HEART FAILURE-A REVIEW

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1. INTRODUCTION

Heart failure (HF) is a condition in which a problem with the structure or function of the heart impairs its ability to supply sufficient blood flow to meet the body's needs (1). It should not be confused with cardiac arrest.

Common causes of heart failure include myocardial infarction and other forms of ischemic heart disease, hypertension, valvular heart disease and cardiomyopathy (2). Heart failure can cause a large variety of symptoms such as shortness of breath (typically worse when lying flat, which is called orthopnea), coughing, ankle swelling and reduced exercise capacity. Heart failure is often undiagnosed due to a lack of a universally agreed definition and challenges in definitive diagnosis. Treatment commonly consists of lifestyle measures (such as decreased salt intake) and medications, and sometimes devices or even surgery.

Heart failure is a common, costly, disabling and deadly condition (2). In developing countries, around 2% of adults suffer from heart failure, but in those over the age of 65, this increases to 6–10% (2, 3). Mostly due to costs of hospitalization, it is associated with a high health expenditure; costs have been estimated to amount to 2% of the total budget of the National Health Service in the United Kingdom, and more than $35 billion in the United States (4, 5). Heart failure is associated with significantly reduced physical and mental health, resulting in a markedly decreased quality of life (6, 7). With the exception of heart failure caused by reversible conditions, the condition usually worsens with time. Although some patients survive many years, progressive disease is associated with an overall annual mortality rate of 10% (8).

2. SIGNS AND SYMPTOMS

2.1 SYMPTOMS

Heart failure symptoms are traditionally and somewhat arbitrarily divided into "left" and "right" sided, recognizing that the left and right ventricles of the heart supply different portions of the circulation. However, heart failure is not exclusively *backward failure* (in the part of the circulation which drains to the ventricle).

There are several other exceptions to a simple left-right division of heart failure symptoms. Left sided *forward* failure overlaps with right sided *backward* failure. Additionally, the most common cause of right-sided heart failure is left-sided heart failure. The result is that patients commonly present with both sets of signs and symptoms.

Left-sided failure

Forward failure of the left ventricle causes congestion of the pulmonary vasculature, and so the symptoms are predominantly respiratory in nature. The patient will have dyspnea (shortness of breath) on exertion (*dyspnée d'effort*) and in severe cases, dyspnea at rest. Increasing breathlessness on lying flat, called orthopnea, occurs. It is often measured in the number of pillows required to lie comfortably, and in severe cases, the patient may resort to sleeping while sitting up. Another symptom of heart failure is paroxysmal nocturnal dyspnea also known as "cardiac asthma", a sudden nighttime attack of severe breathlessness, usually several hours after going to sleep. Easy fatigueability and exercise intolerance are also common complaints related to respiratory compromise.

Compromise of left ventricular *forward* function may result in symptoms of poor systemic circulation such as dizziness, confusion and cool extremities at rest.

Right-sided failure

Backward failure of the right ventricle leads to congestion of systemic capillaries. This helps to generate excess fluid accumulation in the body. This causes swelling under the skin (termed peripheral edema or anasarca) and usually affects the dependent parts of the body first (causing foot and ankle swelling in people who are standing up, and sacral edema in people who are predominantly lying down). Nocturia (frequent nighttime urination) may occur when fluid from the legs is returned to the bloodstream while lying down at night. In progressively severe cases, ascites (fluid accumulation in the abdominal cavity causing swelling) and hepatomegaly (enlargement of the liver) may develop. Significant liver congestion may result in impaired liver function, and jaundice and even coagulopathy (problems of decreased blood clotting) may occur.

2.2 SIGNS

2.2.1 Left-sided failure

Common respiratory signs are tachypnea (increased *rate* of breathing) and increased *work* of breathing (non-specific signs of respiratory distress). Rales or crackles, heard initially in the lung bases, and when severe, throughout the lung fields suggest the development of pulmonary edema (fluid in the alveoli). Dullness of the lung fields to finger percussion and reduced breath sounds at the bases of the lung may suggest the development of a pleural effusion (fluid collection in between the lung and the chest wall). Cyanosis which suggests severe hypoxemia, is a late sign of extremely severe pulmonary edema.

Additional signs indicating left ventricular failure include a laterally displaced apex beat (which occurs if the heart is enlarged) and a gallop rhythm (additional heart sounds) may be heard as a marker of increased blood flow, or increased intra-cardiac pressure. Heart murmurs may indicate the presence of valvular heart disease, either as a cause (e.g. aortic stenosis) or as a result (e.g. mitral regurgitation) of the heart failure.

2.2.2 Right-sided failure

Physical examination can reveal pitting peripheral edema, ascites, and hepatomegaly. Jugular venous pressure is frequently assessed as a marker of fluid status, which can be accentuated by the hepatojugular reflux. If the right ventriclar pressure is increased, a parasternal heave may be present, signifying the compensatory increase in contraction strength.

3. CAUSES

The predominance of causes of heart failure are difficult to analyze due to challenges in diagnosis, differences in populations, and changing prevalence of causes with age.

A 19 year study of 13000 healthy adults in the United States (the National Health and Nutrition Examination Survey (NHANES I) found the following causes ranked by Population Attributable Risk score: (9)

1. Ischaemic Heart Disease 62%
2. Cigarette Smoking 16%
3. Hypertension (high blood pressure)10%
4. Obesity 8%
5. Diabetes 3%
6. Valvular Heart Disease 2% (much higher in older populations)

An Italian registry of over 6200 patients with heart failure showed the following underlying causes: [19]

1. Ischaemic Heart Disease 40%
2. Dilated Cardiomyopathy 32%
3. Valvular Heart Disease 12%
4. Hypertension 11%
5. Other 5%

Rarer causes of heart failure include:

- Viral Myocarditis (an infection of the heart muscle)

- Infiltrations of the muscle such as amyloidosis
- HIV cardiomyopathy (caused by Human Immunodeficiency Virus)
- Connective Tissue Diseases such as Systemic lupus erythematosus
- Abuse of drugs such as alcohol
- Pharmaceutical drugs such as chemotherapeutic agents.
- Arrhythmias

Obstructive Sleep Apnea a condition of sleep disordered breathing overlaps with obesity, hypertension and diabetes and is regarded as an independent cause of heart failure.

Acute decompensated heart failure

Chronic stable heart failure may easily decompensate. This most commonly results from an intercurrent illness (such as pneumonia), myocardial infarction (a heart attack), arrhythmias, uncontrolled hypertension, or a patient's failure to maintain a fluid restriction, diet or medication(10). Other well recognised precipitating factors include anaemia and hyperthyroidism which place additional strain on the heart muscle. Excessive fluid or salt intake, and medication that causes fluid retention such as NSAIDs and thiazolidinediones, may also precipitate decompensation(11).

4. PATHOPHYSIOLOGY

Heart failure is caused by any condition which reduces the efficiency of the myocardium, or heart muscle, through damage or overloading. As such, it can be caused by as diverse an array of conditions as myocardial infarction (in which the heart muscle is starved of oxygen and dies), hypertension (which increases the force of contraction needed to pump blood) and amyloidosis (in which protein is deposited in the heart muscle, causing it to stiffen). Over time these increases in workload will produce changes to the heart itself:

- Reduced contractility, or force of contraction, due to overloading of the ventricle. In health, increased filling of the ventricle results in increased contractility (by the Frank-Starling law of the heart) and thus a rise in cardiac output. In heart failure this mechanism fails, as the ventricle is loaded with blood to the point where heart muscle contraction becomes less efficient. This is due to reduced ability to cross-link actin and myosin filaments in over-stretched heart muscle (11).
- A reduced stroke volume, as a result of a failure of systole, diastole or both. Increased end systolic volume is usually caused by reduced contractility. Decreased end diastolic

volume results from impaired ventricular filling – as occurs when the compliance of the ventricle falls (i.e. when the walls stiffen).

- Reduced spare capacity. As the heart works harder to meet normal metabolic demands, the amount cardiac output can increase in times of increased oxygen demand (e.g. exercise) is reduced. This contributes to the exercise intolerance commonly seen in heart failure. This translates to the loss of one's cardiac reserve. The cardiac reserve refers to the ability of the heart to work harder during exercise or strenuous activity. Since the heart has to work harder to meet the normal metabolic demands, it is incapable of meeting the metabolic demands of the body during exercise.
- Increased heart rate, stimulated by increased sympathetic activity in order to maintain cardiac output. Initially, this helps compensate for heart failure by maintaining blood pressure and perfusion, but places further strain on the myocardium, increasing coronary perfusion requirements, which can lead to worsening of ischemic heart disease. Sympathetic activity may also cause potentially fatal arrhythmias.
- Hypertrophy (an increase in physical size) of the myocardium, caused by the terminally differentiated heart muscle fibres increasing in size in an attempt to improve contractility. This may contribute to the increased stiffness and decreased ability to relax during diastole.
- Enlargement of the ventricles, contributing to the enlargement and spherical shape of the failing heart. The increase in ventricular volume also causes a reduction in stroke volume due to mechanical and contractile inefficiency (12).

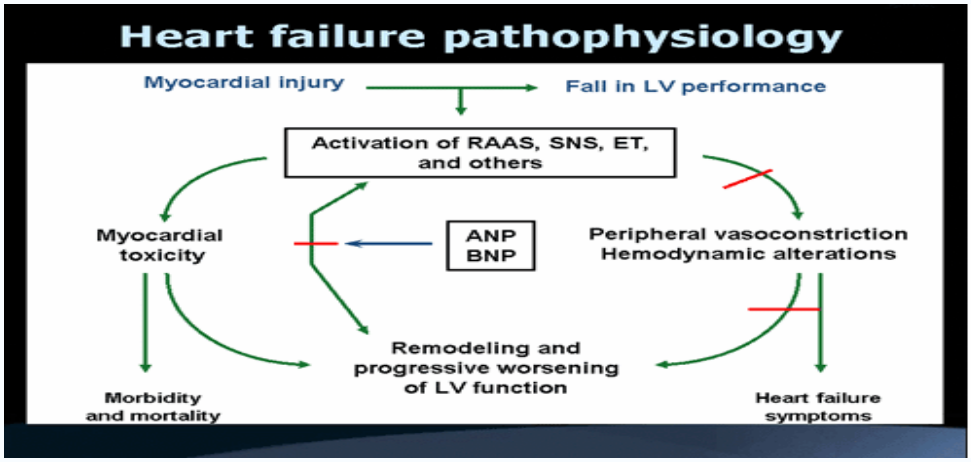

Figure 1. Pathophysiology of Heart Failure

The general effect is one of reduced cardiac output and increased strain on the heart. This increases the risk of cardiac arrest (specifically due to ventricular dysrhythmias), and reduces blood supply to the rest of the body. In chronic disease the reduced cardiac output causes a number of changes in the rest of the body, some of which are physiological compensations, some of which are part of the disease process:

- Arterial blood pressure falls. This destimulates baroreceptors in the carotid sinus and aortic arch which link to the nucleus tractus solitarius. This center in the brain increases sympathetic activity, releasing catecholamines into the blood stream. Binding to alpha-1 receptors results in systemic arterial vasoconstriction. This helps restore blood pressure but also increases the total peripheral resistance, increasing the workload of the heart. Binding to beta-1 receptors in the myocardium increases the heart rate and make contractions more forceful, in an attempt to increase cardiac output. This also, however, increases the amount of work the heart has to perform.
- Increased sympathetic stimulation also causes the hypothalamus to secrete vasopressin (also known as antidiuretic hormone or ADH), which causes fluid retention at the kidneys. This increases the blood volume and blood pressure.
- Reduced perfusion (blood flow) to the kidneys stimulates the release of renin – an enzyme which catalyses the production of the potent vasopressor angiotensin. Angiotensin and its metabolites cause further vasocontriction, and stimulate increased secretion of the steroid aldosterone from the adrenal glands. This promotes salt and fluid retention at the kidneys, also increasing the blood volume.
- The chronically high levels of circulating neuroendocrine hormones such as catecholamines, renin, angiotensin, and aldosterone affects the myocardium directly, causing structural remodelling of the heart over the long term. Many of these remodelling effects seem to be mediated by transforming growth factor beta (TGF-beta), which is a common downstream target of the signal transduction cascade initiated by catecholamines (13) and angiotensin II (14), and also by epidermal growth factor (EGF), which is a target of the signaling pathway activated by aldosterone (15)
- Reduced perfusion of skeletal muscle causes atrophy of the muscle fibres. This can result in weakness, increased fatigueability and decreased peak strength - all contributing to exercise intolerance (16).

The increased peripheral resistance and greater blood volume place further strain on the heart and accelerates the process of damage to the myocardium. Vasoconstriction and fluid retention produce an increased hydrostatic pressure in the capillaries. This shifts of the balance of forces in favour of interstitial fluid formation as the increased pressure forces additional fluid out of the blood, into the tissue. This results in edema (fluid build-up) in the tissues. In right-sided heart failure this commonly starts in the ankles where venous pressure is high due to the effects of gravity (although if the patient is bed-ridden, fluid accumulation may begin in the sacral region.) It may also occur in the abdominal cavity, where the fluid build-up is called ascites. In left-sided heart failure edema can occur in the lungs - this is called cardiogenic pulmonary oedema. This reduces spare capacity for ventilation, causes stiffening of the lungs and reduces the efficiency of gas exchange by increasing the distance between the air and the blood. The consequences of this are shortness of breath, orthopnoea and paroxysmal nocturnal dyspnea.

The symptoms of heart failure are largely determined by which side of the heart fails. The left side pumps blood into the systemic circulation, whilst the right side pumps blood into the pulmonary circulation. Whilst left-sided heart failure will reduce cardiac output to the systemic circulation, the initial symptoms often manifest due to effects on the pulmonary circulation. In systolic dysfunction, the ejection fraction is decreased, leaving an abnormally elevated volume of blood in the left ventricle. In diastolic dysfunction, end-diastolic ventricular pressure will be high. This increase in volume or pressure backs up to the left atrium and then to the pulmonary veins. Increased volume or pressure in the pulmonary veins impairs the normal drainage of the alveoli and favors the flow of fluid from the capillaries to the lung parenchyma, causing pulmonary edema. This impairs gas exchange. Thus, left-sided heart failure often presents with respiratory symptoms: shortness of breath, orthopnea and paroxysmal nocturnal dyspnea.

In severe cardiomyopathy, the effects of decreased cardiac output and poor perfusion become more apparent, and patients will manifest with cold and clammy extremities, cyanosis, claudication, generalized weakness, dizziness, and syncope.

The resultant hypoxia caused by pulmonary edema causes vasoconstriction in the pulmonary circulation, which results in pulmonary hypertension. Since the right ventricle generates far lower pressures than the left ventricle (approximately 20 mmHg versus around 120 mmHg, respectively, in the healthy individual) but nonetheless generates cardiac output exactly equal to the left ventricle, this means that a small increase in pulmonary vascular resistance

causes a large increase in amount of work the right ventricle must perform. However, the main mechanism by which left-sided heart failure causes right-sided heart failure is actually not well understood. Some theories invoke mechanisms that are mediated by neurohormonal activation. Mechanical effects may also contribute. As the left ventricle distends, the intraventricular septum bows into the right ventricle, decreasing the capacity of the right ventricle.

Systolic dysfunction

Heart failure caused by systolic dysfunction is more readily recognized. It can be simplistically described as failure of the pump function of the heart. It is characterized by a decreased ejection fraction (less than 45%). The strength of ventricular contraction is attenuated and inadequate for creating an adequate stroke volume, resulting in inadequate cardiac output. In general, this is caused by dysfunction or destruction of cardiac myocytes or their molecular components. In congenital diseases such as Duchenne muscular dystrophy, the molecular structure of individual myocytes is affected. Myocytes and their components can be damaged by inflammation (such as in myocarditis) or by infiltration (such as in amyloidosis). Toxins and pharmacological agents (such as ethanol, cocaine, and amphetamines) cause intracellular damage and oxidative stress. The most common mechanism of damage is ischemia causing infarction and scar formation. After myocardial infarction, dead myocytes are replaced by scar tissue, deleteriously affecting the function of the myocardium. On echocardiogram, this is manifest by abnormal or absent wall motion.

Because the ventricle is inadequately emptied, ventricular end-diastolic pressure and volumes increase. This is transmitted to the atrium. On the left side of the heart, the increased pressure is transmitted to the pulmonary vasculature, and the resultant hydrostatic pressure favors extravassation of fluid into the lung parenchyma, causing pulmonary edema. On the right side of the heart, the increased pressure is transmitted to the systemic venous circulation and systemic capillary beds, favoring extravassation of fluid into the tissues of target organs and extremities, resulting in dependent peripheral edema.

Regardless of the precipitating event, the common pathophysiologic state that perpetuates the progression of heart failure is extremely complex. Compensatory mechanisms exist on every level of organization from sub-cellular all the way through organ-to-organ interactions. Only when this network of adaptations becomes overwhelmed does heart failure ensue.

In this section, we focus on those adaptations that represent significant therapeutic targets in the treatment of heart failure.

Most important among these adaptations are the

(1) Frank-Starling mechanism, in which an increased preload helps to sustain cardiac performance

(2) Alterations in myocyte regeneration and death

(3) Myocardial hypertrophy with or without cardiac chamber dilatation, in which the mass of contractile tissue is augmented

(4) Activation of neurohumoral systems, especially the release of norepinephrine by adrenergic cardiac nerves

which augments myocardial contractility and includes activation of the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS), and other neurohumoral adjustments that act to maintain arterial pressure and perfusion of vital organs. In acute heart failure, the finite adaptive mechanisms that may be adequate to maintain the overall contractile performance of the heart at relatively normal levels become maladaptive when trying to sustain adequate cardiac performance.

The primary myocardial response to chronic increased wall stress is myocyte hypertrophy, death/apoptosis, and regeneration. This process eventually leads to remodeling, usually the eccentric type. Eccentric remodeling further worsens the loading conditions on the remaining myocytes and perpetuates the deleterious cycle. The idea of lowering wall stress to slow the process of remodeling has long been exploited in treating heart failure patients.

However, the concept of the heart as a self-renewing organ is a relatively recent development. The rate of myocyte turnover has been shown to increase during times of pathologic stress. In heart failure, this mechanism for replacement becomes overwhelmed by an even faster increase in the rate of myocyte loss. This imbalance of hypertrophy and death over regeneration is the final common pathway at the cellular level for the progression of remodeling and heart failure. This new paradigm for myocyte biology has created an entire field of research aimed directly at augmenting myocardial regeneration.

The reduction of cardiac output following myocardial injury sets into motion a cascade of hemodynamic and neurohormonal derangements that provoke activation of neuroendocrine systems, most notably the above-mentioned adrenergic systems and RAAS.

The release of epinephrine and norepinephrine, along with the vasoactive substances endothelin-1 (ET-1) and vasopressin, causes vasoconstriction, which increases afterload, and, via an increase in cyclic adenosine monophosphate (cAMP), causes an increase in cytosolic calcium entry. The increased calcium entry into the myocytes augments myocardial contractility and impairs myocardial relaxation (lusitropy).

The calcium overload may also induce arrhythmias and lead to sudden death. The increase in afterload and myocardial contractility (known as inotropy) and the impairment in myocardial lusitropy lead to an increase in myocardial energy expenditure and a further decrease in cardiac output. The increase in myocardial energy expenditure leads to myocardial cell death/apoptosis, which results in heart failure and further reduction in cardiac output, perpetuating a cycle of further increased neurohumoral stimulation and further adverse hemodynamic and myocardial responses as described above.

In addition, the activation of the RAAS leads to salt and water retention, resulting in increased preload and further increases in myocardial energy expenditure. Increases in renin, mediated by decreased stretch of the glomerular afferent arteriole, reduced delivery of chloride to the macula densa and increased beta1-adrenergic activity as a response to decreased cardiac output. This results in an increase in angiotensin II (Ang II) levels and, in turn, aldosterone levels. This results in stimulation of the release of aldosterone. Ang II, along with ET-1, is crucial in maintaining effective intravascular homeostasis mediated by vasoconstriction and aldosterone-induced salt and water retention.

Research indicates that local cardiac Ang II production (which decreases lusitropy, increases inotropy, and increases afterload) leads to increased myocardial energy expenditure. Ang II has also been shown both in vitro and in vivo to increase the rate of myocyte apoptosis. In this fashion, Ang II has similar actions to norepinephrine in heart failure.

Ang II also mediates myocardial cellular hypertrophy and may promote progressive loss of myocardial function. The neurohumoral factors above lead to myocyte hypertrophy and interstitial fibrosis, resulting in increased myocardial volume and increased myocardial mass, as well as myocyte loss. The increase in myocardial volume results in myocyte slippage, which also results in further increases in myocardial volume and mass.

In the failing heart, increased myocardial volume is characterized by larger myocytes approaching the end of their life cycle.

As more myocytes drop out, an increased load is placed on the remaining myocardium and this unfavorable environment is transmitted to the progenitor cells responsible for replacing lost myocytes. Progenitor cells become progressively less effective as the underlying pathologic process worsens and myocardial failure accelerates. These features, namely the increased myocardial volume and mass, along with a net loss of myocytes, are the hallmark of myocardial remodeling. This remodeling process leads to early adaptive mechanisms, such as augmentation of stroke volume (Starling mechanism) and decreased wall stress (Laplace mechanism), and later, maladaptive mechanisms such as increased myocardial oxygen demand, myocardial ischemia, impaired contractility, and arrhythmogenesis.

As heart failure advances, there is a relative decline in the counterregulatory effects of endogenous vasodilators, including nitric oxide (NO), prostaglandins (PGs), bradykinin (BK), atrial natriuretic peptide (ANP), and B-type natriuretic peptide (BNP). This occurs simultaneously with the increase in vasoconstrictor substances from the RAAS and adrenergic systems. This fosters further increases in vasoconstriction and thus preload and afterload, leading to cellular proliferation, adverse myocardial remodeling, and antinatriuresis with total body fluid excess and worsening congestive heart failure symptoms.

Both systolic and diastolic heart failure result in a decrease in stroke volume. This leads to activation of peripheral and central baroreflexes and chemoreflexes that are capable of eliciting marked increases in sympathetic nerve traffic. While there are commonalities in the neurohormonal responses to decreased stroke volume, the neurohormone-mediated events that follow have been most clearly elucidated for individuals with systolic heart failure. The ensuing elevation in plasma norepinephrine directly correlates with the degree of cardiac dysfunction and has significant prognostic implications. Norepinephrine, while directly toxic to cardiac myocytes, is also responsible for a variety of signal-transduction abnormalities, such as downregulation of beta1-adrenergic receptors, uncoupling of beta2-adrenergic receptors, and increased activity of inhibitory G-protein. Changes in beta1-adrenergic receptors result in overexpression and promote myocardial hypertrophy.

ANP and BNP are endogenously generated peptides activated in response to atrial and ventricular volume/pressure expansion. ANP and BNP are released from the atria and ventricles, respectively, and both promote vasodilation and natriuresis. Their hemodynamic effects are mediated by decreases in ventricular filling pressures, owing to reductions in cardiac preload and

afterload. BNP, in particular, produces selective afferent arteriolar vasodilation and inhibits sodium reabsorption in the proximal convoluted tubule. BNP inhibits renin and aldosterone release and, therefore, adrenergic activation as well. Both ANP and BNP are elevated in chronic heart failure. BNP, in particular, has potentially important diagnostic, therapeutic, and prognostic implications.

Other vasoactive systems that play a role in the pathogenesis of heart failure include the endothelin (ET) receptor system, adenosine receptor system, vasopressin, and tumor necrosis factor-alpha (TNF-alpha). Endothelin, a substance produced by the vascular endothelium, may contribute to the regulation of myocardial function, vascular tone, and peripheral resistance in heart failure. Elevated levels of endothelin-1 (ET-1) closely correlate with the severity of heart failure. ET-1 is a potent vasoconstrictor and has exaggerated vasoconstrictor effects in the renal vasculature, reducing renal plasma blood flow, glomerular filtration rate (GFR), and sodium excretion.

TNF-alpha has been implicated in response to various infectious and inflammatory conditions. Elevations in TNF-alpha levels have been consistently observed in heart failure and seem to correlate with the degree of myocardial dysfunction. Experimental studies suggest that local production of TNF-alpha may have toxic effects on the myocardium, thus worsening myocardial systolic and diastolic function.

Thus, in individuals with systolic dysfunction, the neurohormonal responses to decreased stroke volume result in temporary improvement in systolic blood pressure and tissue perfusion. However, in all circumstances, the existing data support the notion that these neurohormonal responses contribute to the progression of myocardial dysfunction in the long term.

In diastolic heart failure (heart failure with normal ejection fraction [HFNEF]), the same pathophysiologic processes leading to decreased cardiac output that occur in systolic heart failure also occur, but they do so in response to a different set of hemodynamic and circulatory environmental factors that depress cardiac output.

In HFNEF, altered relaxation and increased stiffness of the ventricle (due to delayed calcium uptake by the myocyte sarcoplasmic reticulum and delayed calcium efflux from the myocyte) occur in response to an increase in ventricular afterload (pressure overload). The impaired relaxation of the ventricle leads to impaired diastolic filling of the left ventricle (LV).

An increase in LV chamber stiffness occurs secondary to any one of the following 3 mechanisms or to a combination thereof:

- A rise in filling pressure (ie, movement of the ventricle up along its pressure-volume curve to a steeper portion, as may occur in conditions such as volume overload secondary to acute valvular regurgitation or acute LV failure due to myocarditis)
- A shift to a steeper ventricular pressure-volume curve, occurring most commonly as a result of not only increased ventricular mass and wall thickness, as observed in aortic stenosis and long-standing hypertension, but also due to infiltrative disorders (such as amyloidosis), endomyocardial fibrosis, and myocardial ischemia
- A parallel upward displacement of the diastolic pressure-volume curve, generally referred to as a decrease in ventricular distensibility, usually caused by extrinsic compression of the ventricles.

Whereas volume overload, as observed in chronic aortic and/or mitral valvular regurgitant disease, shifts the entire diastolic pressure-volume curve to the right, indicating increased chamber stiffness, pressure overload that leads to concentric LV hypertrophy (as occurs in aortic stenosis, hypertension, and hypertrophic cardiomyopathy) shifts the diastolic pressure-volume curve to the left along its volume axis so that at any diastolic volume ventricular diastolic pressure is abnormally elevated, although chamber stiffness may or may not be altered. Increases in diastolic pressure lead to increased myocardial energy expenditure, remodeling of the ventricle, increased myocardial oxygen demand, myocardial ischemia, and eventual progression of the maladaptive mechanisms of the heart that lead to decompensated heart failure. Another clinically important process in the development of heart failure is the generation of arrhythmias. While life-threatening rhythms are more common in ischemic versus nonischemic cardiomyopathy, arrhythmia imparts a significant burden in all forms of heart failure. In fact, some arrhythmias even perpetuate heart failure. The most significant of all rhythms associated with heart failure are the life-threatening ventricular arrhythmias. Structural substrates for ventricular arrhythmias common in heart failure, regardless of the underlying cause include

(1) ventricular dilatation,

(2) myocardial hypertrophy,

(3) myocardial fibrosis.

At the cellular level, myocytes may be exposed to increased stretch, wall tension, catecholamines, ischemia, and electrolyte imbalance. The combination of these factors contributes to an increased incidence of arrhythmogenic sudden cardiac death in patients with heart failure.

Diastolic dysfunction

Heart failure caused by diastolic dysfunction is generally described as the failure of the ventricle to adequately relax and typically denotes a stiffer ventricular wall. This causes inadequate filling of the ventricle, and therefore results in an inadequate stroke volume. The failure of ventricular relaxation also results in elevated end-diastolic pressures, and the end result is identical to the case of systolic dysfunction (pulmonary edema in left heart failure, peripheral edema in right heart failure.)

Diastolic dysfunction can be caused by processes similar to those that cause systolic dysfunction, particularly causes that affect cardiac remodeling.

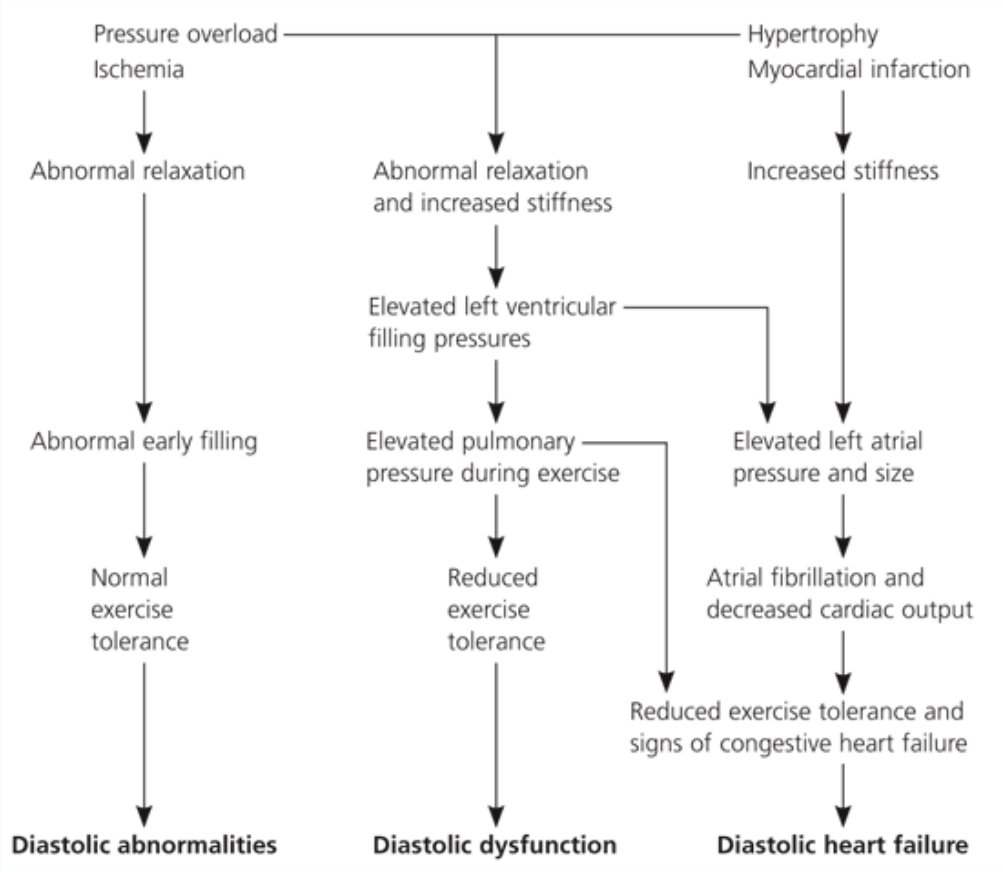

Figure 2. Chronic Heart Failure Program

Diastolic dysfunction may not manifest itself except in physiologic extremes if systolic function is preserved. The patient may be completely asymptomatic at rest. However, they are exquisitely sensitive to increases in heart rate, and sudden bouts of tachycardia (which can be caused simply by physiological responses to exertion, fever, or dehydration, or by pathological tachyarrhythmias such as atrial fibrillation with rapid ventricular response) may result in flash pulmonary edema. Adequate rate control (usually with a pharmacological agent that slows down AV conduction such as a calcium channel blocker or a beta-blocker) is therefore key to preventing decompensation.

Left ventricular diastolic function can be determined through echocardiography by measurement of various parameters such as the E/A ratio (early-to-atrial left ventricular filling ratio), the E (early left ventricular filling) deceleration time, and the isovolumic relaxation time.

Chronic heart failure leads to upregulation of GRK2, both in cardiac myocytes and in adrenal chromaffin cells. In the cardiac myocyte, this results in increased phosphorylation and desensitization (inset) of βARs. This results in reduced catecholamine-induced signaling of these receptors through the G_s protein-AC-PKA signaling pathway, leading to reduced contractility. Thus, in chronic heart failure, increased amounts of circulating (or locally released) catecholamines, present at cardiac βARs, are unable to elicit the procontractile response of these receptors; hence cardiac inotropic reserve diminishes, and a vicious cycle resulting in sympathetic overstimulation of the failing heart ensues. In the adrenal chromaffin cell, increased GRK2 levels result in increased phosphorylation and desensitization (inset) of α_2ARs, diminishing CA-induced, G_i/G_o protein–mediated signaling of these receptors and leading to increased levels of catecholamine secretion and of circulating catecholamines in chronic heart failure. Therefore, simultaneous inhibition of GRK2 in the heart and in the adrenal gland—for example, with a systemically delivered pharmacological inhibitor—could have dual therapeutic efficacy in chronic heart failure, restoring both cardiac inotropic reserve (positive inotropy in the myocardium) and cardiac sympathetic stimulation (sympatholytic activity in the adrenal gland) to normal levels. CA, catecholamine. AC, adenylyl cyclase. ATP, adenosine triphosphate. cAMP, cyclic AMP. PKA, protein kinase A.

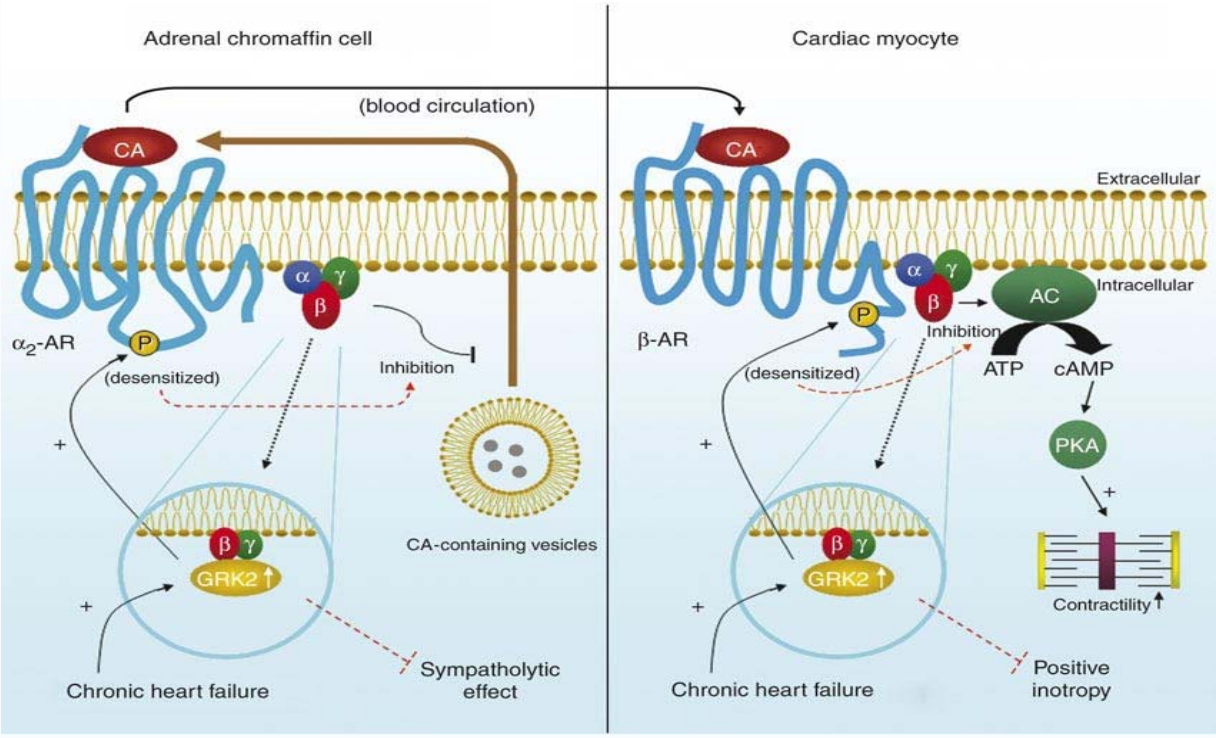

Figure 3. Schematic representation of the pathophysiologic role of GRK2 and the therapeutic potential of its inhibition in heart failure.

5. DIAGNOSIS

Chest x-ray showing an enlarged cardiac silhouette due to congestive heart failure.

Imaging

Echocardiography is commonly used to support a clinical diagnosis of heart failure. This modality uses ultrasound to determine the stroke volume (SV, the amount of blood in the heart that exits the ventricles with each beat), the end-diastolic volume (EDV, the total amount of blood at the end of diastole), and the SV in proportion to the EDV, a value known as the *ejection fraction* (EF). In pediatrics, the shortening fraction is the preferred measure of systolic function. Normally, the EF should be between 50% and 70%; in systolic heart failure, it drops below 40%. Echocardiography can also identify valvular heart disease and assess the state of the pericardium (the connective tissue sac surrounding the heart). Echocardiography may also aid in deciding what treatments will help the patient, such as medication, insertion of an implantable cardioverter-defibrillator or cardiac resynchronization therapy. Echocardiography can also help determine if acute myocardial ischemia is the precipitating cause, and may manifest as regional wall motion abnormalities on echo.

Chest X-rays are frequently used to aid in the diagnosis of CHF. In the compensated patient, this may show cardiomegaly (visible enlargement of the heart), quantified as the *cardiothoracic ratio* (proportion of the heart size to the chest). In left ventricular failure, there may be evidence of vascular redistribution ("upper lobe blood diversion" or "cephalization"), Kerley lines, cuffing of the areas around the bronchi, and interstitial edema.

Electrophysiology

An electrocardiogram (ECG/EKG) is used to identify arrhythmias, ischemic heart disease, right and left ventricular hypertrophy, and presence of conduction delay or abnormalities (e.g. left bundle branch block). An ECG may also diagnose acute myocardial ischemia or infarction (if ST depression or elevation are present).

Blood tests

Blood tests routinely performed include electrolytes (sodium, potassium), measures of renal function, liver function tests, thyroid function tests, a complete blood count, and often C-reactive protein if infection is suspected. An elevated B-type natriuretic peptide (BNP) is a specific test indicative of heart failure. Additionally, BNP can be used to differentiate between causes of dyspnea due to heart failure from other causes of dyspnea. If myocardial infarction is suspected, various cardiac markers may be used.

According to a meta-analysis comparing BNP and N-terminal pro-BNP (NTproBNP) in the diagnosis of heart failure, BNP is a better indicator for heart failure and left ventricular systolic dysfunction. In groups of symptomatic patients, a diagnostic odds ratio of 27 for BNP compares with a sensitivity of 85% and specificity of 84% in detecting heart failure (17).

Angiography

Heart failure may be the result of coronary artery disease, and its prognosis depends in part on the ability of the coronary arteries to supply blood to the myocardium (heart muscle). As a result, coronary catheterization may be used to identify possibilities for revascularisation through percutaneous coronary intervention or bypass surgery.

Monitoring

Various measures are often used to assess the progress of patients being treated for heart failure. These include fluid balance (calculation of fluid intake and excretion), monitoring body weight (which in the shorter term reflects fluid shifts).

6. MANAGEMENT

Treatment focuses on improving the symptoms and preventing the progression of the disease. Reversible causes of the heart failure also need to be addressed: (e.g. infection, alcohol ingestion, anemia, thyrotoxicosis, arrhythmia, hypertension). Treatments include lifestyle and pharmacological modalities.

Acute decompensation

In acute decompensated heart failure (ADHF), the immediate goal is to re-establish adequate perfusion and oxygen delivery to end organs. This entails ensuring that airway, breathing, and circulation are adequate. Immediated treatments usually involve some combination of vasodialtors such as nitroglycerin, diuretics such as furosemide, and possibly non invasive positive pressure ventilation (NIPPV).

Chronic management

The goal is to prevent the development of acute decompensated heart failure, to counteract the deleterious effects of cardiac remodeling, and to minimize the symptoms that the patient suffers. In addition to pharmacologic agents (oral loop diuretics, beta-blockers, ACE inhibitors or angiotensin receptor blockers, vasodilators, and in severe cardiomyopathy aldosterone receptor antagonists), behavioral modification should be pursued, specifically with regards to dietary guidelines regarding salt and fluid intake. Exercise should be encouraged as tolerated, as sufficient conditioning can significantly improve quality-of-life.

In patients with severe cardiomyopathy, implantation of an automatic implantable cardioverter defibrillator(AICD) should be considered. A select population will also probably benefit from ventricular resynchronization.

In select cases, cardiac transplantation can be considered. While this may resolve the problems associated with heart failure, the patient generally must remain on an immunosuppressive regimen to prevent rejection, which has its own significant downsides.

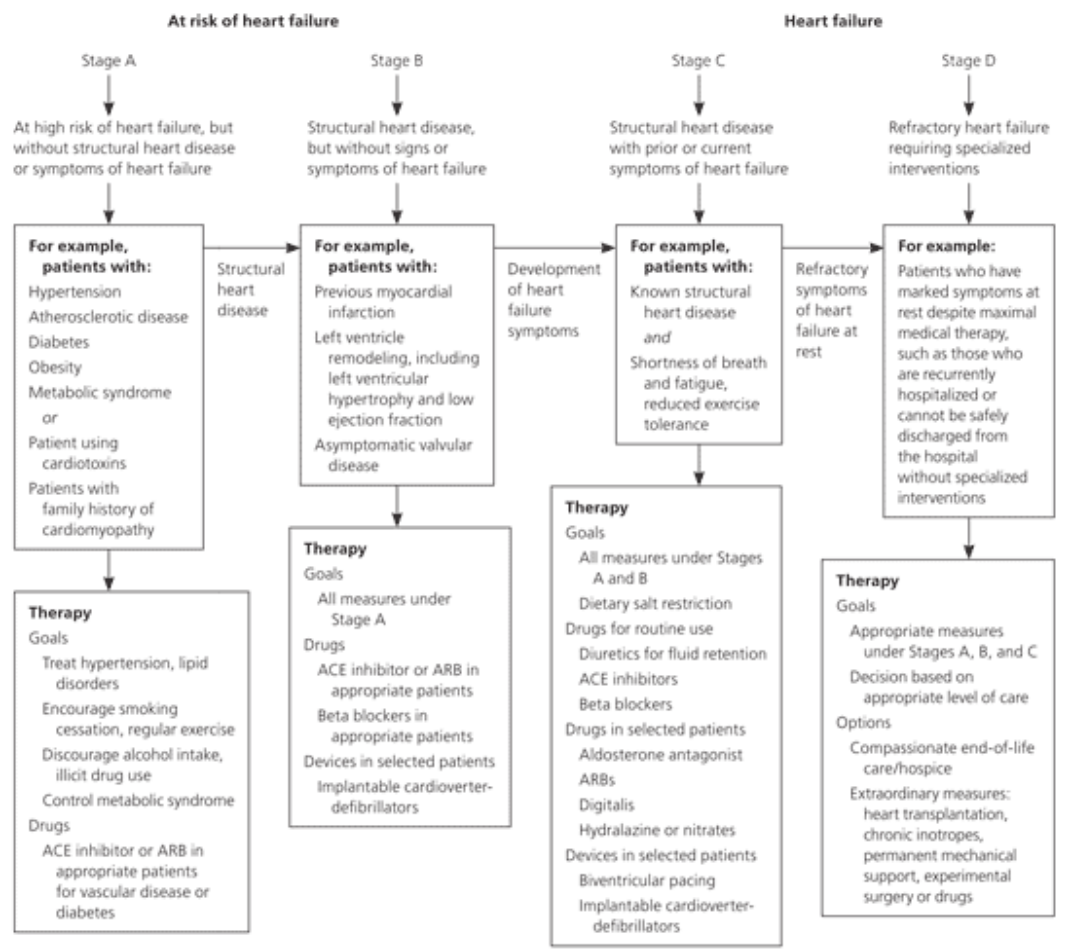

Figure 4. Management of heart failure.

Pharmacological management

There is a significant evidence–practice gap in the treatment of CHF; particularly the underuse of ACE inhibitors andβ-blockers and aldosterone antagonists which have been shown to provide mortality benefit.Treatment of CHF aims to relieve symptoms, to maintain a euvolemic state (normal fluid level in the circulatory system), and to improve prognosis by delaying progression of heart failure and reducing cardiovascular risk. Drugs used include: diuretic agents,vasodilator agents, positive inotropes, ACE inhibitors, beta blockers, and aldosterone antagonists (e.g.spironolactone). Some drugs which increase heart function, such as the positive inotrope Milrinone, lead to increased mortality, and are contraindicated.

6.1 ANGIOTENSIN-MODULATING AGENTS

ACE inhibitor (ACE) therapy is recommended for *all* patients with systolic heart failure, irrespective of symptomatic severity or blood pressure. ACE inhibitors improve symptoms, decrease mortality and reduce ventricular hypertrophy. Angiotensin II receptor antagonist therapy (also referred to as AT_1-antagonists or angiotensin receptor blockers), particularly using candesartan, is an acceptable alternative if the patient is unable to tolerate ACEI therapy. ACEIs and ARBs decrease afterload by antagonizing the vasopressor effect of angiotensin, thereby decreasing the amount of work the heart must perform. It is also believed that angiotensin directly affects cardiac remodeling, and blocking its activity can thereby slow the deterioration of cardiac function.

6.2 DIURETICS

Diuretic therapy is indicated for relief of congestive symptoms. Several classes are used, with combinations reserved for severe heart failure:

- Loop diuretics (e.g. furosemide, bumetanide) – most commonly used class in CHF, usually for moderate CHF.
- Thiazide diuretics (e.g. hydrochlorothiazide, chlorthalidone, chlorthiazide) – may be useful for mild CHF, but typically used in severe CHF in combination with loop diuretics, resulting in a synergistic effect.
- Potassium-sparing diuretics (e.g. amiloride) – used first-line use to correct hypokalaemia.
    - Spironolactone is used as add-on therapy to ACEI plus loop diuretic in severe CHF.
    - Eplerenone is specifically indicated for post-MI reduction of cardiovascular risk.

If a heart failure patient exhibits a resistance to or poor response to diuretic therapy, ultrafiltration or aquapheresis may be needed to achieve adequate control of fluid retention and congestion. The use of such mechanical methods of fluid removal can produce meaningful clinical benefits in patients with diuretic-resistant heart failure and may restore responsiveness to conventional doses of diuretics.[9]

6.3 BETA BLOCKERS

Until recently (within the last 20 years), β-blockers were contraindicated in CHF, owing to their negative inotropic effect and ability to produce bradycardia – effects which worsen heart failure. However, current guidelines recommend β-blocker therapy for patients with systolic

heart failure due to left ventricular systolic dysfunction after stabilization with diuretic and ACEI therapy, irrespective of symptomatic severity or blood pressure. As with ACEI therapy, the addition of a β-blocker can decrease mortality and improve left ventricular function. Several β-blockers are specifically indicated for CHF including: bisoprolol,carvedilol,nebivolol and extended-release metoprolol. The antagonism of β_1 inotropic and chronotropic effects decreases the amount of work the heart must perform. It is also thought that catecholamines and other sympathomimetics have an effect on cardiac remodeling, and blocking their activity can slow the deterioration of cardiac function.

6.4 POSITIVE INOTROPES

Digoxin (a mildly positive inotrope and negative chronotrope), once used as first-line therapy, is now reserved for control of ventricular rhythm in patients with atrial fibrillation; or where adequate control is not achieved with an ACEI, a beta blocker and a loop diuretic. There is no evidence that digoxin reduces mortality in CHF, although some studies suggest a decreased rate in hospital admissions. It is contraindicated in cardiac tamponade and restrictive cardiomyopathy.

The inotropic agent dobutamine is advised only in the short-term use of acutely decompensated heart failure, and has no other uses.

Phosphodiesterase inhibitors such as milrinone are sometimes utilized in severe cardiomyopathy. The mechanism of action is through inhibiting the breakdown and thereby increasing the concentration of cAMP similar to beta adrenoreceptor agonism, resulting in inotropic effects and modest diuretic effects.

6.5 ALTERNATIVE VASODILATORS

The combination of isosorbide dinitrate/hydralazine is the only vasodilator regimen, other than ACE inhibitors or angiotensin II receptor antagonists, with proven survival benefits. This combination appears to be particularly beneficial in CHF patients with an African American background, who respond less effectively to ACEI therapy.

6.6 ALDOSTERONE RECEPTOR ANTAGONISTS

The RALES trial showed that the addition of spironolactone can improve mortality, particularly in severe cardiomyopathy (ejection fraction less than 25%.) The related drug eplerenone was shown in the EPHESUS trial to have a similar effect, and it is specifically labelled for use in decompensated heart failure complicating acute myocardial infarction. While

the antagonism of aldosterone will decrease the effects of sodium and water retention, it is thought that the main mechanism of action is by antagonizing the deleterious effects of aldosterone on cardiac remodeling.

6.7 RECOMBINANT NEUROENDOCRINE HORMONES

Nesiritide, a recombinant form of B-natriuretic peptide, is indicated for use in patients with acute decompensated heart failure who have dyspnea at rest. Nesiritide promotes diuresis and natriuresis, thereby ameliorating volume overload. It is thought that, while BNP is elevated in heart failure, the peptide that is produced is actually dysfunctional or non-functional and thereby ineffective.

6.8 VASOPRESSIN RECEPTOR ANTAGONISTS

Tolvaptan and conivaptan antagonize the effects of antidiuretic hormone (vasopressin), thereby promoting the specific excretion of free water, directly ameliorating the volume overloaded state, and counteracting the hyponatremia that occurs due to the release of neuroendocrine hormones in an attempt to counteract the effects of heart failure. The EVEREST trial, which utilized tolvaptan, showed that when used in combination with conventional therapy, many symptoms of acute decompensated heart failure were significantly improved compared to conventional therapy alone although they found no difference in mortality and morbidity when compared to conventional therapy.

6.9 DEVICES

Patients with NYHA class III or IV, left ventricular ejection fraction (LVEF) of 35% or less and a QRS interval of 120 ms or more may benefit from cardiac resynchronization therapy (CRT; pacing both the left and right ventricles), through implantation of a bi-ventricular pacemaker, or surgical remodeling of the heart. These treatment modalities may make the patient symptomatically better, improving quality of life and in some trials have been proven to reduce mortality.

The COMPANION trial demonstrated that CRT improved survival in individuals with NYHA class III or IV heart failure with a widened QRS complex on an electrocardiogram. The CARE-HF trial showed that patients receiving CRT and optimal medical therapy benefited from a 36% reduction in all cause mortality, and a reduction in cardiovascular-related hospitalization. Patients with NYHA class II, III or IV, and LVEF of 35% (without a QRS requirement) may also benefit from an implantable cardioverter-defibrillator (ICD), a device that is proven to reduce all

cause mortality by 23% compared to placebo in patients who were already optimally managed on drug therapy. Patients with severe cardiomyopathy are at high risk for sudden cardiac death due to ventricular dysrhythmias. Although ICDs deliver electrical shocks to resynchronize heart rhythm which are potentially destressing to the patient, they have not been shown to affect quality of life. The number of (appropriate and inappropriate) shocks seems to be associated to a worse outcome. Although they are expensive, ICDs are potentially cost-effective in this setting.

Another current treatment involves the use of left ventricular assist devices (LVADs). LVADs are battery-operated mechanical pump-type devices that are surgically implanted on the upper part of the abdomen. They take blood from the left ventricle and pump it through the aorta. LVADs are becoming more common and are often used by patients who have to wait for heart transplants.

6.10 SURGERY

The final option, if other measures have failed, is heart transplantation or (temporary or prolonged) implantation of an artificial heart. These remain the recommended surgical treatment options. However, the limited number of hearts available for transplantation in a growing group of candidates, has led to the development of alternative surgical approaches to heart failure. These commonly involve surgical left ventricular remodeling. The aim of the procedures is to reduce the ventricle diameter (targeting Laplace's law and the disease mechanism of heart failure), improve its shape and/or remove non-viable tissue. These procedures can be performed together withcoronary artery bypass surgery or mitral valve repair.

If heart failure ensues after a myocardial infarction due to scarring and aneurysm formation, reconstructive surgery may be an option. These aneurysms bulge with every contraction, making it inefficient. Cooley and coworkers reported the first surgical treatment of a left ventricular aneurysm in 1958. They used a linear closure after their excision. In the 1980s,Vincent Dor developed a method using an circular patch stitched to the inside of the ventricle (the endoventricular circular patch plasty or Dor procedure) to close the defect after excision. His approach has been modified by others. Today, this is the preferred method for surgical treatment of incorrectly contracting (dyskinetic) left ventricle tissue, although a linear closure technique combined with septoplasty might be equally effective.

The multicenter RESTORE trial of 1198 participants demonstrated an increase in ejection fraction from about 30% to 40% with a concomitant shift in NYHA classes, with an early

mortality of 5% and a 5-year survival of 70%. As of yet, it remains unknown if surgery is superior to optimal medical therapy. The STICH trial (Surgical Treatment for IschemiC Heart Failure) will examine the role of medical treatment, coronary artery bypass surgery and left ventricle remodeling surgery in heart failure patients. Results are expected to be published in 2009 and 2011.

The Batista procedure was invented by Brazilian doctor Randas Batista in 1994 for use in patients with non-ischemic dilated cardiomyopathy. It involves removal of a portion of viable tissue from the left ventricle to reduce its size (partial left ventriculectomy), with or without repair or replacement of the mitral valve. Although several studies showed benefits from this surgery, studies at the Cleveland Clinic concluded that this procedure was associated with a high early and late failure rate. At 3 years only 26 percent were event-free and survival rate was only 60 percent. Most hospitals have abandoned this operation and it is no longer included in heart failure guidelines.

Newer procedures under examination are based on the observation that the spherical configuration of the dilated heart reduces ejection fraction compared to the elliptical form. Mesh-like constraint devices such as the Acorn CorCap aim to improve contraction efficacy and prevent further remodeling. Clinical trials are underway. Another technique which aims to divide the spherical ventricle into two elliptical halves is used with the Myosplint device.

6.11 PALLIATIVE CARE AND HOSPICE

Without transplantation, heart failure caused by ischemic heart disease is not reversible, and cardiac function typically deteriorates with time. (In particular, diastolic function worsens as a function of age even in individuals without ischemic heart disease.) The growing number of patients with Stage D heart failure (intractable symptoms of fatigue, shortness of breath or chest pain at rest despite optimal medical therapy) should be considered for palliative care or hospice, according to American College of Cardiology/American Heart Association guidelines.

7. PROGNOSIS

Prognosis in heart failure can be assessed in multiple ways including clinical prediction rules and cardiopulmonary exercise testing. Clinical prediction rules use a composite of clinical factors such as lab tests and blood pressure to estimate prognosis. Among several clinical prediction rules for prognosing acute heart failure, the 'EFFECT rule' slightly outperformed other

rules in stratifying patients and identifying those at low risk of death during hospitalization or within 30 days (18). Easy methods for identifying low risk patients are:

- ADHERE Tree rule indicates that patients with blood urea nitrogen < 43 mg/dl and systolic blood pressure at least 115 mm Hg have less than 10% chance of inpatient death or complications.
- BWH rule indicates that patients with systolic blood pressure over 90 mm Hg, respiratory rate of 30 or less breaths per minute, serum sodium over 135 mmol/L, no new ST-T wave changes have less than 10% chance of inpatient death or complications.

A very important method for assessing prognosis in advanced heart failure patients is cardiopulmonary exercise testing (CPX testing). CPX testing is usually required prior to heart transplantation as an indicator of prognosis. Cardiopulmonary exercise testing involves measurement of exhaled oxygen and carbon dioxide during exercise. The peak oxygen consumption (VO2 max) is used as an indicator of prognosis. As a general rule, a VO2 max less than 12-14 cc/kg/min indicates a poorer survival and suggests that the patient may be a candidate for a heart transplant. Patients with a VO2 max<10 cc/kg/min have clearly poorer prognosis. The most recent International Society for Heart and Lung Transplantation (ISHLT) guidelines also suggest two other parameters that can be used for evaluation of prognosis in advanced heart failure, the heart failure survival score and the use of a criteria of VE/VCO2 slope>35 from the CPX test. The heart failure survival score is a score calculated using a combination of clinical predictors and the VO2 max from the cardiopulmonary exercise test.

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