

Circulation Research

JOURNAL OF THE AMERICAN HEART ASSOCIATION



The ventricular pressure-volume diagram revisited

K Sagawa

Circ. Res. 1978;43;677-687

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

Copyright © 1978 American Heart Association. All rights reserved. Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circres.ahajournals.org>

Subscriptions: Information about subscribing to Circulation Research is online at
<http://circres.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, 351 West Camden Street, Baltimore, MD 21202-2436. Phone 410-5280-4050. Fax: 410-528-8550. Email:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
<http://www.lww.com/static/html/reprints.html>

BRIEF REVIEWS

The Ventricular Pressure-Volume Diagram Revisited

KIICHI SAGAWA

THE PRIMARY purpose of this review is to take the reader back to the classical pressure-volume plane on which a beating ventricle draws a variety of trajectories under conditions of different preload and afterload. In this return visit I hope to show that the contractile state of the ventricle can be traced by focusing attention on the relation of the blood volume *remaining* in this ventricle at the end of systole to the ventricular pressure at that time, just as the passive property of the relaxed ventricle is implied uniquely by the end-diastolic pressure-volume data plotted in the same plane. A somewhat similar contention was expressed earlier by Holt¹. However, I would also indicate that the instantaneous pressure-volume relationship throughout systole provides a simple way to describe the mechanical process of ventricular contraction.

Early Studies on Active Pressure-Volume Relationships

Nearly a century ago, Frank² represented the cycle of ventricular contraction as a loop in a plan defined by pressure (P) in the vertical direction and volume (V) in the horizontal direction (Fig. 1). In the case of *in vivo* contractions, the loop would consist of a vertical ascending segment for the isovolumic contraction phase (a_0 to a_1 in Fig. 1), a curved horizontal segment for the ejection phase during which the pressure may be increasing, unchanging, or decreasing toward the end (a_1 to a_2), a vertical descending segment for the isovolumic relaxation phase (a_2 to a_3), and a horizontal curved segment which represents the filling phase (a_3 to a_0). This loop ($a_0 \rightarrow a_1 \rightarrow a_2 \rightarrow a_3 \rightarrow a_0$) has been called the pressure-volume diagram of the cardiac cycle. Its major use in today's textbooks of physiology is to illustrate the external stroke work that the ventricle does to the loading system represented by the area circumscribed by the loop. Frank, how-

ever, attempted to retrieve much more information from multiple sets of P-V diagrams. First, he connected the peak pressure data points in the P-V plane which a *frog* ventricle generated isovolumically at various volumes (e.g., from a_0 to C in Fig. 1). He called the resultant P-V relation curve the "isometric" maxima curve (the curve $b \rightarrow c \rightarrow$ the origin in Fig. 1). The curve, which should have been called an isovolumic maxima curve, indicated to him that the maximum compressive force that a ventricle can generate was a function of its volume. He also made the ventricle contract without any afterload, maintaining the ventricular pressure constant at the end-diastolic pressure. Frank termed these ejecting contractions "isotonic" contractions (e.g., the segment $a_0 \rightarrow d$ in Fig. 1). To be more accurate, they should have been termed isobaric contractions because, even under a constant transmural pressure, the tension of the ventricular wall muscle decreases as ventricular volume decreases by the Laplace relation. Frank called the P-V relation curve produced by connecting the end-ejection points of the isobaric contractions the "isotonic maxima curve" (the solid curve $b \rightarrow d$ in Fig. 1). As shown schematically in Figure 1, these two maxima curves were separated widely.

Frank's¹ interpretation was that a simple *a priori* relation between length and tension does not exist in cardiac muscle for every moment of its action, but that the mechanical conditions under which muscle has functioned before this instant have a decisive influence. (The last paragraph of Frank's paper³, was translated by C.B. Chapman and E. Wasserman and published in the *American Heart Journal* 58:282-317 and 467-477, 1958.) Since the isovolumic and isobaric maxima curves represent the end-points of systolic activity in two extremely different modes of contraction, Frank² asserted that end-ejection points of the trajectories of natural ventricular contractions would terminate within the space bounded by the isovolumic and isobaric maxima curves (e.g., a_2 of the loop $a_0 \rightarrow a_1 \rightarrow a_2 \rightarrow a_3 \rightarrow a_0$ in Fig. 1). As the indiscriminate use of the

From the Department of Biomedical Engineering, School of Medicine, The Johns Hopkins University, Baltimore, Maryland 21205.

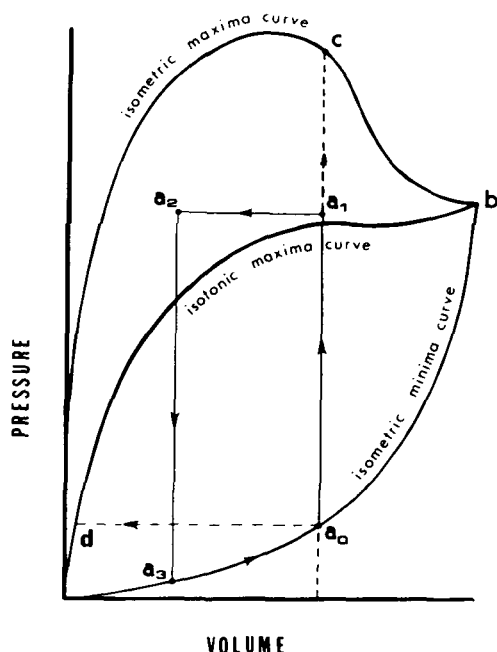


FIGURE 1 Frank's schematic pressure-volume diagram of the frog ventricle. Reproduced from reference 2, but slightly modified for easier understanding, with permission of Urban and Schwarzenberg.

terms such as isometric for isovolumic and isotonic for isobaric indicates, Frank advanced this thought² under the strong influence of similar findings⁴ reported on isometric and isotonic twitch contractions of skeletal muscle.

The wide space between the two maxima curves in the frog ventricle was confirmed by Sulzer⁵ and Reichel^{6,7} in the 1930's (Fig. 2). In addition, Reichel presented two other end-systolic P-V relation curves in the same P-V plane. One is the afterloaded isobaric contraction curve ("Unterstützungskurve," the chain line PE in Fig. 2) which repre-

sents the end-ejection points of a family of isobaric contractions, all from a single end-diastolic volume but afterloaded with various constant pressures. Reichel found that this curve was linear and indistinguishable from a line which connects two end-systolic points, one point being the peak isovolumic pressure at the same volume (P in Fig. 2) and another point being the end-ejection point of a totally isobaric contraction from the identical end-diastolic volume (E in Fig. 2). Another end-systolic relation curve was obtained when the ventricle was made to eject the Ringer's solution at Point Q in Figure 2, into an air-filled chamber, compressing air and thus increasing the afterload pressure as ejection went on. Reichel reported that such an "auxotonic" contraction (auxobaric contraction to be more accurate) also terminated at point F on the same segment of line PE. That is to say that the auxobaric maxima curve coincides with the afterloaded isobaric maxima curve. Apart from the validity of the claim that the segment PE defines both the afterloaded isobaric and auxobaric maxima curves, Sulzer⁵ and Reichel^{6,7} substantiated in the frog's ventricle that isovolumic and isobaric maxima curves are separated, and that contractions in other modes end their systole at a point somewhat between the two curves, a thesis which Frank² advanced earlier. However, Reichel did not observe the descending limb in the isovolumic maxima curve reported by Frank (Fig. 1).

Patterson, Pipe, and Starling⁸ were stimulated by Frank's concept but explored the determinants of stroke volume in the canine heart-lung preparation. They measured mean atrial and mean arterial pressures, using a mercury manometer, and the volume curve recorded by their cardiometer was a combination of left and right ventricular volumes. Thus the relationship between instantaneous pressure and instantaneous volume of a single ventricle could

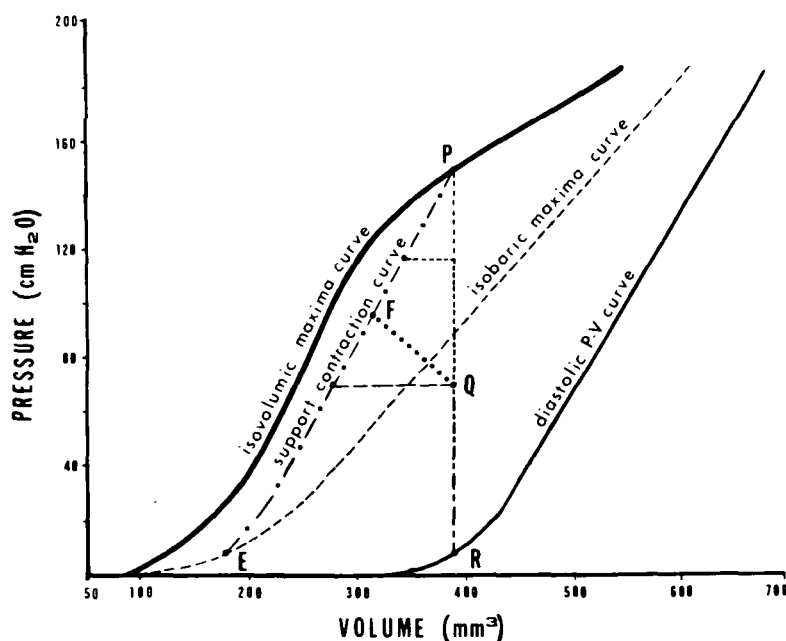


FIGURE 2 Reichel's pressure-volume diagram. Synthesized from two figures published in reference 6. By the courtesy of the authors and with the permission of Urban and Schwarzenberg.

not be monitored in Starling's preparation. As their skillful experiments on the relationship between filling pressure of the ventricle and stroke volume (i.e., the amount of blood *ejected* out) acquired recognition, the cardiologist's attention was turned away from Frank's original thesis on the curves relating the pressure and the blood volume which remained in the ventricle at end systole.

Interestingly, a similar shift of attention occurred in the realm of heart muscle mechanics. The investigators had acquired little systematic knowledge of the absolute length to which heart muscle shortens at the peak of contraction in various modes of twitch before they began to analyze the relation between the velocity (dl/dt) of isotonic shortening and loaded force.

Recent Studies on the Active Pressure-Volume Relation

End-Systolic P-V Relation

Interest in the active pressure-volume relation of the ventricle was revived in the 1960's^{1,9-19} and

accurate data on canine ventricular volume and pressure began to accumulate. Despite considerable differences in volume measurement method, these studies on the *canine* ventricle indicated that, as an approximation, the end-systolic volume to which a ventricle contracts was a linearly increasing function of end-systolic ventricular pressure. Furthermore, unlike Frank², Sulzer⁵, and Reichel^{6,7} the recent investigators did not find wide separation between the end-systolic P-V relation curves of isovolumic and ejecting contractions.

Shown in Figure 3A is a family of P-V diagrams obtained for an excised canine heart.⁹⁻¹¹ The left ventricle was fitted with a balloon which was filled with air and connected to an air chamber. Thus the ventricle contracted auxobarically, compressing air and augmenting the pressure load. When the amount of air in the ventricular loading system was increased from a minimum to larger amounts, the slope of the P-V diagram of the auxobaric contractions decreased from nearly 90° to smaller values. However, the end-systolic P-V data points gathered around a straight line except for one point in the

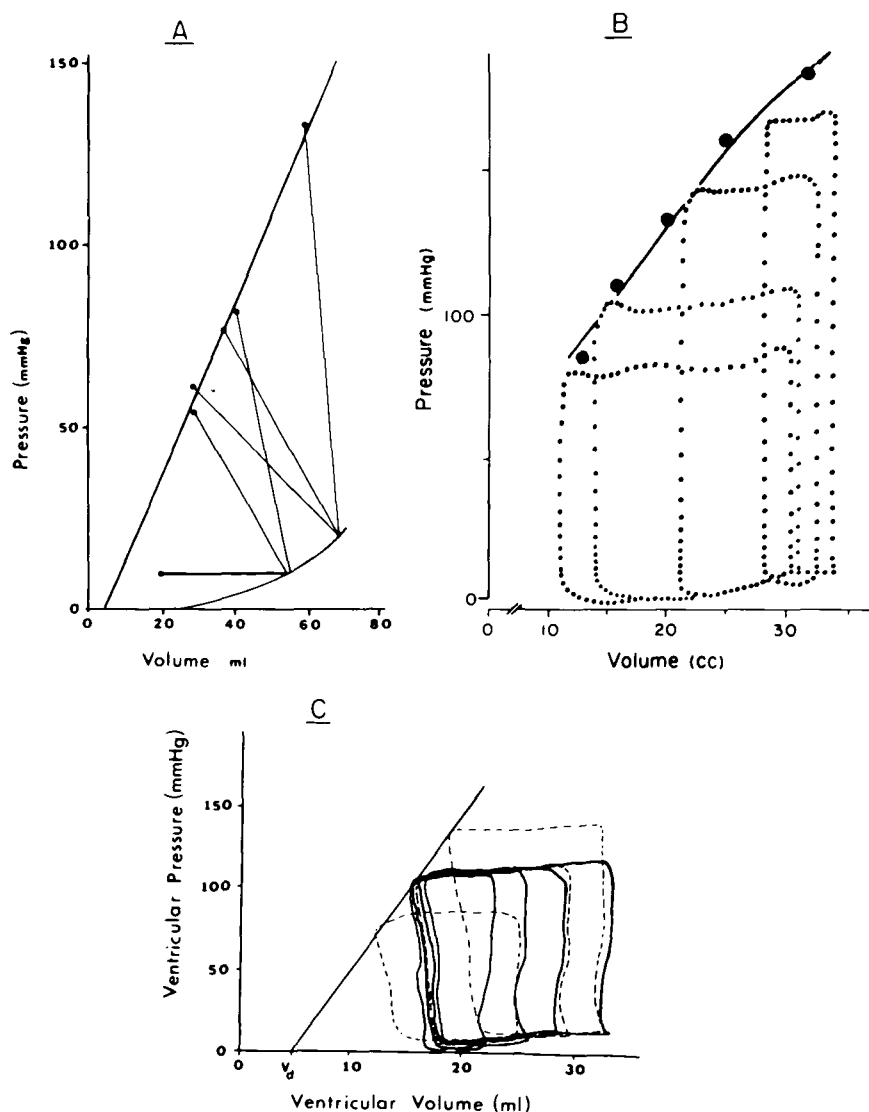


FIGURE 3 Some more recent pressure-volume diagrams in canine ventricles. A: P-V diagram obtained in an isolated left ventricle which was filled with air and connected with an air chamber. The ventricle compressed air during systole. Reproduced from reference 9, by the courtesy of the authors and with the permission of the American Heart Association, Inc. B: P-V diagram obtained in an isolated left ventricle which ejected liquid against a hydraulic servo-controlled loading system. The large circles near the solid line represent the peak isovolumic pressures at various volumes. Reproduced from reference 13, with the courtesy of the authors and permission of the American Physiological Society. C: P-V diagram obtained in a left ventricle ejecting blood. Volume was measured by a cardiometer while venting the right ventricles. Modified from a figure published in reference 19 with the permission of the American Heart Association, Inc.

lower left. Compare this with the line FPE in Figure 2, which is distinct from the isovolumic maxima curve. Shown in Figure 3B are P-V diagrams from a left ventricle which was filled with a fluid and connected to a servo-controlled pump system, which allowed the ventricle to eject the fluid in an isobaric mode at different pressures.^{12,13} The dotted-line loops indicate these variably afterloaded isobaric contractions. The large dots represent peak pressures that the same ventricle reached in isovolumic contractions at various volumes. Note that either these isovolumic pressure points or the left upper corners of the four P-V loops of ejecting beats lie very close to a quasi-linear curve (the thick solid line). Still another example is shown in Figure 3C, where P-V loops were collected from the in situ heart. The left ventricle ejected blood from different end-diastolic volumes, but under a similar systolic pressure (solid-line loops) or under different afterloads (broken-line loops).¹⁴⁻¹⁹ There again, the left upper corners (end-systolic points) of the loops gather around a line. It should be emphasized that in most of these recent studies (1) data from steady state contractions were dealt with, (2) instantaneous ventricular volume was measured with an accuracy which probably is as good as, or even better than, that of biplane cinecardiography, and (3) the contractile state of the ventricle was disturbed minimally by neural or humoral interventions because of the surgical isolation of the heart.

What are the possible reasons for the difference between the earlier and the recent studies? First, it can be a species difference; the frog ventricular muscle may contract quite differently from the mammalian ventricular muscle. Indeed, more recent studies^{20,21} on the frog ventricle reconfirmed the distinction between isovolumic and isobaric maxima curves to an extent similar to that between the line PFE and the isovolumic maxima curve in Figure 2. Second, the frog ventricle does not depend on coronary arteries and obtains O₂ from intraluminal blood. Since the isolated frog ventricles used in those studies obtained O₂ from the Ringer's solution which could not be changed frequently during the determination of P-V relation curve, the myocardium could have been in an ischemic condition. This might be responsible for the observed difference. Third, the difference is, after all, quantitative rather than qualitative. Figures 1 and 2 are both schematic diagrams and it is difficult to assess their quantitative validity. As is obvious in Figure 3, A-C, the superposition of the recently reported end-systolic P-V relation curves for isovolumic and ejecting contractions also is a matter of *approximation* within the limit of spontaneous variations of experimental preparations and measurement errors. In fact, very recent studies,^{22,23} in which end-systolic volume of the isolated canine ventricle was "clamped" at a single value while contraction mode and end-diastolic volume were altered extensively,

indicated that end-systolic pressures after relatively large amounts of ejection were smaller by about 10-20% than those of isovolumic contractions at the identical end-systolic volumes. Therefore, it is fair to say that the studies on the canine ventricle simply indicate a much smaller difference in end-systolic P-V relationship between isovolumic and ejecting contractions than Frank's P-V diagrams from frog ventricle suggested.

The finding that, as an approximation, the end-systolic pressure-volume relationship curve of ejecting beats superimposes on the quasilinear isovolumic end-systolic P-V relation curve implies that, as far as the steady state contraction of the canine left ventricle is concerned, the following simple equation reasonably describes the end-systolic pressure-volume relationship for both isovolumic and ejecting contractions:

$$P_{ES} = E_{ES}(V_{ES} - V_d) \quad (1)$$

Where P_{ES} and V_{ES} are end-systolic pressure and end-systolic volume, respectively. E_{ES} is the slope of the solid lines in Figure 3, A-C, and V_d is the volume axis intercept of these lines. End-diastolic volume, V_{ED} , does not appear in the equation because the end-systolic P-V relation is insensitive to preload. The equation states that, the greater the P_{ES} , the larger V_{ES} will be and, therefore, the smaller the stroke volume from a given V_{ED} (Fig. 3B). The equation further implies that the mode of contraction (i.e., how afterload pressure has changed before the given end-systolic pressure is reached) does not affect C_{ES} at all. Thus, the system represented by Equation 1 has memory of the history of the contractile event within the beat.

The simplified P-V relation described above (Equation 1) had been assumed and used by many modelers of the cardiovascular system²⁴⁻²⁶ even before its experimental verification. Primarily for the sake of simplicity, the modelers conceived the ventricle (and atrium for that matter) as a chamber with time-varying elastance which periodically becomes stiff and soft independently of the loading condition. If the outflow valve opens at a pressure below the peak isovolumic pressure, the chamber will eject a quantity of blood determined by the pressure gradient between the ventricle and aorta and the hydraulic impedance of the junction. When a change in contractility occurs, the model represents it by a change in the magnitude of E_{ES} and time to E_{ES} . The mathematical procedure to represent ventricular contraction by E_{ES} is so easy that it continues to be favored by many theoretical investigators²⁷⁻³⁰ who intend to analyze the complex behavior of the entire cardiovascular system and its control.

A simple example will serve to illustrate how versatile the E_{ES} parameter is in describing pump-performance of the ventricle under various loads. Using Equation 1, one can predict how stroke

volume changes with end-systolic pressure. By definition,

$$\text{Stroke volume (SV)} \equiv V_{ED} - V_{ES}. \quad (2)$$

Rearranging Equation 1 yields

$$V_{ES} = \frac{P_{ES}}{E_{ES}} + V_d. \quad (3)$$

Substituting Equation 3 into Equation 2, we obtain

$$SV = (V_{ED} - V_d) - \frac{P_{ES}}{E_{ES}}. \quad (4)$$

Equation 4 predicts that, in a ventricle with a constant contractile state, stroke volume from a given end-diastolic volume (and therefore ejection fraction as well) decreases linearly with end-systolic pressure. That this is approximately the case was shown by independent studies.^{31,32} Equation 4 also predicts that an increase or decrease in end-diastolic volume should cause a parallel shift of the P_{ES} -SV relation line upward or downward without a significant change in its slope. This proved to be the case in some ventricles, but not exactly so in others.^{31,32}

Effect of Inotropic Intervention on the End-Systolic P-V Relationship

An observed change in the peak pressure of the isovolumically contracting ventricle has been used as a reliable measure of a change in its contractility. The relative increase or decrease in peak isovolumic pressure allows one to quantify the alteration in ventricular contractility by neural (reflex) and humoral agents.^{33,34} However, there has been no way to translate the measured change in this isovolumic pressure index into changes in stroke volume, end-systolic volume, and end-systolic pressure to be expected of a given ejecting ventricle.

By contrast E_{ES} , end-systolic ventricular pressure-volume ratio, allows one to estimate quantitative consequences of the variations in ventricular contractility by physiological mechanisms.^{12,19,35} Figure 4 is an example of the effect of inotropic interventions with epinephrine and isoproterenol infusion on ventricular contractility. The data were obtained from 10 isolated ventricles contracting isovolumically.¹² The infusion increased the value of E_{ES} from 3.86 ± 0.55 to 5.18 ± 1.28 mm Hg/ml and 5.95 ± 0.93 mm Hg/ml, respectively. Since the value of E_{ES} is also valid for ejecting contraction, one can use Equation 4 (as illustrated in Figure 4 by the horizontal arrow) to estimate that SV should increase by about 8 ml with the increase in E_{ES} if end-systolic ventricular pressure were assumed to remain constant at 100 mm Hg. Note that even if P_{ES} changes, the change in SV still can be estimated from E_{ES} and V_{ED} .

Figure 4 also indicates that the V_d did not change significantly with the inotropic intervention.¹² In a

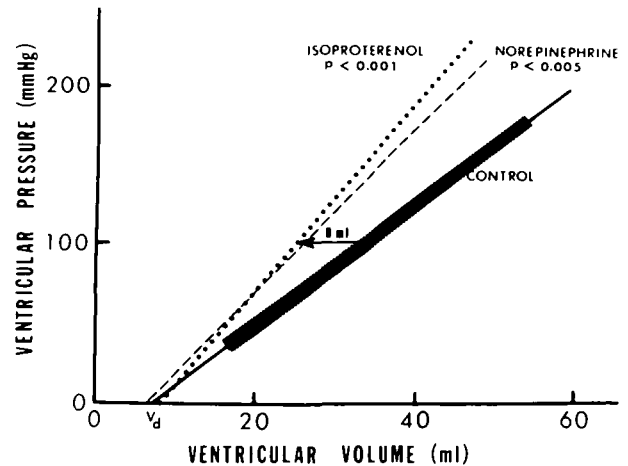


FIGURE 4 Effect of isoproterenol and norepinephrine infusion ($0.2 \mu\text{g}/\text{min}$) on the linear regression of end-systolic pressure on end-systolic volume. The sample standard deviation from the regression in the control condition (5.25 ± 2.64 mm Hg) is shown by the shade. The infusion increased the slope of the regression line (E_{ES}) by about 45% without significant change in volume intercept (V_d). Reproduced from reference 12 with the permission of the American Heart Association, Inc.

recent study,³⁵ the arterial baroreceptor reflexes changed the E_{ES} value, measured again for isovolumic beats, by about $\pm 20\%$ in response to change in the isolated receptor pressure by ± 50 mm Hg from the control pressure of 125 mm Hg. This relatively small change compares favorably with the magnitude of change in cardiac output caused by the carotid sinus baroreceptor reflex measured under a constant mean aortic pressure.³⁶ Severe cerebral ischemia increased E_{ES} to as much as 350% of E_{ES} of the excised, denervated ventricle.³⁵ The full range of nervous control of cardiac contractility as judged by E_{ES} therefore encompasses a 3.5-fold change.

Unlike ejection fraction, E_{ES} is preload independent, as the absence of end-diastolic volume in Equation 1 indicates. Unlike end-systolic volume (which was shown¹⁴ to indicate ventricular contractility only if arterial pressure remains constant), E_{ES} is not affected by changes in systolic arterial pressure because it is a ratio of end-systolic pressure to end-systolic volume of the ventricle. Rearranging Equation 1, one obtains

$$E_{ES} = P_{ES}/(V_{ES} - V_d). \quad (5)$$

If one knows, P_{ES} , V_{ES} , and V_d for a given beat, he can calculate E_{ES} from these values. The measurement of P_{ES} and V_{ES} is relatively easy in intact animals or even in man today. However the determination of V_d requires measurements of many P_{ES} 's and V_{ES} 's from a series of isovolumic and/or ejecting beats under a constant contractile state. This cannot be done easily in man. V_d , "dead vol-

ume," should be distinguished clearly from the unstressed ventricular volume, V_u , i.e., the volume intercept of the passive pressure-volume relation curve. Rushmer³⁷ once proposed to call V_d residual ventricular volume. Usually, V_d is smaller than V_u (5–8 ml as opposed to 15–20 ml in the ventricle of a 20-kg dog). However, the normal V_d for man still is not known and may be significantly small or large in diseased hearts. For example, a concentrically hypertrophied ventricle may have a smaller V_d , whereas a chronically volume-overloaded heart may have a V_d considerably larger than normal. These possible changes in V_d and the derived E_{ES} must be rigorously studied in appropriate animal models of heart disease.

The value of E_{ES} naturally depends on the subject's body size. The human heart is roughly three to four times as large as the heart of the about 20-kg dogs used in those studies.^{12,19} However, both hearts eject blood against approximately the same systolic pressure. Therefore, if the end-systolic volume of man's ventricle were three times as large, Equation 5 indicates that E_{ES} of the normal-human ventricle would have to be $\frac{1}{2}$ of E_{ES} of the normal canine ventricle. For the same reason, we would expect to see some difference in E_{ES} between the adult's and infant's heart, and between an athletic giant's and a sedentary dwarf's heart, even if their heart muscle were in the same normal contractile state. For E_{ES} to be useful for comparison between patients, some normalization of its value must be made to cancel out the size dependence. A normalization with respect to muscle mass, or with an end-diastolic volume measured under a standardized resting condition, may convert E_{max} to a muscle contractility index. This is a clinically important subject for future study.

Instantaneous Pressure-Volume Relation

Extension of E_{ES} to Entire Systole

The time-varying ratio, $E(t)$, of instantaneous ventricular pressure $P(t)$ to instantaneous ventricular volume $V(t)$, as defined below, also appears to be largely insensitive to end-diastolic volume and to the mode of contraction as long as the contractile state of the ventricle remains constant.¹² Mathematically,

$$E(t) = P(t)/[V(t) - V_d(t)] \quad (6)$$

The Equation 6 above is an extension of Equation 5 to the entire period of a cardiac cycle. The statement is *not* valid for the diastolic phase, but it is a reasonable approximation for the systolic phase. The family of lines in Figure 5 are the linear regressions of ventricular pressure on ventricular volume. The data for this regression analysis were collected from many ejecting and isovolumic beats.¹² Each line represents the P-V data specified at a particular time after the onset of contraction. The slope of these curves, $E(t)$, increases with time, reaching the

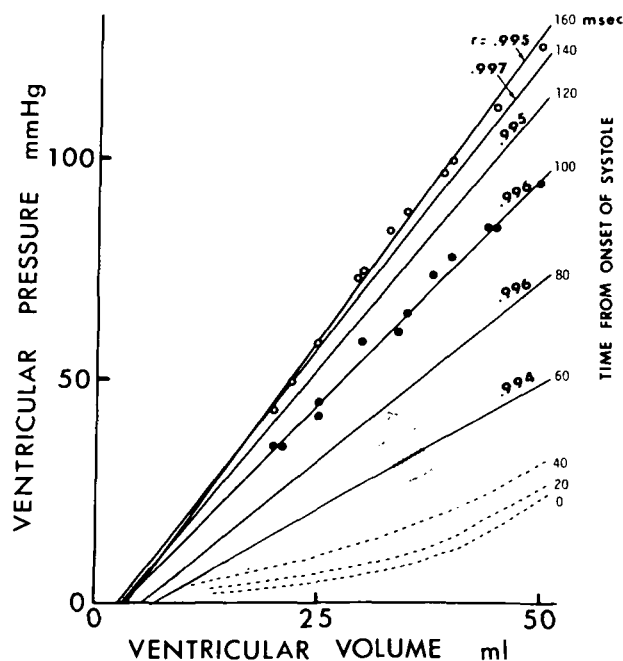


FIGURE 5 Instantaneous relationships between pressure and volume (isochrons) in the ventricle. The shaded arrow indicates that the P-V regression line increases its slope with time during systole. See text for further explanation. Reproduced from reference 47 with the permission of the American Journal of Cardiology.

maximum E_{max} at end-systole. E_{max} is thus exactly the same as E_{ES} in the previous sections. The value of V_d decreases with time in the early phase of systole. However, after about 80 msec, V_d becomes virtually time-invariant. For simplicity, therefore, V_d may be regarded as a constant with the end-systolic value. As mentioned earlier, the end-systolic V_d changed little with inotropic interventions.

Although the time to E_{max} (t_{max}) was also largely insensitive to end-diastolic volume, the average t_{max} for isovolumic contractions was slightly shorter than that for ejecting contractions.¹² This is consistent with the findings for papillary muscle, in which the peak of isometric force is reached earlier than the maximum isotonic shortening.³⁸ Also common between the ventricular P-V relation and the muscle force-length relation is the fact that relaxation proceeds much faster after ejecting contraction and isotonic shortening than after isovolumic contraction and isometric twitch.^{12,38-41}

Concerning Clinical Application

Before concluding this section, a few precautionary words against the use of E_{max} for clinical evaluation of the ventricular state are in order. Serious clinical investigations⁴²⁻⁴⁴ recently have been initiated in patients. The most crucial questions that must be answered are, first, how to estimate the value of V_d in a given patient and, second, how to normalize the calculated E_{max} value to enable a comparison between subjects. One group of inves-

tigators⁴³ disregard V_d by defining $E(t)$ as $E(t) = P(t)/V(t)$ in their clinical studies. If a given subject should have a large V_d , neglecting it would result in a considerable underestimation of the value particularly if end-systolic volume were small. Other studies^{42,44} indicated a significant decrease in E_{\max} with or without an increase in V_d in patients with low ejection fractions. Finally, it always should be remembered that E_{\max} is load-insensitive if and only if the contractile state is not affected by neuro-humoral control mechanisms.

There also has been a recent attempt to evaluate the cardiac state in terms of the ventricular pressure-diameter diagram.⁴⁵ Since the end-systolic volume-diameter relationship is almost linear in the physiological volume range of the normal canine left ventricle,⁴⁶ the end-systolic pressure-diameter ratio E_{\max}^D , might be as useful an indicator of the state of ventricle as the pressure-volume ratio E_{\max} ,⁴⁷ at least in experiments on conscious dogs. However, in ventricles with abnormal lumens, shapes, and/or abnormal regional wall motions, E_{\max}^D is probably much less reliable and less informative than the P-V ratio as an index of the contractile state of the whole ventricle.

Force-Length Relation in Excised Muscle

The relatively simple empirical relation (Fig. 5) which emerges from the plot of instantaneous pressure and instantaneous volume of the ventricle in the P-V plane makes one wonder whether the simplicity is merely a lucky coincidence or whether it derives from some fundamental property of heart muscle. Let us therefore move to the plane of muscle force (F) and length (L) and examine whether a similarly simple relationship can be obtained from the trajectories that heart muscle draws in that plane.

End-Systolic* Force-Length Relation

There is a report⁴⁸ that all the end-systolic* F-L points fell on or near a single curve without regard to the history of the contractile event during systole (Fig. 6A). The authors concluded that the end-systolic F-L relation curve uniquely represents the state of heart muscle.^{48,49} This contrasts the separate end-systolic F-L relation curves associated with different modes of contraction in a twitching skeletal muscle⁴ or single fiber⁵⁰ (Fig. 6B). Findings similar to that in Figure 6A⁴⁸ also were reported in an examination of the relationship between the average midwall muscle force and length, both estimated from the ventricular pressure and volume data.^{1,13,15} Furthermore, it was reported recently that two relationship curves between end-systolic

force and end-systolic sarcomere length, one determined when the sarcomere length was fixed throughout contraction and the other when the sarcomere was allowed to shorten although the muscle length was kept constant, were indistinguishable in the force-sarcomere length plane. If the findings in these reports were born out, they would provide a perfect basis at the muscle and sarcomere level for the insensitivity to past history of the end-systolic pressure-volume relation curve observed in the ventricle by those recent investigators. That the end-systolic F-L relation for the muscle is curvilinear is geometrically consistent with the rectilinear P-V relation for the ventricular chamber.⁵²

There are findings⁵³⁻⁵⁷ to the contrary, however. Quick length change is known to have deactivation effect on the contractile mechanism. The peak isometric force that a papillary muscle develops when it is stretched quickly to a greater length in the middle of systole is smaller than the isometric force generated at the same length from the very beginning.⁵³ This reduction in force becomes considerable when muscle is stretched late in systole. When the mode of contraction suddenly is switched from isometric to afterloaded isotonic contractions,^{54,55} papillary muscles do not shorten to the same length that is expected from the isometric F-L relation curve (Fig. 7). In general, the difference is greater when the afterload is smaller and, therefore, the extent of shortening is greater. According to one report,⁵⁵ the difference varies from muscle to muscle, but the average maximum difference in the extent of shortening was $28 \pm 3\%$ of that expected from the isometric F-L relation. According to another study,⁵⁶ in which the velocity of isotonic shortening of muscle was controlled, the difference between the peak isometric force developed at a muscle length and the force developed at the same length, after various extents of shortening from greater lengths, was a linear function of the extent of preceding shortening. The force deficit amounted to about 10% when the muscle was shortened by 6% of the original length. However, a difference in the speed of shortening did not appear to affect the force deficit.

The diverse results among muscles, even in those isolated muscle experiments and even in a single investigator group, suggest that there is a parameter (or parameters) which has not been adequately controlled. This parameter remains to be discovered. Increasing the contraction frequency from 12 to 60/min markedly shortened the time-to-peak tension, but this did not significantly increase the difference.⁵⁶ Therefore, the limited duration of the active state does not seem to explain the difference between the isometric and isotonic F-L relations at end-systole. Elevation of the muscle bath temperature was found to increase,⁴⁹ have no effect on,⁵⁵ or decrease⁵⁷ the difference. Augmenting contractility by strophanthidin slightly increased the maxi-

* Despite the inappropriateness of using the terms "systole" and "diastole" to refer to the contracting and relaxing phases of twitch of isolated muscle, the analogy with whole ventricle mechanics and the lack of better words causes me to beg the reader's forgiveness. By end-systole I simply mean the peak of contractile activity, whether the activity is measured by force, length or some function of both.

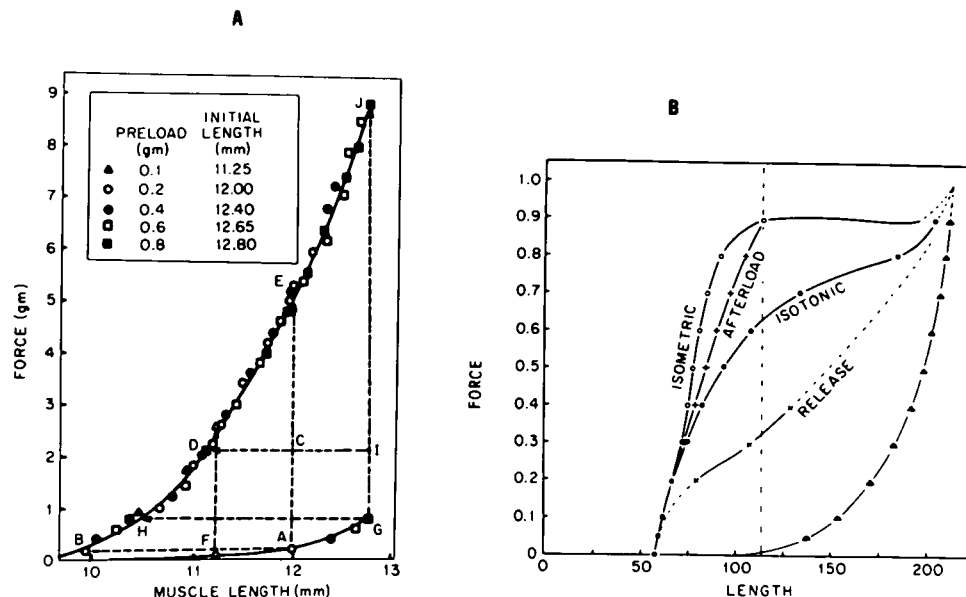


FIGURE 6 Force-length relation of cat papillary muscle (A) and of a single fiber of frog skeletal muscle (B). In the skeletal muscle, the force-length data points in different modes of contraction (isometric, afterloaded, isotonic, and release) resulted in different force-length relationship curves. In heart muscle, no distinct end-systolic relationship curves resulted from different modes of contractions (such as isometric, isotonic, and afterloaded isotonic contractions) Figure 6A was reproduced from reference 48 with the courtesy of the authors and the permission of the American Physiological Society. Figure 6B was reproduced from reference 50 with the courtesy of the authors and the permission of the Danish Academy of Letters and Science.

muscle difference but decreased it in the force region between 0.5 and 2 g.⁵⁵ The discrepancy may be a consequence of a variable degree of facilitatory effect of previous shortening contractions⁵⁸⁻⁶⁰ and/or a variability in the long-term effect of change in preload length.⁶¹ This long-term history-dependent behavior (which develops over many minutes) presents a real difficulty in the precise quantification of mode-dependent differences in the end-systolic F-L relation (i.e., short-term history dependence). An extremely careful experimental design becomes necessary, including control of the number of beats after each change in contraction

mode as well as in the range and direction of alteration of muscle length.

Whatever the reasons for the divergent findings, it is necessary to add a term which integrates the history of muscle length change to Equation 1 for an exact, general description of the end-systolic F-L relation of heart muscle, because heart muscle behaves as though it remembers the immediate past within a twitch. That heart muscle remembers the immediate past has been most clearly demonstrated by the fact that releasing an isometrically contracting muscle just for a few milliseconds but then quickly stretching it back to the previous

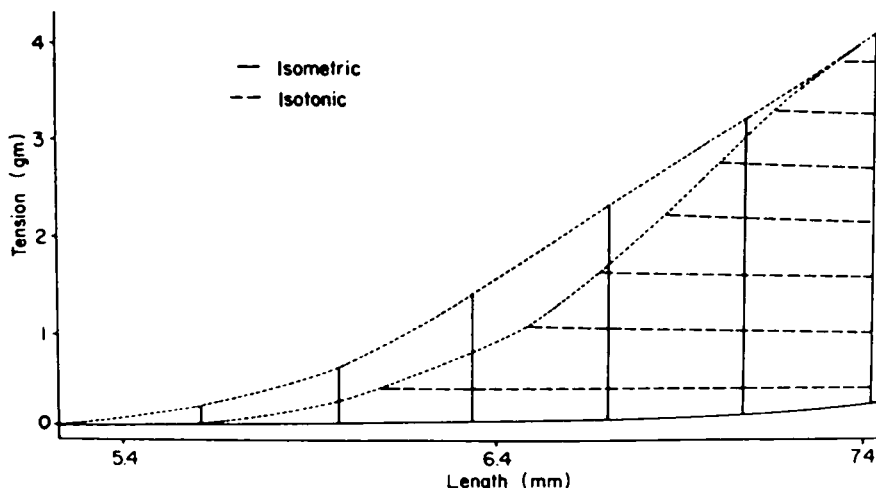


FIGURE 7 End-systolic relation curves from isometric and afterloaded isotonic contractions in a rabbit papillary muscle. Reproduced from reference 54 with the courtesy of the author and the permission of the American Society of Zoologists.

length in the middle of *systole* drastically depresses the subsequent force curve⁶² (see Figure 8 of reference 62).

Instantaneous Force-Length Relation

Some insight into the instantaneous $F(t)$ - $L(t)$ relation of heart muscle can be gained by inspecting instantaneous $F(t)$ - $L(t)$ loops drawn in the force-length plane with the time after the onset of contraction explicitly indicated. Unfortunately, no such plot has been published for heart muscle except for a conceptual analysis of the behavior of the contractile element.⁶³ Merely to suggest the complexity of the relation, an example of unpublished experimental data for a cat papillary muscle⁵⁷ is shown in Figure 8. The filled circles represent data on isometric contractions from various lengths. The broken lines connect isochronous sets of data points at times 135, 270, 405, and 540 msec after the onset of contraction. Except for early systole, a family of linear regression lines fits the isochronous sets of data quite well. We therefore can describe the F - L relation in *isometric* contraction by a formula similar to Equation 6, irrespective of the initial muscle length. However, the similar regression lines for a family of *isotonic* contraction data (broken lines connecting unfilled circles) show that, when muscle shortens, the time-dependent shift of the F - L relation curve lags behind the corresponding shift of isometric curve. The lag seems to be caught up considerably by the end of systole if the afterloaded force is relatively large,⁵¹ but not in the case of isotonic contractions with large extents and velocities of shortening as shown in Figure 8. Even as an approximation, such a simple formula as that obtained from instantaneous ventricular pressure and volume (Equation 6) will not adequately describe the instantaneous $F(t)$ - $L(t)$ relation in which contractions of heart muscle.

It is rather puzzling that the simple isolated papillary muscle gives a more complex F - L relation than the pressure-volume relation of the ventricular chamber which has a more complex architecture. I have no complete explanation for this difference. One possible reason is the difference in the magnitude and speed of perturbation given to the two systems. The length or force perturbation used in muscle experiments is usually large and very quick (a few milliseconds) whereas, in ventricular experiments, the imposed alteration in volume is moderate and quite sluggish compared with the muscle experiments due to the restrictions inherent in the loading system. It generally has been shown in muscle experiments that the smaller the magnitude and speed of perturbation, the milder the depressive (or deactivation) effect on the subsequent contractile process.⁵³

Another possibility is that the history dependence of muscle somehow becomes cancelled out in the ventricle. During an isovolumic contraction of

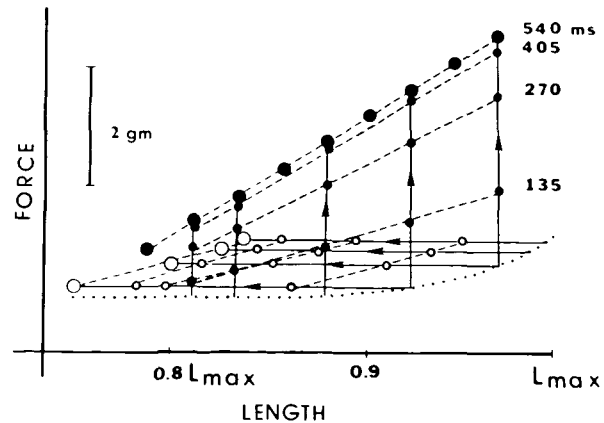


FIGURE 8 Instantaneous force-length relationship curves obtained in a cat papillary muscle. The filled circles represent data at various times after the onset of isometric contraction at various muscle lengths. The open circles represent data at the same instants of time during isotonic contractions from various lengths.

the ventricle the shape and, therefore, regional muscle fiber length, change considerably. That is, muscles are not necessarily contracting isometrically during isovolumic contraction of the ventricle. Complex courses of muscle fibers in various layers of the ventricular wall, its anisotropy, regional differences in the onset of contraction and relaxation, transmural differences in blood flow, force and extent of shortening—some or all of these factors may help to make the complex three-dimensional system behave in a seemingly more simple fashion than its component heart muscle. This must be proven or disproven by further studies. Regardless of the consequence, however, we still can make advantageous use of the phenomenologically simple relationship between ventricular pressure and ventricular volume.

Conclusions

I reviewed ventricular pressure-volume relation and force-length relation of heart muscle. Twisting heart muscle yields complex instantaneous and end-systolic force-length relationship curves which are dependent on the history of the contractile event. In comparison, the canine ventricle seems to yield a considerably simpler pressure-volume-time relation curve. At end-diastole, the relation curve is identical to the nonlinear passive pressure-volume curve. As contraction begins and proceeds, the relation curve increases its slope $E(t)$ and shifts its volume axis intercept $V_d(t)$ to the left (Fig. 5). At the same time it becomes more and more rectilinear. The magnitude of and the time to the maximum (end-systolic) slope of the relation curve (E_{max} and t_{max}) are determined almost entirely by the contractile state of the ventricle; how the ventricle is preloaded and afterloaded (history of contraction) causes minimal difference unless the preload or afterload is excessively unphysiological.

What is described above is a simplified picture of the contraction of the ventricular chamber. Admittedly $E(t)$, or E_{\max} , is a phenomenological parameter of ventricular contraction rather than something directly associated with the fundamental mechanism in the contractile machine of muscle. Effort to find the correspondingly simple F-L relation in heart muscle has yielded unsatisfactory results. On the other hand, E_{\max} should *not* be misconstrued as an *entirely empirical* index with no physiological basis. Having a dimension of volume elastance, it carries a clear notion of active stiffening of ventricular wall. Further, it can be used to predict end-systolic volume (and stroke volume) if end-systolic pressure (and end-diastolic volume) is specified. Because of this feature modelers of the entire circulatory system have used $E(t)$ for many years without experimental data, which are now available at least for the canine left ventricle.

Acknowledgments

This article would have been impossible without the collaboration of my colleagues, Drs. H. Suga, A.A. Shoukas, and K. Nakayama, and Mr. K. Bakalar.

References

- Holt JP: Regulation of the degree of emptying of the left ventricle by the force of ventricular contraction. *Circ Res* 5: 281-287, 1957
- Frank O: Die Grundform des arteriellen Pulses. *Z Biol* 37: 483-526, 1898
- Frank O: Zur Dynamik des Herzmuskels. *Z Biol* 32: 370-447, 1895
- Blix M: Die Laenge und die Spannung des Muskels. (Dritte Abhandlung: Die Zuckungen). *Skand Arch Physiol* 5: 150-172, 1895
- Sulzer R: Die Mechanischen Eigenschaften des Herzmuskels. *Z Biol* 92: 545-554, 1932
- Reichel H: Die Beziehungen zwischen Laenge und Spannung, Volumen und Druck des Herzmuskels. *Z Biol* 99: 63-79, 1939
- Reichel H, Kapal E: Die Mechanik des Herzens bei Aenderung des arteriellen Drucks. *Z Biol* 99: 581-589, 1939
- Patterson SW, Piper H, Starling EH: The regulation of the heart beat. *J Physiol (Lond)* 48: 465-513, 1914
- Monroe RG, French GN: Left ventricular pressure-volume relationships and myocardial oxygen consumption in the isolated heart. *Circ Res* 9: 362-374, 1961
- Monroe RG, Strange RH, LaFarge CG, Levy J: Ventricular performance, pressure-volume relationships and O_2 consumption during hypothermia. *Am J Physiol* 206: 67-73, 1964
- Cross CE, Rieben PA, Salisbury PF: Influence of coronary perfusion and myocardial edema on pressure-volume diagram of left ventricle. *Am J Physiol* 201: 102-108, 1961
- Suga H, Sagawa K: Instantaneous pressure-volume relationships and their ratio in the excised, supported canine left ventricle. *Circ Res* 35: 117-126, 1974
- Weber KT, Janicki JS, Hefner LL: Left ventricular force-length relations of isovolumic and ejecting contractions. *Am J Physiol* 231: 337-343, 1976
- Mitchell JH, Wildenthal K, Mullins CB: Geometrical studies of the left ventricle utilizing biplane cinefluorography. *Fed Proc* 28: 1334-1343, 1969
- Taylor RR, Covell JW, Ross J Jr: Volume-tension diagrams of ejecting and isovolumic contractions in left ventricle. *Am J Physiol* 216: 1097-1102, 1969
- Suga H: Time course of left ventricular pressure-volume. *Jap Heart J* 10: 509-515, 1969
- Suga H: Time course of left ventricular pressure-volume relationship under various extents of aortic occlusion. *Jap Heart J* 11: 373-378, 1970
- Suga H: Left ventricular pressure-volume ratio in systole as an index of inotropism. *Jap Heart J* 12: 153-160, 1971
- Suga H, Sagawa K, Shoukas AA: 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: 314-322, 1973
- Gehl H, Graf K, Kramer K: Das Druckvolumendiagramm des Kaltbluter Herzens. Die Bedeutung des plastischen Elements fuer die Herzmechanik. *Pfluegers Arch* 261: 207-294, 1955
- Soeda Y: Dynamics of the contraction of cardiac muscle in the elastic system. *J Physiol Soc Jap* 22: 287-299, 1960
- Suga H, Yamakoshi K: Effects of stroke volume and velocity of ejection on end-systolic pressure of canine left ventricle: End-systolic volume clamping. *Circ Res* 40: 445-450, 1977
- Suga H, Kitabatake A, Sagawa K: Inotropism dependence and afterload independence of end-systolic pressure at servo clamped end-systolic volume in canine left ventricle. *Circulation* 56: III; 53, 1977
- Warner H: Use of analogue computers in the study of control mechanisms in circulation. *Fed Proc* 21: 87-91, 1962
- Beneken JEW: A mathematical approach to cardiovascular function. The uncontrolled human system. Thesis presented to Inst. TNO Med. Physics, Utrecht Holland, 1965
- Snyder MF, Rideout VC: Computer simulation studies of the venous circulation. *IEEE Trans Biomed Eng* 16: 325-334, 1969
- Suga H: Theoretical analysis of a left-ventricular pumping model based on the systolic time-varying pressure-volume ratio. *IEEE Trans. Biomed Eng* 18: 47-55, 1971
- Green ME, Clark JW, Mohr DN, Bourland HM: A mathematical model of left ventricular function. *Med Biol Eng* 11: 126-134, 1973
- Ghista D, Patel KM, Woo KB, Oliver C: A human left ventricular control system model for cardiac diagnosis. *J Biomech* 5: 365-390, 1972
- Deswysen BA: Parameter estimation of a simple model of the left ventricle and of the systemic vascular bed, with particular attention to the physical meaning of the left ventricular parameters. *IEEE Trans Biomed Eng* 24: 29-38, 1977
- Weber KT, Janicki JS, Reeves RC, Hefner LL, Reeves TJ: Determinants of stroke volume in the isolated canine heart. *J Appl Physiol* 37: 742-747, 1974
- Elzinga G, Westerhof N: The pumping ability of the left heart and the effect of coronary occlusion. *Circ Res* 38: 297-302, 1976
- Levy MN, Ng ML, Zieske H: Cardiac and respiratory effects of aortic arch baroreceptor stimulation. *Circ Res* 19: 930-939, 1966
- Ullrich KJ, Riecher G, Kramer K: Die Druck-volumendiagramm des Warmbluterherzens. Isometrisch Gleichgewichtskurven. *Pfluegers Arch* 259: 481-498, 1954
- Suga H, Sagawa K, Kostiuik DP: Controls of ventricular contractility assessed by pressure-volume ratio, E_{\max} . *Cardiovasc Res* 10: 582-592, 1976
- Kostiuik DP, Sagawa K, Shoukas AA: Modification of the flow-generating capability sinus baroreceptor reflex. *Circ Res* 38: 546-553, 1976
- Rushmer RF: Residual volume of blood in the right and left ventricle. In *Blood Volume and Contractile Protein in Heart Muscle* (World Trends in Cardiology III), edited by AS Cain, Jr. Hoeber-Harper, New York, 1956, 96-103
- Sonnenblick EH: Implications of muscle mechanics in the heart. *Fed Proc* 21: 975-990, 1962
- Parmley WW, Sonnenblick EH: Relation between mechanics of contraction and relaxation in mammalian cardiac muscle. *Am J Physiol* 216: 1084-1091, 1969
- Weisfeldt ML, Scully HE, Frederickson JJ, Rubenstein JJ, Pohost GM, Beierholm E, Bello AG, Daget WM: Hemodynamic determinants of maximum negative dp/dt and periods

- of diastole. *Am J Physiol* **227**: 613–621, 1974
41. Suga H, Yamakoshi K: Reduction of the duration of isovolumic relaxation in the ejecting left ventricle. *J Physiol (Lond)* **267**: 63–74, 1977
 42. Weisfeldt ML, Shoukas AA, Weiss JL, Dashkoff N, Conic P, Griffith LSC, Achuff SC, Ducci H, Sagawa K: E_{max} as a new contractility index in man. *Circulation* **54** (suppl. II): 31, 1976
 43. Clark J Jr, Pruett RC, Baldrige DL, Scrinivasan R, Bourland HM, Cole JS, Brower RW: A functional model for the characterization of the ventricular mechanics of the human subject. *Med Biol Eng Comput* **15**: 335–338, 1977
 44. Grossman W, Braunwald E, Mann T, McLaurin LP, Green LH: Contractile state of the left ventricle in man as evaluated from end-systolic pressure-volume relations. *Circulation* **56**: 845–852, 1977
 45. Mahler F, Covell JW, Ross J Jr: Systolic pressure-diameter relations in the normal conscious dog. *Cardiovasc Res* **9**: 447–455, 1975
 46. Suga H, Sagawa K: Assessment of absolute volume from diameter of the intact canine left ventricular cavity. *J Appl Physiol* **36**: 496–499, 1974
 47. Sagawa K, Suga H, Shoukas AA, Bakalar KM: End-systolic pressure-volume ratio: A new index of contractility. *Am J Cardiol* **40**: 748–753, 1977
 48. Downing SE, Sonnenblick EH: Cardiac muscle mechanics and ventricular performance: Force and time parameters. *Am J Physiol* **207**: 705–715, 1964
 49. Sonnenblick EH: Instantaneous force-velocity-length determinants in contraction of heart muscle. *Circ Res* **16**: 441–451, 1965
 50. Buchthal F, Kaiser E: Rheology of cross striated muscle fiber. *Dan Biol Med* **21**: 1–318, 1951
 51. Pollack GH, Krueger JH: Sarcomere dynamics in intact cardiac muscle. *Eur J Cardiol* **4** (suppl): 53–65, 1976
 52. Suga H, Sagawa K: Mathematical relationship between instantaneous ventricular pressure-volume ratio and myocardial force-velocity relation. *Ann Biomed Eng* **1**: 160–181, 1972
 53. Brady AJ: Time and displacement dependence of cardiac contractility: Problems in defining the active state and force-velocity relations. *Fed Proc* **24**: 1410–1420, 1965
 54. Brady AH: Length-tension relations in cardiac muscle. *Am Zoologist* **7**: 603–610, 1967
 55. Taylor RR: Active length-tension relations compared in isometric, afterload and isotonic contractions of cat papillary muscle. *Circ Res* **26**: 279–288, 1970
 56. Meiss RA, Sonnenblick EH: Controlled shortening in heart muscle: Velocity-force and active state properties. *Am J Physiol* **222**: 630–639, 1972
 57. Nakayama K, Sagawa K, Shoukas AA: Force-length-time relations in heart muscle under various mechanical loadings. (abstr). *Fed Proc* **34**: 412, 1975
 58. Parmley WW, Brutsaert DL, Sonnenblick EH: Effects of altered loading on contractile events in isolated cat papillary muscle. *Circ Res* **24**: 521–532, 1969
 59. Kaufmann RL, Lab MJ, Hennekes R, Krause H: Feedback interaction of mechanical and electrical events in the isolated mammalian ventricular myocardium. *Pfluegers Arch* **324**: 100–123, 1971
 60. Jewell BR, Rovell JM: Influence of previous mechanical events on the contractility of isolated cat papillary muscle. *J Physiol (Lond)* **235**: 715–740, 1973
 61. Parmley WW, Chuck L: Length-dependent changes in myocardial contractile state. *Am J Physiol* **224**: 1195–1199, 1973
 62. Bodem R, Sonnenblick EH: Deactivation of contraction by quick releases in the isolated papillary muscle of the cat. *Circ Res* **34**: 214–225, 1975
 63. Brady AJ: Mechanics of the myocardium. In *The Mammalian Myocardium* chap 6 edited by GA Langer, AJ Brady, New York, John Wiley, 1974, p 163–192