

The heart as a muscle-pump system and the concept of heart failure

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Over the years few subjects have received the attention of physicians and physiologists as the description of cardiac function, and in particular the evaluation of the failing heart. At the turn of the century and from the laboratories of Frank¹ and Starling² emerged the view of the heart as a compression pump. This concept, espoused by Wiggers³ and then by Katz,⁴ likened the heart to a piston-cylinder arrangement and focused on its pressure-volume relations using such displacement terms as stroke volume, cardiac output, and stroke work. In more recent years others, such as Sonnenblick,⁵ Fry and colleagues,⁶ and Levine and Britman⁷ approached this subject from a different vantage point. Here the mechanical properties of cardiac muscle and in particular the behavior of its contractile element were emphasized. The application of these fundamental muscle concepts to the whole heart served to broaden our view of ventricular function. In the diseased heart, however, the confidence with which characteristics of the contractile element could be assessed was challenged.^{8, 9} The controversy focused on the muscle models and simplifying assumptions which were necessary to make such determinations and the fact that supportive experimental data were limited.

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In the past five years a sufficient base of information has been accumulated which permits a more detailed examination of the mechanical properties of the intact myocardium, and in particular its shortening characteristics.^{10, 11-15} The evidence at hand indicates that the heart, in fact, may best be described as an integrated muscle-pump system. The purpose of this review is to elucidate the characteristics of myocardial shortening and in so doing present the heart as a muscle-pump unit. That is, the determinants of wall shortening regulate chamber volume displacement. Finally, the relevance of these behavioral characteristics of the myocardium is addressed with respect to the failing heart and the therapeutic concept of unloading.

The heart as a pump

The traditional view of the heart as a pump has focused on the displacement characteristics of its ventricles. That is, the volume ejected per beat (i.e., stroke volume) or per minute (i.e., cardiac output) has been used to gauge the performance of the heart. The comparison of stroke volume, cardiac output, or stroke work (obtained from the product of mean ejection pressure and stroke volume) to the filling volume of the ventricle represents one such approach which has been termed the *ventricular function curve*.¹⁶ Fig. 1 represents a series of function curves. As the end diastolic volume (EDV) of the normal heart is progressively raised stroke work and stroke volume increase. These increments are attenuated in the failing heart where a plateau and even a decline in work may be apparent. On the other hand, the work performed by the heart may be significantly augmented by such inotropic agents as norepinephrine.

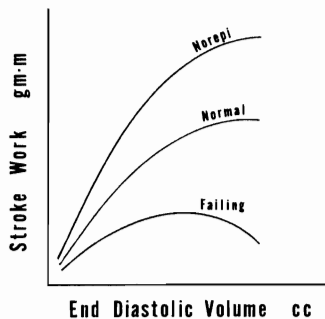


Fig. 1. A series of ventricular function curves for a normal and failing heart and one in which ventricular performance and stroke work have been augmented by norepinephrine (*norepi*).

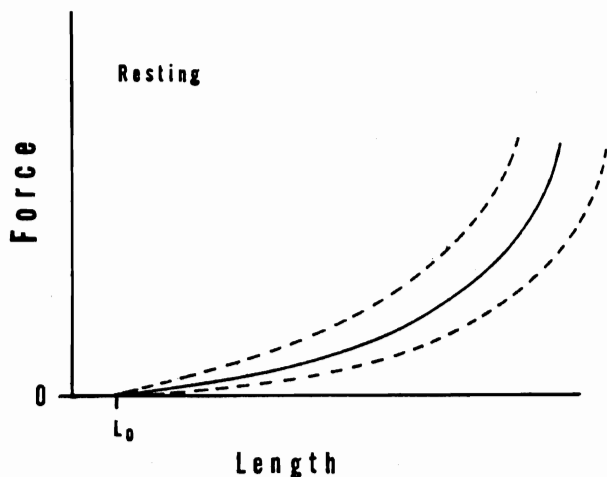
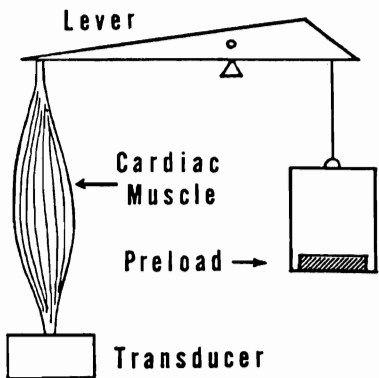


Fig. 2. A schematic representation of an isolated papillary muscle preparation. The weight added to the trough prior to contraction (*preload*) serves to stretch the resting muscle to a given length. The extent to which the muscle will be stretched is dependent on the distensibility of the muscle. As indicated by the resting force-length relation, a stiffer muscle will require a greater distending force to achieve any given length.

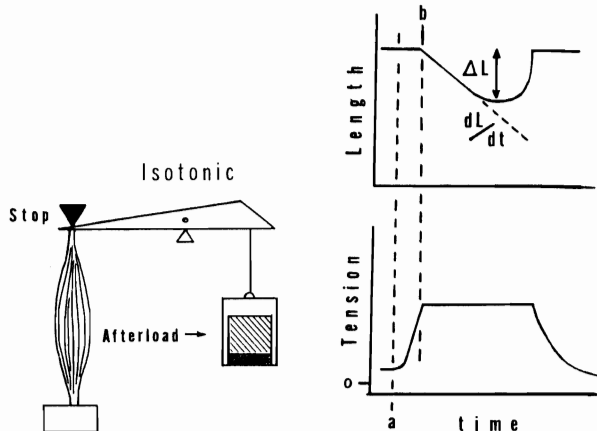


Fig. 3. The addition of the mechanical stop to the lever prevents the muscle from being stretched as additional weights are added to the trough. This weight which represents the grams of force which the muscle must develop and sustain in order to shorten is termed the *afterload*. The extent (ΔL) and rate (dL/dt) of muscle shortening of the afterloaded isotonic contraction may be used to assess the mechanical properties of cardiac muscle.

In basic terms, *work* represents the force required to move an object over a given distance. In the case of the heart, work is equal to the force generated by the heart muscle times the distance the muscular wall shortens. As such, work is a net quantity which does not distinguish between various conditions of force and distance. For example, the same work is performed moving 1,000 Gm. over 3 cm. as 500 Gm. over 6 cm. In addition, work will neither reflect the efficiency nor the energy consumed by the heart in carrying these various but equivalent amounts of work.¹⁷ In the example cited, moving 1000 Gm. over 3 cm. will require more oxygen (i.e., less efficient) than transporting the lesser weight over a greater distance.

The heart as a muscle

Isolated cardiac muscle. The properties of cardiac muscle were first examined some 15 years ago using isolated strips of papillary muscle.⁵ The concepts and terminology which arose as a result of these experiments will first be reviewed and then examined in the intact heart.

Thin papillary muscles taken from the right ventricle of the cat or rabbit were studied with one end of the muscle attached to a force transducer, as shown in Fig. 2, and the other end secured to a level system to monitor muscle

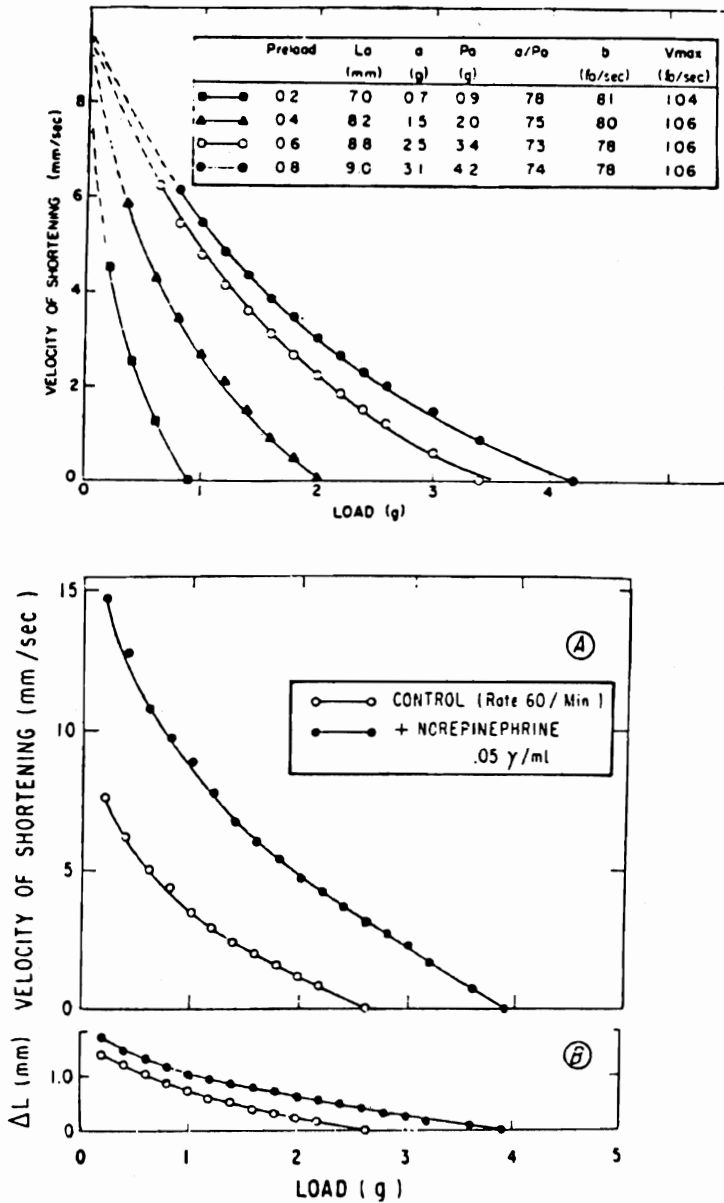


Fig. 4. The response in the velocity and extent (ΔL) of shortening to variations in preload (*upper panel*) and inotropic background (*lower panel*) are presented from the data of E. H. Sonnenblick (Adopted with major modifications from Figs. 10 and 14 of reference 5). Note that for any given preload or contractile state an inverse relation between force and shortening is present.

length. By adding small weights to the trough on the opposite end of the lever the muscle is stretched and a distending force imparted to the muscle. This passive force in grams, which serves to impart a given stretch and length to the muscle has been termed the *preload*. The extent to which the muscle will be stretched by any preload will be a function of the distensibility of the muscle. That is, the stiffer the muscle the greater the

force required to generate any given degree of stretch or muscle length.

Having now established a given length to the muscle, a mechanical stop is placed at the muscle end of the lever to prevent further stretch (see Fig. 3). Electrodes are used to induce a contraction of the muscle. Any additional weights which are now added to the trough will be encountered by the muscle during its contraction. That is, a

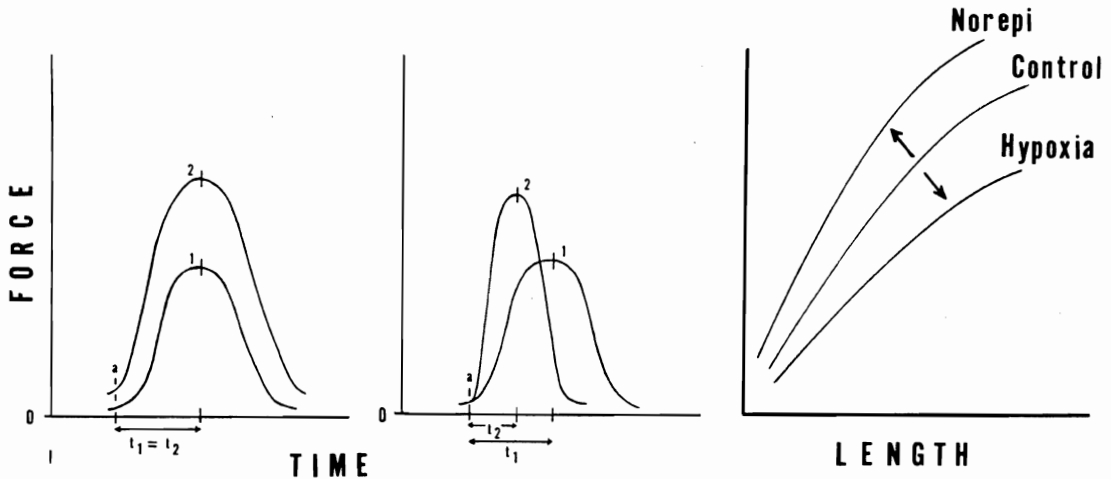


Fig. 5. When the afterload is of such a magnitude that the muscle is unable to shorten, an isometric (constant length) contraction results. These contractions may be studied individually (*left and middle panels*) or collectively (*right panel*) to determine the influence of muscle length or contractile state on the force-generating potential of the muscle.

force must be generated by the muscle which is equivalent to these additional weights if the muscle is to shorten. This shortening load has been termed the *afterload*. During shortening these weights remain stationary in the trough and as a consequence the muscle must generate this same force throughout its contraction (i.e., an *isotonic* contraction). The isotonic contraction of cardiac muscle may be used to assess the properties of cardiac muscle, including the extent (ΔL) and rate (dL/dt) with which it will shorten. For a constant fiber length and preload illustrated in Fig. 4 the extent of shortening (ΔL) declines in a linear fashion as the afterload is progressively raised.⁵ An inverse relation similarly exists between the velocity of shortening (dL/dt) and the load opposing that shortening. The *inverse force-velocity and force-shortening relationships for a given muscle length represent a fundamental property of cardiac muscle*. Another characteristic of muscle is its *length dependent property*.⁵ For example, at any given afterload, the greater the initial length, the larger ΔL and dL/dt . In addition and quite independent of the influence of fiber length and afterload, the extent and rate of muscle shortening are influenced by a number of diverse factors, such as the chemical composition of the perfusate and the temperature of the muscle bath. *This third property of cardiac muscle which is independent of loading and length has been termed the contractile state*. Those factors which influence contractility in a positive or negative fashion are called *inotropic*

stimuli. For example, when the contractile state of muscle is augmented by the addition of a positive inotropic agent, such as norepinephrine, to the perfusate the extent and rate of shortening are increased for any given preload and afterload. Finally, it was these observations on isotonic, afterloaded contractions which served as the conceptual framework for models of cardiac muscle. In these models springlike and contractile elements were arranged in various combinations and the maximal velocity of the unloaded contractile element derived as an index of contractility. However, the dependence on a presumptive arrangement of elements as well as the critical, but unproven assumptions necessary to derive the maximal velocity of contractile element shortening in the intact diseased heart has tempered the enthusiasm for this type of analysis.

Returning again to the isolated muscle preparation (Fig. 5) the afterload may be further raised to a level which does not permit muscle shortening. The muscle, however, is able to develop this force. The generation of force from a constant fiber length without muscle shortening taking place is termed an *isometric contraction*. Like the isotonic contraction the isometric contraction has also been used to describe the mechanical properties of muscle.⁵ For example, the influence of raising the initial fiber length on the isometric force curve may be characterized by an increase in (a) the resting force, (b) the rate of rise of force, and (c) peak force, without (d) a

1) Net Wall Force :
 $\propto [\text{Pressure, Volume}]$

2) Midwall Circumferential
 Fiber Length

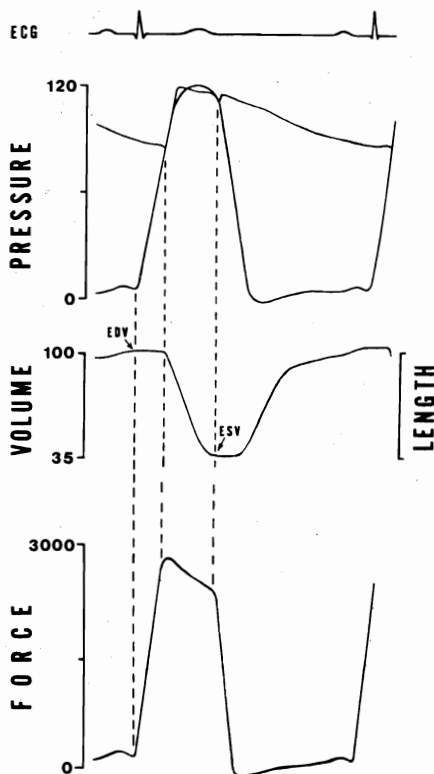
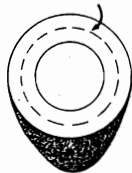


Fig. 6. Net wall force is proportional to chamber pressure and dimension (i.e., as determined by chamber volume and configuration). The time course of ventricular and aortic pressures, chamber volume, fiber length, wall force and the electrocardiogram are given. End-diastolic (EDV) and end-systolic (ESV) volumes have been identified.

change in time from the onset of contraction to peak force ($t_1 = t_2$) taking place. On the other hand, an increase in the contractile state of muscle which is operating from the same resting length may be identified by (a) no change in resting force, (b) an increase in the initial rate of rise of force, (c) an increase in peak force, and (d) a decrease in the time to peak force ($t_2 < t_1$).

In addition to considering the individual isometric contractions their collective appraisal (the force-length relationship) may be used to represent the properties of cardiac muscle. As the muscle is stretched and its length augmented the total force generated becomes greater. For any given length the force-length relation is shifted to the left with positive inotropic stimuli, such as catecholamines or digitalis, or downward and to the right with a negative inotropic intervention (i.e., hypoxia, propranolol).

The intact heart. The intact myocardium surrounding either ventricular chamber may be viewed as a complex arrangement of intertwining strips of muscle. Moreover, it is the mechanical behavior of the muscle fibers comprising the wall

of the ventricle which relates to the pressure and volume events of the cardiac cycle.

These pressure and volume events of cardiac contraction are an integral part of standard physiology textbooks. As shown in Fig. 6 during systole, the ventricle develops pressure that leads to the ejection of blood. The generation of pressure occurs as a result of the force developed by the myocardium. *Chamber pressure and myocardial force however are by no means synonymous.*

Direct measurements of wall force indicate that force is proportional to the pressure and volume (or area) of the respective ventricular chamber.¹⁸ If we envision the ventricle as being divided into two parts by an imaginary plane passing through a cross-sectional area of its chamber and a rim of myocardium, a force is created on either side of the plane. This force, which is equal to the pressure of blood in the chamber times the area of the chamber included in the plane, tends to separate the two halves of the ventricle. In accordance with Newton's law of motion, this force must be counterbalanced by an

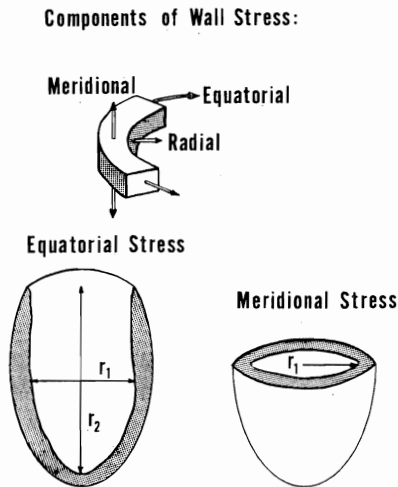


Fig. 7. The components of wall stress are presented and include vectors in the equatorial, meridional, and radial direction. The minor (r_1) and major (r_2) axes of the ventricle have also been identified. See text for discussion.

equal and opposite force existing in the rim of myocardium. Thus myocardial wall force, in grams, may be calculated as the product of chamber pressure and the cross-sectional area of the chamber in the plane. Chamber configuration and volume will determine the size of this subtended area. A circumferential length located in the midwall of the ventricle (see Fig. 6) may be chosen as a simplified representative of fiber length. A further description of the assumptions and rationale implicit in the derivation of these force and length calculations may be found elsewhere.¹²

The terms force, tension and stress have frequently been used interchangeably in the discussion of cardiac mechanics. In the strictest sense this is not correct and deserves further consideration. *Net wall force*, is that force which exists in the rim of myocardium subtended by the plane in question and is independent of (a) the shape, area or thickness of this rim, (b) the orientation of individual fibers or the distribution of forces which they generate, and (c) interfascicular or shearing forces. As such however, it does not describe the distribution of force within the wall or consider that the wall has a finite thickness. *Tension*, which refers to the force existing in a circumferential length of myocardium included in the plane, also does not relate to wall thickness. *Stress*, on the other hand, is a term which may be used for the purposes. Stress indicates the force operative within a cross-sectional area of myocardium subtended by the plane. The three major

directional components of stress, within the segment of myocardium shown in Fig. 7, may be listed as (a) an equatorial, or hoop, stress which runs in a circumferential direction, (b) a meridional stress which traverses the longitudinal direction, and (c) a radial stress which is directed inward toward the chamber. The area of the chamber relevant to equatorial stress is that described by both the minor (r_1) and major (r_2) axes, while meridional stress is related to the smaller area given by the minor axis alone. Thus it is evident that for any given chamber pressure equatorial stress would be greater than its meridional counterpart by a factor of r_2/r_1 .

Returning to Fig. 6, the time course of mechanical contraction may be viewed as follows: At end diastole the fibers have a given stretch or length which is determined by the given wall force. This distending force, which is a function of chamber pressure and myocardial compliance, is analogous to the preload of the isolated muscle preparation. Following depolarization, the ventricle generates pressure leading to the opening of the aortic valve and the ejection of blood. To this point the course of systolic pressure is related to the force developed by the myocardium. Since the magnitude of this wall force is a function of both chamber pressure and volume it is clear that the larger heart must develop more force to generate any given pressure. Even though wall force is greater in the enlarged heart wall stress (i.e., force per unit area of muscle) may be maintained within the normal range by compensatory hypertrophy of the myocardium.^{19, 20} This is particularly true for the patient with compensated failure. The decompensated patient, on the other hand, may have an enlargement in chamber dimension which is greater than the corresponding increment in wall thickness and hence wall stress is greater than normal.

During ejection the myocardium will also sustain a given force. Its value is greatest near the onset of ejection however as chamber volume becomes smaller instantaneous force will decline. This shortening or ejection load is analogous to the afterload of the isolated muscle preparation. However, unlike the constant weight which the muscle lifts after its contraction (i.e., an isotonic load) the force on the normal ventricle has a changing, albeit ever declining, value. We have used the term "allastonic contraction," as proposed by Wiggers,³ for this purpose. The magnitude of this shortening load is a function of

the instantaneous change in chamber size, shape and pressure with the viscoelastic properties of the circulatory system dictating the time course of pressure. As will be discussed in more detail subsequently these impedance characteristics of the vascular bed will influence ventricular loading.²¹

It would seem prudent to define those force and length terms for the intact heart which will be used throughout this review: (a) *instantaneous force* refers to that net wall force which exists at any instant during the cardiac cycle and is dependent on chamber pressure and area at that given instant. The term *load*, which has been used interchangeably throughout the text, denotes this force; (b) *instantaneous length* is that time varying dimension of the midwall circumferential fiber and; (c) *instantaneous shortening load* (i.e., afterload) refers to that force which exists at any instant during ventricular ejection (i.e., from aortic valve opening to closure).

The maximal developed force-length relation.

The maximal wall force which can be developed for any degree of fiber stretch is found in the isovolumetrically beating heart.¹³ This is analogous to the isometric force-length relation of isolated muscle shown in Fig. 5. Under this condition the contraction of the myocardium does not result in a change in chamber volume. An isovolumetric beat however, does not represent an isometric contraction since the ventricle undergoes a change in shape and thus fiber length is not constant. The relationship between maximal developed force and end diastole fiber length is represented in Fig. 8A. It is apparent that as fiber length (i.e., end-diastolic stretch) is increased there is an associated augmentation in developed force. By way of analogy we can consider the elliptical weights and muscles shown in *panel A*. For the muscle length given on the left, a load corresponding to the three weights could be generated but not moved. Consequently, the muscle will not shorten (i.e., an isometric contraction). On the other hand, this load is the maximal force which this length of muscle can develop. By stretching the muscle to a greater length indicated on the right, a larger force, equivalent to the six weights, could be developed, but again not moved. The developed force-length relation provides an expression of the fundamental length-dependent property of cardiac muscle. In this connection, and unlike isolated muscle, a length at which force peaks and then subsequent-

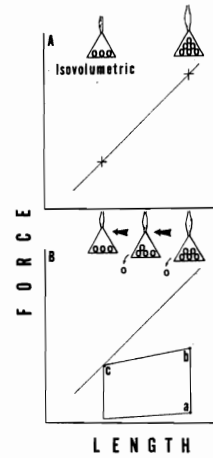


Fig. 8. A, The isovolumetric force-length relation for the intact ventricle. As fiber length is raised, the maximal force which may be developed becomes greater. This is illustrated for the two muscle strips and the weights they are attempting to lift. B, The force-length relations for the isovolumetrically beating and ejecting ventricle are shown. For the load represented at the far right the muscle is able to lift these weights and thereby shorten. During shortening and while muscle length declines, weights are progressively shed from the trough. The muscle ceases shortening when the existing load is maximal for the given instantaneous fiber length.

ly declines, has not been demonstrated for the intact left ventricle operating within the physiological range of filling pressures (i.e., 1 to 25 mm. Hg).¹⁵ Thus, the left ventricle normally functions on the ascending limb of its maximal force-length relation.

Variations in contractile state create nonparallel shifts in the developed force-length relation; positive and negative inotropic interventions raise or reduce the slope of this relation respectively. For example, following the administration of norepinephrine, the ventricle is able to develop a greater force from any equivalent fiber length examined under control conditions. That is, for either muscle length shown in the insert a greater load would be generated following norepinephrine. Alternatively, propranolol attenuates the slope of the force-length relation and thereby reduces the maximal developed load for any given muscle length. Thus, the isovolumetric, developed force-length relation, which is contractile state-dependent, represents the maximal force that can be generated for any given myocardial fiber length. The relevance of this relation to the ejecting heart will now be developed.

The limit to wall shortening. The limit to which the wall will shorten is determined by the isovolumetric force-length relation for a given

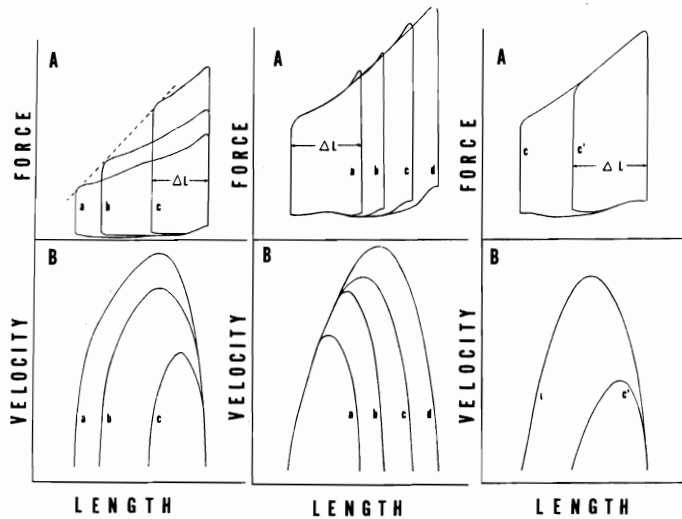


Fig. 9. The trajectories of wall force, the velocity of fiber shortening, and fiber length are shown for the following: (*left panel*) contractions of equivalent instantaneous shortening length moving three different instantaneous shortening loads or afterloads; (*middle panel*) contractions having similar trajectories of ejection force with different instantaneous shortening lengths; and (*right panel*) two contractions of equivalent instantaneous length and shortening load in which myocardial contractile state has been reduced from control (beat *c'*), with propranolol (beat *c'*). Adopted and greatly modified from Ref. 14.

contractile state.^{10, 13} That is, the wall force which exists at any end systolic length equals the maximal force which that length can sustain. To illustrate this further a force-length loop representing an ejecting contraction is given in *panel B* of Fig. 8 together with the corresponding isovolumetric force-length relationship. From an end-diastolic length denoted as point *a* the ventricle generates an isovolumic force prior to ejection. Fiber shortening (i.e., ventricular ejection) commences at point *b* and continues until point *c* is reached. The course of this contraction is described as *abc*. From the opening of the aortic valve to its closure the ventricle must shorten against a force whose magnitude is time varying and determined by the response in chamber pressure and dimension. Note that the end-systolic point *c*, falls on the isovolumetric force-length line. Under these conditions the ventricle may be envisioned as the muscle beginning its contraction from the fiber length shown at the far right of *panel B*. This length is equivalent to its counterpart in *panel A*, however here the load at onset contraction is less. Hence, the muscle will be able to shorten. As shortening commences weights begin to fall from the trough (i.e., force is decreasing). At the intermediate shortening length shown the muscle is moving a smaller load than that present at the onset. Weights continue to fall from the trough as the muscle shortens. Muscle

shortening ceases when its given length (point *c*) can no longer move the existent load. In the example given the muscle length and load indicated at end-systole is equivalent to that shown for the isovolumetric state above.

The equivalence of the end-systolic and isovolumetric force-length relations can also be shown by altering the time course of the ejection force from that shown in Fig. 8*B*. That is from the same onset ejection force (point *b*) and initial length the instantaneous force opposing shortening (i.e., the shortening load) may be varied by controlling the rate with which the weights fall from the trough. For example, if we induce more weights to leave the trough the muscle shortens at a much reduced load and a greater degree of shortening is permitted. Alternatively, retarding the rate at which the weights are shed will impose an additional load in comparison to that moved by the muscle under the conditions shown in the figure and hence shortening will be attenuated. Consequently, from a given end-diastolic length, three different end-systolic lengths are obtained. In each case, shortening ends when the ejecting force-length relation corresponds to a point on the isovolumetric force-length relation.

Finally, the equivalence of the isovolumetric and end-systolic force-length relations has been verified for either positive (e.g., norepinephrine) or negative (e.g., propranolol) variations in

contractile state.¹⁵ Therefore regardless of its particular contractile state, the ejecting ventricle contracts within the confines of its isovolumetric, developed force-length relation. In view of the fact that the end-systolic and isovolumetric force-length relations are equivalent, we^{13, 15} and others^{10, 22-23} have suggested that the end-systolic relation might provide a useful clinical estimate of contractile state.

Although the isovolumetric force-length relation defines the limits of shortening, the extent to which the ventricle will shorten is determined by the instantaneous course of systolic force and length. In contrast, end-systolic length is independent of initial length and onset ejection force. That is the heart does not have a memory of these initial conditions. Therefore end-diastolic length and onset ejection force only serve to determine the starting points of the contraction.

Determinants of shortening. The importance of instantaneous force and length on the extent (and velocity) of midwall circumferential fiber shortening has been alluded to above. To examine this further three variably loaded contractions and the respective trajectories of force, velocity, and length have been illustrated in *the left hand panel* of Fig. 9. Each contraction originates from the same resting length. The isovolumetric relation is represented by the dotted line. In each case the extent of shortening (i.e., the change in length, ΔL) and the velocity of shortening is determined by the *instantaneous force* opposing that shortening. For beat *a* having the smallest shortening load, ΔL will be greater than that found for beats *b* or *c*. The velocity-length relations are indicated in *panel B*. For these contractions which traverse over equivalent instantaneous ejection lengths, it is clear that the *maximum and instantaneous velocity of shortening, as well as the extent of shortening, are determined by the instantaneous shortening load.*¹⁴ This load-dependent aspect of fiber shortening, which is not represented by work, represents a fundamental property of the intact ventricular myocardium.

A second property of wall shortening relates to its fiber length. The importance of *instantaneous length* in determining the extent and rate of shortening is illustrated in *the middle panel* of Fig. 9. Here end-diastolic fiber length was progressively raised by increasing end diastolic pressure from 2 mm. Hg (beat *a*) to 10 mm. Hg (beat *d*). For each increment or onset contraction length a

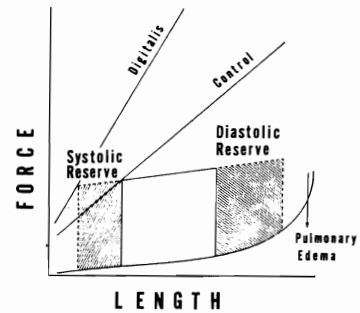


Fig. 10. The concept of cardiac reserve is diagrammatically represented. The reserve or increment in stroke volume which is derived as the ventricle is progressively stretched represents the heart's diastolic reserve while that increment in stroke volume which accompanies a shift in contractile state and the maximal force-length relation represents the systolic reserve.

greater resting force, instantaneous length, maximal velocity, and degree of shortening (ΔL) were observed. The instantaneous shortening load however follows a common path so that each contraction terminates at a constant end systolic length. Consequently, the response in shortening for these beats traversing a path of equivalent instantaneous force indicates that the *rate and extent of shortening are a function of instantaneous length*. This is another expression of the length-dependent (Frank-Starling) property of heart muscle which is not considered in the traditional work calculation.

Thus, the instantaneous velocity and extent of shortening for any given contractile state is determined by both instantaneous force and length. In addition to these two fundamental properties of heart muscle a third property which is independent of instantaneous force and length, that is *myocardial contractile state*, must also be considered. The response in shortening following the pharmacological depression of the contractile state by propranolol is illustrated in *the right hand panel* of Fig. 9 where control (beat *c*) and beta blockade (beat *c'*) data are given. As would be predicted, the end-systolic force-length relation after propranolol (not shown) has been shifted to the right. Hence for comparable conditions of instantaneous length and force, the instantaneous velocity and extent of shortening following propranolol are reduced. These alterations in shortening are analogous to those observed for the failing heart (vide infra). A positive inotropic agent, such as norepinephrine or digitalis, causes a shift in the opposite direction, i.e., the end-systolic force-length relation

moves to the left and a greater rate and extent of shortening are observed for any given length or load.

The heart as a muscle-pump system

The concept of cardiac reserve. The ability of the heart to raise its output or stroke volume has been referred to as its reserve capacity. These reserves, which are analogous to the inspiratory and expiratory reserves of the lung, may be visualized as follows (see Fig. 10): the heart's *diastolic reserve* reflects the increment in shortening which is possible when the ventricle draws on its fiber length capabilities (i.e., chamber dilatation). By raising diastolic stretch into the cross-hatched area, designated diastolic reserve in Fig. 10, stroke volume is raised. The ventricle, for example, may draw on this reserve compensatorily during increments in arterial pressure or venous return, or following a compromise in myocardial contractility. Its limits are determined physiologically by the levels of accompanying pulmonary hydrostatic pressure and edema formation.

The *systolic reserve* is brought to bear during positive shifts in contractile state. That is, a contraction which is induced to shorten beyond its present end systolic volume, as would occur following the administration of digitalis, will utilize this reserve. End-diastolic volume need not be influenced. The maximal force-length relation, on the other hand, is shifted to the left. The extent of this shift, which again determines the new limits to this augmented shortening, is dependent on (a) the strength of the applied stimulus (i.e., the amount of digitalis given or the use of several positive inotropic interventions in combination) and (b) the state of the myocardium (i.e., a failing heart responding to a lesser degree than a normal ventricle). A severely compromised heart in which the isovolumetric force-length relation has been greatly reduced may, in fact, be refractory to such agents.

As a pump the ventricle generates pressure and displaces volume. It should now be apparent that these properties of the heart as a pump may be expressed in terms of the development of muscle force and fiber shortening respectively. In this context the heart's pumping characteristics are an expression of the behavior of the muscle fibers which comprise its wall.

Commencing with the opening of the aortic valve, the myocardium must accelerate the column of blood, with its given inertia, into the vascular system. Up to this point in their contraction the fibers have already been loaded by a force proportional to chamber pressure and dimension. Under normal circumstances the load imposed by the outflow tract and semilunar valve will be negligible. The force on the contracting fibers, however, is influenced by the resistance and capacitance elements of the vasculature. The force resulting from the resistive component is a function of the velocity of fiber shortening (i.e., ejection rate), whereas that force attributable to the capacitive portion is related to the extent of fiber shortening or the volume ejected.

This heart-vessel interaction may also be viewed as a feedback control of myocardial contraction.²¹ For example, an increment in stroke volume (and ejection rate) leads to an increase in aortic impedance (decreased capacitance) and, subsequently, in wall force. As a result of this increased load subsequent contractions have an attenuated stroke volume. Contrariwise, if an increment in aortic impedance were the initial event, the accompanying reduction in stroke volume should lead to both a greater end-systolic and end-diastolic chamber volume. As a consequence of this increase in fiber length, stroke volume would be restored to original levels. In the failing heart in which systemic perfusion is not maintained at adequate levels, peripheral resistance is raised to preserve arterial pressure. The pharmacological reduction of this increased resistance using vasodilators has been utilized to unload such a heart (vide infra). This coupling between the heart and vascular bed necessitates that cardiac fibers be able to react not only to beat to beat variations in filling volume and arterial impedance, but also that they adjust instantaneously to differences in length and load. That this is indeed possible has been presented in the previous section.

In addition to the influence of pressure on ventricular loading, the change in ventricular dimension represents an important determinant of shortening load. The alteration in dimension for any given load will be a function of the geometrical configuration of the chamber as well as myocardial contractile state. In the normal heart the reduction in radius throughout ejection

permits wall force to decline despite the fact that chamber pressure increases. Burch and colleagues²⁴ have pointed out some years ago that as the heart enlarges it loses this advantage. For example, the extent of shortening by fibers compromising the wall of a large spherical ventricle is less than that associated with an equivalent stroke volume from a smaller chamber. Thus the marked abbreviation in shortening in the enlarged and failing ventricle will contribute significantly to instantaneous load for any given condition of arterial pressure. This important aspect of the failing heart will be discussed further below.

According to the traditional pump concept, the performance of the ventricle may be gauged from the stroke volume to end-diastolic volume relationship. Stroke volume may be raised by the augmentation in filling volume (Frank-Starling response) or myocardial contractile state (e.g., catecholamines or digitalis). Stroke volume, however, is also dependent on arterial pressure.¹¹ Elevations in systolic pressure, and concomitantly, in wall force serve to reduce the ejected fraction or stroke volume from any given diastolic volume. Alternatively, a reduction in impedance, as with aortic or mitral regurgitation or an arteriovenous shunt, allows for a greater ventricular emptying.

The product of stroke volume and aortic pressure, which approximates stroke work, has also been utilized to assess pump function. As mentioned previously, the relationship of work to end-diastolic volume (or end-diastolic pressure) has been termed the *ventricular function curve*. Now that the muscular properties of the myocardium are understood, the origins of this relation, which are critical to understanding its meaning, may be elucidated. For any given contractile state the extent to which a fiber will shorten will depend on its instantaneous length and force. Taking the instantaneous force trajectory shown in *the middle panel* of Fig. 9, for example, increments in end-diastolic and instantaneous length result in progressive elevations in stroke volume (or shortening), thereby describing the shortening-length relation. A number of such linear shortening-length relationships derived for a series of force trajectories (F), where $F_1 < F_2 < \dots < F_n$, have been given in Fig. 11. The slope of each shortening-length relation is

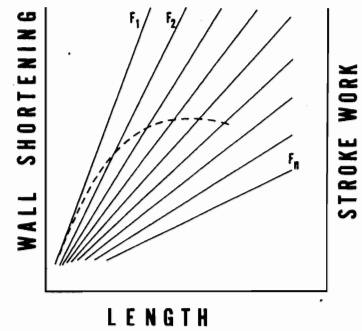


Fig. 11. The traditional ventricular function curve is derived from the shortening-length relations obtained for a series of instantaneous force trajectories where $F_1 < F_2 < \dots < F_n$.

reduced as the absolute level of the force trajectory is increased. However, in the intact animal, or in man, it is obviously not possible to maintain these rigidly controlled conditions of loading when deriving a function curve. For example, when the circulating volume is expanded using dextran, both the intracardiac and intravascular (capacitance) space are expanded. Consequently, arterial pressure, chamber dimension, and instantaneous force increase on a continuous basis. The resultant work to diastolic volume (or fiber length) relation thereby traverses these shortening-length relations as indicated by *the dotted line* in Fig. 11. Alterations in myocardial contractile state for any given heart or differences in contractility between hearts produce a series or family of function curves. Despite these limitations, the absolute level of stroke work has, in fact, been found to provide a useful clinical estimate of the degree of ventricular dysfunction following acute myocardial infarction.²⁵⁻²⁶

The failing heart

As we have used the term here, heart failure refers specifically to a compromised contractile state of the left ventricle which is accompanied by an inadequate forward flow to accommodate the needs of the peripheral circulation. Because ventricular emptying is less, signs and symptoms of pulmonary venous hypertension may also be present. The reduction in contractile state and the decreased slope of the isovolumetric force-length relation accounts for the decline in both the extent and rate of fiber shortening for any condition of length or load. The force-length loop given in Fig. 9 for propranolol would be illustrative of this circumstance. This attenuation

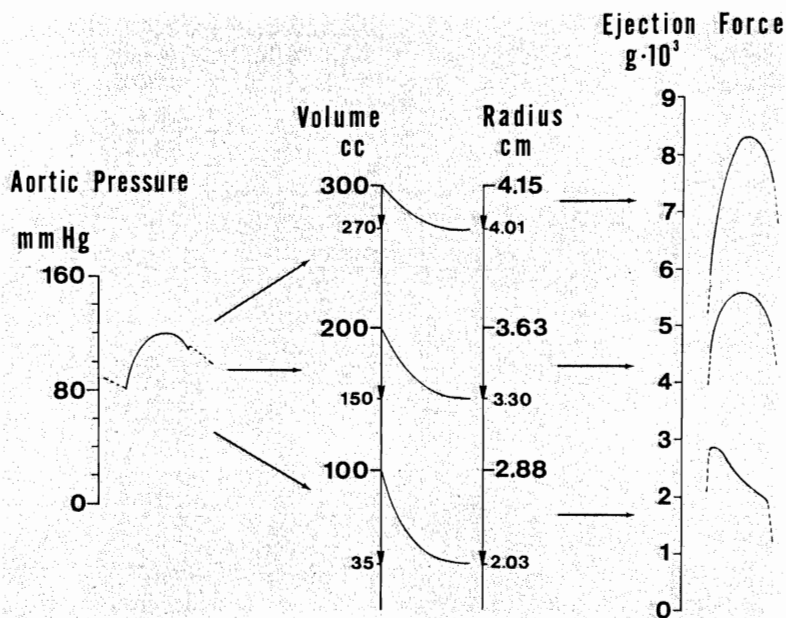


Fig. 12. The response in ventricular dimension represents an important determinant of instantaneous shortening load or afterload. In the normal heart the reduction in chamber radius permits wall force to decline during ejection. In the failing ventricle, enlarged to two and three times its normal size, it loses this advantage and an abnormal load must be sustained by the shortening fibers.

in shortening implies that the slope of the shortening-length relation is also reduced. Translated into terms of the heart's function as a pump, stroke volume, ejection fraction, and ejection rate will be reduced.

The depression in the maximal force-length relation itself represents a reduction in the heart's systolic reserve. In other words, the ability of positive inotropic agents, such as digitalis, to shift this relation to the left and permit greater shortening becomes attenuated. In addition, the inherent toxicity and rate of renal clearance of digitalis limits the extent of its daily administration. A critical reduction in systolic reserve exists when the failing ventricle becomes refractory to such agents. It is here that increments in shortening may only be achieved by manipulating instantaneous force (i.e., the concept of unloading) such as with vasodilators.²⁷⁻²⁸ Each decrement in the developed force-length relation will also attenuate the ability of the heart's diastolic reserve to restore stroke volume. That is, the increment in shortening which is possible through chamber dilatation (i.e., greater fiber length) becomes less as the limits to shortening are reduced.

In this connection one other point deserves comment. The reduction in chamber dimension or radius during ejection is abbreviated in the

enlarged, failing ventricle. That is, the change in ventricular size from end-diastole to end-ejection is less than under normal conditions. This circumstance may be accounted for by (a) the reduced stroke volume of the failing heart, and (b) the fact that its end-diastolic chamber size is enlarged. In this connection, recall that for any given stroke volume the extent of shortening of fibers encompassing a large ventricle is less than that of a smaller chamber. When wall motion becomes severely attenuated, creating an essentially invariant chamber dimension, the absolute level of systolic force remains high (i.e., essentially unchanged from its onset value or even increasing throughout the ejection period). This sustained shortening load further decreases the degree of wall shortening. As shown in Fig. 12, the enlargement of the ventricular chamber (two- and three-fold normal size) and a reduction in contractile state both account for the abnormally high and sustained shortening load. Reducing chamber size and thereby instantaneous force in such a heart with a diuretic, by venesection, or vasodilator permits an increase in shortening without influencing contractility. According to the traditional viewpoint, this increment in stroke volume represents an ascent from a depressed position on the ventricular function curve.

The concept of unloading. Positive inotropic agents, such as digitalis, aimed at improving contractile state, forward flow, and the symptoms of pulmonary venous hypertension have long been the mainstay for treating the compromised ventricle. In the chronically failing, enlarged heart characterized by a marked reduction in its maximal force-length relation (i.e., a limited systolic reserve) it may no longer be possible to augment shortening by such measures (i.e., refractory failure). Alternatively, in the acutely ischemic, failing heart these agents unfavorably augment metabolic demand and thereby may increase infarct size. Under either circumstance, it is necessary to work within the heart's given contractile state while providing for conditions which favor a greater degree of fiber shortening. This is accomplished by reducing instantaneous shortening load, or more specifically by lowering the pressure and radius variables of systolic wall force. Toward this end a number of vasodilators have received much recent attention.²⁷⁻²⁸ The cardio-circulatory effects of these agents, however, differ depending on their relative influence on the systemic resistance and venous capacitance vessels. Despite these relative differences, chamber volume and pressure are both perturbed throughout the cardiac cycle following the administration of these agents. Hence instantaneous load will be altered. Therefore it is not appropriate to consider that any particular vasodilator will exclusively influence end-diastolic force or shortening load. This is not meant to imply, however, that there would not necessarily be a predominant effect as in the case of hydralazine, where its pharmacological action is directed almost entirely at arterial smooth muscle and thereby shortening load.

The response of any ventricle to these agents will depend on its size, distensibility, and contractile state. These factors, plus the cardiocirculatory effects of the individual vasodilators, deserve consideration when selecting among these agents for any given patient. For example, in the enlarged failing ventricle with high filling pressure, nitroprusside and phentolamine provide a significant reduction in systemic arterial and ventricular end-diastolic pressures while stroke volume (i.e., wall shortening) is raised. In these hearts the increment in fiber shortening induced by the reduction in instantaneous systolic force is greater than the moderate, counteracting reduc-

tion in instantaneous fiber length. However, when the reduction in filling pressure (i.e., to levels < 10 mm. Hg) and length is marked, stroke volume declines or does not change. Here the attenuation in fiber length or diastolic reserve predominates and outweighs the reduction in instantaneous force. In similar fashion, stroke volume could be expected to decline when filling pressure is reduced in a noncompliant ventricle. However, under these conditions the extent of venodilation required to significantly reduce pressure is much less.

The appropriate selection of a particular vasodilator should therefore be based on filling pressure, ventricular size, and cardiac output. Obviously, the degree of urgency and the given clinical state of the patient in heart failure, as well as the route of vasodilator administration will also dictate the choice of agent. For the enlarged ventricle with elevated filling pressure (> 15 mm. Hg) and an abnormally high shortening load, it would be preferable to choose an agent(s) which would significantly reduce both chamber dimension and systolic pressure. Nitroprusside or the combination of hydralazine and isosorbide dinitrate would appear appropriate for this purpose. The noncompliant ventricle would seemingly derive a greater benefit from hydralazine since the reduction in filling pressure will be less pronounced.

Conclusion

The heart functions as an integrated muscle-pump system so that the determinants of myocardial fiber shortening regulate the volume displaced from the chamber. In this review we have attempted to unite these two concepts of performance by examining the ventricle as a pump as well as the behavioral characteristics of its circumferentially oriented fibers. The isovolumetric force-length relation, which depends on the contractile state of these fibers, describes the maximal force attainable for any degree of fiber stretch. It further establishes the limits to fiber shortening. During ejection the extent and rate of fiber shortening are determined by the instantaneous trajectories of wall force (i.e., a function of chamber pressure and dimension) and fiber length, as well as by the contractile state of the myocardium. These properties of the myocardium may be utilized to describe the heart as a pump, including the derivation of the ventricular

function curve. Finally, the relevance of these relationships in characterizing the failing heart is emphasized. Specifically, the attenuation in slope of the maximal force-length relation and the sustained shortening load of the enlarged chamber account for the reduced output of the compromised ventricle. Vasodilators may be used to lower this abnormal shortening load, thereby unloading the failing ventricle and permitting greater fiber shortening and forward flow.

REFERENCES

1. Frank, O.: Zur Dynamik des Herzmuskels, *Ztschr. Biol.* **32**:370, 1895.
2. Starling, E. H.: *The Lincarc Lecture on the Law of the Heart*, London, 1918, Longmans, Green.
3. Wiggers, C. J.: *Pressure Pulses in the Cardiovascular System*, New York, 1928, Longmans, Green.
4. Katz, L. N.: The Lewis A. Conner Memorial Lecture. The Performance of the Heart, *Circulation* **21**:483, 1960.
5. Sonnenblick, E. H.: Implications of muscle mechanics in the heart, *Fed. Proc.* **21**:975, 1962.
6. Fry, D. L., Griggs, D. M., and Greenfield, J. C.: Myocardial mechanics: Tension-velocity-length relationships in heart muscle, *Circ. Res.* **14**:73, 1964.
7. Levine, H. J., and Britman, N. A.: Force-velocity relations in the intact dog heart, *J. Clin. Invest.* **43**:1383, 1964.
8. Pollack, G. H.: Maximum velocity as an index of contractility in cardiac muscle, *Circ. Res.* **26**:111, 1970.
9. Noble, M. I. M.: Problems concerning the application of concepts of muscle mechanics to the determination of the contractile state of the heart, *Circulation* **45**:252, 1972.
10. Suga, H., Sagawa, K., and Shoukas, A. A.: Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio, *Circ. Res.* **32**:314, 1973.
11. Weber, K. T., Janicki, J. S., Reeves, R. C., Hefner, L. L., and Reeves, T. J.: Determinants of stroke volume in isolated canine heart, *J. Appl. Physiol.* **37**:742, 1974.
12. Weber, K. T., Janicki, J. S., Reeves, R. C., and Hefner, L. L.: Factors influencing left ventricular shortening in isolated canine heart, *Am. J. Physiol.* **230**:419, 1976.
13. Weber, K. T., Janicki, J. S., and Hefner, L. L.: Left ventricular force-length relations of isovolumic and ejecting contractions, *Am. J. Physiol.* **231**:337, 1976.
14. Weber, K. T., and Janicki, J. S.: Instantaneous force-velocity-length relations in isolated dog heart, *Am. J. Physiol.* **232**:H241, 1977.
15. Weber, K. T., and Janicki, J. S.: Instantaneous force-velocity-length relations: Experimental findings and clinical correlates, *Am. J. Cardiol.* **41**:740, 1977.
16. Sarnoff, S. J., and Berglund, E.: Ventricular function, *Circulation* **9**:706, 1954.
17. Weber, K. T., and Janicki, J. S.: Myocardial oxygen consumption: The role of wall force and shortening, *Am. J. Physiol.* **233**:H421, 1977.
18. Hefner, L. L., Sheffield, L. T., Cobbs, G. C., and Klip, W.: Relation between mural force and pressure in the left ventricle of the dog, *Circ. Res.* **11**:654, 1963.
19. Sandler, H., and Dodge, H. T.: Left ventricular tension and stress in man, *Circ. Res.* **13**:91, 1963.
20. Hood, W. P., Rackley, C. E., and Rolett, E. L.: Wall stress in the normal and hypertrophied human left ventricle, *Am. J. Cardiol.* **22**:550, 1968.
21. Milnor, W. R.: Arterial impedance as ventricular after-load, *Circ. Res.* **36**:565, 1975.
22. Sagawa, K., Suga, H., Shoukas, A. A., and Bakalar, K. M.: End systolic pressure/volume ratio: A new index of ventricular contractility, *Am. J. Cardiol.* **40**:748, 1977.
23. Grossman, W., Braunwald, E., Mann, T., McLaurin, L. P., and Green, L. H.: Contractile state of the left ventricle in man as evaluated from end-systolic pressure-volume relations, *Circulation* **56**:845, 1977.
24. Burch, G. E., Ray, C. T., and Cronvich, J. A.: The George Fahr Lecture. Certain mechanical peculiarities of the human cardiac pump in normal and diseased states, *Circulation* **5**:504, 1952.
25. Weber, K. T., Ratshin, R. A., Janicki, J. S., Rackley, C. E., and Russell, R. O.: Left ventricular dysfunction following acute myocardial infarction, *Am. J. Med.* **54**:697, 1973.
26. Weber, K. T., Janicki, J. S., Russell, R. O., Rackley, C. E.: Identification of high risk subsets of acute myocardial infarction, *Am. J. Cardiol.* **41**:197, 1978.
27. Chatterjee, K., Parmley, W. W., Ganz, W., Forrester, J., Walinsky, P., Crexells, C., and Swan, H. J. C.: Hemodynamic and metabolic responses to vasodilator therapy in acute myocardial infarction, *Circulation* **48**:1183, 1973.
28. Cohen, J. N., and Franciosa, J. A.: Vasodilator therapy of cardiac failure, *N. Engl. J. Med.* **297**:27, 254, 1977.