Heart Failure and Innovative Therapies

Mohamed Abdelkhalek

1. INTRODUCTION

Heart failure is a clinical syndrome, where the heart is unable to provide sufficient blood flow to meet the energy requirements, or accommodate systemic venous return. It is accompanied with symptoms, signs and evidence of structural, or functional deviation from normal heart conditions. Cardio-vascular disease still remains a major cause of death worldwide. Simultaneously, advancements in technology has given us a much better picture of the underlying physiological causes and mechanisms underlying the disease. From rapid improvements in high fidelity digital imaging, to advances in genetic sequencing and computational simulations of cardio phenomena. The challenge is how to assimilate the various methods and multi-disciplinary techniques , in order to confidently assist clinicians in making life changing decisions, affecting patients health and quality of life.

2. PATHOPHYSIOLOGY

When discussing heart failure, it is useful to formulate distinction between different states and stages of the condition and the underlying bio-molecular mechanisms that can help identify the variety of causes that lead to injury of the myocardium. [2]

2.1 Acute and Chronic Heart Failure

Its important to mention the distinction between a sudden onset of heart failure for eg; after a heart attack, where part of the myocardium dies leaving the heart function impaired, And the gradual onset of heart failure, where damage to the heart muscle is progressive over time, and symptoms are usually less severe until an acute attack occurs. Such a classification is essential as they have very different clinical presentations and also disparate treatment plans. [2]

2.2 Systolic and Diastolic Heart Failure

Similarly ,Another distinction is made between systolic and diastolic impairment; Usually assessed by ejection fraction. Where systolic failure means the heart muscle cannot contract properly thus decreasing its ejection of blood. While a diastolic problem entails inability of the heart fill up with blood efficiently. [2]

2.3 Compensatory Mechanisms

When discussing biological dynamic systems such as the cardio-vascular system. one must recognize the importance of the complex feedback loops that determine the effective behaviour underlying the dynamics of heart function. Therefore, it is very important to recognize the highly variable environment of the system due to these evolving and sometimes competing mechanisms, and realize that such compensatory mechanisms, under certain conditions may qualify as a pathway from adaptation to disease. [8]

2.4 Ventricular Remodeling

The mechanism by which the cardiac cells are able to sense the filling state of the chambers, and translate this input into a change in cellular function (Frank Starling Mechanism). Many parameters of myocyte behaviour may be affected, such as contractility, membrane voltage, or even gene expression. It is important to note that this mechanism though it enables the cardiac muscle to adapt to variety of external disturbances may lead to abnormalities further on. [9]

2.5 Vascular Remodeling

The response of muscular arterial resistance to shear stress, the myogenic tone. Is countered by the endothelial dilation of the vascular wall in response to flow. This mechanisms are facilitated by biochemical agents such as extracellular matrix and cell structure proteins and nitrous oxide release. [?]. Such mechanical-cellular interactions are also important during the embryonic development, and are responsible for the final form and function, of heart structure and dynamics through the alteration vascular cells phenotype.

3. CLINICAL DIAGNOSIS AND TREATMENT

It is important to recognize the current clinical methodology when dealing with patients with possibility of Heart Failure. From the identification of the particularity of the disease, towards how evidence of a specific ailment is obtained. And finally, what course of action can be taken for treatment of the patient.[4]

3.1 Classification

It is easier to discuss heart failure in terms of functional classification, according to degree of symptoms. The NYHA[1] describes a system with four classes from **class I** where patients exhibit no symptoms even under physical activity, to **class IV** where patient are incapable of carrying out any physical activity without discomfort.

3.2 Constitutional Symptoms And Signs

The diagnosis of HF typically starts with the patent's medical history, as well as observation of symptoms and signs such as breathlessness, elevated jugular venous pressure, or more uncommon symptoms and signs, such as nocturnal cough and signs like tachycardia and irregular pulse.

3.3 Clinical Investigation

Following classification of HF based on symptoms and signs, investigation is needed to ascertain exact cause of ailment affecting the heart system. Echocardiograpy, ECG, blood count and chemistry investigation is common methods in **class I** with X-RAY and measurement of natriuretic peptides [2] in more advanced classes for all patients. Furthermore, in certain select patients CMR, cornary angiography and catheterization is recommended. For patients that are going to undergo mechanical circulatory support for example. [4]

3.4 Drug Therapy

Treatment strategy when using drugs aims for relieving symptoms, improve life quality and increase cardio performance. For improving the conditions in case of systolic heart failure, three main neurohumoral antagonists are considered an ACE Inhibitor, Beta Blocker and an MRA. For patients with advanced diastolic heart failure no pharmacological treatment has yet been shown to reduce mortality rates. However, treatment of hypertension and myocardial ischema is important to improve symptoms and physical activity through rate limiting Calcium Channel Blockers and Beta Blockers. [4]

3.5 Cardio Assist Devices and Surgical Interventions

In more advanced cases of heart failure where therapy through chemical agents is inadequate or not fast enough other options may be considered. Mechanical assist devices vary from non surgical options such as ICDS and CRTS that affect the cardio excitation sequence to surgical implantable options namely mechanical pump devices like LVADS, artificial valves and implantable pacemakers. Surgical interventions include vascular/ventricular reconstrucion, vavular surgery and heart transplantation. [4]

[1]NYHA: New York Heart Association functional classification of Heart Failure

[2]A family of hormones secreted in increased amounts when the heart is diseased

4. INNOVATIVE THERAPIES

By understanding the complex feedback loops of the cardiovascular system in the macro and the molecular. We can decide on therapeutic methods that integrate with the existing adaptive mechanisms, which would not only provide safer treatments, but can provide a pathway from the abnormal structure or function to the restoration of the healthy state. In what follows I will discuss some innovative therapeutic methods that demonstrate such an approach.

4.1 Cardiac Contractility Modulation

Cardiac contractility modulation (CCM) is a novel approach for improving ventricular function in patients with advanced systolic heart failure. A small programmable implantable, under the skin, impulse generator that resembles a pacemaker is the central part of the CCM system. CCM therapy does not aim at altering the cardiac activation sequence; it modulates contractility instead. by delivering high- energy electrical impulses to the myocardium during in sync with cardio excitation sequence. By altering the membrane potential, these signals augment Ca2+ influx through the L-type calcium channels, thereby increasing Ca2+- induced calcium release from the sarcoplasmatic reticulum, which in turn augments myocardial contractility. Furthermore, CCM normalizes cardiac mRNA expression by the up-regulation of fetal and down-regulation of adult genes. Genes responsible for sarcoplasmic calcium cycling and contractile proteins are targeted. By reactivating the fetal pattern of gene expression, the heart adjusts to lowered cardiac energy resources. This reversal is one of the mechanisms potentially underlying the clinical improvements observed under CCM. [7] [5]

4.2 Left Ventricular Assist Devices and Drug Therapy

The molecular, cellular, biochemical, and structural changes occurring in the myocardium, mentioned above, have been studied extensively in patients with heart failure. One intriguing feature of remodeling is that at least some of its manifestations can occasionally be reversed. For increasing the probability of recovery, A combined therapy that consists of a left ventricular assist device and drugs known to enhance reverse remodeling, followed by the use of the drugs that increase the cardiac output. Clinical improvements in patients undergoing the treatment was associated with improvement in hemodynamics, exercise capacity, and quality of life. The first stage of the mechanical, drug therapy is to reverse ventricular remodeling. Since, mechanical pump assist devices have been shown to reduce release of biochemical agents responsible for ventricular remodeling, it is possible to accelerate restoration of normal ventricular architecture using drugs that target the biochemical and genetic processes responsible for the remodeling. [3]

4.3 Surgical Intervention Planning With Simulation Methodolgies

Aortic valve replacement is a surgical intervention by which the patient who has either (aortic valve stenosis or aortic valve regurgitation) undergoes a procedure to replace the damaged valve with an artificial one. An issue is raised on the long term durability of such valves as altered aortic root hemodynamics may induce complications such as vascular wall degeneration(through vascular remodeling mechanisms), paravavular leakage and aortic rupture . A novel approach aims at simulating fluid dynamics of an artificial heart valve, in specific geometry captured from a patient,that may undergo the surgery. And assess the new condition of hemodynamic parameters such as stress distribution and geometrical changes in comparison with healthy patient data-sets. With that it is possible to evaluate surgery decision, as well as evaluate post surgery conditions and plan accordingly[10] [1]. Furthermore, research on complex reconstructive cardio-vascular surgeries, show that the geometric conditions of the repair site, is a main factor in determining post operative outcomes, such as cardiac output[6].

4.4 Conclusion

To overview we have looked at the pathophysiology of heart failure with the underlying compensatory mechanisms that are activated. Then, we have looked at current state of clinical diagnosis and treatment methodologies. Finally, we observed how select therapeutic treatments take advantage of the complex mechanical, molecular and genetic processes with respect to clinical direction in order to solve certain

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