

Review Article

The pathophysiology of heart failure

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Abstract

Heart failure is a clinical syndrome that results when the heart is unable to provide sufficient blood flow to meet metabolic requirements or accommodate systemic venous return. This common condition affects over 5 million people in the United States at a cost of \$10–38 billion per year. Heart failure results from injury to the myocardium from a variety of causes including ischemic heart disease, hypertension, and diabetes. Less common etiologies include cardiomyopathies, valvular disease, myocarditis, infections, systemic toxins, and cardiotoxic drugs. As the heart fails, patients develop symptoms which include dyspnea from pulmonary congestion, and peripheral edema and ascites from impaired venous return. Constitutional symptoms such as nausea, lack of appetite, and fatigue are also common. There are several compensatory mechanisms that occur as the failing heart attempts to maintain adequate function. These include increasing cardiac output via the Frank–Starling mechanism, increasing ventricular volume and wall thickness through ventricular remodeling, and maintaining tissue perfusion with augmented mean arterial pressure through activation of neurohormonal systems. Although initially beneficial in the early stages of heart failure, all of these compensatory mechanisms eventually lead to a vicious cycle of worsening heart failure. Treatment strategies have been developed based upon the understanding of these compensatory mechanisms. Medical therapy includes diuresis, suppression of the overactive neurohormonal systems, and augmentation of contractility. Surgical options include ventricular resynchronization therapy, surgical ventricular remodeling, ventricular assist device implantation, and heart transplantation. Despite significant understanding of the underlying pathophysiological mechanisms in heart failure, this disease causes significant morbidity and carries a 50% 5-year mortality. © 2012 Elsevier Inc. All rights reserved.

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1. Definition and epidemiology

Heart failure (HF) describes the complex clinical syndrome where the heart is incapable of maintaining a cardiac output (CO) that is adequate to meet metabolic requirements and accommodate venous return [1,2]. There are multiple etiologies leading to this final common clinical pathway, which carries a 50% 5-year mortality rate and is responsible for over one third of all deaths in the United States from cardiovascular causes [3].

Worldwide, cardiovascular disease is on the rise and continues to be the leading cause of death [4]. Each year, there are approximately 500,000 new cases in the United States and 2 million new cases of HF diagnosed worldwide,

leading to a prevalence of over 5 million in the United States and 22 million people across the globe [3,4].

By the age of 40, people in the United States have a one in five chance of developing HF, and it affects 10 people per 1000 over the age of 65 [3]. HF is more common in males until the age of 65 when the prevalence is equal among the sexes [3]. African Americans have the highest prevalence of HF at 4.6 per 1000 person-years, followed by Hispanic, Caucasian, and Asian Americans at 3.5, 2.4, and 1.0 per 1000 person-years, respectively [5]. HF patients take on average six HF-related medications, and 78% have at least two hospital admissions per year, leading to an annual cost of \$10–38 billion [3,6,7].

2. Etiology

Heart failure is caused by a loss of a critical quantity of functional myocardial cells after injury to the heart from a

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number of causes. The most common etiologies are ischemic heart disease, hypertension, and diabetes [3,8]. Three quarters of all HF patients have preexisting hypertension, and this risk factor alone doubles the risk of developing HF compared to normotensive patients [8]. Less common, but important, causes of HF in order of decreasing prevalence are cardiomyopathies, infections (e.g., viral myocarditis, Chagas' disease), toxins (e.g., alcohol, cytotoxic drugs), valvular disease, and prolonged arrhythmias.

3. Signs and symptoms

The signs and symptoms of HF are the result of the clinical sequelae of inadequate CO and lack of efficient venous return [1]. Dyspnea, cough, and wheezing result from increased pressure in the pulmonary capillary bed due to ineffective forward flow from the left ventricle. Lower extremity edema, as well as ascites, occurs when the right ventricle is unable to accommodate systemic venous return. Fatigue is common as the failing heart cannot sustain enough CO to meet the body's metabolic needs and conserves blood flow to the heart and brain. Nausea and lack of appetite may also occur as blood is shifted from the gastrointestinal tract to the more vital organs. Palpitations can occur as the failing heart tries to accommodate for the lack of flow with a faster heart rate (HR).

4. Functional classification and disease progression

HF is commonly classified using the New York Heart Association (NYHA) classification system which places patients in one of four classes based upon the physical disability caused by their HF (Table 1) [9]. Currently, the NYHA classification is used not only to document functional cardiac status but also as an entry criterion for clinical trials of medications and devices. Patients with NYHA Class I HF have cardiac disease without any limitations or symptoms with ordinary activity. Those in NYHA Class II have a slight limitation of physical activity; they are comfortable at rest, but ordinary physical activity will result in fatigue, palpitation, dyspnea, or angina. NYHA Class III patients are still comfortable at rest but have marked limitation of physical activity with symptoms occurring with less than ordinary activity. NYHA Class IV patients may have symptoms at rest and are unable to carry out any physical activity without symptoms. According to the National Heart, Lung, and Blood Institute, 35% of patients have Class I HF, followed by 35% with Class II, 25% with Class III, and 5% with Class IV HF [2]. Mortality rises as patients progress through the various NYHA classifications [10].

More recently, a new system was developed by the American College of Cardiology (ACC) and the American Heart Association (AHA) that emphasizes both the evolution and progression of the disease process (Table 1) [11]. This classification system recognizes that there are established

Table 1
NYHA and ACC/AHA classifications of HF

NYHA classification	
Class I	No symptoms with ordinary activity
Class II	Slight limitation of physical activity Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea, or angina
Class III	Marked limitation of physical activity Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation, dyspnea, or angina
Class IV	Unable to carry out any physical activity without discomfort Symptoms of cardiac insufficiency may be present even at rest
ACC/AHA classification	
Stage A	Patient at high risk for developing HF with no structural disorder of the heart
Stage B	Patient with structural disorder of the heart without symptoms of HF
Stage C	Patient with past or current symptoms of HF associated with underlying structural heart disease
Stage D	Patient with end-stage disease who requires specialized treatment strategies

risk factors for HF as well as structural prerequisites for the development of HF. Patients in Stage A are at high risk for developing HF but do not have any structural disorders of the heart. Stage B patients have structural disorder without any symptoms of HF. Those in Stage C have past or current symptoms of HF which are associated with underlying structural heart disease. Stage D patients are those who have end-stage HF who require specialized treatment strategies. There are some overlaps between this system and the NYHA system; Stage A corresponds to pre-HF, Stage B to NYHA Class I, Stage C to NYHA Class II and III, and Stage D to NYHA Class IV HF. This four-stage classification scheme underscores the principle that therapeutic interventions before the development of LV dysfunction can result in a reduction in morbidity and mortality from HF.

5. Pathophysiology

5.1. Normal cardiac physiology

The amount of blood pumped by the heart over a given time period is known as cardiac output, which is in turn the product of HR and stroke volume (SV) and is typically 4–8 L/min [12,13]. In addition, other factors such as synergistic ventricular contraction, ventricular wall integrity, and valvular competence all affect CO (Fig. 1).

SV is defined as the amount of blood ejected by the ventricle per heartbeat, and is usually 1 cc/kg or approximately 60–100 cc [12,13]. SV is affected by three main

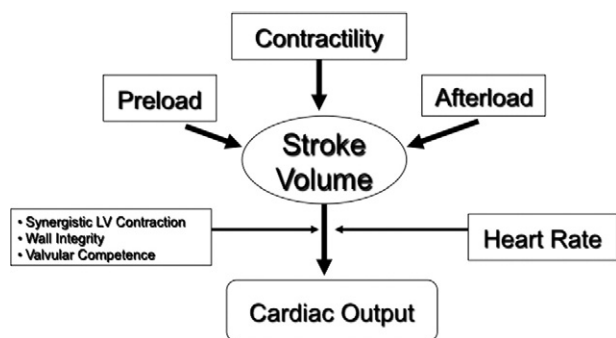


Fig. 1. Factors affecting CO.

factors: preload, which is the amount of myocardial fiber stretch at the end of diastole; afterload, which is the resistance that must be overcome in order for the ventricle to eject blood; and contractility, which is the inotropic state of the heart independent of the preload or the afterload.

5.2. Left ventricular dysfunction

Left ventricular (LV) dysfunction can be divided into two categories: systolic dysfunction (impaired ventricular contraction and ejection) and diastolic dysfunction (impaired relaxation and ventricular filling). Although there are many etiologies of HF, some tend to more adversely affect systolic or diastolic function, though 70% of patients with HF have systolic dysfunction compared to 30% with diastolic dysfunction [14]. In addition, most patients with systolic dysfunction also have a component of diastolic dysfunction. Whether or not a patient with HF has systolic or diastolic dysfunction depends on the ejection fraction (EF), which is defined as the amount of blood pumped from the ventricle in one heartbeat. If the EF is <40%, it is systolic dysfunction, and if it is >40%, it is diastolic dysfunction.

LV systolic dysfunction is defined as an LVEF less than 40% (Fig. 2). The leading cause of LV systolic dysfunction is loss of functional myocardium due to ischemic disease and infarction. Uncontrolled hypertension leading to excessive pressure overload is another leading factor. Volume overload due to valvular incompetence, and impaired contractility

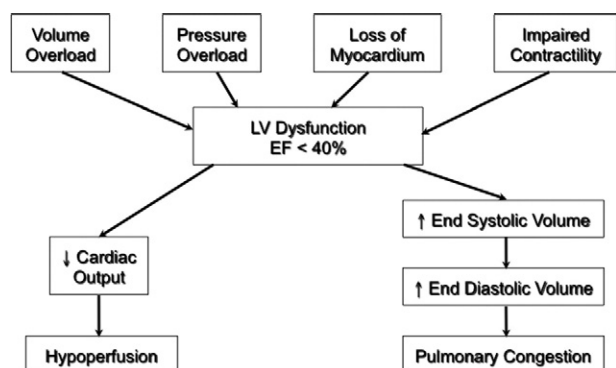


Fig. 2. Left ventricular dysfunction.

Table 2
Signs and symptoms of LV failure

LV dysfunction	
Symptoms	Signs
Dyspnea on exertion	Basilar rales
Paroxysmal nocturnal dyspnea	Pulmonary edema
Tachycardia	S3 gallop
Hemoptysis	Pleural effusion
	Cheyne–Stokes respiration

from cardiotoxins and cardiotoxic drugs are also contributors. The consequence of LV dysfunction is decreased CO which in turn leads to global hypoperfusion. In addition, LV dysfunction causes an increase in the amount of blood in the ventricle and therefore an increase in both end-systolic and end-diastolic volumes. This in turn leads to an increase in LV end-diastolic pressure (LVEDP) which causes elevations in left atrial pressures which in turn lead to increases in the pressure of the capillaries in the lungs. This elevated pressure in the lungs forces fluid out of the pulmonary capillaries and leads to pulmonary congestion and the major clinical symptom of dyspnea.

It is important, however, to understand that the symptoms of systolic and diastolic HF are the same, and whether a patient has systolic or diastolic dysfunction depends on the EF. Patient symptoms must correlate to their physical signs in order for them to be diagnostic of HF. These signs and symptoms of LV dysfunction are all the result of increased left atrial pressure and pulmonary congestion (Table 2).

5.3. Right ventricular dysfunction

The most common cause of right ventricular (RV) failure is LV failure. As the RV fails, there is a similar increase in the amount of blood in the ventricle, which in turn leads to elevated right atrial pressure and increased pressure in the vena caval system which impairs venous drainage from the body. This leads to increased pressure in the liver, the gastrointestinal tract, and the lower extremities and to the clinical signs and symptoms of abdominal pain, hepatomegaly, and peripheral edema. (Table 3). Other causes of RV failure include arrhythmic RV cardiomyopathy/dysplasia.

Table 3
Signs and symptoms of RV failure

RV dysfunction	
Symptoms	Signs
Abdominal pain	Peripheral edema
Anorexia	Jugular venous distension
Nausea	Abdominal–jugular reflex
Bloating	Hepatomegaly

6. Compensatory mechanisms

Mean arterial pressure (MAP) is closely regulated and is defined as the product of CO and total peripheral resistance (TPR). A patient with HF has decreased CO which in turn leads to a decrease in MAP and therefore decreased tissue perfusion. The body thus tries to maintain adequate tissue perfusion and compensates to bring MAP back to normal using several mechanisms including the Frank–Starling mechanism, neurohormonal activation, and ventricular remodeling. While initially beneficial, the long-term effects of these mechanisms serve to worsen HF in a vicious cycle.

6.1. Frank–Starling mechanism

The Frank–Starling mechanism plays an important compensatory role in the early stages of HF (Fig. 3) [15]. This graph depicts CO as a function of LVEDP which is directly related to LV end-diastolic volume (LVEDV or preload). Point A is on the curve which represents a healthy patient with a normal heart. On this curve, as preload (LVEDV) increases, this leads to an increase in LVEDP which causes a stretch in the myocardium which responds with an increase in CO which is known as the Frank–Starling mechanism. There is a limit to this increase in CO; with increasing amounts of preload, the resultant increase in CO is lessened as the curve flattens out. Points B and C are on another curve which represents a patient with systolic dysfunction. This curve is below that of the normal heart because the failing heart is unable to contract as it once did and, thus, SV falls and there is an increase in LVEDV (preload). Initially, at point B, which is on the ascending portion of the curve, this increase in preload leads to a compensatory increase in CO, although there is less impact as a similar increase in preload would have on the normal heart. As this patient's HF increases as indicated

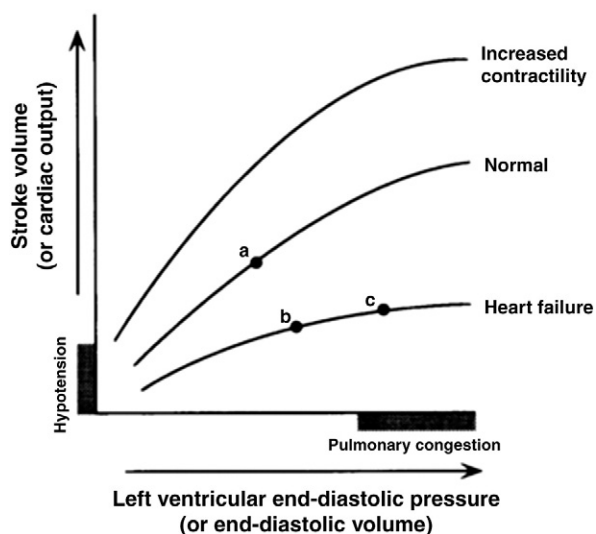


Fig. 3. The Frank–Starling mechanism.

by point C, SV only increases slightly for the increase in LVEDV. Eventually, this curve becomes flat and even downwards as the heart muscle decompensates and the compensatory mechanism is exhausted. At this point, increasing LVEDV and LVEDP lead to pulmonary congestion with a depressed CO.

6.2. Neurohormonal activation

Neurohormonal activation plays an important role in the maintenance of MAP and in the compensation during early stages of HF [16]. Recalling that MAP is the product of CO and TPR, neurohormonal activation serves to augment MAP by increasing TPR. In addition, many neurohormones also promote sodium and water retention, which maximizes SV and augments CO via the Frank–Starling mechanism.

The decrease in MAP seen in HF leads to a stimulation of the sympathetic nervous system (SNS) and release of catecholamines (norepinephrine and epinephrine) [17]. This stimulation has direct effects on the heart (increased HR and contractility) and on the peripheral vasculature (vasoconstriction) which increase SV and TPR, respectively, increasing MAP.

The effects of the sympathetic nervous system are mediated through three receptors: β_1 , β_2 , and α_1 . In HF patients, both β_1 and β_2 receptors are activated and, along with the α_1 receptors, eventually lead to myocardial toxicity, the effects of which are seen by decreased EF, arrhythmias, and tachycardia due to overstimulation by the SNS [17]. In the peripheral vasculature, activation of the β_1 and α_1 receptors leads to activation of the renin–angiotensin–aldosterone system (RAAS) which causes vasoconstriction, sodium retention, and thirst, also augmenting MAP [17].

The kidneys secrete renin in response to this sympathetic activation as well as due to reduced renal blood flow from a decrease in MAP [18]. Renin then acts on angiotensinogen in the liver to make angiotensin I. Circulating angiotensin I is converted by angiotensin-converting enzyme (ACE) in the lungs to angiotensin II which directly increases vasoconstriction and promotes the release of aldosterone. The end results of the activation of this particular neurohormonal system are to facilitate release of norepinephrine, promote sodium reabsorption, stimulate vasopressin release, and increase contractility.

Vasopressin is synthesized in the hypothalamus and secreted by the posterior pituitary gland. Its release is facilitated by angiotensin II formation and is also controlled via a negative feedback loop. When MAP falls in HF, this is detected by central baroreceptors which decrease their inhibitory impulses to the hypothalamus, thereby lifting the negative regulation and leading to an increase in vasopressin release. Increased vasopressin causes vasoconstriction as well as increased water retention, both of which augment the decrease in MAP in HF [18].

Although important in the compensation during early-stage HF, long-term results of the activation of these

neurohormonal systems result in ventricular remodeling which further hastens myocardial dysfunction.

6.3. Ventricular remodeling

The chronic hemodynamic stresses on the heart lead to alterations in the size, shape, structure, and function of the ventricle in a process known as remodeling [19]. As remodeling occurs, there are changes in ventricular mass, composition, and volume and its overall geometry changes as it becomes less elliptical and more spherical. These geometric changes initially are compensatory as a failing heart enlarges to increase ventricular volume which leads to greater SV and higher CO despite a reduced EF. Myocardial wall thickness and overall ventricular mass are also increased, which initially leads to increased contractility.

The remodeling process in HF is progressive and eventually becomes detrimental. As the ventricle continues to enlarge and the myocardium hypertrophies, this leads to increased wall tension and fibrosis which eventually impair contractility. The long-term process of remodeling also leads to an increase in myocardial apoptosis. In addition, there is significant contractile dyssynchrony in the dilated and remodeled ventricle leading to less effective pumping.

6.4. Other neurohormones

There are other neurohormonal mechanisms at work in HF. The first includes the natriuretic peptides atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and c-type natriuretic peptide (CNP) which serve to counteract the vasoconstricting effects of the other neurohormonal systems previously discussed [20]. ANP and BNP are found in the atria and ventricles, respectively, and are released following atrial or ventricular stretch. CNP is found predominantly in the central nervous system. These hormones act directly on blood vessels to cause vasodilation;

cause salt and water excretion; and inhibit secretion of renin, aldosterone, and vasopressin. Elevated BNP in particular is thought to be one of the first signs of HF and is used to follow the progression of disease.

In addition, there are endothelium-derived vasoactive substances that are produced by the vascular endothelium and act locally to promote vasodilation (nitric oxide, bradykinin, and prostacyclin) or vasoconstriction (endothelin I) [21]. Cytokine production also increases in HF and include tumor necrosis factor α , interleukin 1α , interleukin 6, and interferon α [22]. These small molecules are negative inotropes and decrease contractility, and elevated levels are associated with worse clinical outcomes.

6.5. Summary of the effects of the adaptive response to HF

The neurohormonal mechanisms that are activated in HF are identical to those that are triggered when MAP and CO are threatened in situations like intense physical exercise or hemorrhage. In these circumstances, the neurohormonal mechanisms are successful at reversing these temporary hemodynamic abnormalities, and their activity eventually subsides. In contrast, however, this neurohormonal activation never turns off in HF. These systems are constantly on in an attempt to compensate for the failing heart's inability to maintain normal cardiovascular homeostasis. The chronic presence of these circulating neurohormones exacerbates the hemodynamic abnormalities present in HF which encourage further remodeling and neurohormone release and further hemodynamic deterioration. Continued progression of HF eventually leads to a critical reduction in blood flow to all vital organs. In this final phase, the body maximizes all of its vasoconstrictive mechanisms in an attempt to redirect blood flow to these critical organ systems, which only add to the hemodynamic burden of the failing heart; thus, ventricular function progressively deteriorates, and terminal HF ensues. A vicious cycle develops whose end result is progressive ventricular dysfunction and death (Fig. 4).

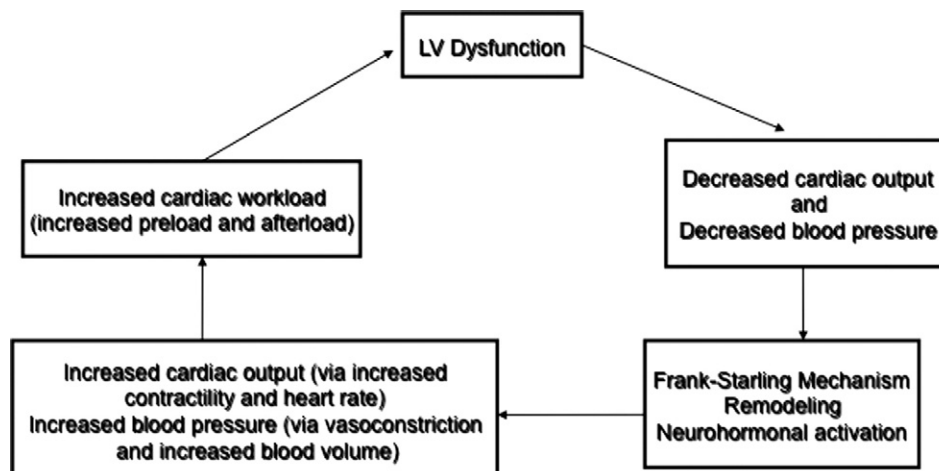


Fig. 4. The vicious cycle of HF.

7. Assessment of the patient with HF

The assessment of a patient with HF begins with documenting the history of HF symptoms, performing a physical examination, and obtaining laboratory and other diagnostic tests to ascertain the severity of disease. The type of cardiac dysfunction (systolic vs. diastolic) should be established, and the etiology should be determined to see if this is a reversible process. With this information, patients can be provided with both a prognosis and an appropriate treatment plan.

Initial workup should include an electrocardiogram to identify the presence of infarct or ischemia, hypertrophy, arrhythmias, or conduction disturbances which are common in patients with HF. Chest x-ray is useful to determine the size of the heart and presence of pulmonary congestion or pleural effusions. Laboratory examination is helpful to identify signs of end-organ dysfunction of the liver or kidney as well as any electrolyte imbalances or neurohormonal activation. Echocardiography is invaluable to define cardiac function (EF), geometry (ventricular mass, shape, and chamber size), any valvular abnormalities (insufficiency or stenosis), and wall motion abnormalities (hypokinesis, dyskinesis, or akinesis).

8. Treatment of the patient with HF

The details of the treatment of the patient with HF are beyond the scope of this review. The basic guidelines presented here are based upon the ACC/AHA guidelines (Fig. 5) [23].

General measures for the treatment of HF include both lifestyle modification as well as medical therapies (Table 4). Patients should be encouraged to lose excess weight, to abstain from tobacco and alcohol use, and to improve their

Table 4
General measures for the treatment of HF

Lifestyle modifications	Medical therapy
Weight reduction	Treatment of hypertension, hyperlipidemia, diabetes, and arrhythmias
Smoking cessation	Coronary revascularization
Avoidance of alcohol and other cardiotoxins	Anticoagulation
Exercise	Immunization
	Sodium restriction
	Daily weights and close outpatient monitoring

physical condition through exercise as tolerated. Medical therapies include treatment of hypertension, dyslipidemia, diabetes, and arrhythmias, as well as sodium and water restriction. Revascularizable coronary artery disease should be treated as appropriate.

Pharmacologic management of HF includes many medications that are designed to counteract the deleterious effects of the compensatory mechanisms that have previously been discussed [24,25]. Digoxin has been used to treat HF for over 200 years and acts to enhance inotropy of cardiac muscle and also reduces activation of the SNS and RAAS. Diuretics such as furosemide relieve fluid retention (pulmonary congestion and peripheral edema) and improve exercise tolerance. ACE inhibitors such as captopril and enalapril block the conversion of angiotensin I to angiotensin II, which reduces activation of the RAAS. Angiotensin receptor blockers such as valsartan, losartan, and candesartan are used in patients who cannot tolerate ACE inhibitor therapy and work directly on the angiotensin receptors that are the final downstream target of the RAAS pathway. β -Blocking agents such as carvedilol and metoprolol are used to protect the heart and vasculature from the deleterious effects of overstimulation of the SNS

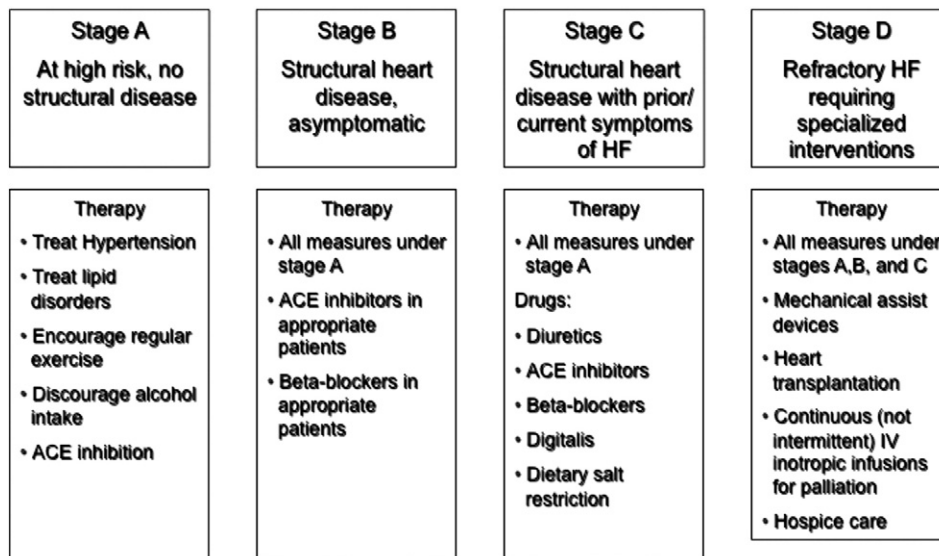


Fig. 5. Current management of HF. IV, intravenous.

and to help slow the heart down to allow for more efficient contraction. Aldosterone antagonists such as spironolactone also directly inhibit the RAAS. Inotropic agents such as milrinone provide direct stimulation of myocardium to increase contractility.

Surgical management includes cardiac resynchronization therapy (CRT), coronary revascularization, surgical ventricular remodeling (SVR), ventricular assist device (VAD) implantation, and heart transplantation. Reversible ischemic heart disease can provide more functional myocardium and improve pump efficiency. CRT aims to improve ventricular efficiency by simultaneously pacing both ventricles. SVR attempts to surgically restore the normal geometry of the ventricle. VAD augments the decreased CO in HF, and heart transplantation replaces the failing heart with a new functional organ.

9. Outcomes

HF continues to remain a significant cause of mortality among patients with this disease. As patients progress through the NYHA stages of HF, mortality increases [10]. Deaths due to HF itself (as a percentage of all deaths) increase from 12% for patients in NYHA Class II to 26% in Class III to 56% in Class IV. Another significant and related factor for mortality is sudden cardiac death (SCD), which occurs more frequently in earlier-stage HF and may be suitable for early intervention to prevent this lethal outcome. The risk of SCD is highest among Class II HF patients (64%) and decreases to 59% and 33% in Class III and Class IV patients, respectively, as the rate of mortality due to HF itself becomes more frequent among these patients.

10. Summary

HF remains a significant problem in the United States and worldwide, contributing to significant morbidity and mortality at a high cost to society and the medical system. Basic understanding of the mechanisms behind the adaptive response to HF has identified several pathways of compensation that have been targeted for pharmacologic and surgical therapies aimed at ameliorating this devastating disease. Further research is needed to identify novel targets to improve survival among patients with HF.

References

- [1] American Heart Association. Heart failure. Accessed on 6/6/2011; Available from: http://www.heart.org/HEARTORG/Conditions/HeartFailure/Heart-Failure_UCM_002019_SubHomePage.jsp.
- [2] NHLBI. What is heart failure? Accessed on 6/6/2011; Available from: http://www.nhlbi.nih.gov/health/nci/Diseases/Hf/HF_All.html.
- [3] Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, et al. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. *Circulation* 2011;123:e18–209.
- [4] World Health Organization. Cardiovascular disease. Accessed on 6/6/11; Available from: <http://www.who.int/mediacentre/factsheets/fs317/en/index.html>.
- [5] Bahrami H, Kronmal R, Bluemke DA, Olson J, Shea S, Liu K, et al. Differences in the incidence of congestive heart failure by ethnicity: the multi-ethnic study of atherosclerosis. *Arch Intern Med* 2008;168:2138–45.
- [6] English MA and Mastrean MB. Congestive heart failure: public and private burden. *Crit Care Nurs Q* 1995;18:1–6.
- [7] Havranek EP, Abraham WT. The health care economics of heart failure. *Heart Fail* 1998;14:10–8.
- [8] Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, et al. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation* 2002;106:3068–72.
- [9] The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston: Little, Brown, & Co., 1994.
- [10] MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;353:2001–7.
- [11] Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman AM, Francis GS, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the International Society for Heart and Lung Transplantation; Endorsed by the Heart Failure Society of America. *Circulation* 2001;104:2996–3007.
- [12] Klabunde RE. Cardiovascular physiology concepts. 2nd ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2012.
- [13] Mohrman DE, Heller LJ. Cardiovascular physiology. New York: McGraw-Hill, 2010.
- [14] Lilly LS, the faculty of the Harvard Medical School. Pathophysiology of heart disease: a collaborative project of medical students and faculty. 5th ed. Baltimore: Lippincott Williams & Wilkins, 2011.
- [15] Westerhof N, O'Rourke MF. Haemodynamic basis for the development of left ventricular failure in systolic hypertension and for its logical therapy. *J Hypertens* 1995;13:943–52.
- [16] Lee CS, Tkacs NC. Current concepts of neurohormonal activation in heart failure: mediators and mechanisms. *AACN Adv Crit Care* 2008;19:364–85.
- [17] Chaggar PS, Malkin CJ, Shaw SM, Williams SG, Channer KS. Neuroendocrine effects on the heart and targets for therapeutic manipulation in heart failure. *Cardiovasc Ther* 2009;27:187–93.
- [18] Rea ME, Dunlap ME. Renal hemodynamics in heart failure: implications for treatment. *Curr Opin Nephrol Hypertens* 2008;17:87–92.
- [19] Curry CW, Nelson GS, Wyman BT, Declerck J, Talbot M, Berger RD, et al. Mechanical dyssynchrony in dilated cardiomyopathy with intraventricular conduction delay as depicted by 3D tagged magnetic resonance imaging. *Circulation* 2000;101:E2.
- [20] Kim HN, Januzzi AL. Natriuretic peptide testing in heart failure. *Circulation* 2011;123:2015–9.
- [21] Boulanger CM. Secondary endothelial dysfunction: hypertension and heart failure. *J Mol Cell Cardiol* 1999;31:39–49.
- [22] Chen D, Assad-Kottner C, Orrego C, Torre-Amione G. Cytokines and acute heart failure. *Crit Care Med* 2008;36:S9–16.
- [23] Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. 2009 focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 2009;119:e391–479.
- [24] Hencin MY. Heart failure in clinical practice. London: Springer-Verlag London Limited, 2010.
- [25] Young JB. Clinical management of heart failure. 3rd ed. West Islip: Professional Communications, Inc., 2009.