10. PATHOPHYSIOLOGY OF HEART FAILURE

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Introduction

Congestive heart failure has been considered a syndrome characterized by pulmonary and/or systemic venous congestion accompanied by a low cardiac output. Recently, however, it has become clear that a broad definition of this sort has confused understanding of this syndrome. The term *congestive* itself ensures that venous congestion is present, but we now know that severe heart failure may exist with normal or even low ventricular filling pressures. Also, pulmonary or systemic venous congestion may be severe in some patients with perfectly normal hearts. Thus, drawing a distinction between myocardial failure, on the one hand, and congestive failure, on the other, has provided a clearer understanding of the syndrome.

In this discussion of the pathophysiology of heart failure, particular emphasis is placed on the primary deficiencies of cardiac contraction that initiate the heart's compensatory mechanisms. These mechanisms result in chamber dilatation, myocardial hypertrophy, and alterations in adrenergic nervous system activity. It is ultimately the failure of these compensatory mechanisms that causes heart failure to lead to congestion. However, before theories of the pathogenesis of the deficiency of cardiac contraction leading to heart failure are presented, it is necessary to understand the determinants of ventricular performance, how they relate to component muscle function, and how they are altered by disease.

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Determinants of Stroke Volume

PRELOAD

Starling's observation that "the mechanical energy set free on passage from the resting to the contracted state is a function of the muscle fibers' length, i.e., the area of chemically active surfaces," underlies our current concepts of the length–active tension curve in isolated muscle and the effect of end-diastolic pressure on stroke volume or stroke work in the intact ventricle (the Frank-Starling relationship). Shifts in the ventricular function curve, as shown in figure 10–1, can also be used to demonstrate changes in contractility of the ventricle. Thus, the concept of ventricular function is useful in evaluating clinical changes due to either load or contractility. In the intact heart, ventricular end-diastolic wall stress is analogous to the preload of isolated muscle and within physiologic loads ultimately determines the resting length of sarcomeres in the ventricular wall. However, unlike the relation between muscle length and developed force in isolated muscle, where developed force reaches a maximum at a particular length and then declines, in the normal ventricle the ascending limb of ventricular function continues above the range of normal end-diastolic pressures (12–14 mmHg). Also, at end-diastolic pressures greater than 20 mmHg, or in certain

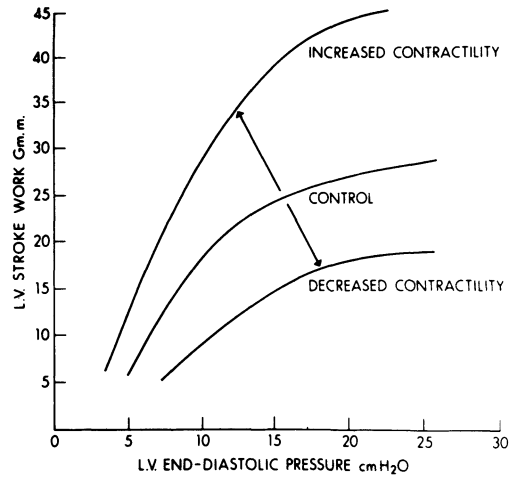

FIGURE 10–1. Diagrammatic representation of ventricular function curves expressed as the relation between left ventricular end-diastolic pressure and stroke work. Note that increasing or decreasing underlying myocardial contractility shifts the entire curve as well as changes its shape. It should be noted that the afterload, which can also change the shape and position of these curves, was kept constant during the experimental determination of these curves. (Reproduced by permission [1].)

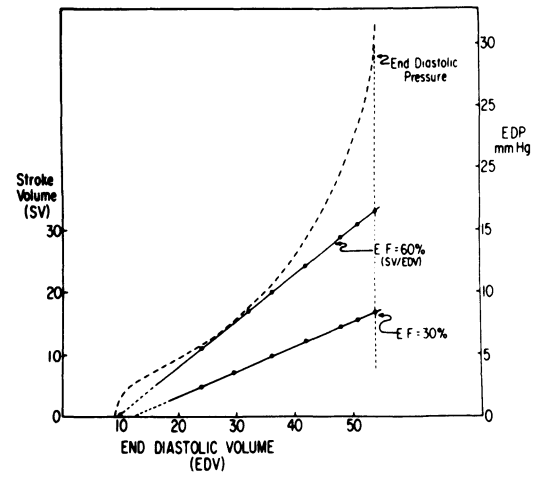

FIGURE 10–2. The relation between stroke volume and end-diastolic volume (both in ml) for a normal and a depressed left ventricle (solid lines). The slope of each line, SV/EDV, approximates the ejection fraction (EF) and is reduced from 60 to 30%. However, the EF is not a constant number since the linear relation does not intersect the origin. The nonlinear relation between end-diastolic pressure (EDP) and EDV is also shown (dashed line and right ordinate). At higher filling pressures, filling pressure rises substantially without significant increments in diastolic volume.

disease states, the predicted relation between midwall sarcomere lengths and diastolic wall stress is not always found [1, 2].

The increases in preload that are associated with increases in both the extent and velocity of midwall shortening combine to produce an increase in stroke volume. If end-diastolic volume is plotted against stroke volume to describe ventricular function, the slope of the ventricular function curve is the ejection fraction [3] (figure 10–2). However, the relation between end-diastolic pressure and stroke volume is nonlinear. Therefore, ejection fraction is dependent on lower end-diastolic pressure (figure 10–3). Thus, the usefulness of ejection fraction as a preload-independent index of ventricular function is limited.

The relationships between stroke volume or stroke work versus end-diastolic pressure or volume have been used to describe ventricular function curves [4]. Clinically the most useful relationship is between end-diastolic pressure and stroke volume. These relationships, which describe the response of the ventricle to changes in preload and contractile state, are also altered by changes in aortic pressure (afterload). Thus, multiple factors can participate in changes in stroke volume and stroke work.

A properly timed atrial contraction augments ventricular filling and preload. This elevates end-diastolic pressure and volume prior to ventricular contraction and thus importantly contributes to the magnitude of the stroke volume. Conditions associated with ineffective atrial contraction (atrial fibrillation) or improperly sequenced atrial contraction (complete heart block or atrioventricular dissociation) result in a reduction of the portion of preload contributed by atrial contraction.

Thus, alterations in preload, operating through changes in end-diastolic sarcomere length, serve as an important determinant of intact ventricular performance and provide the basis of wall force–midwall length relations and end-diastolic pressure–stroke volume curves.

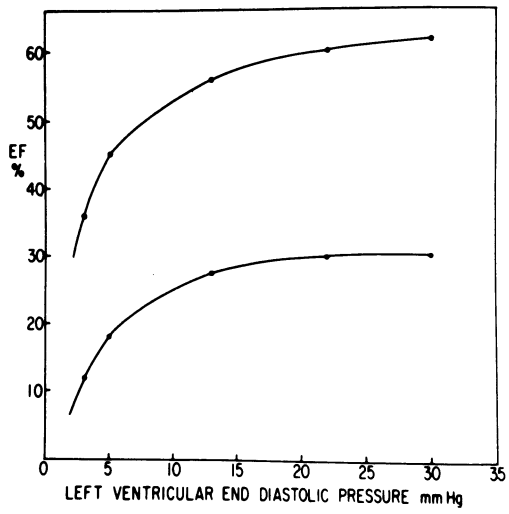

FIGURE 10–3. The relation between ejection fraction (EF) and left ventricular end-diastolic pressure. The data are derived from those shown in figure 10–2. The EF is only slightly dependent on end-diastolic pressure at high filling pressures but is highly dependent on end-diastolic pressure at lower ones. The upper limits of the normal end-diastolic pressure is approximately 12 to 14 mmHg.

The mechanism underlying the response of heart muscle to changes in preload provides a functional reserve capable of balancing the outputs of two ventricles under conditions of acute stress, exercise, hypovolemia, or cardiac failure, or during normal maneuvers such as respiration.

AFTERLOAD

Afterload is the stress (force per unit area) distributed in the ventricular wall during ventricular ejection. In the intact heart, viscous and inertial properties of the blood, ventricular volume, and wall thickness, as well as the peripheral vascular resistance, contribute to the stress maintained in the ventricular wall during ejection. The wall force developed during ejection, the afterload, influences the quantity of blood ejected by the ventricles. For example, abrupt increases or decreases in peripheral vascular resistance inversely alter the stroke volume and do so even when end-diastolic volume is independently controlled [5]. Afterload is never constant during ventricular ejection but continually declines as ventricular volume and midwall radius decrease, as predicted by the Laplace relation ($T = P \cdot r/2h$, where P is pressure, r is radius, and h is wall thickness of the ventricle). This type of contraction with continuously varying load is termed an auxotonic contraction.

Increasing the afterload results in a reduction of stroke volume as well as the extent in velocity of wall shortening (figure 10–4). If the afterload is rapidly varied during the course of a single ejection, an instantaneous force-velocity-length relation can be determined. Decreasing or increasing afterload causes an immediate inverse change in the velocity and extent of midwall shortening as well as the ejected volume. Also, in a manner analogous to what occurs in isolated muscle, the intact left ventricle reaches a point at end-systole that is near the isovolumetric

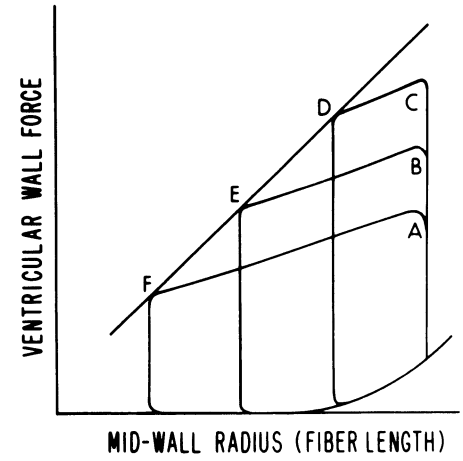

FIGURE 10–4. Effects of changes in afterload, created by increasing impedance to ejection, on the midwall-radius–wall force relations during normal contraction with preload held constant. Lines C-D, B-E, and A-F show decreasing midwall radius and wall force during ejection at three levels of afterload. This is the basic principle underlying the concept of E_{max}. There is an inverse relation between wall force during ejection and the extent of midwall shortening. Not shown, but occurring simultaneously, are reciprocal changes in the rate of midwall shortening with load (force-velocity relation). Note that at end-ejection (points D,E,F), wall force and radius coincide with the isovolumic radius-wall force line, describing underlying myocardial contractility.

length–active tension curve regardless of the imposed afterload (figure 10–4). This relationship has recently been explored as a specific index of ventricular contractility [5].

The low impedance to ventricular ejection produced by mitral regurgitation, a patent ductus arteriosus, a ventricular septal defect, or an arteriovenous shunt can result in an increased ejection fraction through a reduction in ventricular afterload in the patient with normal ventricular contractility. Increases in afterload, such as that produced by an infusion of angiotensin to elevate the systemic blood pressure, lead to compensatory alterations in both preload and the contribution of ventricular volume to afterload, which result in the maintenance of stroke volume in the normal heart [6]. In diseased hearts, however, stroke volume and stroke work fall with similar elevations in afterload. This response of the diseased heart depends on the degree of reduction of ventricular contractility as well as the capability of making adjustments in preload. Thus, in the intact circulation when there is relative hypovolemia and/or a depressed ventricular contractility, a given increase in afterload will cause a reduction in stroke volume that does not occur when contractility is higher or when preload can increase adequately.

An understanding of the effects of afterload is crucial to an appreciation of the effects of chronic systemic or pulmonary arterial hypertension, the consequences of obstruction to ventricular ejection by valvular disease such as aortic or pulmonic stenosis, or the effects on hemodynamics of mitral or aortic regurgitation. Pharmacological or surgical manipulation of afterload in these conditions constitutes the primary modes of therapy.

VENTRICULAR CONTRACTILITY

Ventricular contractility is a concept derived from isolated cardiac muscle studies and reflects the intensity of activation of the myofibrils during contraction. In mechanical terms, contractility can be described in isolated heart muscle as a surface that is generated during contraction by the interrelated variables of muscle force, velocity, and length, at any instant. Thus, for any fiber length and instantaneous total load on the muscle, there is a unique velocity of shortening; the greater the contractility, the greater this velocity will be. From another point of view, at a given level of contractility and total load, the muscle can shorten to a particular end-systolic length. When load is changed, velocity and extent of shortening change reciprocally, but the limits to mechanical performance (i.e., maximum force development or rate of shortening) are set by the level of contractility. Thus, the term *ventricular contractility* has a different connotation from the term *ventricular performance,* and it is useful to identify a change in contractility as an alteration in cardiac function that is independent of changes in ventricular performance, such as those caused by alterations in either preload, afterload, or both.

Under conditions where preload, afterload, and contraction frequency are controlled, the administration of a positive inotropic agent such as norepinephrine shortens the duration of contraction and increases the velocity and extent of wall shortening and increases stroke volume. These changes are depicted in figure 10–5, where wall

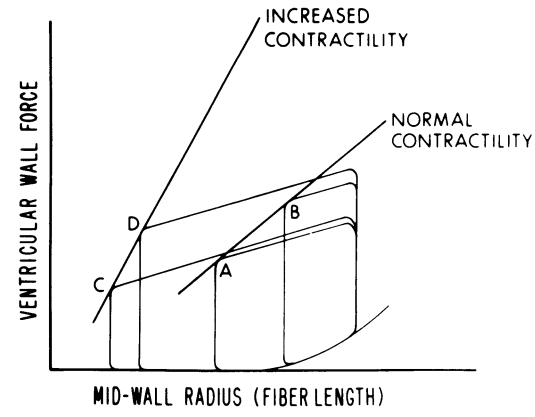

FIGURE 10–5. Effects of augmentation of contractility on the radius-wall force relation during contraction. Shown are two isovolumic radius-wall force lines defining normal (line A-B) and increased contractility (line C-D). The effects of this contractility change on the extent of midwall shortening at two different levels of afterload are shown. Note that extent of shortening is increased at both levels of afterload, but proportionately more at the higher afterload. Not shown, but also occurring with increased contractility, is a rise in the rate of wall shortening and a fall in the total duration of systole.

force–radius loops derived from two levels of afterload and a normal and increased level of contractility are shown. As can be seen, with augmentation of contractility the line relating end-systolic radius and wall force is shifted upward and to the left of normal. This results in an improvement of the rate and extent of wall shortening during ejection, leading to improvement in indices of ventricular performance, such as the ejection fraction. Acute administration of negative inotropic agents such as pentobarbital and propranolol has been shown to produce opposite effects. A wide variety of intrinsic and extrinsic factors have been shown to alter the level of inotropic state of the ventricles. These include autonomic nerve impulses, drugs such as sympathomimetic amines, beta-adrenergic blocking agents, the cardiac glycosides, theophylline derivatives, anesthetic agents, and hormones such as glucagon and thyroid hormone.

In the intact ventricle, a premature depolarization in the form of an atrial or ventricular extrasystole results in a contraction whose strength decreases with increasing prematurity of the extrasystole. The contraction following the extrasystole is more forceful than normal due to an increase in the level of contractility. This phenomenon, postextrasystolic potentiation, has been shown to be independent of variations in diastolic filling of the ventricle [7]. Use has been made of this phenomenon in the cardiac catheterization laboratory where the application of timed premature beats has demonstrated motion in previously motionless areas of the ventricular wall, where contractility is reduced but not absent. This technique gives a reliable estimate of the myocardial contractility reserve and it provides useful prognostic information in conditions associated with regional abnormalities of myocardial contractility such as ischemic heart disease.

HEART RATE

Heart rate can be considered the fourth major determinant of cardiac performance. Increasing the frequency of contraction exerts a positive inotropic effect through operation of the interval-strength relation, although this effect is less prominent in the intact conscious state than in the anesthetized animal or depressed heart. In the normal subject, artificially varying the heart rate between 60 and 160 beats per minute has little effect on the cardiac output despite increasing contractility. Tachycardia produces a reduction in the duration of diastolic filling, but increases of contractility, induced by the frequency change, tend to restore normal filling dynamics through contractility-mediated reduction in the duration of systole.

WALL STRESS–RADIUS–FLOW RELATIONSHIPS

The ventricle, in addition to ejecting a stroke volume from a given end-diastolic volume, delivers this stroke volume with a velocity determined by the instantaneous volume of the ventricle and resistance to ejection [8]. Thus, when the end-diastolic volume is augmented, there is an increase in stroke volume as well as in the rate at which the blood leaves the ventricle. When the arterial pressure is increased, the velocity of ejection of blood and the extent of ventricular emptying are reduced. Furthermore, an inotropic intervention will increase both the stroke volume and the velocity of ejection. The stroke power, which is the product of the stroke volume and the aortic pressure divided by the duration of ejection (i.e., stroke work per unit time), is also increased at any end-diastolic volume; but as with stroke work, stroke power remains pressure dependent.

DIASTOLIC PROPERTIES OF THE VENTRICLE

Before considering the diastolic properties of the intact ventricle, it is essential to define the terms that are used to describe it. Stress is the force per unit cross-sectional area; strain results from the application of a stress and is the fractional or percentage change in dimension or size from the unstressed dimension; elasticity is a property of recovery of a deformed material after removal of a stress. Use of the terms *stress* and *strain* allows normalization of values so that the property of tissues obtained from organs of different sizes and shapes can be compared. Isolated cardiac muscle, like most biological materials, exhibits a curvilinear relation between diastolic stress and strain and does not obey Hooke's law (linear stress-strain relation); this

property is responsible for the nonlinear pressure-volume curve of the intact ventricle. Elastic stiffness defines the instantaneous ratio of stress to strain at any given point on the curve relating stress to strain. The stiffness constant is the slope of the straight line relating these stress-strain ratios to the corresponding stress. The term *stiffness* has also been used when referring to the stiffness of the whole ventricular chamber and may be expressed in its simplified form as the ratio of change in pressure (dP) to change in volume (dV).

The term *compliance,* which has been used interchangeably with the term *distensibility,* represents the inverse of elastic stiffness. That is, it refers to the ratio of a change in strain relative to a change in stress. Simplifying this, ventricular compliance may be referred to as the ratio of dV to dP.

The diastolic pressure-volume curve for the normal ventricle is typically curvilinear, having a relatively small slope at low ventricular end-diastolic pressures and becoming steeper at the upper limit of normal end-diastolic pressure and above (10 to 20 mmHg). It approximates an exponential relation, and as the chamber becomes progressively filled during each diastole, instantaneous ventricular compliance (dV/dP) decreases. The slope of the line relating dV/dP to P represents the elastic stiffness constant of the whole chamber, and while it does not represent the stiffness constant of the muscle of the ventricular wall, its slope has been shown to be relatively independent of ventricular shape and therefore may be useful for detecting changes in wall stiffness.

Although instantaneous compliance varies as the heart fills, an alteration in the compliance of the whole chamber can be identified by a change in the shape and position of the entire curve relating ventricular diastolic volume to pressure. It has been demonstrated, when incomplete relaxation due to tachycardia is excluded, that acute interventions that alter myocardial contractility (other than myocardial ischemia) do not significantly shift the pressure volume relation of the left ventricle. Volume loading and elevation of arterial pressure cause no apparent shift in the ventricular diastolic pressure-diameter relationship during the slow phase of ventricular filling. However, during the rapid phases of filling, under some circumstances, inertial and viscous properties appear to influence compliance significantly.

In the intact heart, alterations in the filling of one ventricle can substantially alter the diastolic pressure-volume relation of the opposite ventricle [9, 10, 11, 12]. Therefore, when right ventricular volume is changing significantly, changes in left ventricular end-diastolic pressure may not be a reliable guide even to directional changes of the diastolic pressure-volume curve of the ventricle. Studies in which the pericardium is left intact have shown that not only the end-diastolic pressure, but also the shape of the left ventricle, is altered by increased right ventricular filling with encroachment of the interventricular septum on the left ventricular cavity.

MUSCLE MECHANICS IN THE INTACT HEART

Since all of the determinants of ventricular performance reflect the properties of the underlying myocardium, indexes of performance have been derived using principles of muscle mechanics obtained in studies of isolated cardiac muscle. The hemodynamic parameters of pressure, flow, and volume reflect to a degree the activity of the underlying myocardial force velocity and length. In table 10–1, these variables have been portrayed with the measurements that are made during the preejection and ejection phases of systole. As noted, the hemodynamic measurements reflect one or more of these variables but no single measurement encompasses them all, and no one reflects only two of three, independent of the third. In general, these indices have been developed to describe the contractility of the intact heart independent of its performance. However, it should be appreciated that these indices are only approximations dependent on oversimplified assumptions and difficult measurements. While the principles may appear clear from isolated muscle, the direct translation into unstable tools of the intact heart is difficult.

Heart Failure

For the purpose of this discussion, heart failure will be considered as the pathophysiologic state

TABLE 10–1. The usefulness of various measures of function in the intact heart as contractility indices

Index	Contractility Variables			Load dependence*	
	Force	Velocity	Displacement	Volume (Preload)	Pressure (Afterload)
Stroke volume	+	0	+	+	+
Ejection fraction	+	0	+	+	+
Ejection time	0	+	0	+	+
Ejection rate (SV/time)	+	+	+	+	+
Rate of pressure development	+	+	0	+	+
Rate of fiber shortening (Vcf)	+	+	0	+	+
V_{max}	0	++	0	0	0
Peak V_{CE}	+	+	0	+	0
E_{max}	+	0	+	0	0

*Zero indicates load independence and therefore theoretically greater usefulness.
V_{max} = maximum velocity of shortening.

in which an abnormality of myocardial function is responsible for the failure of the heart to pump blood at a rate commensurate with the body's metabolic requirements during exercise. Reductions in myocardial function leading to depression of the cardiac output may result from a primary abnormality in the heart muscle (i.e., cardiomyopathy) or may be secondary to ischemia produced by obstructive coronary artery disease. Also, myocardial failure may result secondarily from anatomic lesions of the cardiac valves or pericardium that interfere with cardiac filling or emptying, or from severe or prolonged disorders of cardiac rate or rhythm.

In the presence of a defect in myocardial contraction induced by one or more of the factors outlined in table 10–2, the heart is dependent on three principal compensatory mechanisms to maintain its normal function as a pump (figure 10–5). First, the Frank-Starling phenomenon is activated and an increased preload (i.e., elevated end-diastolic volume) acts to sustain cardiac stroke volume. Second, myocardial hypertrophy occurs, which increases the mass of contractile tissue. Third, increased catecholamines are released by adrenergic cardiac nerves and the adrenal medulla, augmenting myocardial contractility (table 10–3). These compensatory mechanisms have a limited potential and ultimately fail. The development of the syndrome of heart failure, thus, is a direct consequence of the limited ability and ultimate failure of these compensatory mechanisms [13].

CONTRACTILITY OF HYPERTROPHIED AND FAILING MYOCARDIUM

When an excessive load, either a volume or a pressure load, is imposed on the ventricle, the development of myocardial hypertrophy provides for the reduction of stress per unit area of muscle toward normal values through an increase in myocardial mass, and permits the ventricle to sustain the burden. However, with prolonged overloads and greater degrees of hypertrophy, the ventricle ultimately fails. Results of early studies of myocardial contractility in patients and experimental animals with various forms of ventricular overload were variable and inconclusive because of limitations inherent in assessing intrinsic contractility of the intact

TABLE 10–2. Primary etiology of myocardial failure

Work Overloads	
Increased Pressure Load	
·High "central" resistance eg. valvular stenosis	
·High "peripheral" resistance eg. hypertension	
Increase Volume Load	
·Valvular regurgitation	
·High output: A-V shunt, Thyrotoxic	
Oxygen Deprivation	Akinesis
Hypoxia and Ischemia	Asynergy
	Dysynergy
Infarction and/or fibrosis	
Myocardopathy	
Idiopathic: hereditary or acquired	
Viral	
Metabolic: eg. EtOH, Cobalt	

TABLE 10–3. Secondary compensations of myocardial failure

Compensation	*Mechanism*	*Limit*
Volume	Length—Tension Curve Sarcomere	Structure of Sarcomere
		"Fibril Slippage" Laplace Relation (T = P × r)
Hypertrophy	Muscle Mass	Total force, but force/unit mass. Actomyosin ATPase
Sympathetic Drive	Norepinephrine Release	NE depletion tyrosine hydroxylase

heart [14–19]. For this reason there has been substantial interest in the analysis of isolated muscle behavior in experimental models of pressure or volume overload.

Pulmonary artery banding in a variety of mammalian species, producing right ventricular pressure overload and hypertrophy with progression to overt ventricular failure, has been studied extensively [20, 21]. Right ventricular hypertrophy and failure both reduced the maximum velocity of shortening (V_{max}) and index of contractility below values obtained in muscles from normal animals. The changes were more marked in muscles from animals with heart failure than in those that had hypertrophy alone (figure 10–6). Heart failure clearly depressed maximum isometric tension, but hypertrophy without failure produced only mild depressions of peak force. Thus, ventricular hypertrophy in the absence of failure in this experimental model was associated with a depression of contractility per unit area of myocardium. Ventricular compensation preventing development of signs of heart failure was maintained by an increase in muscle mass. The precise alterations in subcellular function regulating myocardial contraction during the development of hypertrophy and failure have been studied in detail [22–26]. Multiple defects appear to occur, which include defects in energy production, calcium metabolism, and membrane function [27].

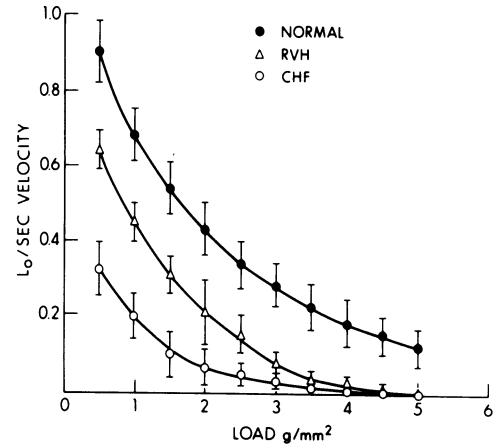

FIGURE 10–6. Force-velocity relations of three groups of cat papillary muscles: normal, right ventricular hypertrophy without failure (RVH), and right ventricular hypertrophy with congestive heart failure (CHF). Velocity is expressed in muscle lengths per second (L_O/sec). Note the parallel depression of the lower load velocity with the development of hypertrophy and failure.

The contractile performance of the intact right ventricle of the same animals revealed depressions of function that paralleled the muscle function studies [21]. Wall force development by the right ventricle at equivalent end-diastolic fiber lengths was significantly lower than normal in animals with heart failure. Reducing or augmenting the end-diastolic volume in the heart failure group demonstrated that the relation between end-diastolic volume and stroke volume or stroke work was shifted downward and to the right of the normal curves, indicating a depression of performance. Thus, during the development of heart failure, ventricular volume increases and the performance of the ventricle returns to near normal values through movement to the right and upward along a depressed ventricular function curve. Ventricular performance is thus preserved in the face of a reduction in over-all contractility at the expense of an increased end-diastolic pressure, volume, and fiber length.

More recently, experimental models of pressure-overload hypertrophy and failure have been reexamined, and the results of muscle studies related to the type, duration, and severity of

the overload as well as to the degree of abruptness with which it was applied to the ventricle. Newer models, such as renovascular hypertension in rats, provide more clinically relevant temporal relationships between the application of the overload and the development of myocardial hypertrophy, consequent alterations in ventricular function, and their reversibility upon relief of the overload [28, 29].

In studies of muscle removed from animals with chronic volume overload (atrial septal defect), contractility was normal and exhibited none of the changes in the force-velocity or length-tension curves noted in muscles obtained from animals with pressure-overload hypertrophy [30]. Thus, the nature of the stress responsible for inciting the hypertrophy appears to play a critical role in determining whether or not hypertrophy is detrimental to myocardial contractility. Following the development of an arteriovenous fistula, the left ventricular end-diastolic pressure rises and stabilizes while the left ventricular end-diastolic diameter increases progressively and the wall thickens. With chronic adjustment to the shunt and to the elevated diastolic filling, myocardial function, as reflected in measurements of mean velocity of circumferential fiber shortening, remains normal. However, worsening of the shunt and hence the development of signs of congestive failure are uniformly associated with depressions of myocardial contractility. Thus, the development of hypertrophy with primary chamber enlargement in volume overload alters ventricular geometric relations in a way that allows maintenance of normal wall stress as well as optimal sarcomere length, permitting an enhancement of overall myocardial performance while contractility remains normal [31–33]. With further overload, however, these mechanisms of compensation are inadequate [33].

As a result of the compensatory mechanisms serving the heart, ventricular performance usually is not markedly affected until the development of signs and symptoms of congestive heart failure. Therefore, indices of ventricular contractility, reflecting the intrinsic state of the myocardium itself, have been sought to define more precisely the course of myocardial deterioration in various myocardial diseases as well as to provide an early indication of the need for either pharmacologic or surgical therapy. The search for the ideal index of ventricular contractility, defined in mechanical terms, has been hampered by both incomplete understanding of ventricular contraction and significant assumptions required before analysis of ventricular function in terms of isolated muscle mechanics can be undertaken [34, 35]. When studied, nearly all indices of ventricular contractility are performance-dependent, which means their sensitivity in detecting a change in contractility is diminished to the extent they are influenced by preload, afterload, and heart rate, important determinants of ventricular performance. However, despite these obstacles, ejection-phase indices such as the ejection fraction (ratio of stroke volume to end-diastolic volume) and the velocity of circumferential fiber shortening have clinical usefulness [36]. By definition, these indices remain incomplete and their limitations require continual consideration when they are applied to a clinical problem. With more precise information on ventricular contraction dynamics, it is hoped that more sensitive indices will emerge, permitting the early detection of myocardial failure, and allowing therapy to begin before compensatory mechanisms are exhausted.

ADRENERGIC NERVOUS SYSTEM IN HEART FAILURE

The third form of compensation for failure of myocardial contraction is augmented sympathetic nervous system activity with increased release of norepinephrine into the myocardium. It is well known that an increase in norepinephrine release augments myocardial contractility and participates in the regulation of cardiac performance during acute stress or exercise in the normal state. During early stages of heart failure, urinary excretion of catecholamines is elevated [37]. However, during sustained loads on the myocardium with developing myocardial failure, the myocardium becomes depleted of its catecholamine stores. This depletion is related to failure of the adrenergic nerves of the heart. Thus, with chronic failure, the myocardium becomes effectively denervated due to progressive failure of the sympathetic nerve endings of the heart to synthesize, store, and release cate-

cholamines. The myocardial catecholamines are most depleted in situations where the myocardium is most depressed. This does not mean, however, that a loss of myocardial catecholamine stores per se leads directly to heart failure, since pharmacologic depletion of myocardial catecholamines stores in the normal state does not alter basal contractility [38]. However, in heart failure with depression of myocardial contractility, the ability to augment contractility by localized catecholamine release is lost even though the responsiveness of the myocardium to circulating catecholamines is normally sustained. While there is augmentation of the circulating catecholamines from peripheral nerves and the adrenal glands in the presence of heart failure, the degree to which this circulating store of catecholamines serves to support contractility of the heart is unknown. However, it is now recognized that use of beta-adrenergic blockade in severe myocardial failure may be limited by further depression of the heart, which could be related in part to blockade of the action of these circulating catecholamines [29].

Chronic elevations of circulating catecholamines also affect the peripheral vascular resistance in patients with congestive heart failure, often producing a significant increase in order to maintain blood pressure [39]. This results in an increased impedance to ventricular ejection, which in combination with a dilated heart results in significant elevations of afterload and decreasing ventricular performance.

Pathophysiology of Heart Failure

Myocardial failure resulting in ventricular dysfunction and ultimate depression of cardiac pump performance remains a fundamental, unsolved clinical problem. It invariably leads to a limitation of normal activities and early death of the patient. Indeed, the presence of myocardial failure appears to be the primary determinant of short-term or long-term patient survival, independent of the etiology or whether treatment is medical or surgical [36].

The syndrome of heart failure may be considered in relation to two conditions (table 10–4). The first is myocardial failure, either diffuse or segmental, characterized by a decrease in speed and force of muscle contraction. When the amount of myocardial depression is great enough, it is translated into a decrease in the reserves of pump function and ultimately into pump failure. Pump failure is then defined as the inability to provide a cardiac output on demand that is adequate to meet the peripheral needs during exercise. The second condition is congestive heart failure, which reflects systemic responses to an inadequate pump, characterized by augmented sympathetic nervous system activity, renal vasoconstriction, and activation of the renin-angiotensin system with peripheral congestion and edema (figure 10–7).

TABLE 10–4. The myocardial and systemic components of heart failure

Myocardial Failure
Decrease in force development and shortening.
2° to myocyte loss and hypertrophy --- pump failure (CO on demand).
Congestive Failure
Peripheral effects of failure of pump to meet peripheral needs.
Sympathetic tone and renin-angiotensin activity.
Peripheral congestion, edema, and/or fatigue.

Experimental heart failure has been studied in several animal models, all of which are characterized by hemodynamic pressure or volume overload. In these models, the time between the creation of the hemodynamic overload and the appearance of myocardial failure depends on the type of overload created (pressure or volume), the abruptness with which it is applied, and the severity of the overload created. Whereas initial hypertrophy in response to the hemodynamic overload tends to normalize the load per unit of myocardium and maintain pump performance early in the course, myocardial failure ultimately develops in most, but not all, instances. Whether or not depression of myocardial function ensues has correlated significantly with the severity of the overload and the extent of resultant myocardial hypertrophy [40]. The contribution of other factors—such as age of the host, when the overload occurs, and concurrent vascular disease —is not clear.

From early studies of the mechanical correlates of acute pulmonary artery banding in the

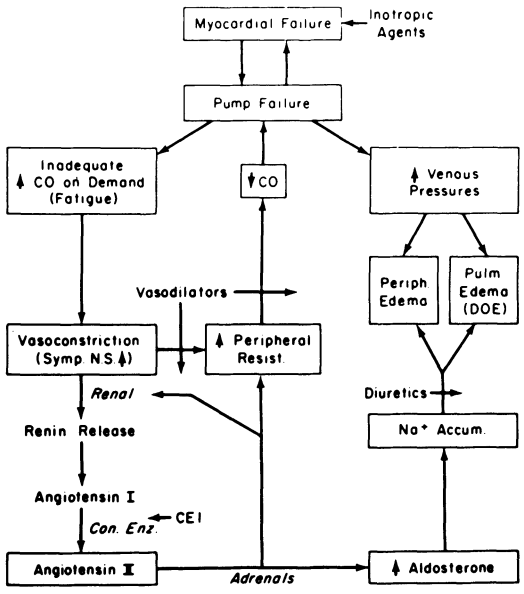

FIGURE 10–7. Systemic response to myocardial and pump failure. This figure depicts the body response to a lowered cardiac output and elevated venous pressures. Adrenergic-mediated vasoconstriction leads to increases in renin production and direct increases in peripheral resistance. Elevated vascular resistance further reduces cardiac output and angiotensin-mediated aldosterone production leads to Na^+ accumulation and worsening pulmonary and venous congestion.

cat [20], it is clear that moderate degrees of obstruction of the pulmonary artery lead to right ventricular hypertrophy but not ventricular failure. With more severe obstruction, a greater systolic pressure overload is produced and more severe hypertrophy occurs as well as right ventricular failure. Studies of papillary muscles removed from hypertrophied hearts without congestive failure showed decrements in the maximum velocity of shortening of unloaded myocardium (V_{max}), but not in peak force development (P_0). Ultrastructural and biochemical studies done in the same preparation showed little histologic change aside from cell enlargement, little or no change in mitochondrial function, and increase in connective tissue [41] and a significant decrease in the rate-limiting enzymatic step for muscle shortening, namely actomyosin ATPase [42]. A slowing of calcium binding by the sarcoplasmic reticulum from such preparations has also been found [35]. As the systolic overload was increased further, additional myocardial failure as well as ventricular failure occurred, characterized by a fall in force production as well as a further decrease in velocity of the isolated papillary muscle [43]. In addition to a further decline in actomyosin ATPase, catecholamine depletion occurred in the heart with failure of cardiac nerves to synthesize, store, or release norepinephrine [43, 44].

Not all experimental systolic overloads have resulted in a clear-cut depression of myocardial function. This may be explained, at least in part, by variations in the severity and duration of the overload. Moreover, most studies of hypertrophy have involved the acute imposition of the load. This may produce initial pump failure with focal myocardial damage and subsequent recovery with residual scarring and hypertrophy. In studies of a more physiologic model of systolic pressure overload, renovascular hypertension, it has been found that V_{max} falls as a function of hypertrophy, yet force development is well maintained [28, 40]. Thus, systolic (renal) hypertension in the rat, which mimics hypertensive hypertrophy of humans, is associated with changes in contractile properties of the myocardium characterized by a decrease in V_{max}, a prolongation of the duration of contraction, and a decrease in relaxation rate [28, 40]. Actomyosin ATPase rates fall pari passu with these mechanical events [28]. Of greater importance, all of these contractile changes are reversible when the hypertension is corrected [63].

It has recently been shown that experimental diabetes mellitus in the rat leads to contractile changes characterized by a decrease in V_{max} and slowed relaxation [64]. Once again this is associated with a decrease in actomyosin ATPase [61] and reduced rates of calcium binding by isolated sarcoplasmic reticulin [62]. These alterations are reversed by treatment of diabetic rat with insulin [45].

Diastolic overloads (volume overload) impose a change in diastolic volume without an increase in the systolic load on the myocardium. An increase in ventricular mass occurs but does not produce the same fall in contractility as is observed following systolic overloads [30, 46]. The reason for this discrepancy is not known, but one explanation is that diastolic overload

may not lead to the same degree of cell enlargement during hypertrophy. However, with substantial volume overloads, sarcomeres in the wall of the heart are stretched to the limit of their length-tension curve and "plastic" alterations occur leading to further dilatation [47]. Further, when volume is increased without unloading of tension in the wall by increased ventricular emptying, the tension in the wall rises as a result of the Laplace relation and hypertrophy ensues. This may then lead to late declines in contractility from this secondary tension overload. All of the changes in mechanics described are subject to reversal upon removal of the overload [48–50].

Of essential pathophysiological importance to the problem of myocardial failure is the understanding of what factors lead to irreversible depression of myocardial function and ultimate pump failure in the face of a compensatory hypertrophic response to various pump overloads. Recent studies in four different forms of cardiomyopathy have produced some insight into this question. These forms of cardiomyopathy include the hereditary cardiomyopathy that occurs in the Syrian hamster [51]; the cardiomyopathy that develops in the hypertensive-diabetic heart [52] and in human diabetic hearts [53]; and renovascular hypertension [28, 40]. Histological studies in each type of myopathy have all shown regions of fibrosis, myocytolysis, and even calcification adjacent to regions of severely hypertrophied but normal-appearing muscle [51].

The hereditary cardiomyopathic Syrian hamster develops focal myocardial necrosis beginning as early as 1 month of age, which leads to eventual myocardial failure within a year. Studies of isolated muscle from such hearts have demonstrated substantial decrements in force development as early as 50 days after birth with subsequent restoration of total force development as compensatory hypertrophy develops [54]. In contrast, V_{max} was preserved early but later fell as the hypertrophic process progressed. Such findings are consistent with an early loss of myocytes producing a fall in force with V_{max} unchanged, with later changes reflecting progressive hypertrophy of the remaining cells characterized by a decline in V_{max}. Continued progression of the latter process eventuates in a congestive cardiomyopathy and death of the animal. Treatment of young Syrian hamsters with the calcium channel blocker verapamil, during the period when the animals normally develop focal myocardial necrosis (30 to 44 days of age), prevented the myocytolytic lesions and abolished the microvascular hyperreactivity [55]. Thus, in this case a drug was capable of preventing the development of a cardiomyopathy.

Although vascular hyperreactivity may provide a rational explanation for the early pathologic lesions in the Syrian hamster, it is felt that these microcirculatory lesions are not limited to this model. Very similar abnormalities have been demonstrated recently in the hypertensive-diabetic rat, an experimental model of human disease [53, 56]. The animals in this model develop focal, discrete areas of fibrosis in the myocardium, similar to those seen in the Syrian hamster. Perfusion of these hypertensive-diabetic rats with silicone rubber solutions in vivo has also revealed a multiplicity of constrictions, tortuousities, and true microaneurysms [56, 57] (figure 10–8). Whether or not these lesions can be prevented with a calcium channel blocker such as verapamil is currently under study. Microvascular constriction has also been demonstrable with postmortem perfusions of human diabetic hearts [53]. In this investigation, typical microaneurysms similar to those seen in diabetic retinas were observed, but in addition, focal vascular constrictions, identical to those reported in the Syrian hamster studies, were also seen. Constricted lesions following microfill injection have also been demonstrated in renal hypertensive rats [57].

Since microvascular hyperreactivity is present in the Syrian hamster, the hypertensive diabetic rat, the human diabetic heart [56], and the renovascular hypertensive rat, and leads in all models to focal cell necrosis and subsequent fibrosis, it has been speculated whether such circulatory lesions are a feature of congestive cardiomyopathy in general (figure 10–9). Most human forms of cardiomyopathy have focal myocardial fibrosis as their most significant pathological feature [58, 59]. Thus, since adult myocardial cells do not

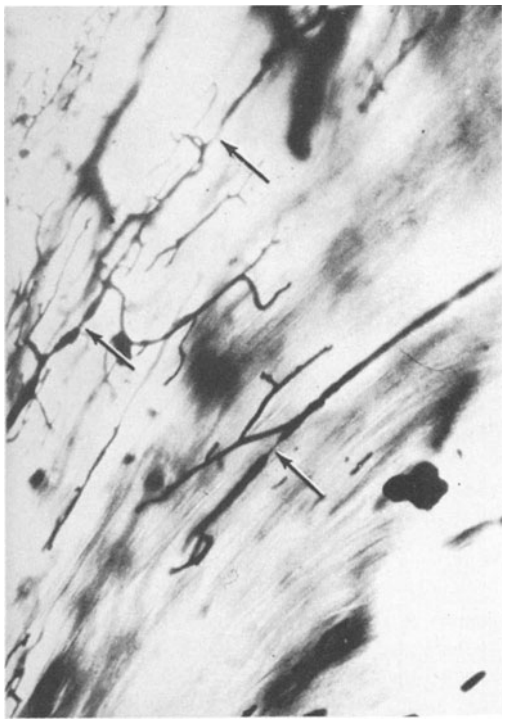

FIGURE 10–8. High-powered micrograph of myocardium removed from a hypertensive-diabetic rat after silicone-rubber solution was perfused into the coronary circulation in vivo. Note the many constrictions, tortuousities, and true microaneurysms, as noted by arrows, in the coronary arterioles.

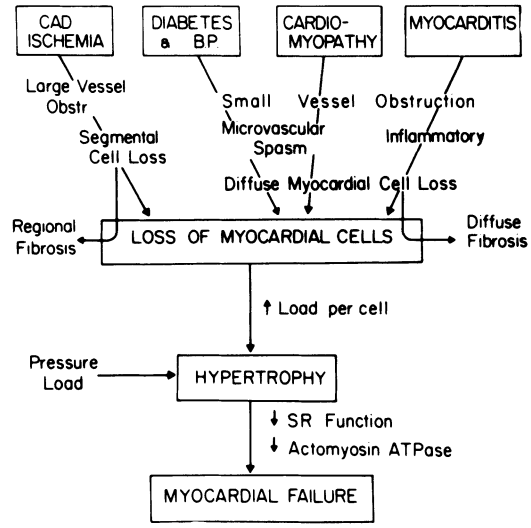

FIGURE 10–9. The concept of hypertrophic myopathy. Hypothesis showing relation of etiologic entities of coronary disease, diabetes, hypertension, cardiomyopathy, and myocarditis to the ultimate loss of myocardial cells, which in these pathologic states is the stimulus for secondary myocardial hypertrophy and loss of contractility of the remaining cells to develop.

proliferate, microvascular spasm with focal myocytolytic necrosis will result in decreased numbers of ventricular myocytes. This will increase the load borne by the remaining myocytes, leading to their compensatory hypertrophy. Subsequently, in later stages of the cardiomyopathy, one would expect to find areas of focal necrosis and fibrosis intermingled with hypertrophied myocardium. Severe hypertrophy that results from this underlying microvascular process and the persistent hemodynamic overload result in extremely large cells in which activation is impaired and actomyosin ATPase activity is reduced. Widespread fibrosis also has substantial effects on overall ventricular compliance. Dilatation of the heart may then be superimposed in an attempt to compensate for decreased myocardial function. Thus, what began as widespread focal and even unrecognized myocyte necrosis, secondary to microvascular hyperreactivity and spasm, may terminate as hypertrophic myopathy characterized by large ventricular myocytes with impaired contractility, ultimately producing myocardial failure (figure 10–9).

Conclusion

The current concept of the systemic response to myocardial failure is summarized in figure 10–7. Myocardial failure eventually ensues after cardiac compensatory mechanisms have been exhausted. An essential consideration relative to therapy and outcome of the process leading to myocardial failure depends on what is reversible and what is irreversible (table 10–5). Reversible factors include hypertrophy when the load is removed prior to substantial cell loss. Ischemia is reversible until necrosis and cell loss occur, whether the result of large vessel obstruction or spasms. Once myocyte loss has occurred, an irreversible process develops that depends on the extent of further cell loss for its progression [60].

TABLE 10–5. Reversible and irreversible factors in heart failure

Reversible
Hypertrophy
Volume increase—elastic
Ischemia*—Large vessel (CAD)
Small vessel (Spasm)
Irreversible
Myocardial cell loss and fibrosis
Segmental
Diffuse focal
Volume increase—dilatation
With "plastic" changes ("fiber slippage")
Catecholamine depletion (?)

*Ischemia includes both large vessel obstructive disease and microvascular spasm prior to myocardial necrosis.

Current therapy for the treatment of myocardial failure, as well as the systemic response to myocardial failure (congestive heart failure), has traditionally involved medication aimed at improving the contractile function of myocardial cells as well as relieving the hemodynamic effects of the systemic response to myocardial failure. However, these medications provide palliative relief and in no way reverse the abnormality of the activating system or contractile proteins of the myocardium that are observed in the presence of severe hypertrophy. Moreover, the process of microvascular spasm and loss of cardiac cells with further fibrosis may be proceeding and may even be worsened by inotropic therapy. Although the need for palliative therapy in heart failure is not questioned, we as physicians must remain critically aware that the initial lesion, namely myocyte loss, causing an ultimate downhill course for the myocardium is not being approached directly by these medications. Alternatively, it is possible that agents that affect microvascular spasm and perhaps other yet unknown factors may ultimately improve myocardial performance by preventing progression of the primary disease. These considerations strongly suggest that interest should shift from continued therapeutic attempts to bolster the already irreversibly damaged heart to attempts to identify patients with certain forms of cardiomyopathy at an earlier stage of the disease, when an opportunity to truly affect the long-term outcome exists.

References

1. Sonnenblick, E.H. and Skelton, C.L. Reconsideration of the ultrastructural basis of cardiac length-tension relations. *Circ. Res.* 35:517–526, 1974.
2. Spiro, D. and Sonnenblick, E.H. Comparison of the ultrastructural basis of the contractile process in heart and skeletal muscle. *Circ. Res.* 15 (Suppl. 2):14–24, 1964.
3. Sonnenblick, E.H. and Strobeck, J.E. Derived indices of ventricular and myocardial function. *N. Engl. J. Med.* 296:978–983, 1977.
4. Sarnoff, S.J. and Berglund, E. Ventricular function. I. Starling's law of the heart studied by means of simultaneous right and left ventricular function curves in dogs. *Circulation* 9:706–718, 1954.
5. Sagawa, K., Suga, J., Shoukas, A., and Bakalar, K. End-systolic pressure/volume ratio: A new index of ventricular contractility. *Am. J. Cardiol.* 40:-748–753, 1977.
6. Ross, J., Jr. Afterload mismatch and preload reserve: A conceptual framework for analysis of ventricular function. *Prog. Cardiovas. Dis.* 18:-255–264, 1976.
7. Lendrum, B., Feinberg, H., Boyd, E., and Katz, L.N. Rhythm effects on contractility of beating isovolumic left ventricles. *Am. J. Physiol.* 199:-115–124, 1960.
8. Gault, J.H., Ross, J., and Braunwald, E. Contractile state of the left ventricle in man: Instantaneous tension-velocity-length relations in patients with and without disease of left ventricular myocardium. *Circ. Res.* 22:451–463, 1968.
9. Ross, J., Jr. Acute displacement of the diastolic pressure-volume curve of the left ventricle: Role of the pericardium and the right ventricle. *Circulation* 59:32–37, 1979.
10. Gibson, D.G. and Brown, D.J. Relation between diastolic left ventricular wall stress and strain in man. *Brit. Heart J.* 36:1066–1078, 1974.
11. Glantz, S.A. Ventricular pressure-volume indices change with end-diastolic pressure. *Circ. Res.* 39:-772–785, 1976.
12. Tyberg, J.V., Misbach, G.A., Glantz, S.A., Morres, W.Y., and Parmley, W.W. A mechanism for shifts in diastolic, left ventricular pressure-volume curve: The role of the pericardium. *Eur. J. Card.* 7 (Suppl.):163–173, 1978.
13. Braunwald, E., Ross, J., Jr., and Sonnenblick, E.H. *Mechanism of Contraction in the Normal and Failing Heart,* 2nd ed. Boston: Little, Brown, 1976).
14. Braunwald, E., Welch, G.H., Jr., and Sarnoff, S.J. Hemodynamic effects of qualitatively varied experimental mitral regurgitation. *Circ. Res.* 5:539–550, 1957.
15. Grant, C., Greene, D.G., and Bunnell, I.L. Left ventricular enlargement and hypertrophy. A clin-

ical angiocardiographic study. *Am. J. Med.* 39:-895–904, 1965.
16. Hood, W.P., Jr., Rackley, C.E., and Rolett, E.L. Wall stress in the normal and hypertrophied human left ventricle. *Am. J. Cardiol.* 22:550–558, 1968.
17. Urschel, C.W., Covell, J.W., Sonnenblick, E.H., Ross, J., Jr., and Braunwald, E. Myocardial mechanics in aortic and mitral valvular regurgitation: The concept of instantaneous impedance as a determinant of the performance of the intact heart. *J. Clin. Invest.* 47:867–883, 1968.
18. Urschel, C.W., Covell, J.W., Graham, T.P., Clancy, R.L., Ross, J., Jr., Sonnenblick, E.H., and Braunwald, E. Effects of acute valvular regurgitation on the oxygen consumption of the canine heart. *Circ. Res.* 23:33–43, 1968.
19. Welch, G.H., Jr., Braunwald, E., and Sarnoff, S.J. Hemodynamic effects of quantitatively varied experimental aortic regurgitation. *Circ. Res.* 5:546–556, 1957.
20. Spann, J.F., Jr., Buccino, R.A., Sonnenblick, E.H., and Braunwald, E. Contractile state of cardiac muscle obtained from cats with experimentally produced ventricular hypertrophy and heart failure. *Circ. Res.* 21:341–354, 1967.
21. Spann, J.F., Jr., Covell, J.W., Eckberg, D.L., Sonnenblick, E.H., Ross, J., Jr., and Braunwald, E. Contractile performance of the hypertrophied and chronically failing cat ventricle. *Am. J. Physiol.* 223:1150–1157, 1972.
22. Alpert, N.R. and Gordon, M.S. Myofibrillar adenosine triphosphate activity in congestive failure. *Am. J. Phys.* 202:940–946, 1962.
23. Chidsey, C.A., Weinbach, E.C., Pool, P.E., and Morrow, A.G. Biochemical studies of energy production in the failing human heart. *J. Clin. Invest.* 45:40–50, 1966.
24. Conway, G.F. and Roberts, J.L. Comparison of molecular weight of myosin from normal and failing dog hearts. *Am. J. Physiol.* 208:243–249, 1965.
25. Katz, A.M. Biochemical "defect" in the hypertrophied and failing heart. *Circulation* 47:1076–1079, 1973.
26. Olson, R.E., Ellenbogen, E., and Iyengar, R. Cardiac myosin and congestive heart failure in dog. *Circulation* 24:471–482, 1961.
27. Entman, M.L., VanWinkle, B., Tate, C.A., and Mc Millin-Wood, J.B. Pitfalls in Biochemical Studies of Hypertrophied and Failing Myocardium. In Braunwald, E. (ed.), *Congestive Heart Failure: Current Research and Clinical Applications,* New York: Grune & Stratton, 1982, pp. 51–64.
28. Capasso, J., Strobeck, J.E., and Sonnenblick, E.H. Myocardial mechanical alterations during gradual onset long-term hypertension in rats. *Am. J. Physiol.* 241:H435–H441, 1981.
29. Epstein, S.E. and Braunwald, E. The effect of beta-adrenergic blockade on patterns of urinary sodium excretion: Studies in normal subjects and in patients with heart disease. *Ann. Int. Med.* 65:-20–27, 1966.
30. Cooper, G., IV, Puga, F., Zujko, K.J., Harrison, C.E., and Coleman, H.N. Normal myocardial function and energetics in volume-overload hypertrophy in the cat. *Circ. Res.* 32:140–148, 1973.
31. Grossman, W., Jones, D., and McLaurin, L.P. Wall stress and patterns of hypertrophy in the human left ventricle. *J. Clin. Invest.* 56:56–64, 1975.
32. McCullagh, W.H., Covell, J.W., and Ross, J., Jr. Left ventricular dilatation and diastolic compliance changes during chronic volume overloading. *Circulation* 45:943–951, 1972.
33. Ross, J., Jr. Adaptations of the left ventricle to chronic volume overload. *Circ. Res.* 35 (Suppl. 2):64–70, 1974.
34. Gunther, S. and Grossman, W. Determinants of ventricular function in pressure overload hypertrophy in man. *Circulation* 59:679–688, 1979.
35. Sordahl, L.A., McCollum, W.B., Wood, W.B., and Schwartz, A. Mitochondrial and sarcoplasmic reticulum function in cardiac hypertrophy and failure. *Am. J. Physiol.* 224:497–502, 1973.
36. Cohn, P.F., Gorlin, R., Cohn, L.H., and Collins, J.J., Jr. Left ventricular ejection fraction as a prognostic guide in surgical treatment of coronary and valvular heart disease. *Am. J. Card.* 34:136–141, 1974.
37. Chidsey, C.A., Braunwald, E., and Morrow, A.G. Catecholamine excretion and cardiac stores of norepinephrine in congestive heart failure. *Am. J. Med.* 39:442–451, 1965.
38. Spann, J.F., Jr., Sonnenblick, E.H., Cooper, T., Chidsey, C.A., Willman, V.L., and Braunwald, E. Cardiac norepinephrine stores and the contractile state of heart muscle. *Circ. Res.* 19:317–325, 1966.
39. Higgins, C.B., Vatner, S.F., Franklin, D., and Braunwald, E. Effects of experimentally produced heart failure on the peripheral vascular response to severe exercise in conscious dogs. *Circ. Res.* 31:186–194, 1972.
40. Strobeck, J.E., Aronson, R.S., Capasso, J.M., and Sonnenblick, E.H. Hypertensive hypertrophy effects on cardiac contractile and electrophysiological behavior. *Proceedings of the Second US-USSR Joint Symposium on Hypertension.* Dept HEW, NIH 80-2016, pp, 107–123, 1980.
41. Buccino, R.A., Harris, E., Spann, J.R., Jr.; and Sonnenblick, E.H. Response of myocardial connective tissue to development of experimental hypertrophy. *Am. J. Physiol.* 216:425–428, 1969.
42. Chandler, B.M., Sonnenblick, E.H., Spann, J.R., and Braunwald, E. Association of depressed

myofibrillar adenosine triphosphatase and reduced contractility in experimental heart failure. *Circ. Res.* 21:717–725, 1967.
43. Spann, J.F., Jr., Chidsey, C.A., Pool, P.E., Sonnenblick, E.H., and Braunwald, E. Mechanism of norepinephrine depletion in experimental heart failure produced by aortic constriction in the guinea pig. *Circ. Res.* 17:312–321, 1965.
44. Chidsey, C.A., Kaiser, G.A., Sonnenblick, E.H., and Braunwald, E. Cardiac norepinephrine stores in experimental heart failure in the dog. *J. Clin. Invest.* 43:2386–2393, 1964.
45. Fein, F.S., Strobeck, J.E., Malholtra, A., Scheuer, J., and Sonnenblick, E.H. Reversibility of diabetic cardiomyopathy with insulin in rats. *Circ. Res.* 49:1251–1261, 1981.
46. Mehmel, H.C., Mazzoni, S., and Krayenbuchl, H.P. Contractility of the hypertrophied human left ventricle in chronic pressure and volume overload. *Am. Heart J.* 90:236–240, 1975.
47. Bishop, S.P. Structural Alterations of the Myocardium Induced by Chronic Work Overload. In *Comparative Pathophysiology of Circulatory Disturbances,* Blood (ed.). New York: Plenum Press, 1972, pp. 289–314.
48. Coulson, R.L., Yazdanfar, S., Rubio, E., and Spann, J.R. Recuperative potential of cardiac muscle following relief of pressure overload hypertrophy and right ventricular failure in the cat. *Circ. Res.* 40:41–49, 1977.
49. Jouannot, P. and Hatt, P.Y. Rat myocardial mechanics during pressure-induced hypertrophy development and reversal. *Am. J. Physiol.* 229:355–364, 1975.
50. Sasayama, S., Ross, J., Franklin, D., Bloor, C.M., Bishop, S., and Dilly, R.R.B. Adaptations of the left ventricle to chronic pressure overload. *Circ. Res.* 38:172–178, 1977.
51. Strobeck, J.E., Factor, S.M., Bhan, A., Fein, F., and Sonnenblick, E.H. Hereditary and acquired cardiomyopathies in experimental animals. Mechanical, biochemical and structural features. *Ann. NY Acad. Sci.* 317:59–88, 1979.
52. Factor, S.M., Minase, T., and Sonnenblick, E.H. Microvascular abnormalities in the hypertensive-diabetic rat heart. *Circulation* 62 (Suppl. III):III–247 (Abstract), 1980.
53. Factor, S.M., Okun, E.M., and Minase, T. Capillary microaneurysms in the human diabetic heart. *N. Engl. J. Med.* 320:384–388, 1980.
54. Forman, R., Parmley, W.W., and Sonnenblick, E.H. Myocardial contractility in relation to hypertrophy and failure in myopathic Syrian hamster. *J. Mol. Cell. Cardiol.* 4:203–211, 1972.
55. Factor, S.M., Cho, S., and Sonnenblick, E.H. Verapamil treatment of cardiomyopathic Syrian hamster: Effects on the microcirculation and the extent of myocardial necrosis. *Fed. Proc.* 40:758, 1981.
56. Factor, S.M., Minase, T., and Sonnenblick, E.H. Clinical and morphological features of human hypertensive-diabetic cardiomyopathy. *Am. Heart J.* 99:446–458, 1980.
57. Factor, S.M., Bhan, R., Minase, T., and Sonnenblick, E.H. Hypertensive-diabetic cardiomyopathy in the rat: An experimental model of human disease. *Am. J. Pathol.* 102:219–228, 1981.
58. Olsen, E.G.J. The pathology of cardiomyopathies. A critical analysis. *Am. Heart J.* 98:385–392, 1979.
59. Roberts, W.C. and Ferrans, V.J. Pathologic anatomy of the cardiomyopathies: Idiopathic dilated and hypertrophic types, infiltrative types and endomyocardial disease with and without eosinophilia. *Human Path.* 6:287–342, 1975.
60. Sonnenblick, E.H., Factor, S.M., Strobeck, J.E., Fein, F., and Capasso, J. The Pathophysiology of Heart Failure: The Primary Role of Microvascular Hyperreactivity and Spasm in the Development of Congestive Cardiomyopathies. In Braunwald, E. (ed.), *Congestive Heart Failure: Current Research and Clinical Applications.* New York: Grune & Stratton, 1982, pp. 87–97.
61. Malholtra, A., Penpargkul, S., Fein, F.S., Strobeck, J.E., and Sonnenblick, E.H. Effect of streptozotocin-induced diabetes in rats on cardiac contractile proteins. *Circ. Res.* 49:1243–1250, 1981.
62. Penpargkul, S., Fein, F., Sonnenblick, E.H., and Scheurer, J. Depressed cardiac sarcoplasmic reticular function from diabetic rats. *J. Mol. Cell. Cardiol.* 13:303–309, 1981.
63. Capasso, J., Strobeck, J.E., Malholtra, A., Scheuer, J., and Sonnenblick, E.H. Contractile behavior of rat myocardium after reversal of hypertensive hypertrophy. *Physiology* 242:H882–H889, 1982.
64. Fein, F., Kornstein, L., Strobeck, J.E., and Sonnenblick, E.H. Altered myocardial mechanics in diabetic rats. *Circ. Res.* 47:922–933, 1980.