Heart Failure and Abnormal Ventricular Function*
Pathophysiology and Clinical Correlation (Part 1)
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From the clinical standpoint, heart failure should be considered a symptom complex rather than a specific disease, and intelligent management dictates that its cause and pathophysiologic features be understood before therapeutic efforts are begun. It is the intent of this review to provide a diagnostic framework of heart failure and to integrate both new and old concepts of abnormal ventricular function in relation to heart failure states.

In this review, the term "heart failure" refers to the pathophysiologic state in which an abnormality of heart muscle (myocardial failure) inhibits the performance of the heart as a pump, so that either delivery of blood to the tissues becomes impaired or circulatory congestion occurs, or both may happen. Other disease processes—eg, constrictive pericarditis—also can cause heart failure, but without necessarily involving the myocardium.

PATHOPHYSIOLOGY OF HEART FAILURE

Heart failure may involve the left or the right ventricle or both and may be caused by systolic or diastolic ventricular dysfunction or both (Fig 1 and 2). It may be symptomatic or asymptomatic and may manifest varying degrees of clinical compensation. In some patients, low-output symptoms may predominate and occur without congestive symptoms; in others, the converse may occur, and some patients may have varying degrees of both low-output and congestive symptoms.

Systolic or diastolic failure of either ventricle may ultimately produce increased end-diastolic (filling) pressures which, in turn, may cause symptoms that reflect venous congestion (Fig 1 and 2).

Abnormal response to exercise may be a more sensitive index of ventricular systolic dysfunction than is a measure of resting function, such as ejection fraction. The correlation between resting ejection fraction and objective measures of exercise tolerance (for example, oxygen consumption) is poor. Ejection fraction—defined as the ratio of stroke volume to end-diastolic volume—cannot be strictly equated with forward cardiac output because conditions may affect end-diastolic volume differently than they affect stroke volume. Also, cardiac output—defined as the product of heart rate and stroke volume—may be maintained if there is sufficient chronotropic reserve. These factors, for example, may account for the apparent paradox of an asymptomatic patient with an ejection fraction of 20 percent. Mitral regurgitation, commonly found in dilated hearts, causes a portion of the stroke volume to be ejected backward into the left atrium. In this case also, even though ejection fraction is normal or even increased, it will not correlate with forward cardiac output, because the latter will be decreased by an amount equivalent to the regurgitant volume.

With severe degrees of left ventricular failure, the length-tension curve (Fig 3) becomes progressively depressed (shifted downward and to the right), so that cardiac output becomes inadequate to meet resting body requirements. Left ventricular end-diastolic pressure and pulmonary capillary wedge pressure increase to levels that cause pulmonary congestion or even frank pulmonary edema.

The clinical manifestations of heart failure vary with the age of the patient, the extent and rate of development of abnormal cardiac performance (systolic or diastolic or both), the precipitating causes of heart failure, and the specific cardiac chambers involved. Individual responses to the abnormalities in cardiac function also vary widely. For nearly equivalent degrees of low cardiac output and increased filling pressures, some patients will be markedly symptomatic and others less so. From the clinical standpoint, cardiac output in the resting state is a relatively insensitive index of overall cardiac function. Increases in left ventricular filling pressure with subsequent pulmonary congestion can occur while cardiac output remains normal.

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The following sequence of events frequently occurs in the failing heart: (1) left ventricular end-diastolic volume and end-diastolic pressure increase; (2) volume and pressure in the atrium behind the failing ventricle increase (the respective atrium contracts more vigorously—Starling's law of the atrium); (3) pressure in the venous bed behind the failing ventricle increases, resulting in pulmonary venous hypertension for left ventricular failure and systemic venous hypertension for right ventricular failure; and (4) capillary pressure in the respective venous circulation increases with transudation of fluid from the capillary bed into the interstitial spaces (pulmonary or systemic), resulting in increased extracellular fluid volume and edema (lungs, liver, subcutaneous tissues, serous cavities). Many of the symptoms and manifestations of heart failure result from this pathophysiologic sequence. Transudation of fluid across capillary beds may be modified by variable lymphatic flow rates (clearance mechanism), the state of the vascular endothelium (porosity), and the other Starling forces that govern transcapillary flow—such as, tissue pressure and plasma oncotic pressure. These factors presumably account for the observation that some patients may tolerate chronically increased left ventricular end-diastolic and pulmonary capillary wedge pressures without developing pulmonary congestion.

Even though the systemic and pulmonary circulations are connected both anatomically and physiologically, it is useful from the conceptual standpoint to separate the left and the right heart in terms of their respective functions, systolic or diastolic or both (Fig 1). According to this concept (right-sided vs left-sided heart failure), excess fluid may become localized behind the specific cardiac chamber initially affected. Thus, symptoms of pulmonary congestion (such as dyspnea, paroxysmal nocturnal dyspnea, and orthopnea) tend to predominate in patients with primarily left ventricular involvement. Although some patients with left ventricular failure may exhibit sodium and
fluid retention in the absence of increased systemic venous pressure, marked peripheral edema usually is associated with right ventricular failure. When caused by isolated left heart failure, peripheral edema presumably is due to activation of the renin-angiotensin-aldosterone system with consequent sodium and fluid retention.

With right ventricular failure, pressures increase in the right atrium and systemic venous circuit. This increase in systemic venous pressure is manifested clinically by various combinations of peripheral edema, congestive hepatomegaly, and, when severe, ascites (Fig 2). Jugular venous pressure is almost always increased under these circumstances, an important point in the differentiation of cardiac from noncardiac causes of hepatomegaly and ascites. Left heart failure may cause a secondary form of pulmonary hypertension, ultimately causing right ventricular failure as well. A common clinical scenario then would consist of a patient describing the following sequence: symptoms of left heart failure followed, after a variable period (days to weeks), by symptoms of right heart failure. This pathophysiologic sequence is of diagnostic importance because it tells the clinician that the left ventricle was initially responsible for the cardiac failure and focuses the differential diagnosis on disease processes that primarily affect the left ventricle or its valves (mitral or aortic or both).

When there are features of both left and right heart failure, the term "biventricular failure" is often used. Both ventricles are connected by a common muscle wall (the ventricular septum), and the muscle bundles of both ventricles are continuous. Thus, although the hemodynamic burden initially may involve only one ventricle, with time the other ventricle often becomes abnormal also. Functional tricuspid regurgitation (secondary to dilatation of the tricuspid annulus) frequently accompanies right ventricular failure of any cause and adds to the systemic venous congestion.

As the heart fails, various compensatory mechanisms come into play: (1) the Frank-Starling mechanism or "preload reserve," consisting of increased preload achieved by cardiac dilatation (lengthening of sarcomeres to provide optimal overlap between myofilaments) and resulting in increased cardiac output; (2) reflex sympathetic cardiac stimulation (increased release of catecholamines by cardiac adrenergic nerves and the adrenal gland) resulting in increased contractility and heart rate; and (3) myocardial hypertrophy leading to increased myocardial muscle mass, which in turn tends to counteract increased ventricular wall stress.

The importance of the "preload reserve" mechanism in maintaining pump performance under systolic stress will depend on where the ventricle lies on the active length-tension curve at the start of stress (Fig 3). For example, the ventricular muscle fibers may already be operating at nearly maximal length; therefore, only limited "preload reserve" exists, and the ventricle must rely on increased contractility (inotropic reserve) and increased heart rate (chronotropic reserve) to augment cardiac output. If drugs with negative inotropic properties are administered (for example, β-adrenergic blockers or verapamil), cardiac decompensation may occur. Conversely, when ventricular end-diastolic pressure and volume are decreased, significant improvement in cardiac pump performance can result from therapeutic increases in preload (for example, IV administration of fluids). A decrease in preload (for example, by the administration of diuretics) may relieve congestion symptoms but at the "physiologic expense" (Fig 3) of a further decline in pump performance. This observation may partly explain the apparent poor response of some patients treated with the combination of vasodilators and diuretics.

To maintain normal levels of ventricular systolic wall stress (defined for a simple spherical model as the product of ventricular chamber dimension, or radius, and ventricular systolic pressure divided by ventricular wall thickness), the overloaded ventricle may increase its muscle mass.

The degree of hypertrophy may or may not be sufficient to offset the increased wall stress. Dilated ventricles may be associated with an increased ventricular radius-to-wall thickness ratio and thus with "inadequate hypertrophy" in response to a chronic hemodynamic load.

There is an approximate inverse relationship between afterload and muscle fiber shortening when preload is held constant (force-shortening or force-velocity relationship) (Fig 4); experimentally, with preload held constant, increase in afterload leads to decreased myocardial muscle shortening and vice
versa. The intact normal heart can compensate for an increased afterload by use of its "preload reserve" mechanism, and muscle shortening is not appreciably affected. The failing heart is sensitive to changes in afterload and is responsive to afterload reduction—for example, as provided by vasodilator therapy. Among patients with heart failure of equivalent degrees, the responses to vasodilator therapy are variable, however. An excessive preload response may offset the potential improvement achieved by afterload reduction. Hypotension, orthostatism, and tachycardia are clinical clues that the hemodynamics are being affected adversely by unloading agents. For the treatment of heart failure, one has to balance afterload and preload reduction carefully, especially in severe heart failure states, and invasive hemodynamic monitoring (Swan-Ganz catheter) at times is required for this purpose.

Some of the improvement noted with afterload reduction may be due to decrease in left ventricular chamber dimension and, therefore, mitral annular size. This, in turn, lessens the degree of secondary mitral regurgitation and improves forward cardiac output.

The ventricular end-systolic pressure-volume relationship is useful as a relatively load-independent index of contractility. By manipulation of preload and afterload, a family of pressure-volume loops can be obtained (Fig 5). The slope of the line connecting the end-systolic pressure-volume points is an expression of ventricular contractility. The relationship shifts to the left with increased contractility and to the right with decreased contractility. End-systolic wall stress can be substituted for end-systolic pressure on the ordinate to give an end-systolic stress/end-systolic volume relationship. Although useful from the research standpoint, its clinical application thus far has remained limited. Attempts at simplifying the pressure-volume data to a single index of contractility have met conceptual difficulties. Nevertheless, the pressure-volume relationship concept does provide a view of ventricular pump performance that theoretically separates contractility from loading conditions.

In comparison with other sophisticated techniques, measurement of end-systolic volume is relatively simple and is useful clinically; it can be measured by radionuclide techniques and also can be approximated by echocardiographically determined end-systolic dimensions. A large end-systolic volume or dimension suggests either significant volume overload or decreased systolic function due to a depressed contractile state.

The hemodynamic derangements provoked by cardiac failure stimulate complex and variable physiologic reactions including increased sympathetic nervous system activity, increased plasma renin activity, and release of atrial natriuretic factor.

Although the release of atrial natriuretic factor from overloaded atria would tend to cause natriuresis and compensate for sodium and fluid retention, the other compensatory responses may have an adverse effect on overall cardiac performance. These neurohumoral...
concentrations, which, in turn, increases the afterload of the failing ventricle. As a part of a complex compensatory response to decreased cardiac output and perfusion pressure in heart failure, the renin-angiotensin system is activated which, in turn, causes peripheral vasoconstriction. Angiotensin II also facilitates the action of catecholamines in peripheral tissues and causes constriction of the efferent arterioles in the renal glomerulus. The latter effect serves to maintain net glomerular filtration rate. The addition of an inhibitor of angiotensin-converting enzyme leads to decreased circulating levels of angiotensin II, counteracts vasoconstriction, and prevents efferent arteriolar constriction in the glomerulus. Treatment with angiotensin-converting enzyme inhibitors generally improves hemodynamics, relieves symptoms, and increases survival in patients with myocardial failure.

Although renal function usually improves with treatment, presumably because of increased cardiac output and renal blood flow, occasional patients demonstrate progressive renal insufficiency. Systemic hypotension and renal hypoperfusion as well as the decrease in efferent arteriolar tone contribute to the decrease in glomerular filtration rate. The increase in cardiac output secondary to the decrease in peripheral resistance may or may not compensate for these changes. However, if intravascular volume is depleted, if there is known renal insufficiency (especially if there is renal artery stenosis), or if there is excessive vasodilation, renal function is more likely to decrease. Thus, caution is needed when treatment with these drugs is begun, especially in patients who are volume depleted—e.g., have been treated with large doses of diuretics—or who have preexisting systemic hypotension. Decreasing the diuretic dose prior to initiating therapy with the enzyme inhibitor may allow sufficient intravascular volume repletion. Long-acting enzyme/inhibitors—e.g., enalapril—to prolong the effects on glomerular efferent arteriolar tone may be less well tolerated than shorter-acting agents—e.g., captopril.14

REFERENCES