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Review Article

Pathophysiology and Management of Chronic Heart Failure

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Abstract: Chronic heart failure refers to a clinical state of systemic and pulmonary congestion resulting from inability of the heart to pump as much blood as required for the adequate metabolism of the body. The commonest causes of heart failure are coronary artery disease, hypertension and diabetes, however, hypertension and diabetes have been found to be stronger risk factors in elderly women and coronary artery disease and smoking are stronger risk factors in elderly men. Pathophysiologically, heart failure is either an inadequate cardiac output for the organism's metabolic demands or an adequate cardiac output that is due to neurohormonal compensation, which means the inability of the heart to supply blood to the tissues according to their needs without additional strain. The pharmacological treatment of chronic heart failure with reduced ejection fraction is now based on four classes of drugs that have been proven to reduce mortality among heart failure patients such as angiotensinogen converting enzyme inhibitors or angiotensin II receptor blockers, beta-blockers, aldosterone antagonists and sodium-glucose co-transporter 2 inhibitors. Angiotensinogen converting enzyme inhibitors or angiotensin II receptor blocker therapy should be initiated at a low dose with very gradual up titration, monitoring renal function and serum potassium levels closely. Chronic heart failure treatment with direct inhibitors of aldosterone receptors brought about a significant improvement in terms of survival and hospitalizations.

Keywords: Chronic heart failure; Pathophysiology; Management.

INTRODUCTION

Chronic heart failure, a clinical syndrome in which abnormalities of ventricular function and neurohormonal regulation lead to pulmonary venous congestion, exercise intolerance, and decreased life expectancy, remains the one major cardiovascular disorder that has increased both in incidence and prevalence in recent years [1]. Chronic heart failure (CHF) induces change in the molecular architecture of the myocardium. Consequently, contractility and synchronicity of systolic and diastolic function are compromised, posing significant problems when metabolic demand is increased. Optimal cardiac function during exercise is dependent on an ability to increase heart rate and contractility, to compensate for decreased filling time of the left ventricle, which ultimately reduces stroke volume [2, 3]. Heart failure affects around 26 million people worldwide and around 50% of patients die within 5 years of diagnosis [4]. A broad array of biological pathways contributes to the development and progression of heart failure (HF), including neuro-hormonal and remodeling mechanisms. In addition to being a syndrome encompassing activation of cardiovascular disease-related mechanisms, heart failure may also be viewed as a systemic disorder with alterations to metabolism, immune response, haemostasis/ fibrinolysis, and iron homeostasis [5-7]. Chronic heart failure (CHF) is a significant and growing health-care challenge, as increasing numbers of people live longer and survive ischaemic heart disease [8]. Heart failure is characterised by cardiomyocyte energy depletion due to mitochondrial dysfunction and adenosine triphosphate depletion, leading to abnormal calcium handling and impaired contractile function [9]. One of the most prevalent diseases worldwide is chronic heart failure (CHF). It is linked with low quality of life and notable morbidity/mortality [10, 11]. Chronic heart failure (CHF) incidence and prevalence increases with age. Heart failure (HF) is a leading cause of hospitalization and accounts for approximately 7% of cardiovascular deaths [12]. Currently, approximately 64.3

million people in the world are suffering from cardiac insufficiency; its increase in incidence over the past three decades could be assigned to significant changes in the demographics of the world population, HF management, and the incidence and survival of illnesses predisposing to HF [13-15].

Etiological factors

The commonest causes of HF are coronary artery disease (CAD), hypertension and diabetes, however, hypertension and diabetes have been found to be stronger risk factors in elderly women and CAD and smoking are stronger risk factors in elderly men. The concomitant diseases such as atrial fibrillation, valvular heart disease, diabetes, chronic kidney disease, arrhythmias, anemia, chronic obstructive pulmonary disease (COPD), depression, thyroid pathologies, congenital cardiomyopathies, inflammatory diseases and excessive alcohol intake, obesity, arthritis, sensory impairment, and cognitive dysfunction substantially add to the complexity of HF care. It has been shown that 2/3 of elderly patients with HF have more than two non-cardiac co-morbidities and over 25% of them have more than six comorbidities [16-18].

Pathophysiology

Heart failure (HF) is the pathophysiological state in which the heart is unable to pump blood at a rate commensurate with the requirements of metabolizing tissues, or can do so only from an elevated filling pressure. A complex series of neurohormonal changes takes place as a result of the two principal haemodynamic alterations occurring in this condition: reduction of cardiac output and atrial hypertension. In the early stages of acute systolic failure, these changes are heightened adrenergic drive, activation of the renin angiotensin aldosterone axis, and augmented release of vasopressin and endothelin are truly compensatory, maintaining perfusion to vital organs and increasing the inadequate arterial blood volume. As HF becomes chronic, several of these compensatory mechanisms can cause undesirable effects such as excessive vasoconstriction, increased afterload, excessive retention of salt and water, electrolyte abnormalities, and arrhythmias [19-21]. Exercise intolerance at both maximal and submaximal effort is the hallmark of progressive heart failure, and it is associated with worsened quality of life and increased risk of adverse clinical outcomes. Two extracardiac factors ("peripheral factors") abnormal metabolic vasodilation in skeletal muscle and abnormal skeletal muscle substrate use in the pathogenesis of exercise intolerance at maximal and submaximal effort in patients with chronic systolic heart failure have its role [22, 23]. Submaximal exercise endurance capacity is determined by factors that link oxygen delivery, substrate use, and ventilation in response to increased metabolic demand during exercise. In patients with chronic systolic heart failure, available evidence suggests that submaximal exercise is limited not by reduced nutritive blood flow, but rather by impaired substrate use in skeletal muscle. Patients with chronic heart failure demonstrate reduced percentage of type I (oxidative slow-twitch) muscle fibers, reduced skeletal muscle aerobic enzyme activity, reduced skeletal muscle mitochondrial volume density, reduced skeletal muscle mass, and reduced skeletal muscle mitochondrial oxidative capacity independent of nutrient blood flow when compared with control populations. Endurance performance at submaximal exercise levels is determined by the efficiency of mitochondrial conversion of oxygen to adenosine triphosphate and efficiency of the conversion of adenosine triphosphate to physical work. Decreased work efficiency during submaximal exercise has been reported in subjects with chronic systolic heart failure when compared with control subjects without heart failure [24-27].

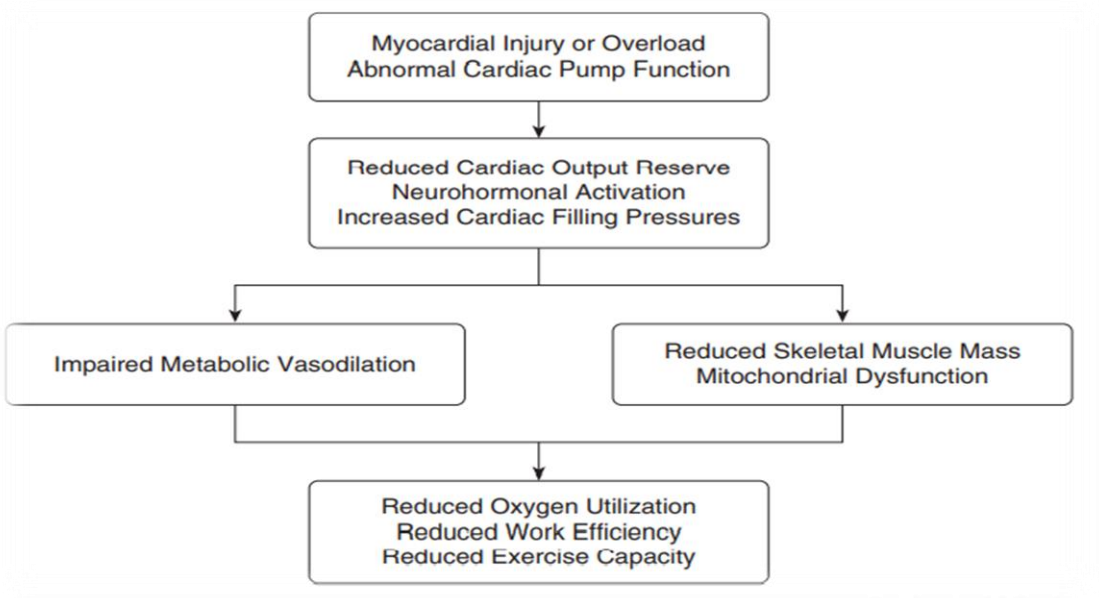

Figure 1: Pathophysiology of exercise intolerance in patients with chronic systolic heart failure

A combination of hemodynamic factors related to impaired cardiac pump function (reduced cardiac output reserve, neurohormonal activation, and increased cardiac filling pressures) and extracardiac factors that limit skeletal muscle oxygen use (impaired metabolic vasodilation, reduced skeletal muscle mass, and mitochondrial dysfunction) contribute to impairment of both submaximal and maximal exercise capacity in patients with chronic systolic heart failure.

Excess interstitial fibrosis is an important detrimental aspect of chronic LVH and chronic heart failure (CHF). Oxidative stress is well known to be pro-fibrotic in many organs, and recent work suggests that nicotinamide adenine dinucleotide phosphate 2 (Nox2) oxidase-derived ROS are centrally involved in the development of interstitial cardiac fibrosis. A similar inhibition of interstitial fibrosis was found in a model of aldosterone infusion, either in Nox2 knockout mice or in animals treated with nicotinamide adenine dinucleotide phosphate (NADPH) oxidase inhibitor, apocynin. Interstitial cardiac fibrosis was also inhibited in Nox2 knockout mice subjected to aortic banding. Multiple underlying mechanisms are likely to be involved in these Nox2-dependent pro-fibrotic effects, including increased expression of pro-fibrotic growth factors and genes, increased activation of nuclear factor KB (NF-kB), activation of matrix metalloproteinases, and inflammatory cell infiltration [28, 29]. Cytokines form a vast array of relatively low molecular weight, pharmacologically active proteins. These substances are secreted by different cell types for the purpose of altering either their own function (autocrine) or that of adjacent cells (paracrine). The most important cytokines implicated in the progression of CHF are tumour necrosis factor a (TNFa), interleukin (IL) 1, and IL-6. These cytokines share some of their major characteristics (redundancy), and all act in a proinflammatory sense [30].

Nitric Oxide

Nitric oxide (NO) is a lipophilic, freely diffusible, soluble gas, which has a short half-life of less than four seconds in biological solutions. Its nearly ubiquitous involvement has resulted in an explosion in the NO field in the last years. NO is produced from the amino acid L-arginine by nitric oxide synthase (NOS), and it reacts with O2 in aqueous solutions yielding the relatively inert nitrate ($NO3_2$) and nitrite ($NO2_2$). However, NO also reacts with oxygen derived free radicals, namely superoxide anion, to form the toxic peroxynitrite ($ONOO_2$). NO is produced by a group of well characterised isoforms of nitric oxide synthase (NOS). Three isoforms have been identified. (1) The endothelial (constitutive) isoform (cNOS, also known as NOS_3) produces a continuous amount of NO, which acts as a vasodilator. In endothelial cells, cNOS is mainly found in the membrane of caveolae, small invaginations, which are characterised by the presence of a marker protein termed caveolin. After synthesis in the endothelium, NO diffuses across the cell membrane and enters vascular smooth muscle cells to induce muscle relaxation [31, 32].

Tumour necrosis factor a

TNFa is associates observed that mean (SEM) serum concentrations of TNFa were higher in CHF patients than in healthy subjects. They also demonstrated that those patients with high concentrations of TNFa were more often suffering from cardiac cachexia. TNFa exerts its effects via TNFa receptors (TNFR), which are expressed by almost all nucleated cells. Two TNFRs have so far been identified. TNFR-1 is more abundantly expressed and appears to be the main signalling receptor. The majority of deleterious effects caused by TNFa seem to be mediated via this receptor, whereas TNFR-2 appears to have a more protective role in the heart. Proteolytic cleavage by TNFa converting enzyme (TACE) yields the soluble forms. The role of soluble TNFRs is sometimes to stabilize the TNFa molecule, thus potentiating its detrimental long term actions. However, higher concentrations of TNFRs appear to inhibit TNFa activity. It is thought that high plasma concentrations of soluble TNFRs primarily indicate a history of raised TNFa values. The reproducibility of plasma concentrations of soluble TNFRs is higher than that of TNFa itself. This may be the reason why soluble TNFRs predict short term and long term prognosis better than TNFa in CHF patients [33-35].

Natriuretic Peptides

Both are released in response to pressure or volume overload means ANP and BNP plasma concentrations are elevated in patients with heart failure. It balances the effects of the RAAS by causing natriuresis, diuresis, vasodilation, decreased aldosterone release, decreased hypertrophy, and inhibition of the SNS and RAAS [34].

C Reactive Protein

C reactive protein (CRP) was so named because it reacts with the somatic C polysaccharide of Streptococcus pneumoniae. CRP specifically binds to specific microbial polysaccharides (phosphocholine moieties), which gives this substance a host defensive role. Upon binding to these structures, CRP activates the classical complement pathway and opsonises ligands for phagocytosis. CRP is exclusively produced in the liver. It is secreted in increased amounts within six hours of an inflammatory stimulus and is therefore regarded as a marker of acute inflammation [36].

Renin- angiotensin aldosterone system

The RAA system is activated in patients with heart failure. Similar to the sympathetic nervous system, initial activation may be important to maintain cardiac output in a damaged heart by increasing preload through sodium

retention and volume expansion. Perfusion also may be maintained by vasoconstriction [37]. Angiotensin II Effects of ATII are mediated by the activation of specific angiotensin receptors, AT1 and AT2. Both receptors have high affinity for ATII but are functionally distinct. They are located throughout the body including the kidneys, brain, endothelium, and heart. Binding of ATII to AT1 and AT2 receptors may produce biologic effects that may be important to the pathophysiology of heart failure. The AT1 receptor-signaling pathway interacts with both adenylate cyclase and the G protein system. Stimulation of the AT1 receptor causes activation of several phospholipases, leading to an increase in inositol 1,4,5 triphosphate, which stimulates intracellular calcium release and vasoconstriction [38-40].

Aldosterone

Aldosterone may play a significant role in the pathophysiology of heart failure that goes beyond sodium and water retention. Circulating or plasma concentrations of aldosterone are produced in the adrenals. Angiotensin II stimulation of the AT1 receptor increases aldosterone secretion, although other mechanisms also may do this, such as plasma potassium, adrenocorticotropic hormone, and endothelin, and decreased metabolic clearance [41].

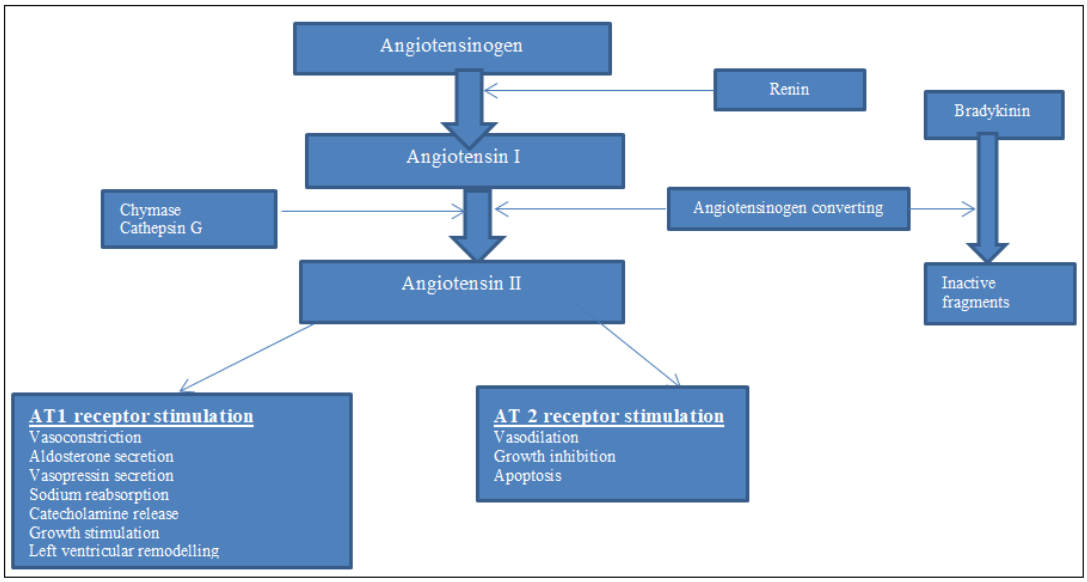

Figure 2: The mechanism by which renin-angiotensin-aldosterone system cause heart failure

Diagnostic Criteria

Heart failure is usually associated with dyspnoea, fatigue, and fluid retention. Symptoms alone cannot be relied on in making the diagnosis: a careful history and physical examination need to be supplemented by further tests. Diagnosis requires consideration of the underlying abnormality of the heart, the severity of the syndrome, the aetiology, the precipitating and exacerbating factors, the identification of concomitant disease relevant to management, and an estimation of prognosis. The following investigations should be carried out in a patient with suspected heart failure: Twelve lead electrocardiography (check chamber hypertrophy, low-voltage QRS morphologic characteristics with ST-T wave abnormalities may suggest myocardial inflammatory disease or pericarditis) ; Chest radiography (check cardiac enlargement, increased pulmonary vascular bed); Blood biochemistry (including urea, creatinine, glucose, electrolytes), haemoglobin, thyroid and liver function tests, and blood lipids; Urinalysis to detect proteinuria or glycosuria; Cardiac imaging usually a transthoracic echocardiogram, which can rapidly provide detailed information about the structure and function of the cardiac chambers, valves, and pericardium; Hyponatremia: serum sodium <130 mEq/L; Serum creatinine may be increased due to hypoperfusion [42, 43].

HF classification

Many clinical classification systems have been proposed to classify severity of HF and guide patient management. The most popular system is the New York Heart Association (NYHA) classification that ranges from essentially asymptomatic patients (NYHA I) to mild (NYHA II, slight limitation in physical activity), moderate (NYHA III, symptoms on light exercise) and severe HF (NYHA IV, breathless at rest. The staging system is meant to complement, not replace, the widely used New York Heart Association (NYHA) classification, which is organized according to severity of symptoms. The latter remains useful because severity of symptoms has a robust correlation with survival and quality of life [44].

Table 1: NYHA classes focus on exercise capacity and symptoms of HF

NYHA class	Degree of clinical impairment
I	No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue and palpitations
II	Slight limitation of physical activity. Comfortable at rest but, ordinary physical activity results in undue breathlessness, fatigue and palpitations
III	Marked limitation of physical activity. Comfortable at rest but, less than ordinary physical activity results in undue breathlessness, fatigue and palpitations
IV	Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken discomfort is increased

The updated ACC/AHA guidelines for evaluating and managing HF include a new, four-stage classification system emphasizing the progression of the disease. The new guidelines include patients with "preclinical" stages of HF with the hope of slowing (and perhaps reversing) progression of disease. The ACC/AHA classification system recognizes the progressive course of HF and identifies those at risk, reinforcing the importance of neurohormonal antagonism in an attempt to arrest disease progression [45].

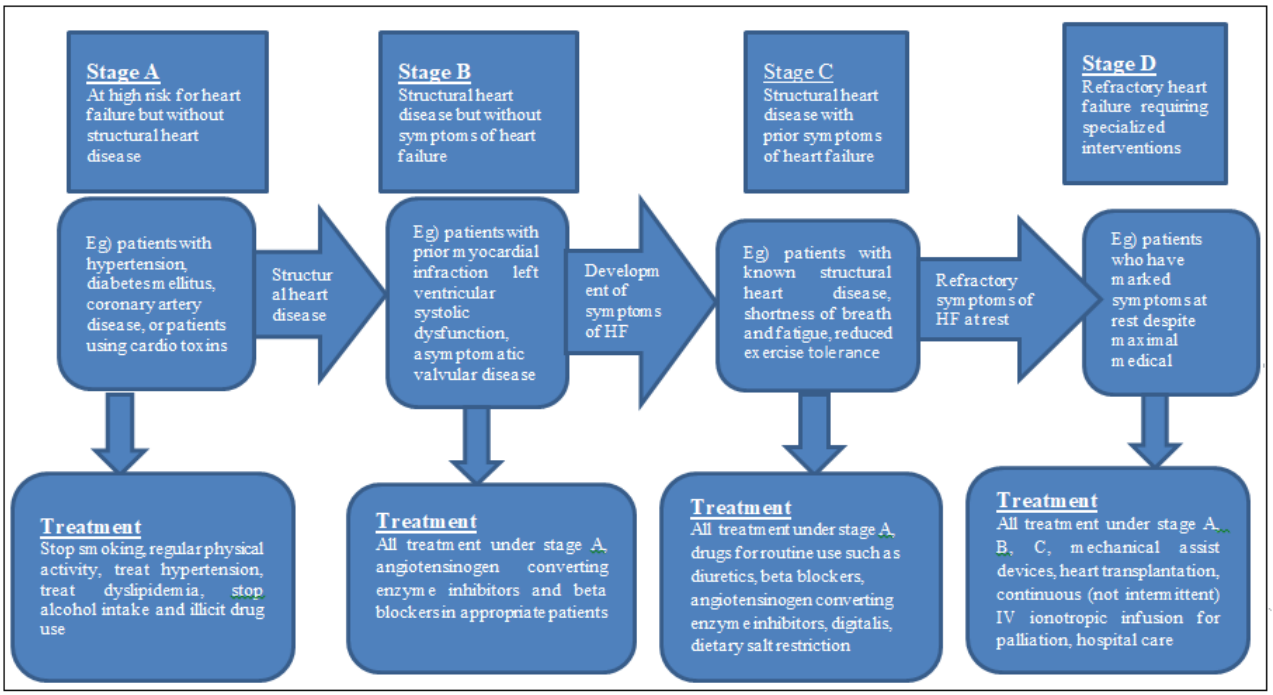

Figure 3: Stage and treatment of chronic heart failure

Management

Modern treatment aims to control symptoms and prolong life by blocking the neurohormonal activation and controlling the fluid retention. Goal of therapy are improve quality of life, relieve or reduce symptoms, treating underlying cause, prevent or minimize hospitalizations, slow disease progression, and prolong survival [46].

Lifestyle management

Lifestyle changes can have an important impact. Ready to cook meals and convenience foods contain large amounts of salt and may increase the dose of diuretic needed to control fluid retention. All patients should be discouraged from adding salt to their food and should try to reduce the amount of salt they add during cooking. Severe salt restriction (< 2 g/day) is rarely necessary. Regular aerobic exercise should be encouraged, as it improves peripheral muscle function and exercise tolerance in patients with heart failure. If alcohol is the cause of the heart failure then abstinence is essential. Smoking cessation should be encouraged. Restrictions on activities within the context of the specific diagnosis and the patient's ability, cardiac rehabilitation, restriction of fluid and sodium intake, infection prevention, weight monitoring and competitive and strenuous sports activities are usually contraindicated [47]. Self-management is integral to achieving best patient outcomes: to reduce mortality and improve quality of life. Self-management in CHF usually involves behavioural adaptation. Patients may need to learn new behaviours, such as learning how to monitor and manage symptoms and complex medical regimens. Patients may also need to abstain (e.g. cease smoking), adapt (e.g. restrict

their sodium, cholesterol and fluid intake) and maintain (e.g. exercise regularly) other behaviours. While targets have been recommended for best CHF management practice (such as to restrict fluid to 1.5 litres per day and to monitor weight changes > 2 kgs over three days), these need to be individualized according to the patient symptom and disease status profile and reset regularly [48].

Pharmacological Treatment

Pharmacology needs to be carefully selected for a multitude of reasons. First, there are physiological age-related changes that influence drug pharmacokinetics and pharmacodynamics. Ageing is also associated with a change in body composition, which results in a lower volume of distribution and higher plasma concentrations of hydrophilic drugs, while the plasma concentrations of lipophilic drugs tend to decrease. Second, these patients often have multiple other co-morbidities which increases the risk of drug side effects (renal, liver dysfunction, orthostatic hypotension) and conflicts with HF treatment guidelines e.g., angiotensin-converting enzyme inhibitors (ACEI) with orthostatic hypotension. The presence of cognitive impairment makes treatment compliance more challenging and is a marker of poorer outcome. Polypharmacy also increases the risk of drug-drug interactions. Patients with CHF, on average take 10 medications with significant risk for adverse drug reactions. Third the presence of social and economic issues, frailty and caregiver burden needs all to be taken into account when choosing a plan management. The pharmacological treatment of chronic HFrEF is now based on four classes of drugs that have been proven to reduce mortality among HF patients such as ACE inhibitors or angiotensin II receptor blockers (ARBs), beta-blockers, aldosterone antagonists and odium-glucose co-transporter 2 (SGLT-2) inhibitors (SGLT2-inhibitors) [49-53].

Diuretics

Mechanism of actions: Decrease reabsorption of water and sodium by the kidney; decrease circulating blood volume; decrease pulmonary fluid overload and ventricular filling pressure.

Diuretics have been found to be of major importance for symptomatic treatment and maintenance of euvolemia. Diuretics are the most effective means of removing fluid retention, and their introduction often produces rapid symptomatic relief. Diuretics should be prescribed in all patients with symptoms/signs of pulmonary or systemic congestion. The mainstay for managing the symptoms of fluid overload is diuretics. Loop diuretic inhibit a specific ion transport protein, the Na+-K+-2Cl- symporter on the apical membrane of renal epithelial cells in the ascending limb of the loop of Henle [54, 55].

Angiotensinogen converting enzyme inhibitors/Angiotensin II receptor blockers

ACEIs have cardiac remodeling function independent of after load reducing effect, reduced morbidity and mortality in adult patients and aldosterone reducing effect which decrease in retention of sodium and water. ACE inhibitors improve symptoms, slow disease progression, and decrease mortality in patients with HF and reduced LVEF. ACE inhibitors should also be used to prevent the development of HF in at-risk patients. ARBs are used only in patient's stage A, B, or C HF who are intolerant of ACEIs. Candesartan and valsartan are FDA-approved for HF and are the preferred agents. ACEI or angiotensin receptor blocker (ARB) therapy should be initiated at a low dose with very gradual up titration, monitoring renal function and serum potassium levels closely. CHF treatment with direct inhibitors of aldosterone receptors brought about a significant improvement in terms of survival and hospitalizations. Small increases in the serum creatinine level (0.5 mg/mL) do not mandate discontinuation of ACEI or ARB but should prompt careful assessment of volume status and consideration of a reduction in diuretic dosages [56-58].

Beta-blockers

β-blockers slow disease progression, decrease hospitalizations, and reduce mortality in patients with HF. use of β-blockers in all stable patients with HF and a reduced LVEF in the absence of contraindications. β-Blockers are also recommended for asymptomatic patients with a reduced LVEF (stage B) to decrease the risk of progression to HF. β-blockers should be started in very low doses with slow upward dose titration. Metoprolol CR/XL, carvedilol, Nebivolol and bisoprolol are the only β-blockers shown to reduce mortality in large HF trials. Beta-blockers have shown to improve survival by 26% and 49% (low dose and high dose respectively) if added to an ACEI by improving LV function [59].

Digoxin

Mechanism of actions: Inhibition of the sodium-potassium adenosine triphosphatase (NA^+/K^+ ATPase) pump-rise in intracellular calcium (Ca^{++}) and sodium (NA^+) coupled with the loss of intracellular potassium (K^+), increased force of myocardial muscle contraction net positive inotropic effect, increases the automaticity of Purkinje fibers but slows conduction through the atrioventricular (AV) node. Digoxin has positive inotropic effects, but its benefits in HF are related to its neurohormonal effects. Attenuates the excessive SNS activation and Improving impaired baroreceptor function. Digoxin does not improve survival in HF patients. Digoxin is indicated as an adjunct for rate control in atrial fibrillation and for HF with advanced systolic dysfunction as an inotropic agent in New York Heart Association (NYHA) class III or IV. While it may improve function and quality of life, it does not impact survival [60].

Spironolactone

There are benefits to the use of aldosterone antagonists for treatment of systolic HF. Low doses (not more than 25 mg/d) are recommended in patients with severe systolic HF without significant renal dysfunction [contraindicated in chronic kidney disease (CKD) stage 4 and 5 not on dialysis]. Inhibits aldosterone and enhances potassium retention, dose is 2-3mg/kg/24hrs in 2-3 divided doses and improve survival in patients with advanced heart failure *via* a mechanism that is independent of diuresis [61, 62].

Statins

Statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) block the rate limiting step in cholesterol biosynthesis in the liver and other tissues. These drugs are administered orally, are well tolerated, and generally safe. It has been reported that statins can improve the prognosis of coronary artery disease irrespective of serum cholesterol values, which gave rise to the idea that effects beyond cholesterol lowering so called pleiotropic effects exist. Indeed, some substances from this group have been shown to improve endothelial function by inducing cNOS gene transcription. Some statins might be able to reduce vascular production of reactive oxygen species. Moreover, statins have been found to reduce C reactive protein values after myocardial infarction and in hypercholesterolaemia. Moreover, statins might decrease the production of TNFa, IL-1, and IL-6 from macrophages [63, 64]. Quality of life and exercise capacity increased significantly in the statin-treated patients. In addition, there was a trend towards increased LVEF and improved endothelial function [65].

B-type natriuretic peptide

The cardiac-derived natriuretic peptide BNP and its related peptides may be such markers. Given that myocardial stretch stimulates BNP production and release, that the heart is the major source of BNP, and that BNP can easily be measured in plasma, there is a straightforward rationale for evaluating circulating BNP as a biomarker for cardiac overload [66].

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors (Empagliflozin) has glucuretic, diuretic and natriuretic properties, which means that through SGLT inhibition, it decreases blood glucose, causes osmotic diuresis and reduces sodium load. Approximately 80 g of glucose is excreted every day due to SGLT2 inhibition if the patient maintains normal renal functions. As SGLT2-inhibitors work in the proximal tubules, they increase the delivery of fluid and electrolytes to the macula densa, which activates tubuloglomerular feedback leading to afferent glomerular arteriole vasoconstriction. This result in a reduction in intraglomerular hypertension, diminishes glomerular hyperfiltration, attenuates albuminuria and thereby decelerates the progression of diabetic as well as non-diabetic chronic kidney disease. Although a decrease in eGFR may be initially observed during empagliflozin treatment, it is followed by stabilization after a longer period of time. Empagliflozin treatment is associated with many beneficial effects, such as weight loss despite increased food intake, largely due to body fat loss, improvement of endothelial dysfunction and arterial stiffness, reduction in blood pressure in diabetic patients and alleviation of the early signs of nephropathy in diabetic animal models; on the other hand, empagliflozin preserved body weight in models of type 1 diabetes. Patients with type 2 diabetes were observed to have lost weight and reduced their blood pressure, as well as improved glycemic control after undergoing empagliflozin treatment in monotherapy or as an addition to other medication [67-70]. Empagliflozin causes osmotic diuresis and reduces both intravascular and interstitial volume; thus it can cause symptomatic hypotension, especially in patients on hypotensive drugs, the elderly, patients with renal impairment and patients with low systolic blood pressure. SGLT2-inhibitors may interact with loop diuretics commonly used in patients with HF; thus, an adjustment of doses is required [71].

Nitrates and hydralazine

Reduce systemic vascular resistance (SVR) and increase stroke volume and cardiac output. They also provide additional benefits by interfering with the biochemical processes associated with HF progression. Improve mortality, hospitalizations for HF, and quality of life in African-Americans who receive standard therapy. The combination is also appropriate as first-line therapy in patients unable to tolerate ACEIs or ARBs [72].

Alpha and beta adrenergic agonists

They are usually given in an intensive care setting. Long term use may increase morbidity and mortality

Dopamine: β agonist predominantly but has α agonist effect at higher doses. Less chronotropic and arrythmogenic and selective renal vasodilation

Dobutamine: Dopamine derivative, have direct inotropic effect and moderate reduction of PVR. It can be used in adjunct with dopamine eliminate vasoconstrictive effect and less risk of rhythm disturbance [73].

Cardiac Surgery

Heart transplantation can transform a very sick patient, but owing to the shortage of donor organs and the general level of comorbidity in many patients with heart failure this is not an option for the vast majority. Xenotransplantation using a genetically modified pig heart remains a distant prospect. The design of implantable mechanical assist devices is improving, and these provide a "bridge" to transplantation or may tide a patient over until recovery from myocarditis. Some patients have survived several years with such devices [74].

CONCLUSION

Chronic heart failure (CHF) incidence and prevalence increases with age. Heart failure (HF) is a leading cause of hospitalization and accounts for approximately 7% of cardiovascular deaths. The pathophysiology of chronic systolic heart failure is fundamentally determined by the failure of the circulatory system to deliver sufficient oxygen for metabolic needs, and it is best explained by a complex interplay between intrinsic abnormalities of ventricular pump function and extra cardiac factors that limit oxygen use in metabolically active tissues. Modern treatment aims to control symptoms and prolong life by blocking the neurohormonal activation and controlling the fluid retention. Diuretics have been found to be of major importance for symptomatic treatment and maintenance of euvolemia. Diuretics are the most effective means of removing fluid retention, and their introduction often produces rapid symptomatic relief.

Abbreviations

ACEI: Angiotensinogen converting enzyme inhibitors; ARB: Angiotensin receptor blocker; BNP: B-type natriuretic peptide; CAD: Coronary artery disease; CHF: Chronic heart failure; COPD: Chronic obstructive pulmonary disease; eGFR: Estimated glomerular filtration rate; HFrEF: Heart failure with reduced ejection fraction; IL: Interleukin; LVH: Left ventricular hypertrophy; LVEF: Left ventricular ejection fraction; NF-KB: Nuclear factor-kB; NYHA: New York Heart Association; NADPH: Nicotinamide adenine dinucleotide phosphate; iNOS: Inducible nitric oxide synthase; ROS: Reactive oxygen species; SGLT2-inhibitors: Sodium-glucose co-transporter 2 (SGLT-2) inhibitors; TNFa: Tumour necrosis factor a;

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