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Pathophysiology of Heart Failure

Mihai Gheorghide, MD,* and Jeffrey B. Lakier, MD*

Heart failure occurs when the heart is unable to maintain a cardiac output sufficient to satisfy the oxygen requirements of the body despite adequate blood volume and hemoglobin content. Regardless of the initial cause of heart failure and in spite of compensatory mechanisms, patients often follow a course of worsening heart failure that is characterized by a low cardiac output, high filling pressures, and increased peripheral vascular resistance. In addition to persistence of the initiating event, cardiac deterioration may be caused or aggravated by a variety of factors including depletion of cardiac norepinephrine stores, down-regulation of myocardial beta-adrenergic receptors, microvascular spasm with resultant further cellular necrosis, and subendocardial ischemia perpetuating myocardial failure. (Henry Ford Hosp Med J 1986;34:153-5)

Heart failure occurs when the heart is unable to maintain a cardiac output sufficient to satisfy the oxygen requirements of the body despite adequate blood volume and hemoglobin content (1). Myocardial failure, heart failure without myocardial failure (eg, tricuspid stenosis and constrictive pericarditis which interfere with cardiac filling, or rhythm disturbances), and circulatory volume overload resulting from abnormal salt and water retention without a disturbance of cardiac function per se (2) all may result in the clinical syndrome of heart failure. This review focuses on the pathophysiology of heart muscle dysfunction that causes myocardial failure.

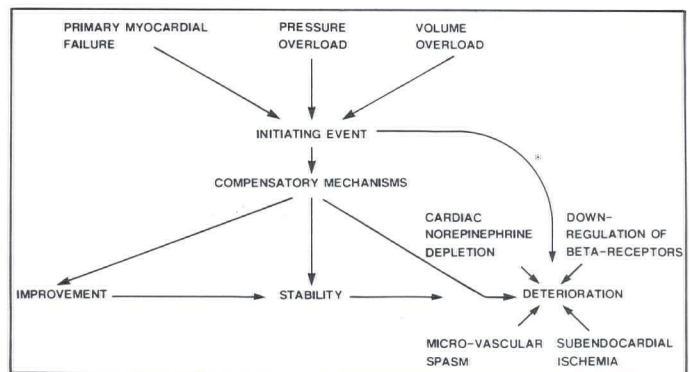
Myocardial Failure

Three different mechanisms may be responsible for myocardial failure (3): 1) primary myocardial failure (cardiomyopathy) in which cardiac contractility is severely compromised secondary to either a quantitative loss of myocardial cells due to destruction or replacement and/or a qualitative defect in myocardial cells; 2) failure due to pressure overload (ie, in aortic stenosis) in which the principal cause of the reduced stroke volume is obstruction to ventricular ejection; and 3) failure due to volume overload in which a significant portion of the total ejected cardiac output fails to reach the peripheral tissues due to regurgitation into the atrium (mitral regurgitation) or into the ventricle (aortic regurgitation) (Figure).

Despite considerable effort directed toward clarifying the fundamental processes involved in myocardial contractile deterioration, a distinct biochemical defect responsible for heart failure has not been identified (4).

Myocardial failure, which frequently develops gradually, is preceded by a phase in which the whole heart, or the remaining viable portion, hypertrophies and dilates (5). This permits compensation for the loss of myocardial cells or hemodynamic overload. Why the initial compensatory hypertrophy and dilatation progress to myocardial failure is unknown (6). Available data suggest that the alteration in the function of myocardial cells and

not their increased size is responsible for this course of events (5). Chronic ischemia (7,8), mitochondrial dysfunction (9), depletion of myocardial energy supplies (10), defective myocardial energy utilization (11), and abnormalities in excitation-contraction coupling (12) are all possible mechanisms. Recent interest has focused on the role of abnormalities in calcium transport in heart failure (13). Theoretically, defective calcium transport could interrupt maximal excitation-contraction coupling by several mechanisms: decreased calcium availability to the sarcolemma, decreased calcium transport across this membrane, altered calcium release or uptake by the intracellular sarcoplasmic reticulum, or decreased calcium removal from the contractile protein.



Figure—Pathophysiology of heart failure. *Persistence of a primary etiology for the initial event (eg, alcohol, aortic stenosis, persistent ischemia) will result in further deterioration.

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Compensatory Mechanisms

Regardless of the etiology of heart failure, several circulatory adjustments tend to compensate for the fall in cardiac output. The initial adjustment to a decrease in contractility or volume overload is cardiac dilatation. As the preload increases, a limited increase occurs in sarcomere length, and additional sarcomeres are recruited to augment ventricular function. This represents the Frank-Starling mechanism (14). However, this mechanism may not operate in patients with severely dilated ventricles when further ventricular dilatation may cause secondary mitral or tricuspid insufficiency (15,16) and increase in wall tension which may further reduce stroke volume (17). In addition, subendocardial ischemia may supervene (18).

A second compensatory mechanism is fluid retention. Plasma volume is increased due to reabsorption of salt and water by the kidneys (3). The origins of the sodium retention include elevations in renal venous pressure, redistribution of the diminished renal blood flow toward the juxtamedullary nephron, activation of the renin-angiotensin-aldosterone system (19), and lack of the natriuretic substance. In chronic heart failure, antidiuretic hormone titers are high despite augmented stretch of left atrial receptors which normally inhibit the release of this hormone (20-22).

Circulating catecholamines (23) which augment myocardial contractility and blood pressure comprise a third mechanism. Finally, myocardial hypertrophy (24) may occur, providing a fundamental compensatory mechanism when an excessive pressure or volume load is imposed on the heart.

Regardless of the initial cause of heart failure and despite compensatory mechanisms, patients often follow a course of worsening heart failure that is characterized by a low cardiac output, high filling pressures, and increased peripheral vascular resistance (25).

Possible Causes for Further Myocardial Deterioration

In addition to persistence or progression of the initiating event, cardiac deterioration may be caused or aggravated by a variety of factors including depletion of cardiac norepinephrine stores, down-regulation of myocardial beta-adrenergic receptors, microvascular spasm with resultant further cellular necrosis, and subendocardial ischemia perpetuating myocardial failure (Figure).

Depletion of cardiac norepinephrine stores

The role of catecholamines in heart failure is discussed in detail by Goldstein in this issue of the Journal (26). Control subjects have a modest adrenergic tone, low levels of plasma catecholamines, and a significant store of myocardial norepinephrine (25). With mild degrees of heart failure, plasma catecholamine levels rise only moderately, and myocardial norepinephrine supplies are not depleted (25). With chronic severe heart failure, plasma catecholamines are increased markedly and myocardial norepinephrine stores are diminished (27).

Experimentally, after the production of heart failure in dogs (28), ventricular norepinephrine concentration falls markedly and the infusion of norepinephrine does not raise cardiac nor-

epinephrine stores. The reduced capacity to retain administered norepinephrine is probably due to a reduction in the total number of neurones in the heart (1). This may be responsible for loss of the adrenergic support which could intensify the severity of the heart failure.

Down-regulation of beta-receptors

Compensatory adrenergic stimulation in patients with heart failure occurs for a limited period (29). In chronic heart failure the activity of endogenous catecholamines is rapidly terminated through uptake into intraneuronal and extraneuronal sites where metabolic degradation occurs (29). Brief exposure to adrenergic agonists transforms the active form of the beta-adrenergic receptor to a low-affinity form that interferes with production of adenylate cyclase (30). Prolonged exposure to adrenergic agonists results in a significant decrease in beta-receptor density in the cell membrane. This phenomenon is called receptor down-regulation (29). Because of a decrease in beta-receptor density, circulating catecholamines no longer stimulate the failing heart to the same degree, and myocardial failure progresses (30,31).

The high levels of catecholamine observed in patients with severe heart failure (32) in the presence of decreased beta-receptors on cell membranes of smooth muscle may actually reduce cardiac output by increasing peripheral resistance through unopposed alpha-adrenergic stimulation. Available data suggest that there could be a group of patients with heart failure in whom long-term beta-adrenergic blockade will improve myocardial function and prolong life (33,34). The benefit that has been observed from beta-blocker therapy may be the result of up-regulation of beta-adrenergic receptors, allowing restoration of catecholamine responsiveness which results in improved myocardial function.

Microvascular spasm

Dilated cardiomyopathy may possibly begin with focal transient microvascular spasm that causes myocyte necrosis and, subsequently, fibrosis (35). Factor et al (36) showed that the Syrian hamster develops focal myocardial necrosis beginning at one month of age, which leads to eventual ventricular failure within one year. Those authors demonstrated that transient spasm of small blood vessels, probably secondary to vasoactive substances, may cause myocytolytic necrosis. According to Sonnenblick et al (35), verapamil, a channel calcium antagonist, prevents the focal necrosis and fibrosis in the Syrian hamster myocardium. The similarity of this disease to human and experimental cardiomyopathy suggests that microvascular spasm may be a common denominator in many different cardiomyopathic syndromes. The perfusion defects (37) seen on thallium-201 scans of patients with idiopathic dilated cardiomyopathy may represent areas of myocardial fibrosis and scarring resulting from microvasospasm.

Subendocardial ischemia

Studies (38,39) suggest that in patients with a dilated cardiomyopathy the subendocardial muscle first loses its ATP, followed by vacuolization and finally fibrosis. This progressive deterioration can be due partly to insufficient coronary blood flow to the subendocardium, which initiates a vicious cycle

that worsens the heart failure and further decreases coronary blood flow (18). This hypothesis has some implications in the therapeutics of heart failure. Decreasing ventricular size, lowering left ventricular end-diastolic pressure, or decreasing heart rate may improve subendocardial perfusion and correct the imbalance of energy supply and demand (39). Benefits of beta-blocker therapy in patients with idiopathic dilated cardiomyopathy (33) may be partly related to increased subendocardial flow resulting from an increase in diastolic time (decreased heart rate) and transmural redistribution of blood from the subepicardium to the subendocardium (40).

In the last ten years important progress has been made in the development of pharmaceutical agents for the management of patients with chronic heart failure. Research has been directed toward improving abnormal hemodynamics in these patients. Although symptomatic improvement may result from the augmentation of cardiac output when inotropic and vasodilating agents are employed, survival may not be altered (31). Survival is determined by the amount of myocardial damage and its progression, which may not be affected by such agents (41). To have a favorable impact on duration as well as quality of life, future research will need to focus on not only improving cardiac hemodynamics but also preventing further myocardial cell loss or dysfunction, especially in the early stages of heart failure.

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