Heart Failure: Past, Present, Future
Karki DB,1 Bhattarai TR,2 Rayamajhi A3

ABSTRACT
There are 23 million people with heart failure in the world. Heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) need to be identified before advising treatment of heart failure. Coronary artery disease, dilated cardiomyopathy, valvular heart disease, and hypertension are the common causes of heart failure. Diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and nephrilysin receptor blockers have been found to reduce mortality in heart failure. Natural compensatory mechanisms such as release of various vasoconstrictors and vasodilators in heart failure come into action to improve symptoms for some time. Ultimately compensatory mechanisms fail to work and patients reach end-stage heart failure. Mechanical circulatory support devices are recommended as a bridge treatment before heart transplant. The only option at this stage is heart transplant which is not feasible easily in the low and middle-income countries. Though end-stage heart failure treatment with inotropic drugs improves symptoms for a short period, various trials have shown increased mortality with their uses. On-going research on heart failure is expected to come out with more effective treatment of heart failure in future.

KEY WORDS
Cardiac output, Cardiac transplant, Heart failure

INTRODUCTION
Foxglove or Digitalis purpurea was first used to treat swelling of the legs due to congestive heart failure by Scottish physician William Withering in 1785.1 Digitalis and diuretics were the only treatment for heart failure in the past. Digoxin is still used in the treatment of atrial fibrillation and heart failure. Though it can decrease heart rate and hospitalization, it does not seem to have mortality benefit. Digitalis Investigation Group (DIG) has shown that digoxin has no mortality benefit.2 Currently, digoxin has a class IIa indication in the ACC/AHA (American College of Cardiology/American Heart Association) 2013 heart failure guidelines but class IIb indication in the European society of cardiovascular heart failure guidelines.3,4 Heart rate control with digoxin in hypotensive heart failure patients may be considered as beta-blockers can not be given in hypotension and verapamil or diltiazem have negative inotropic effects. Digoxin has an inotropic property and acts by inhibiting the sodium-potassium adenosine triphosphatase pump and preventing the transport of sodium from the intracellular to the extracellular space. This in turn raises the intra-cellular calcium by decreasing its efflux resulting in the inotropic action of digoxin. Worsening of symptoms of heart failure on stopping digoxin has been shown by Randomized Assessment of Digoxin on Inhibitors of Angiotensin-Converting Enzyme (RADIANCE) trial.5

Many effective pharmacological and non-pharmacological treatments have been introduced to treat heart failure at present. Despite the recent advances in the treatment of heart failure, patients do not seem to have a good prognosis. Millions of people die of heart failure every year worldwide.6 Scientists could be expected to invent a curative treatment of heart failure in the future. Such a treatment would make cardiac muscle work normally and help patients to live a long and healthy life. Studies are being carried out in pigs on gene therapy and Intra-cardiac injection of bone marrow stem cells. Gene packed in engineered viruses are injected into the artery. Gene is expected to regulate cardiac proteins in heart failure and improve myocardial contraction. Regeneration of cardiac muscles could be achieved in the future.
The prevalence of heart failure has been estimated to be 23 million in the world. People with heart diseases live longer because of the effective modern treatment and as a result of this, the prevalence of heart failure has increased in recent years. According to a Framingham study, the prevalence of heart failure in men is 8 per 1000 at age 50 to 59 years, to 66 per 1000 at age 80 to 89 years. These prevalence rates indicate that heart failure is common with increasing age.7

The prevalence of heart failure mentioned here is of symptomatic patients and does not include left ventricular dysfunction only. Left ventricular dysfunction as indicated by left ventricular ejection fraction (LVEF) of ≤ 40 percent is also called systolic heart failure but only 50 % of such patients are symptomatic.8 Fifty percent of patients with heart failure have diastolic dysfunction with preserved systolic function (LVEF ≥ 50%).9 Prevalence of heart failure with preserved left ventricular ejection fraction increases with increasing age and is more common in women.10-12

According to the Framingham study, at age 40, the lifetime risk of developing heart failure for both gender is one in five.13 Mortality from heart failure with preserved left ventricular systolic function (HFpEF) is 30 percent lower than that of heart failure with reduced left ventricular systolic function (HFrEF).14

Definition
Heart failure is a common clinical syndrome resulting from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. Heart failure may be caused by diseases of the myocardium, pericardium, endocardium, heart valves, blood vessels, or metabolic disorders.15

Causes
The prevalence of the causes of heart failure differs from one study to another because of different diagnostic criteria. The prevalence of heart failure also differs in developed and developing countries. Heart failure due to rheumatic heart disease is more common in developing countries. Diabetes and obesity are also known causes of heart failure.

According to the Italian registry, the following are the causes of heart failure with their prevalence.16
1. Ischemic heart disease 40 percent
2. Dilated cardiomyopathy 32 percent
3. Primary valvular heart disease 12 percent
4. Hypertensive heart disease 11 percent
5. Other 5 percent

Among the other causes of heart failure, chemotherapy like the anthracycline group of drugs doxorubicin results in congestive heart failure due to the generation of free radicals by mitochondrial redox cycling. Also among 1-4% of patients treated with targeted therapy trastuzumab, which is commonly used in Her-2 positive breast cancer patients results in heart failure as serious side effects. So baseline cardiac monitoring before giving these chemotherapies is a must.17,18

Classification of heart failure
HFrEF and HFpEF are important types of heart failure from a clinical and prognostic point of view.

American College of Cardiology and American Heart Association (ACC/AHA) task force 2013 has divided heart failure into the following four stages.9 This classification helps in the management of patients with heart failure
Stage A: People are at high risk of developing HF but have no heart disease or symptoms.
Stage B: Presence of structural heart disease but without signs or symptoms of HF.
Stage C: Presence of structural heart disease with prior or current symptoms of HF.
Stage D: Presence of refractory heart failure requiring specialized interventions.

Heart failure is also divided into New York Heart Association (NYHA) I, II, III, and IV class according to the severity of symptoms. In class II, symptoms like difficulty in breathing occur during ordinary activity (walking at a normal pace). Patients with NYHA class I become short of breath on doing more than ordinary activity (running for a bus). Less than normal activity (walking from one room to another) produces NYHA class III symptoms. Patients are symptomatic even at rest in NYHA class IV symptoms.19

Pathophysiology of heart failure
Diastolic heart failure is also known as heart failure with preserved left ventricular ejection fraction (HFpEF). In HFpEF, left ventricular ejection fraction (LVEF) is ≥ 50 percent. In heart failure with reduced systolic function also called systolic heart failure or HFrEF, LVEF is ≤ 40 percent. Patients have dyspnea when pulmonary capillary wedge pressure (PCWP) rises in heart failure. PCWP indirectly reflects left atrial pressure which can be guessed by echocardiography. E/e’ ratio is measured by pulse wave Doppler echocardiography and tissue doppler. E/e’ ratio > 15 suggests a PCWP of > 15 mm Hg when e’ is the mean of medial and lateral left mitral annulus early diastolic velocities.20 The sympathetic nervous system, the renin-angiotensin-aldosterone system, and antidiuretic hormone are stimulated in response to both systolic and diastolic heart failure.21-23

Endothelin is a vasoconstrictor secreted from the vascular endothelial cells in heart failure. Neurohormonal activation due to low cardiac output and hypotension increases systemic blood pressure by vasoconstriction. Cardiac output is increased due to contraction of the myocardium and an increase in heart rate by neurohormonal activation.
An increase in blood pressure and cardiac output help in the maintenance of perfusion of vital organs.

Vasodilators such as a natriuretic peptide, nitric oxide, prostaglandins, and bradykinins produced in heart failure can not fully counteract the vasoconstriction due to stimulation of the sympathetic and renin-angiotensin-aldosterone system.24-26

Low cardiac output with low blood pressure stimulates the production of norepinephrine. Alpha-2 receptors normally inhibit the release of norepinephrine. Downregulation of alpha-2 receptors in heart failure also increases the production of norepinephrine.27

Because of systemic and pulmonary vasoconstriction and increased venous tone due to sympathetic activity, left ventricular preload is increased. This also helps in maintaining cardiac output initially. However, chronic sympathetic stimulation leads to downregulation of beta receptors resulting in a decrease inotropic and chronotropic action of the myocardium.

Renal vasoconstriction is produced by norepinephrine at afferent glomerular arterioles. This increases glomerular filtration despite a fall in renal blood flow. Sodium reabsorption from the proximal tubule is increased by norepinephrine and angiotensin II. Aldosterone is produced due to the stimulation of the adrenal gland by angiotensin II. Aldosterone increases the absorption of sodium. The resulting sodium retention produces swelling of the limbs and ascites.

Stimulation of cardiac beta-1 and to a lesser extent beta-2 adrenergic receptors on the cardiac myocytes increases the contractility of the heart. These receptors also mediate the adverse effects of norepinephrine on the viability of myocytes. Stimulation of beta-1 receptors also leads to myocyte necrosis.

In heart failure, there is a selective reduction in the density of beta-1 receptors but not of beta-2 receptors on the cardiac myocytes.28 In heart failure, the heart is mainly dependent on beta-2 receptors for inotropic support. Beta-2 receptors exert an anti-apoptotic effect which is opposed by the pro-apoptotic action of the beta-1 receptor.29 The beta-blockers may act by reducing beta-2 receptor-mediated norepinephrine release in the heart. This effect is greater with the non-selective beta-blockers compared to selective beta-blockers.30

Renin angiotensin system

Hypotension in heart failure reduces the stretch of afferent glomerular arterioles, also decreases chloride in macula densa and beta-1 receptors. All these factors in heart failure are known to stimulate the production of renin from the juxtaglomerular cells. Renin converts angiotensinogen into angiotensin I which is converted to angiotensin II by angiotensin converting enzyme. Angiotensin II has a similar action to norepinephrine and stimulates the production of aldosterone from the adrenal gland. Angiotensin is also produced from the heart, kidney, blood vessels adrenal glands, and brain. Because of this, plasma aldosterone level may be normal in heart failure but it is present in different organs as mentioned above. and causes sodium retention.21

Cardiac angiotensin II and angiotensin converting enzyme (ACE) are increased in heart failure in proportion to its severity.31-35

Antidiuretic hormone, Endothelin, Natriuretic peptides, and Nitric oxide in heart failure.

Carotid sinus and aortic arch baroreceptors are stimulated due to low cardiac output in heart failure and anti-diuretic hormone (ADH) is produced with increased thirst. Increased ADH in the blood promotes water reabsorption. Increased water intake due to thirst expands extracellular volume and produces hyponatremia which is a well-known finding in heart failure.

Endothelin is a vasoconstrictor produced by endothelial cells and is increased in heart failure. Increased plasma endothelin level has a deleterious effect on the heart.

Natriuretic peptides are vasodilators and are increased in heart failure in response to increasing left ventricular filling pressure. Secubitril- Valsartan is used in the treatment of heart failure.

Secubitril is known to inhibit the enzyme nepri lysin which is responsible for the degradation of natriuretic peptides. This results in an increased plasma level of natriuretic peptide, which is beneficial in heart failure.

Nitric oxide is a vasodilator produced in endothelial cells by nitric oxide synthase from L-arginine. Increase free radicals in heart failure may inactivate nitric oxide. Vitamin C has been found to improve endothelial function in HF.36

However, Nitric oxide action on the myocardium is either beneficial or deleterious. Endothelial nitric oxide synthase (eNOS) is found to limit left ventricular dysfunction and remodeling.37

Nitric oxide is also found to lower myocyte energy production by directly affecting mitochondrial function and reducing myocardial inotropic function.38

Clinical manifestations of HF

The patients with heart failure usually present to the clinicians with a history of exercise intolerance, loss of weight, volume overload, hypotension, and signs of inadequate perfusion such as low pulse pressure and fatigue. Hypotension in heart failure is associated with increased mortality.39-41 Drugs known to benefit patients with heart failure may not be. tolerated in hypotensive patients. Hyponatremia is common in heart failure and is associated with a worse prognosis.42,43

In the early stage of heart failure, dyspnoea is observed only during exertion. However, as the disease progresses, dyspnoea is noticed with less exertion and ultimately even
at rest. Accumulation of fluid in the interstitial space and the alveoli activates juxtacapillary receptors which in turn stimulate rapid shallow breathing. Paroxysmal nocturnal dyspnoea (PND) is a common symptom of heart failure. PND refers to acute shortness of breath and coughing that occurs at night and awakens the patient from sleep, usually, 1-3 hours after the patient goes to bed.

Cheyne Stokes respiration is also known as periodic breathing is found in advanced heart failure and is usually associated with low cardiac output. It is caused by a diminished sensitivity of the respiratory center to arterial PCO2. There is an apneic phase which is followed by a fall in arterial Po2 and a rise in PCO2. These blood gas changes stimulate the depressed respiratory center resulting in hyperventilation.

Physical examination

Systolic blood pressure may be low, normal, or high. Sinus tachycardia is a non-specific finding due to increasing adrenergic activity. Pulse pressure may be diminished reflecting a reduction of stroke volume. Cool extremities and peripheral cyanosis is caused by excessive adrenergic activity.

Examination of the jugular vein provides an estimation of right atrial pressure. Sustained abdominal pressure for > 1 minute produces elevated Jugular venous pressure and is called abdominojugular reflux.

Examination of the lung may reveal bilateral basal crackles or crepitation. In pulmonary edema, crackles are widely heard over both lungs and may be accompanied by expiratory wheeze. Crackles are frequently absent in chronic heart failure because of increased lymphatic drainage. bilateral pleural effusion is often found in chronic heart failure. Unilateral pleural effusion is common on the right side.

The point of maximum impulse is displaced lateral and downwards in left ventricular enlargement. Right ventricular heave may be found in right ventricular hypertrophy. The pulmonary second sound may be palpable in the pulmonary area. A fourth and third heart sounds can be found. Depending upon the causes of heart failure, systolic and diastolic thrills and murmurs are heard.

**Framingham Diagnostic Criteria for Heart Failure**

**Major criteria**

1. Acute pulmonary edema. (bilateral crackles)
2. Cardiomegaly
3. Hepatomegaly
4. Neck vein distension. (Raised JVP > 16 cm of water)
5. Paroxysmal nocturnal dyspnoea or orthopnea
6. Third heart sound - LA pressure = 15 mm Hg

**Minor criteria**

1. Ankle edema
2. Dyspnoea on exertion
3. Hepatomegaly
4. Nocturnal cough
5. Pleural effusion
6. Tachycardia - > 120 bpm (Weight loss > 4.5 kg in 5 days with treatment)

Two major or one major and two minor criteria are required for the diagnosis of heart failure. Six-minute walk test < 300 m indicates the severity of heart failure and poor prognosis.

**Diastolic heart failure with preserved LVEF (HFpEF)**

Diastolic dysfunction is one of the criteria for the diagnosis of heart failure with preserved left ventricular function (HFpEF). E/A(E=early diastole wave, A=wave by atrial contraction) ratio of less than one is usually used for the diagnosis of diastolic dysfunction even at the present moment. A reduced mitral E/A ratio with normal annular Tissue Doppler velocity in persons > 60 years of age does not indicate diastolic dysfunction and should not be used to diagnose diastolic dysfunction.

The diagnostic criteria recommended by the American Society of Echocardiography and the European Association of Cardiovascular imaging should be followed in the assessment of diastolic function. Though diastolic dysfunction can be diagnosed by cardiac catheterization, its diagnosis by echocardiography is simple and cost-effective. The echocardiographic diagnostic criteria of diastolic dysfunction in patients with normal and reduced LVEF are different. These criteria will be briefly outlined here. Systolic and diastolic blood pressure control with antihypertensive drugs are recommended in patients with HFpEF.

Probable diastolic heart failure = 1. Clinical heart failure. 2. Borderline LVEF
Possible diastolic heart failure. =1. Clinical heart failure. 2. Borderline LVEF
E/A. More than 2 is due to high LVEDP, atrial contraction is ineffective)

**Diagnostic criteria of diastolic dysfunction with normal LVEF**

Four following echocardiographic criteria are needed
for the evaluation of diastolic function with normal LVEF. Septal and lateral e’ annular velocities are measured by Tissue Doppler.\textsuperscript{49}

1. Average E/e’ ratio > 14: average of septal and lateral e’
2. Septal e’ annular velocity < 7 cm per second or
Lateral e’ annular velocity < 10 cm per second
3. Tricuspid regurgitation velocity > 2.8 m/s
4. Left atrial volume index ≥ 34 ml/m²

Less than 50 percent of negative findings indicate normal diastolic function.

More than 50 percent of positive findings indicate diastolic dysfunction. If 50 percent of the findings are positive, the diastolic function can not be determined

**Diagnostic criteria of diastolic dysfunction in patients with reduced LVEF (HFrEF)**

Mitral inflow velocity by Pulse Wave Doppler should be recorded. If E/A ratio is ≤ 0.8 with mitral E velocity of ≤ 50 cm/s, grade 1 diastolic dysfunction with normal LA pressure is diagnosed. If E/A ratio is ≥ 2, grade 11 diastolic dysfunction with increased LA pressure is the diagnosis.

If E/A ratio is ≤ 0.8 with E velocity > 50 cm/s or E/A ratio > 0.88 and < 2, three other following echo-criteria should be evaluated.

**Three criteria are as follows**

1. Average E/e’ > 14
2. TR velocity > 2.8 m/s
3. LA volume Index > 34 ml/m²

If 2 of 3 or all 3 of the above criteria are negative, grade 1 diastolic dysfunction with normal LA pressure is diagnosed. If 2 of 3 or all 3 of the above criteria are positive, grade 11 diastolic dysfunction with increased LA pressure is the diagnosis. If one criterion is positive and one criterion is negative, diastolic grading cannot be determined. LA volume Index should not be applied as a diagnostic criterion of diastolic dysfunction in the case of athletes, mitral stenosis, and atrial fibrillation.

Before the introduction of the above criteria for the diagnosis of diastolic dysfunction by the American Society of Echocardiography, an E/A ratio of less than 1 was commonly used to diagnose LV diastolic dysfunction.

The prevalence of HFpEF increases with age and is more common in women and 35% of patients with heart failure have been found to have a normal LVEF.\textsuperscript{50-54} Nearly half of the heart failure patients have HFpEF.\textsuperscript{21} Dyspnoea and fatigue in patients with HFpEF is considered to be due to elevated left atrial and pulmonary venous pressure.\textsuperscript{55,56} Systemic hypertension and atrial fibrillation are more common in HFpEF compared to HFrEF. Left ventricular volume is normal in HFpEF. BNP > 100 pg/ml and NT-pro BNP (Brain Natriuretic Peptide) > 300 pg/ml are diagnostic of HFpEF or HFrEF. However normal levels of natriuretic peptides do not rule out HFpEF.

Beta-blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers do not decrease mortality in heart failure with preserved ejection fraction. Resynchronization therapy is also not effective.\textsuperscript{57} Hypertension, lung disease, coronary artery disease, atrial fibrillation, obesity, anemia, and sleep disorders are associated and have an impact on the clinical course of HFpEF. These conditions should be treated with appropriate medicines.

**Heart failure with reduced LVEF (HFrEF)**

Heart failure with a reduced ejection fraction of < 40% is also called systolic heart failure. In systolic heart failure, the left ventricle is dilated and signs and symptoms of heart failure are present. In heart failure with preserved ejection fraction, signs and symptoms of heart failure are present but the left ventricle is not dilated. The dilatation of the left ventricle and its remodeling can be reversed with the appropriate treatment of diseases causing heart failure. One of the causes of heart failure with reduced ejection fraction is systemic hypertension. Patients with hypertensive heart failure treated with beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor-neprilysin antagonist, or mineralocorticoids receptor antagonists have survival benefits. Therefore hypertensive patients should be treated with these drugs. If blood pressure is not controlled with these drugs, a loop diuretic, nitrates, hydralazine, amlodipine, or alpha-blockers can be added.\textsuperscript{58}

Ischemic heart disease is the number one cause of mortality worldwide. The most common cause of heart failure with reduced ejection fraction in developed countries is coronary artery disease. Beta-blockers are useful drugs in relieving angina and improving heart failure. Revascularization procedures such as percutaneous coronary angioplasty or coronary artery bypass graft surgery can relieve symptoms and improve heart failure.\textsuperscript{59}

In symptomatic heart failure patients, sodium restriction (3 gram per day) and fluid restriction (1.5 - 2 liter per day) is advised.\textsuperscript{1} Smoking should be stopped completely. Alcohol restriction is also advisable in heart failure. Anemia if present should be treated with appropriate medicines depending upon its cause. Overweight, patients are advised to reduce their weight by regular exercise and diet control. Pneumococcal and influenza vaccines are recommended for heart failure patients.

Dilated cardiomyopathy and valvular heart disease also can cause refractory heart failure and need treatment. Valvular heart disease may require valve replacement.
2017 ACC/AHA/HFSA on heart failure

Recommendations for investigations and treatment based on the 2017 ACC/AHA/HFSA updated guidelines are mentioned below.

Biomarkers: BNP or NT-Pro BNP estimation
1. Class IIa BR (BR= moderate evidence) recommendation for prevention of HF
2. Class IA recommendation for diagnosis of HF
3. Class I A recommendation for Prognosis

Stage C HFrEF treatment with ACE inhibitors, ARB, ARNI
1. ACE-I: class I A
2. ARB: Class IA
3. ARNI: Class I BR

Recommendation for Ivabradine: Class Iia BR

Stage C HFpEF treatment recommendation
1. Systolic & diastolic BP control: Class I B
2. Use of diuretics to control volume overload: Class I C
3. Coronary revascularization: Class Iia C
4. AF management. Class IIa. C-LD recommendation
5. Use of beta-blocker, ACE-I, ARB to control BP: Class IIA C
6. Use of aldosterone receptor antagonist in patients with GFR > 30 ml/min, creatinine < 2.5 mg/dl and potassium < 5 milli E/L: Class IIb BR

Anemia associated with HF

IV iron in iron deficiency anemia: Class IIb BR recommendation: new evidence consistent with therapeutic benefit. Erythropoietin has no therapeutic benefit.

Sleep-disordered breathing

1. Sleep assessment: Class IIA. C-LD recommendation
2. Obstructive sleep apnea: use of C-PAP(Continuous Positive Airway Pressure) is class Iib B-R
3. In patients with NYHA class II- 1V symptoms and central sleep apnea, adaptive servo-ventilation causes harm: Class III B-R recommendation.

Updated ACC/AHA 2020 Performance and Quality measures for Heart failure

Some of the changes made in ACC/AHA 2020 from ACC/AHA 2017 guidelines are as follows.
1. Assessment of left ventricular ejection fraction is recommended in outpatient follow-up.
2. Documentation of patient’s symptoms and level of activity in outpatient visit includes NYHA class, KCCQ (Kansas City Questionnaire), and 6-minute walk test.
3. Mineralocorticoid inhibitor is recommended in HF with LVEF ≤ 35% with NYHA class II-IV symptoms.
4. Hydralazine/isosorbide dinitrate is recommended in HF with EF ≤ 45% in black, African Americans.
5. Device therapy is recommended to heart failure patients with LVEF ≤ 35% not responding to medical treatment of ≥ 3 months.

Initial treatment of heart failure

Loop diuretics are introduced first in patients in volume overload. Angiotensin-converting enzyme inhibitors are initiated during the optimization of diuretic therapy. Angiotensin receptor blockers can be given to those patients who can not tolerate ACE inhibitors because of cough. These drugs are initiated at low doses and gradually increased. Angiotensin receptor neprilysin inhibitors can be used in place of ACE inhibitors. Beta-blockers are initiated after the patient is stable on ACE inhibitors or ARB.

Treatment of refractory heart failure

Patients with chronic heart failure with severe symptoms despite maximum guideline-directed treatment are considered to have refractory or stage D heart failure. These patients are treated with vasodilators and inotropes. Dialysis can also remove fluid by ultrafiltration. Mechanical circulatory support, surgical procedures, cardiac transplant. and palliative care is another modality of treatment of refractory heart failure.

Medical management consists of the treatment of volume overload with increasing doses of loop diuretics. Metolazone and spironolactone orally may be needed if loop diuretics are not effective.

Vasopressin receptor 2 antagonists (Tolvaptan) can be used in patients with significant hyponatremia (≤ 120 mEq/L). This drug should not be used in patients with liver disease. It also should not be used for more than 30 days. Tolvaptan improves hyponatremia but does not affect mortality. The usual recommended dose of Tolvaptan is 15 mg per day orally. Severe heart failure patients with hypotension not responding to an adequate dose of diuretic and having increase left ventricular filling pressure can be treated with IV nitroglycerin and nitroprusside. Patients with symptomatic hypotension and evidence of organ hypoperfusion should be treated with IV inotropes.

Dobutamine

Dobutamine is a catecholamine with beat1 and beta2 adrenergic agonist properties, which improve myocardial contraction. It is used in patients with severe heart failure with hypotension. Its half-life is only 2 minutes and its usual dose is 0.25 to 0.75 microgram/kg body weight/minute with a maximum dose of 20 microgram/kg body weight/minute. The beta-blocker should be discontinued while using dobutamine. Inotropic drugs have no mortality benefit.
**Milrinone**

Milrinone is a phosphodiesterase inhibitor that can be given with beta-blocker to heart failure patients without hypotension. It is an alpha and beta-agonist and has both inotropic and vasodilator effects on the systemic and pulmonary vasculature. It is known to reduce pulmonary artery and LV filling pressures. Its half-life is 2-3 hours and the initial dose is 0.125 microgram/kg/min. Maximum dose is 0.75 microgram/kg/min. In renal impairment, dose should not exceed 0.25 microgram/kg/min. It is given via a central venous catheter. Milrinone prevents the degradation of cyclic adenosine monophosphate (cAMP) within the cells by inhibiting phosphodiesterase 3 intracellular enzyme. An increased level of cAMP increases the action of protein kinase A, which leads to an influx of calcium into the cells. Increase intracellular calcium stimulates myocardial contraction. Inotropic drugs have no mortality benefit as shown by the UPTIME- HF trial, ADHERE registry, and PROMISE trial.63,64

**Noradrenaline**

Noradrenaline has both alpha and beta-agonist properties and produces an inotropic effect and peripheral vasoconstriction. Tachycardia and cardiac arrhythmias can occur. It should be given via a central venous catheter as skin necrosis can occur if peripheral veins are used. It’s usual dose is 0.3-1 microgram/kg/min. Noradrenaline is given in severe heart failure with hypotension.

**Dopamine**

Dopamine in < 3 microgram/kg/minute has a vasodilator effect. In doses between 3-10 microgram/kg/min, it has both inotropic and chronotropic effects. In higher doses of 10-20 microgram/kg/min, it has alpha-receptor mediated vasoconstrictor activity and increases afterload, which is not desired in severe LV dysfunction.

**Levosimendan**

Levosimendan is a calcium sensitizing agent. It reduces preload and afterload and is widely used in Europe but not approved in the USA by FDA.

**Omecamtiv mercarbil**

Omecamtiv mercarbil is a new inotropic agent and works as a cardiac-specific myosin activator. It increases LVEF and stroke volume. LV end-systolic and end-diastolic volumes are reduced. This drug may prove effective in the treatment of end-stage heart failure in the future.

**Ivabradine in heart failure**

Ivabradine is beneficial in reducing hospitalization in symptomatic heart failure patients with reduced LVEF of ≤ 35% and sinus rhythm having heart rate ≥ 70 bpm (COR = 11a, LOE = B-R). It inhibits the If channel in the sinoatrial node prolongs diastolic time, and increases stroke volume. 5 mg tablets are available and 5 - 7.5 mg twice daily can be given. The dose of this drug should be adjusted according to heart rate. Initially, it should be started in smaller doses and increased gradually.65

**Dapagliflozin in heart failure**

Dapagliflozin is a SGLT2 inhibitor used in type 2 diabetes mellitus and also approved in the treatment of heart failure. This drug reduces mortality and hospitalization in heart failure.66

**Cardiac Resynchronization Therapy (CRT). Intracardiac Difibrillator (ICD (CRT-P, CRT-D)**

Cardiac Resynchronization Therapy (CRT) is a modality of cardiac pacing used in patients with systolic dysfunction and dyssynchronous ventricular activation. Biventricular pacing activates both left and right ventricles simultaneously. CRT is also combined with the implantable cardiac defibrillator and is called CRT-D.

Electrical dyssynchronous is indicated by a wide QRS complex. Approximately one-third of patients with heart failure and reduced LVEF have a wide QRS complex of > 120 ms. Mortality in patients with reduced ejection fraction increases with increasing QRS duration.67,68 Left bundle branch block of any cause increases the mortality. However, the right bundle branch block is not associated with increase mortality.69

CRT improves systolic LV function, promotes LV reverse remodeling, and decreases LV size. The left ventricle becomes less spherical. Blood pressure, cardiac output, and LVEF are increased.70 Heart failure patients with reduced LVEF of ≤ 35% should be evaluated for CRT-P or CRT-D after 3 months of optimum medical therapy. Reversible causes of heart failure such as myocardial ischemia, tachycardia-induced cardiomyopathy, or diseases of the thyroid gland also should be treated before considering CRT.

**Surgical treatment in refractory heart failure**

The following surgical procedures have been done for end-stage heart failure.

1. Coronary artery bypass surgery
2. Reconstructive cardiac surgery: LV volume reducing surgery
3. Cardiomyoplasty: Latissmus Dorsi muscle is wrapped around the heart and stimulated by a pacemaker. This procedure is not recommended now.
4. Mitral valve repair or valve replacement.

**Mechanical circulatory support**

The following cardiac assist devices in decompensated heart failure can be used. Cardiac power output (CPO) helps in choosing cardiac assist devices and using inotropic drugs in the management of refractory heart failure.71

1. Intra-aortic balloon pump: Increases myocardial oxygen, cardiac output (CO) Mean Blood Pressure (MBP): decreases Left Ventricular End Diastolic Pressure (LVEDP): Cardiac
Power Output (CPO) improved by 10%

2. Tandem heart: Left atrium to the common iliac artery, Increase in CO, MBP, decrease in LVEDP, CPO improved by 80%, effective when CPO > 0.53

3. Impella devices: 2.5 and 5 devices, Unloading LV into the aorta, Increase in CO, MBP, decrease in LVEDP: CPO improved by 50% in 2.5 devices and 100% in Impella 5 device

4. Extra Corporeal Membrane Oxygenation (ECMO): Mini cardiopulmonary bypass, Right atrium to the aorta, (veno arterial) - ECMO, useful in a very sick patient.

Cardiac Power Output (CPO) is calculated as follows

\[ \text{CPO} = \frac{\text{Cardiac output} \times \text{Mean Blood Pressure}}{451} \]

Value < 0.6 indicates hemodynamic compromise: mechanical circulatory support may be needed in this category of patients

Value < 0.53: not comparable with life

Value. Around 1: benefited by inotropes

CPO helps in the management of symptomatic patients with severe heart failure.

Heart failure therapy timelines

Pre - 1980: Non Pharmacologic treatment (bed rest, fluid restriction, diuretics) only available.

The 1980s: pharmacological treatment - digitalis, diuretics, Vasodilators, inotropes

The 1990s: pharmacological and, neurohormonal intervention

The 2000s: devices - CRT, ICD, LVAD, and others

2010 - 2020: gene therapy, intracardiac bone marrow stem cell injection

Cardiac transplant

Cardiac transplantation has now become an established treatment for end-stage heart failure. Dr. Christian Barnard carried out the first human-to-human heart transplant on 3rd December 1967 at Groote Schuur hospital in Cape Town. Mr. Luis Washkansky was the first South African to undergo a heart transplant.

In India, the first heart-lung transplant was performed at Chennai by Dr. K M Cherian in 1999. He was also the first surgeon to perform the first coronary artery bypass surgery in India in 1975. A peak VO2 of ≤ 12 ml/kg/min indicates severe heart failure and is used as the criterion of cardiac transplantation.73

Exercise in heart failure

European Society of Cardiology 2021 guidelines on heart failure recommend exercise to all patients with heart failure to improve quality of life and reduce hospitalization.73

Prognosis

Mortality increases with increasing age. Prognosis is better in women compared to men. According to the Framingham heart study, median survival after diagnosis was 3.2 years in women and 1.7 years in men. After 5 years, 38% of women and 25% of men with heart failure were alive. Serum albumin ≤ 3.4 mg/dl is associated with a worse prognosis in heart failure.75 Despite the advances in the treatment of heart failure in recent years, its prognosis is not good.

REFERENCES


34. Dzau VJ. Tissue renin-angiotensin system in myocardial hypertrophy and failure. Archives of internal medicine. 1993 Apr 26;153(8):937-42.


73. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2011 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. European heart journal. 2021 Sep 21;42(36):3599-726.
