Pathophysiology of Congestive Heart Failure

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Heart failure is a clinical syndrome characterized by impaired structure and/or function of the heart, leading to dyspnea and fatigue at rest or with exertion. The pathophysiology of heart failure is complex, and there is no single lesion. Any form of heart disease can lead to heart failure. Most heart failure can be explained by well-recognized etiologic factors, though ostensibly healthy patients may harbor risk factors for the later development of heart failure. A fundamental response to myocardial injury or altered loading conditions includes "remodeling" of the heart, so that the size, shape, and function of the affected chamber is grossly distorted. This is accompanied by a constellation of biologic changes, best recognized in advanced cases of heart failure. These multiple alterations may be primary or secondary events but, nonetheless, add importantly to the morbidity and mortality of the patients. More emphasis should be placed on recognition and correction of risk factors related to the development of heart failure.
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There are few clinical syndromes that have undergone both the conceptual and epidemiologic transformation that has occurred with heart failure. The entire concept of what the heart failure syndrome is, how it begins, how it naturally unfolds, and how its primary phenotypic expression is manifested has undergone radical change since the 1970s. This has occurred simultaneously with a large increase in incidence, largely attributed to the aging of the Western population. For many years, heart failure was defined as a clinical syndrome in which the amount of blood pumped by the heart was insufficient

to meet the demands of the various organ systems. Although this concept persists in some circles and is generally correct, we now know that the syndrome of heart failure is far more complex. Heart failure is now more broadly defined as a clinical syndrome characterized by dyspnea and fatigue, at rest or with exertion, due to structural and/or functional abnormalities of the heart. Strictly speaking, there must be a fundamental problem with the heart in the syndrome of heart failure.

Like all common clinical syndromes, including anemia and renal failure, heart failure is not a standalone diagnosis. There is always an etiology, though in many cases the precise etiology is not uncovered. For example, it is now clear that as many as 30% of patients with "idiopathic dilated cardiomyopathy" have genetic bases for their heart failure.[1] However, there are multiple genes involved, with a large number of molecular changes that are not apparent under the microscope. Our understanding of the basis of heart failure at the cellular and molecular levels is still evolving. Although it is likely that any form of heart disease can ultimately lead to heart failure, the more common causes in the Western world continue to be coronary artery disease, poorly controlled hypertension, valvular heart disease, primary "idiopathic" cardiomyopathy, genetic cardiomyopathies, and cardiomyopathies due to lymphocytic inflammatory myocarditis or other infiltrative disorders. Toxic cardiomyopathy due to cocaine, amphetamine, and ephedrine use and various chemotherapies is also recognized as a growing problem.

Terminology and Semantic Difficulties

There has been a long-standing problem regarding how to define and classify heart failure. More recently, the syndrome of heart failure has been divided into two broad classes: cases in which systolic function is preserved (so-called *diastolic heart failure*) and cases in which there is obvious impairment of systolic function with a low ejection fraction and a dilated left ventricle. The definition and natural history of these two broad categories of heart failure have been the subject of numerous reports.[2–5]

Diastolic heart failure is largely a product of the aging population, occurring in patients with long-standing hypertension and left ventricular hypertrophy; however, it may also occur in patients with hypertrophic and restrictive cardiomyopathy, some of whom may be quite young. Patients with diastolic heart failure tend be older, more often female, have increased left ventricular wall thickness, smaller left ventricular cavities, preserved systolic function by echocardiography, and impaired diastolic function, often with some element of mitral regurgitation.

Conversely, patients with systolic heart failure tend to have large, dilated ventricles and markedly impaired systolic function. They frequently manifest mitral regurgitation and tricuspid regurgitation, usually on the basis of dilated ventricles and disruption of the normal papillary muscle architecture (so-called *functional regurgitation*).

The aim of this brief report is to discuss the fundamental pathophysiology of the syndrome of dilated cardiomyopathy with impaired systolic function. The epidemiology and clinical natural history of this syndrome are well described in a number of recent publications[4] and, therefore, will not be addressed.

The Beginning of the Problem: The Index Event

Heart failure syndrome always begins with an index event. The index event may be clinically silent, such as the expression of a genetic mutation, or obvious, such as the catastrophic, sudden loss of a large mass of contractile tissue from acute myocardial infarction. The index event could be the explosive onset of fulminant viral myocarditis, or it may be prolonged and insidious, such as occurs with valvular heart disease. The phenotypic expression of left ventricle dilation and impaired systolic function can also be slow to develop, such as a pressure- or volume-overloaded state from valvular or coronary heart disease. The clinical picture can also be more rapidly progressive, as sometimes occurs with familial cardiomyopathy.[6] By the time patients are seen in the clinic with shortness of breath and fatigue, the late stages of the syndrome are often manifest. Heart failure frequently passes through an asymptomatic, latent phase that is concealed from the patient and the physician.[7,8] Unfortunately, because asymptomatic left ventricular dysfunction is often not visible to the practicing physician, these patients do not usually receive treatment. Although it is not certain that the early introduction of drugs such as angiotensin-converting enzyme (ACE) inhibitors and possibly β-adrenergic receptor blockers slow or reverse the progression of the earli-

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est form of heart failure, data from the prevention arm of the SOLVD (Studies of Left Ventricular Dysfunction) study suggest that patients with asymptomatic left ventricular dysfunction may benefit from ACE inhibitors.[9] Asymptomatic patients with no structural heart disease who are at risk to develop heart failure (stage A) include those with coronary artery disease, diabetes mellitus, hypertension, or a family history of cardiomyopathy, and those who harbor risk factors for the development of coronary artery disease. Early pharmacologic interdiction in such patients may pay broad dividends later, but this remains to be proved.

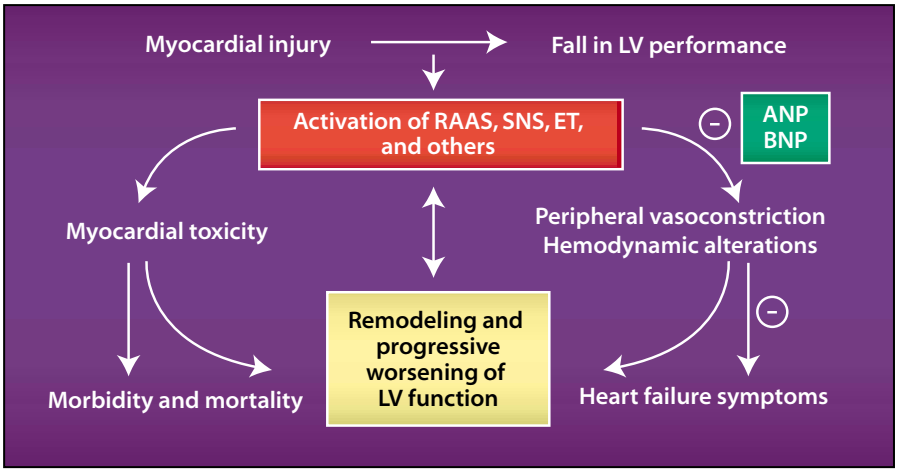

Figure 1. *Heart failure: a response to injury. LV, left ventricle; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system; ET, endothelin; ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide.*

Response to the Index Event

The "response to injury" concept suggests that all injured tissue responds in a mechanistically adaptive manner to ensure cellular and, thus, organ survival.[10] In the heart, adaptive systemic processes have evolved over hundreds of millions of years and include conservation of effective circulating blood volume and protection of blood pressure and flow to vital organs. At the cellular level, the wounded heart is no different than other tissue, in that there is often an initial inflammatory response to the injury followed by a healing phase, which includes the deposition of collagen and, in many cases, hypertrophy of adjacent, viable cardiac myocytes (Figure 1). However, cardiac myocytes, which are highly complex, terminally differentiated cells, do not appear to undergo exuberant cell division in response to injury. Nevertheless, data suggest that some mature cardiac myocytes undergo cell division,[11,12] at least more than what was previously considered to be the case.[13,14] In addition to myocardial necrosis and subsequent hypertrophy of adjacent viable cells, apoptosis occurs in an unspecified number of cardiac cells,[15,16] which likely contributes to cell drop-out and, thus, further impairment of cardiac systolic function.[17] The quantitative contribution of apoptosis to impairment of systolic function and subsequent left ventricular remodeling is still the subject of considerable debate.[18,19]

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The type of myocardial "injury" response may be highly variable and is dependent on the inciting factors. For example, the myocardial response to chronic, severe mitral regurgitation or chronic aortic regurgitation is quite different from the response to long-term excessive afterload, as might occur in untreated hypertension or severe aortic stenosis. Rather than an acute injury to the heart, valvular insufficiency imposes chronically perverse loading conditions, in which there are unrelenting, abnormal molecular signals that are sensed by the cardiac myocytes and fibroblasts, leading to myocyte hypertrophy and progressive dilation (remodeling) of the heart with an increase in collagen deposition (Figure 2). In chronically elevated, volume-overloaded states, the cardiac myocytes enlarge mainly by elongation because of an increase of new sarcomeres in series. Chronic volume-overloaded states, which are characteristic of valvular insufficiency and coronary artery disease, typically result in eccentric elongation of cardiac myocytes and obvious chamber enlargement. Changes in the geometry of the left ventricle may distort the relationship of the papillary muscles to the mitral and tricuspid leaflets, leading to additional mitral and tricuspid insufficiency, which only serves to worsen the volume overload. Experimental data suggest that elongation of cardiac myocytes contributes to dilation of the chamber,[20] thus providing the structural abnormality that may help form the basis of impaired systolic function. In all likelihood, the increase in

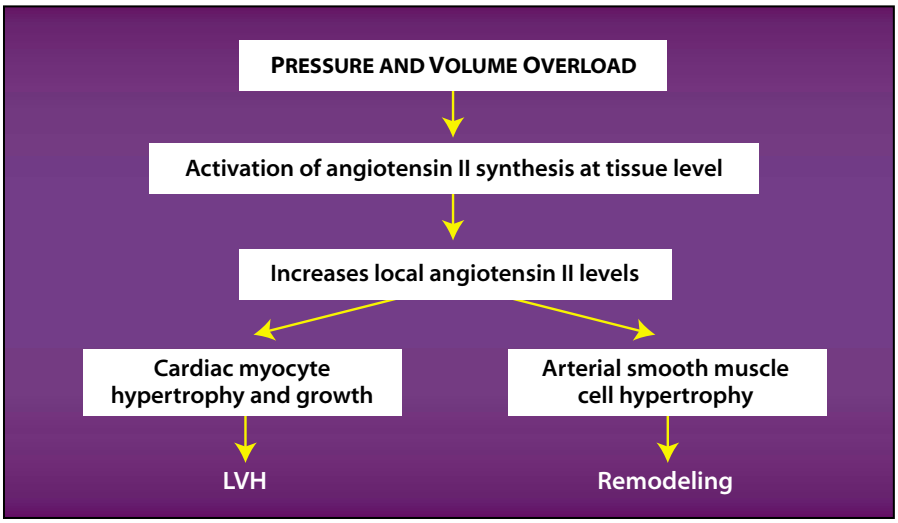

Figure 2. *Response to pressure and volume loading of the left ventricle. LVH, left ventricular hypertrophy. Reproduced from Dahlof B. Effect of angiotensin II blockade on cardiac hypertrophy and remodeling: a review.* J Hum Hypertens. *1995;9(suppl 5):S37–S44.*

chamber size initially serves to maintain stroke volume despite an obvious reduction in ejection fraction. However, over time, the progressive chamber enlargement is attended by insufficient hypertrophy, leading to increased wall stress and, thus, an obligatory impairment of systolic function.[21]

Unlike with a chronic volume-overloaded state, longstanding, severe excessive afterload results in myocyte hypertrophy characterized by an increase in the cross-sectional thickness of the cells. This is often referred to as *concentric hypertrophy*. Of course, the hypertrophic response of the cardiac myocytes to unusual loading conditions can be a hybrid state between eccentric and concentric hypertrophy. For example, the largest human cardiac myocytes are seen in patients with long-standing, severe aortic regurgitation.[22] Myocytes from these patients are much longer and somewhat thicker than normal myocytes.

Genetic mutations may lead to abnormal sensing and signaling of loading conditions to the cardiac myocyte cell nucleus.[23–25] The altered phenotype may involve microtubules, cytoskeleton, or the interaction of the extracellular matrix and integrins and their transduction of mechanical signals to the cell nucleus. Full expression of the heart failure phenotype in genetically driven dilated cardiomyopathy may require a combination of environmental factors (eg, altered load) and genetically altered structural factors (eg, abnormal cytoskeleton). It is unlikely that genetic cardiomyopathies are due to single mutations. The variable penetrance may be related to important environmental interaction (ie, altered loading conditions) with dysfunctional proteins.

Propagation of the Syndrome

A constellation of many factors converge to provide the abnormalities of heart structure and function that lead to the phenotypic expression of heart failure. There is no single molecular "lesion" of heart failure. Rather, there are many factors that drive the left ventricular remodeling process, which is fundamentally a response to injury and/or abnormal loading conditions and is now considered to be the core lesion of heart failure. The hypothesis that cardiac remodeling is the hallmark of heart failure is supported by the well-known fact that the only drugs that improve survival in the syndrome also reverse or limit left ventricular remodeling. To date, such drugs include only those that block the renin-angiotensin-aldosterone system (ACE inhibitors, angiotensin-receptor blockers, and aldosterone-receptor blockers) or the sympathetic nervous system (β-adrenergic blockers).

Primary Causes or Secondary Epiphenomena?

There are other important pathophysiologic changes that occur in the heart failure syndrome, but it has been difficult to understand whether these are secondary to the left ventricular remodeling process or primary causes of the heart failure syndrome.[26] Such changes include downregulation of the sarcolemma β-adrenergic receptor density and, in some cases, uncoupling of the receptor–adenyl cyclase system. There is a generalized reversion of the heart to the so-called *fetal genetic program*. This is associated with observed alterations in β-myosin heavy-chain and other contractile proteins; overexpression of counter-regulatory hormones, such as B-type

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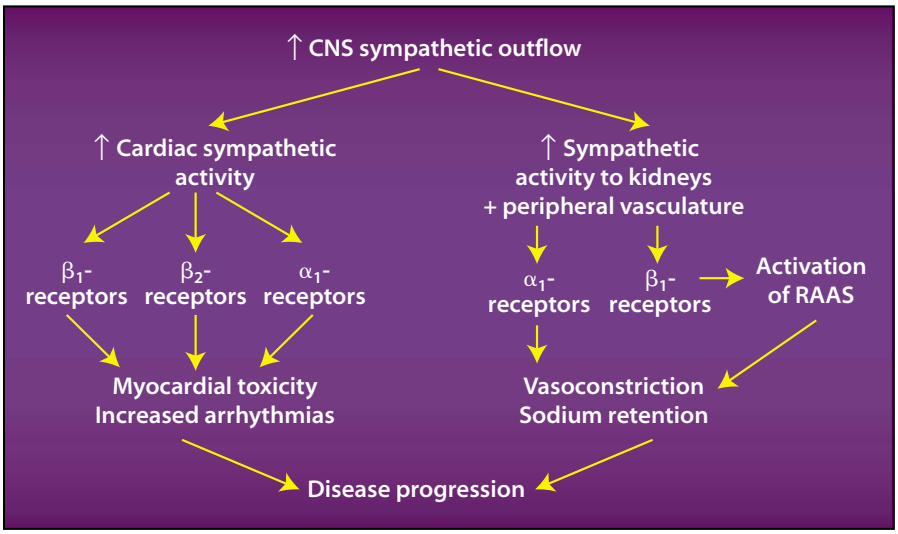

Figure 3. *Effects of sympathetic action in heart failure. CNS, central nervous system; RAAS, renin–angiotensin–aldosterone system. Adapted with permission from Packer M. Beta-adrenergic blockade in chronic heart failure: principles, progress, and practice.* Prog Cardiovasc Dis. *1998;41(1 suppl 1):39–52.*

natriuretic peptide, in the heart; excessive activation of the sympathetic nervous system and renin-angiotensin-aldosterone system; reduction of parasympathetic nervous system activity; altered reflex control mechanisms; impaired endothelial function; and alteration of skeletal muscle biochemistry (Figure 3). At the cellular level, there may be changes in cardiac metabolism, including preferential use of glucose over free fatty acids, as a consequence of reversion back to the fetal program. The maintenance of calcium transport across the sarcolemma and the sarcoplasmic reticulum, as well as the subsequent exit of calcium for myocardial contraction, is also grossly altered. This can result in disturbances of electrical synchrony and impaired myocyte contraction. Patchy fibrosis can lead to intraventricular conduction delay, common in 25%–30% of patients with heart failure. Such conduction delays are associated with myocardial dyssynchrony, which is believed to cause cellular dysfunction and worsening heart failure.[29] Alteration of calcium transients, coupled with excessive sympathetic activity and diuretic-induced hypokalemia, may also converge to promote cardiac arrhythmias. It is now well recognized that about one third of patients with heart failure die suddenly and unexpectedly, often from lethal arrhythmias. Sudden death from arrhythmias is seemingly more common in less symptomatic New York Heart Association class II patients, often striking down younger patients in the earlier stages of heart failure. Medical therapy to prevent serious arrhythmias has been lacking, but implantable cardiac defibrillators can prolong life in certain subsets of patients.[27] Resynchronization therapy with left-sided pacing can restore cardiac synchrony in some patients and is associated with improved systolic function and clinical outcomes,[28] suggesting that desynchronization may be pathophysiologically important in heart failure.[29]

Another late clinical manifestation of heart failure is impaired reflex control mechanisms. For example, patients with advanced heart failure are unable to mount an appropriate tachycardia in response to exercise, vasodilation, or orthostasis. Parasympathetic nervous system derangement is also abnormal, as demonstrated by impaired heart-rate recovery following exercise. Activation of the renin-angiotensin-aldosterone system leads to retention of salt and water by the kidney, which can be offset to some extent by release of B-type natriuretic peptide from the heart. As the heart failure syndrome advances, patients become less physically active, and there can be substantial salt and water retention, leading to edema. Many patients eventually die with what is referred to as *progressive pump dysfunction*, which includes hypotension, low cardiac output, and multiorgan dysfunction. Classification of death is quite problematic in patients with heart failure, with approximately one third dying suddenly, one third dying from progressive pump failure, and one third dying in unclassified manners, usually from arrhythmias occurring in the setting of terminal hemodynamic decompensation.

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The epidemiologic factors that drive the heart failure syndrome are well understood and include coronary artery disease, hypertension, valvular heart disease, and infiltra-

tive heart disease. However, many patients with dilated cardiomyopathy demonstrate no inciting factor. It remains unclear why the genetic expression of dilated cardiomyopathy occurs when it does in any given patient; it may occur early in life, during midlife, or even late in life. Expression of polymorphism and mutations can be strongly influenced by environmental factors. This may explain why two patients with similar-sized myocardial infarction may develop dissimilar degrees of heart failure.

The Prevention of Heart Failure

We now know that certain risk factors put patients at risk for the development of heart failure. Such factors include hypercholesterolemia, coronary artery disease, poorly controlled hypertension, left ventricular hypertrophy, and diabetes mellitus. Although unproven, it is likely that aggressive, early management of these risk factors may delay the onset of heart failure or, in some cases, prevent heart failure. Such a strategy would likely be far more successful and economical than the current process of waiting for symptomatic heart failure to occur and then prescribing multiple drugs and devices. Currently, physicians are merely delaying the progression of heart failure for a few months without being given a chance to actually prevent its root causes. Clearly, a strategy of aggressive, front-loaded management of risk factors is needed for the prevention of heart failure.

Summary

Heart failure is a clinical syndrome characterized by impaired heart structure and/or function, leading to dyspnea and fatigue at rest or with exertion. Its pathophysiology is complex, and there is no single lesion. Any form of heart disease can lead to heart failure. Most heart failure can be explained by well-recognized etiologic factors, though ostensibly healthy patients may harbor risk factors for the later development of heart failure. Early recognition and correction of these risk factors would likely provide for a more robust favorable outcome. Many cases previously considered to be "idiopathic" dilated cardiomyopathy are now recognized to be due to a variety of genetic mutations, many of which likely require some interaction of environmental factors to express the full phenotype. A fundamental response to myocardial injury or altered loading conditions includes "remodeling" of the heart, so that the size, shape, and function of the affected chamber is grossly distorted. This is accompanied by a vast constellation of biologic changes, best recognized in advanced cases of heart failure. These multiple alterations may be primary or secondary events but, nonetheless, add substantially to the morbidity and mortality of patients. Unfortunately, most of our current therapies are provided to the patient toward the end of the natural history of the syndrome, rather than at the beginning. Ultimately, more emphasis should be placed on recognition and correction of risk factors related to

Main Points

- Heart failure is broadly defined as a clinical syndrome characterized by dyspnea and fatigue, at rest or with exertion, due to structural and/or functional abnormalities of the heart.
- The more common causes of heart failure in the Western world are coronary artery disease, poorly controlled hypertension, valvular heart disease, primary "idiopathic" cardiomyopathy, genetic cardiomyopathies, and cardiomyopathies due to lymphocytic inflammatory myocarditis or other infiltrative disorders.
- Patients with systolic heart failure tend to have large, dilated ventricles and markedly impaired systolic function. They frequently manifest mitral regurgitation and tricuspid regurgitation, usually on the basis of dilated ventricles and disruption of the normal papillary muscle architecture.
- There is no one index event in heart failure: index events can be clinically silent (eg, expression of a genetic mutation) or obvious (acute myocardial infarction), explosive (fulminant viral myocarditis) or prolonged and insidious (valvular heart disease). Heart failure often passes through an asymptomatic, latent phase that is frequently concealed from the patient and the physician.
- As heart failure syndrome advances, patients become less physically active, and there can be substantial salt and water retention, leading to edema. Many patients eventually die from progressive pump dysfunction, which includes hypotension, low cardiac output, and multiorgan dysfunction.
- Aggressive, early management of the risk factors of heart failure (hypercholesterolemia, coronary artery disease, poorly controlled hypertension, left ventricular hypertrophy, and diabetes mellitus) may result in the delay of onset of heart failure or, in some cases, the prevention of heart failure.

the development of heart failure. This will likely prove to have the most profound public health effect. ■

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