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AN OVERVIEW OF CONGESTIVE HEART FAILURE AND ITS NOVEL TREATMENT APPROACHES

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ABSTRACT

Congestive heart failure (CHF) is a common clinical disorder that results in pulmonary vascular congestion with reduced cardiac output and describes the inability of the heart to meet the needs of organs and tissues for oxygen and nutrients. The risk factors include coronary artery disease, myocardial infarction, hypertension, abnormal heart valves, heart muscle diseases, congenital heart disease, etc. It can also be caused due to smoking, high fat diet, lack of exercise and obesity. Although major improvements in medical and device treatments like beta blockers, Angiotensin converting enzyme (ACE) inhibitors, Angiotensin receptor blockers (ARBs), Digoxin, Device therapies, and Heart transplantation. Heart Failure (HF) remains a syndrome with high morbidity mortality, poor quality of life, high health care costs. Some of the novel treatment approaches including Cardiac contractility modulation, inter atrial stunt devices, Algisyl in the treatment of heart failure, Stem cell therapy, Omnecamtiv mecabril, Ivabradine and Sacubitril/valsartan, CHF treatment devices, Vericiguat, Neuregulin and their stages in the clinical trials were reviewed in this article. Even with the best care heart failure may be fatal and hence the novel approaches in the treatment need safety interventions and future potential.

Keywords: Congestive heart failure, Inter atrial shunt devices, Ventricular assists devices,Neuregulin, Cardiac resynchronization therapy**.**

INTRODUCTION

Congestive heart failure (CHF) is a common clinical disorder that results in pulmonary vascular congestion and reduced cardiac output failure [1]. Heart failure(HF) describes the inability of the heart to adequately meet the needs of organs and tissues for oxygen and nutrients [2,3]. CHF will also develop some other conditions when the chambers of the heart become stiff and fail to fill and or pump blood properly. The term 'congestive' relates to improperly pumped blood extremities [4]. CHF remains as single most common cause of mortality and morbidity in the developed world with as many hospitals annually treating heart failure represents a major component of the health care budget of every developed nation.[5]

Epidemiology:

HF incidence and prevalence increases with age. While 50% of patients with HF are over 75 years of age and also with an age of 61 years [6]. According to the Centers for Disease Control and Prevention (CDC), about 5.1 million people experience heart failure and about 550,000 new cases are diagnosed each year in the United States [7,8]. In India the estimated prevalence of HF is about 8-10 million individuals and the mortality is about 0.1-0.16 million people per year [9] . In Europe every year about 3.5 million people are newly diagnosed with hf. The only way of avoiding this new pandemic is through prevention, which is the collective responsibility of health care professionals [10].

Etiology:

There are many risk factors that leads to heart failure and the conditions include Coronary artery disease, Myocardial infarction, Hypertension, Abnormal heart valves, Heart muscle diseases, congenital heart disease, severe lung disease, obesity, Diabetes, Sleep apnea [11]. The Non-etiological predisposing causes have no direct cause and relationship with HF. Which includes age, sex, obesity, cardiomegaly, reduced vital capacity, cigarette smoking, proteinuria and anomalies in baseline electrocardiogram. Tobacco is also considering as a main cause for the HF [12]. Some of the Characteristic findings in children with heart failure such as like impaired cardiac function causes arrhythmias, structural heart disease, myocardial dysfunction and the Noncardiac causes of congestive heart failure include processes that increase the preload and afterload by reducing the oxygen-carrying capacity of the blood [13].

Pathophysiology of heart failure:

HF is a global problem which varies between the developed and developing world. So, the syndrome of HF is an abnormality in cardiac structure, function, rhythm, or conduction and the determinants of cardiac output includes heart rate and stroke volume. This stroke volume is further determined by the preload and afterload. These variables are important in understanding the pathophysiologic results of heart failure and possible treatments [14].

Mechanisms Involved in Heart Failure: There are a number of circulatory mechanisms in HF and both are Central, Peripheral [15].

- In Haemodynamic model, there is actually a reduction in the intrinsic contractility of cardiac muscle and it was reflected in a reduction in force development in cardio- renal model, Renal sodium and water retention are main components of the HF syndrome because it plays a critical role in the origin of dyspnea and edema. In Neuro humoural model a prolonged activation of the adrenergic nervous

system and of the renin-angiotensin-aldosterone system causes incomplete remodelling of the ventricles and further myocardial injury [16].

- The Neurohormonal Activation is by Decreased Contractility and Stroke Volume along with this there is an increased sympathetic nervous system activation and Renin-Angiotensin – Aldosterone then finally everything was increased that is System heart rate contractility, blood volume and Cardiac output [17]. There are several mechanisms which occurs as failing heart to maintain enough function and thus include increasing cardiac output via frank starling mechanism [18] . In that frank starling mechanism there is cardiac performance and increased preload. Factors affecting the mechanism are venous return, peripheral resistance for filling force and cardiac nutrition, calcium for pumping force [19].

Classification of Heart Failure:

The classification is based upon the characteristic function of the heart in diseased condition and it is shown in Table 1.

Table 1: Different types of heart failure and their characteristics shown [20]

TYPE	CHARACTERISTICS
Diastolic dysfunction	Normal myocardial contractility and diminished early diastolic filling
Systolic dysfunction	Impairement of myocardial contractility and low ejection fraction
High output heart failure	Increased cardiac output and ejection fraction
Low cardiac output syndrome	Fatigue and reduced contractility
Right heart failure	Rt-atrial and ventricular dilation and also reduced Rt-side contractility
Left heart failure	Dyspnea, pulmonary vascular congestion and reduced Lt-side contractility
Bivenricular failure	Dyspnea and bilateral reduced contractility

Clinical Manifestations:

Four major assesments for the cardiac dysfunction are Resting sinus tachycardia, Narrow pulse pressure, Diaphoresis and Peripheral vasoconstriction and three major manifestations for volume overload in patients with HF are Pulmonary congestion , Peripheral edema and Elevated jugular venous pressure [21].

Diagnostic Tests: It includes Invasive and Non-Invasive tests.

Invasive tests:

The Invasive test indicates with entering into body through fine, flexible catheters which are inserted into an artery or vein and reach the heart via the aorta or the vena cava.

Right heart catheterization is done by using Swan-Ganz catheter which can be safely pass from the femoral vein through the inferior vena cava and then through the right heart.

Left heart catheterization may include both ventriculography and a coronary angiography. This Ventriculography allows for assessing of regional left ventricular wall motion, ejection fraction, aneurysm formation and thrombus can be seen. Whereas in Coronary angiography is the "gold standard" for visualization of coronary anatomy to identify the coronary lesions, stenoses and also sometimes thrombus [22].

Noninvasive tests:

The Non-invasive indicates without entering into the body although it does not rule out the use of intravenous administered pharmacological agents. These include Chest X-Ray, Focussed Trans thoracic echo, Comprehensive Trans thoracic echo, Trans esophageal Echo, CT-Scan [23].

Guidelines from the American College of Cardiology and the American Heart Association identify four stages for progression of heart failure such as Stage A have no structural abnormalities, Stage B have structural heart disease, Stage C have structural abnormalities, Stage D have end-stage heart failure and require mechanical circulatory support for infusion of ionotropic agents, cardiac transplantation, or hospice care [24].

Laboratory tests:

Lab blood tests are important for evaluation of people with heart failure which can be helpful to identify causes of heart failure that is by the organs or through medicines. Tests includes complete blood count, Serum creatinine and albumin, Blood urea nitrogen, Brain natriuretic peptide, Urinalysis, lipid test, Liver function tests, Thyroid tests, Blood glucose levels, Electrolytes [25].

Clinical Studies with Heart Disease:

Purpose of this study was to evaluate the measurement of heart rate which was undertaken in this studies by assessing the repeatability and the ability of entire analysis of an study of heart rate measurements by various methods, conditions and also by determining whether a single heart rate measurement at rest is representative of the circadian and between subsequent days of heart rate [26] .

Novel Approaches in the Treatment of Cardiac Failure:

Although major improvements in medical and device treatments, HF remains a syndrome with high morbidity and mortality, poor quality of life, high health-care costs [27]. Generally aimed to treat the HF underlying cause- high blood pressure(BP), to reduce symptoms, to prevent further cardiac damage, and improve quality of life [25]. Multiple medical therapies, device treatments are available and it includes beta-blockers, angiotensin-converting enzyme(ACE) inhibitors and angiotensin receptor blockers, aldosterone antagonists, and combination of ARB/neprilysin blockers, ivabradine), Digoxin and device therapies [27]. Heart transplantation remains as the only option in some cases but due to shortage of donars and gravity of operation it remains as a last means of treatment [28].

Multiple treatments are available but there exists many drawbacks of existing therapies which provide the need for novel approaches and targets in the treatment of heart failure to reduce mortality and increase the life expectancy [29].

Cardiac Contractility Modulation (CCM):

In addition to the medical treatments, device therapies help in increasing the life expectancy in heart failure conditions. Although internal cardiac defibrillator (ICD) is indicated to prolong survivals in heart failure patients whereas Chronic resynchronization therapy(CRT) can improve symptoms in patients with low ejection fraction and wide QRS duration (150 ms or more.) but was not useful in patients with normal. Thus to improve function and symptoms in patients with moderate-to-severe systolic dysfunction and normal or mildly prolonged QRS duration in heart failure patients who were on optimal medical treatment(OMT), this CCM wiil be beneficial [29].

Mechanism of action:

CCM delivers a biphasic high-voltage signal to the right ventricular septum during the absolute refractory period without raising oxygen consumption, thereby improving cardiac efficiency. once the signals are generated, they cause phosphorylation of phospholamban, activation of L-type calcium channels,

restitution of the sodium/calcium exchanger, upregulation of metallomatrix proteins, and reduction in basement membrane fibrosis within minutes of initiation of signals, ejection fraction and cardiac contractility typically rise [29].

IASD-Inter atrial shunt devices:

Heart failure with normal ejection fraction accounts for ~50% of heart failure conditions. Main clinical hallmark in these patients is increased left atrial pressure, studies show that percutaneously delivered atrial devices are the novel therapeutic approach to reduce left atrial pressure and also reveal that Device insertion was associated with improved symptoms, functional capacity and a substantial drop in NTproBNP. Creation of a left–right atrial shunt with either the V-Wave or IASD seems to be safe in the mid-term and may cause symptomatic improvement in some carefully selected patients with heart failure and raised left atrial pressure(LAP). However careful attention is needed. The studies are in progress [30].

Algisyl in treatment of heart failure:

Therapeutic options for severe advanced heart failure was refractory to pharmacological therapies which were limited and the several animal studies, Computer simulations reveal that addition of non contractile material to the failing myocardium can reduce elevated myofibril stress.[28] ALGISYL-LVR is a proprietary biopolymer gel that is injected into strategic areas of left ventricular(LV) free walls.

mechanism of action:

Augment HF clinical trial reveals the long term benefits of LV augmentation with algisyl in advanced HF patients. 12 month Follow up results shows improvement in exercise capacity, increased cardiac output, functional capacity and improvement in peak Volume oxygen and increased LV functioning [31,32].

limitations:

Overall incidence of all adverse events was approximately three-fold higher for patients receiving the Algisyl device compared with patients maintained on standard medical therapy alone further future studies need to focus on this strategy.

Stem cell therapy:

Advances in understanding of molecular basis for myocardial dysfunction along with improvements in gene technology, there is a tremendous increase in the application of gene based therapy in heart failure conditions [33] .Even with the optimum medical therapy of the heart failure condition is often fatal which supports regenerating heart tissue as an ideal option for the phase I clinical trial showed good results by using patients own thigh muscle cells in making patches and glued on to the surface of heartmuscle. [28,34].

In the phase III clinical trials of autologous stem cells was launched for successful progression in future gene therapies. The targets for gene therapy include beta adrenergic system, calcium channel cycling pathway, and cytokine mediated cell proliferation [34].

Ixmyelocel-T is an expanded, muticellular therapy using CD 90+ mesenchymal stem cells and CD 45+ CD 14+ autofluoroscent + macrophages. Early clinical phases of this therapy has shown improvement in clinical, symptomatic, functional and quality of life outcomes in HF associated with ischemic dilated cardiomyopathy [35].

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Two new Drugs (Ivabradine and Sacubitril/Valsartan) for HF:

The American Heart Association and Heart Failure Society of America have added Corlanor (ivabradine) and Entresto (sacubitril/valsartan) medications. The Ivabradine works by slowing the heart rate while Sacubitril/Valsartan works to relax blood vessels, allowing better blood flow and decreases the productive stress on heart. Therefore, adding Corlanor to beta blocker therapy can better control heart rate and help prevent hospitalizations. Entresto represents an evolution in heart failure treatment and what was formerly considered part of the foundation in treating heart disease and heart failure is by the use of angiotensin-converting enzyme, or ACE- inhibitors. Recent compelling data demonstrate that if you treat patients in a traditional manner with therapy, which includes the ACE inhibitor, and then replace that ACE inhibitor with this new combination, remarkably, patients don't just do a little bit better, they do substantially better [39].

New treatment for HF by removing excess of fluid from lymphatic system:

In the Ohio State of US, a new treatment study was done for hf patients. Generally, Edema is the major symptom for the heart failure and this lymphatic system typically drains up to two gallons of fluid per day. Catheter was inserting internally into lymphatic system and this device is placed in the neck and the treatment continues at the bedside using a machine that helps circulate some of the blood, with the help of a diuretic medication which bypasses the kidneys and filters water and salt from the body. However, these treatments can have unwanted side effects such as low blood pressure and worsening kidney function [40].

HF treatment devices:

Mechanical therapies and surgical interventions are more commonly adopted treatments by physicians in hospitalization cases but these devices used for the treatment of congestive heart failure includes Implantable Cardioverter Defibrillators (ICD) consists of a Subcutaneous ICD and Transvenous ICD. The cardiac resynchronization therapy (CRT) consists of CRT- Pacemakers and CRT-defibrillators whereas for the ventricular assist devices (VADs) consist of Right and left VAD's [41] .

Vericiguat in patients with worsening HF:

Study called as Socrates study which was Soluble by the guanylate Cyclase stimulator in HF patients with an preserved ejection fraction to determine tolerability and optimal dose regimen. Randomized, placebo-controlled double-blind and Phase2b dose-finding study were done in patients with Heart failure preserved Ejection fraction. Vericiguat was well tolerated just did not change NT-proBNP and LAV at 12 weeks compared with placebo but associated with improvements in quality of life in patients with Heart failure preserved Ejection fraction (HFpEF). Effects of vericiguat in patients with HFpEF warrant further study possibly with higher doses, longer follow-up and additional endpoints. Clinical Summary Score was improved in the vericiguat 10 mg arm by mean 19.3 ± 16.3 points [median 19.8 (interquartile range 10.4–30.7)] from baseline (mean difference from placebo 9.2 points) [42].

Neuregulin – heart failure therapy:

The beta isoform of Neuregulin-1(NRG-1β) as a heart failure therapy and mediator of reverse modeling along with its receptors (ErbB2-4) for cardiac development. NRG-1β, as well as the ErbB2 and ErbB4 receptors are also essential for maintenance of adult heart function.

Animal studies and ongoing clinical trials have demonstrated beneficial effects of two forms of recombinant NRG-1β on cardiac function as heart failure therapies, endogenous NRG-1β/ErbB signaling

appears to play a role in restoring cardiac function after injury.NRG-1β acts on the vasculature, interstitium, cardiac fibroblasts, hematopoietic and immune cells. Clinical trials evaluate two isoforms of NRG-1β as a possible therapy for cardiovascular disease. We will review and advance the hypothesis of endogenous NRG-1β is a mediator of reverse remodelling. NRG's role as a regulator of progenitor cell populations and as an adjunct in regenerative therapies also warrants further investigation. The ongoing program examining the clinical translation of recombinant NRGs promises to further light up the role and potential of multipotent growth factor [43].

Conclusion:

CHF was proven to be the vital cause of mortality in the developed nations. Clinicians and investigators are now considering many novel treatment approaches to improve the quality of life in HF patients. The new upcoming research needs special focus on detailed pathophysiology, co morbidities of HF and limitations of novel treatment approaches.

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