart failure is the complex interaction of the immune system, cytokine activation, and the nitric oxide system. In spite of development of number of molecules acting on specific targets, even today, one has to rely on the currently available anti-hypertensives, lipid lowering, anti-diabetic, and antithrombotic drugs for cardiovascular protection in the event of diabetic cardiomyopathy. In the early stages we carried out animal and clinical studies on proper selection of anti-diabetics and anti-hypertensives related to cardioprotection, justifying use of selective ACE inhibitors and calcium channel blockers in NYHA class 1 cardiac failure. Similarly metformin was reported to be relatively cardio protective as compared to sulfonylureas, giving rise to a new era for insulin sensitizers. Further, clinical studies in patients undergoing coronary artery bypass surgery in NYHA Class-2 and Class-3 heart failure, suggested suitability of perindopril and ramipril over other ACE inhibitors. We also reported that adenosine and sodium nitroprusside administered sequentially as intracoronary boluses are effective in establishing TIMI and TMP flow grade-3 in most of the patients. Monitoring of pulmonary artery pressure in NYHA Class 3 and Class 4 heart failure patients showed that while metoprolol was effective in most of these patients, some patients did not show improvement possibly because of gene polymorphism.

Recently some newer Short-term therapies have come up but all are in the stage of clinical trials

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<thead>
<tr>
<th>Name</th>
<th>Mechanism</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Cinaciguat</td>
<td>Heme-independent activation of soluble guanylatecyclase</td>
<td>22</td>
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<tr>
<td>Chimeric natriuretic peptidesx</td>
<td>More selective venodilator than BNP</td>
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<td>Relaxin</td>
<td>Systemic and renal vasodilator</td>
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<tr>
<td>Istaroxime</td>
<td>stimulation of membrane-bound Na-K/ATPase sarcoendoplasmic</td>
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**Macronutrients in Heart Failure**

In the last few years, numerous epidemiological and interventional studies have shown that dietary omega-3 fatty acids exert beneficial CV effects. The recent publication of the GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto del Miocardio) trial has expanded these observations to patients with chronic HF, showing mortality and morbidity benefits. The proposed mechanisms include anti-inflammatory and haemodynamic effects, as well as CV remodelling, neurohormonal inhibition, and arrhythmia suppression. Micronutrients are essential cofactors for energy transfer and include molecules such as thiamine, amino acids, L-carnitine, and coenzyme Q10.

**REFERENCES:**


