Determinants of Cardiac Performance

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Sequential experimental studies are reviewed which, when properly integrated, confirm the concept that the responses of the ventricles, however measured, are determined by the initial length of fibers, provided that the functional state of the myocardium is not altered. Some of the established factors are discussed which may obscure the evidence that this basic law is of importance under normal and pathologic conditions.

During the past 50 years progress in the study of heart disease has been achieved over different pathways. Among these is the clinical application of instrumentation and technics originally designed in, and limited to, physiologic laboratories. Since my entry into medical school in 1901 I have witnessed the successive employment of sphygmographs, phlebographs, apex beat recorders, sphygmomanometers, plethysmographs, roentgenographs, electrocardiographs, and phonocardiographs. Some of these have not survived the dictates of experimental fashions and are known to the present generation only as museum pieces or text figures, if at all. They were retired from the armamentarium of clinicians because the information gained did not appear commensurate with the time and effort required for their proper use. With the development of high fidelity pressure recorders in laboratories and the demonstrated safety of arterial punctures and cardiac catheterization in hospitals we have entered an era in which circulatory derangements are being intensively studied through the interpretation of cardiac outputs and of pressure pulses recorded directly from the cardiac chambers and large vessels. The interpretation of circulatory dynamics by such procedures requires not only a comparison of data from human subjects in health and disease, but also the utilization of information derived from more controllable experiments on animals. We can obviously not hope to comprehend the processes through which we die unless we understand the mechanisms which keep organisms alive.

The purposes of this review are (1) to restate briefly some important experimental results on cardiac performance, (2) to re-examine concisely the deductions, theories and concepts of cardiac behavior to which they have given rise, and (3) to attempt a resynthesis of evidence into a modern physiologic concept of myocardial regulation. Such a process of "modernization" involves a divestment of factual data from theories and the integration of successive discoveries with classical ones of the past. When this is done it frequently happens, as in this instance, that very old laws of cardiac behavior have merely been given more extended applications, rather than that essentially new ones have been discovered.

Three Classic Discoveries

1. In 1869 a young American, Dr. H. P. Bowditch, undertook the study of physiology in Ludvig's laboratory in Leipzig. His investigation on the apex of the frog's ventricle published in 1871 has become a classic in physiology. He showed that if the condition of the heart muscle remains unaltered, the contractions remain equal regardless of the strength of stimuli applied. As Ranvier expressed it, the heart's motto is "all or none." The paradox that the ventricles can obviously alter the vigor of their contractions, under normal as well as pathologic conditions, was explained by another observation in the same investigation, namely, that excitation of the resting frog's ventricle by successive shocks of the same intensity at short intervals results in a progressive increase in amplitude of contractions. The phenomena called "treppe" or "staircase" is obviously occasioned by the fact that...
each stimulus exerts a beneficial aftereffect on the responsiveness of cardiac muscle.

Summarizing, the law of all or none implies that cardiac muscle either does not contract at all or responds to the fullest extent, but the magnitude of the all or none response is determined by the inherent "condition" of the muscle.

2. In 1884, Howell and Donaldson presented unequivocal evidence that the heart itself has intrinsic mechanisms by which its output is nicely adjusted to the venous input. Using the Newell Martin heart-lung preparation, it was found that augmentation of venous inflow to a heart weighing 76 Gm. caused the cardiac output to increase from 480 to 1964 cc. per minute, the stroke volume from 5.2 to 21.6 cc., and the right atrial pressure from 10 to 60 cm. of blood. The compensation for increasing volumes of venous return was not quite perfect, however; increases in output of the left ventricle lagged progressively behind the available supply of blood in the venous reservoirs. Upon reducing venous inflow so that atrial pressure fell to the original level of 10 cm. of blood, cardiac output dropped to 400 cc. and the stroke volume to 2.38 cc., which indicated that the performance had deteriorated slightly after a short period of strain.

3. In 1895, O. Frank published his investigations on "the dynamics of heart muscle." His object was "to correlate as far as possible the mechanical reactions of cardiac muscle with the well known responses of skeletal muscle previously established by A. Fick, J. von Kries, and Blix." It should be recalled that these investigators had established a relationship between the force of contraction and the degree of stretch and tension under which skeletal muscles were placed previous to stimulation, that is, the so-called initial length and tension. Frank recorded isometric and isotonic contractions of the frog's atria and ventricle during various degrees of diastolic filling and pressure. He found that, within limits, stepwise increases in diastolic volume and pressure just before contraction—hereafter called the presystolic volume and pressure—determine the magnitude of the all or none response. These studies emphasized that the cardiac response to artificial or natural excitation is determined wholly by hemodynamic events which precede excitation.

Years of experimentation have not only confirmed the basic laws of cardiac behavior founded upon these observations, but they have also elucidated the many variables which tend to obscure their operation in the control of the mammalian heart under normal and pathologic conditions.

THE LAW OF UNIFORMITY OF BEHAVIOR

In 1906, Y. Henderson succeeded in improving previously used plethysmographic technics sufficiently to establish patterns of ventricular filling and emptying under different circulatory conditions. A study of cardiometric records led Henderson and his associates to the conclusions (1) that the ventricles have a fixed pattern of relaxation which determines their diastolic capacity as long as the venous supply is at normal levels, and (2) that further increase in venous supply cannot augment ventricular filling and systolic discharge. Such a concept set an extremely low limit to the cardiac response to increasing initial tension and length. According to this view also the only way in which greater volumes of venous blood could be pumped to the aorta would be through an increase in heart rate. According to his "law of uniformity of behavior," cardiac output increases progressively up to rates of 180 per minute, thereafter becoming stationary and, during extreme tachycardia, diminishing rapidly.

A reappraisal of Henderson's work indicates that his analysis of ventricular volume curves gives a valuable geometric plan for evaluating the effect of cycle length on systolic discharge and cardiac output; but his conclusion that increased venous return cannot augment ventricular filling does not seem to have been supported by valid experimental evidence. Henderson was unquestionably correct in his deduction that ventricular filling occurs largely in early diastole as a result of A-V pressure differences, but he underestimated the additional quantity of blood that the atria inject into the ventricles, partly because the slower
beats in his experiments were obtained during vagus stimulation and therefore associated with depression of atrial contraction.

**The Applicability of Laws of Initial Tension and Length to Mammalian Hearts**

In 1914 the writer\(^5\) reported experiments which demonstrated that every increase or decrease in volume of blood returning to the right atrium simultaneously alters the initial tension, height, and contour of the right intraventricular pressure curve. These experiments were the first to demonstrate that the reactions established for the frog’s ventricle are also applicable to the naturally beating right ventricle of dogs. In brief, the conclusion was reached that the gradient of the isometric pressure rise and the peak systolic pressure are determined by changes in the initial tension, as long as marked changes in inherent contractility are not simultaneously produced by experimental procedures.

Concurrently and quite independently, other investigators, notably Starling and his associates\(^5\) and Straub,\(^4\) investigated the effect of changes in initial tension and length on the response of isolated hearts. Since the work of Starling and his group has aroused the greatest attention in relation to clinical studies, a reappraisal of their investigations and conclusions should be of timely interest. These investigators utilized their well known heart-lung preparation\(^5\) which was designed to control heart rate, mean arterial pressure and venous inflow, and to vary any one of these factors at a time. This was of signal importance despite the facts that the individual factors cannot be controlled as independently as the British investigators believed and that the dynamic conditions under which the heart operates deviate somewhat from those which exist in the body.\(^1-17\) The important results and conclusions pertinent to our discussion can be summarized as follows:

1. When arterial resistance and venous inflow were kept constant—within limits of the preparation—variations in heart rate from 60 to 160 per minute caused no significant changes in cardiac output per minute (Markwalder and Starling\(^15\)), a conclusion diametrically opposed to that of Henderson and his associates.\(^9\) The inference was drawn—and later it was supported in a measure by registration of volume curves—that ventricular filling is not dominated by a fixed pattern of relaxation and elastic resistance to filling pressures (Patterson, Piper and Starling\(^11\)).

2. At constant heart rate and mean arterial pressure, progressive augmentation of venous inflow caused progressive increases in diastolic size (stretch), systolic discharge, and cardiac output per minute up to a critical atrial pressure (compensation). Beyond this, systolic discharge and cardiac output decreased (decompensation). These results were interpreted as follows: A compensatory increase in stroke volumes takes place *as long as the ventricles can undergo additional distention*. When no further distention is possible, owing to limitations imposed by the elastic ventricular stretch or the restraining action of the pericardium,\(^18\) the rapidly increasing presystolic tension exerted on individual fibers hinders the development of contractile force, and systolic discharge diminishes (Patterson, Piper and Starling\(^11\)).

3. During the compensatory state, that is, while cardiac output increased with augmenting venous supply—pressures rose *pari passu* in both atria, slowly at first and thereafter at a progressively increasing rate. During the stage of decompensation (when cardiac output of the left ventricle began to decline) pressure rose rapidly in the right atrium but fell in the left (right heart failure) (Patterson and associates\(^11\)).

4. The fatigued or depressed heart could have an output equal to that of a fresh heart but required a higher atrial pressure and greater presystolic ventricular distention. The corollary follows that, at controlled heart rates, the competence of the myocardium may be tested by comparing the systolic discharge at equivalent venous pressures or by determining the venous pressure required to produce equivalent stroke volumes. This procedure has been used by Krayer\(^16\) in the heart-lung preparation and by the author\(^19\) in the intact animal.
5. In some experiments in which simultaneous volume and pressure curves from the ventricles were recorded, it appeared that considerable increase in presystolic ventricular size took place, while the presystolic or initial tension in the left ventricle remained unchanged or actually fell (Patterson, Piper and Starling). However, at the time these investigators worked it was not realized that slight shifts in the entire pressure curve cannot be excluded unless a base line for optical pressure curves is simultaneously recorded. From their observations the inference seemed warranted that the presystolic size (stretch) of the ventricles is not determined solely by actual filling pressures (mean atrial pressures), but is affected also by inherent variations in their rate of relaxation and elastic or tonic resistance to stretching. On the whole, they believed that the mammalian ventricle, unlike that of the frog studied by Frank, rarely reaches a state of "static relaxation" before the succeeding beat supervenes.

From these observations, Starling's oft quoted "law of the heart" was derived. There is a general impression that the graphic representation of the law, often reproduced, was based on data from these experiments. The careful reader will discover the frank statement that the published curves are reproductions of graphs previously published by Blix and by O. Frank (Patterson, Piper and Starling). "So far our analysis of the mechanical condition of the heart's contraction does not differ essentially from Frank's classical exposition of the mechanical events affecting contraction of the frog's heart. In this work, however, Frank was dealing with contractile tissue which had long periods of diastole, so that it had reached a static condition before the beginning of systole, and he found that the energy set free in the excited condition (as measured by the tension set up) was proportional to the initial, i.e., diastolic, tension on the muscle. But in this case it is not easy to decide whether the determining factor is really the initial tension or the initial length of the muscle fibres...."

"In the mammalian heart we are dealing with an organ which is contracting rapidly and rhythmically, such contraction being a necessary condition for the preservation of its functional activity. The condition of the heart therefore as to both tension and length of its muscle fibres is altering continuously during diastole from one beat to the next."

"In Frank's experiments on the frog's heart, the initial length was proportional to the initial tension, so that the augmentation of energy set free on contraction might have been due either to the increased tension or to the increased length. In our experiments we have found that it is length rather than tension which determines the energy of contraction.

"We thus find no constant connection between the diastolic tension and the succeeding contraction, though as a rule these two quantities will be altered together. But we do find a direct proportion between the diastolic volume of the heart (i.e., the length of its muscle fibres) and the energy set free in the following systole.

"The law of the heart is therefore the same as that of skeletal muscle, namely, that the mechanical energy set free on passage from the resting to the contracted state depends on the area of 'chemically active surfaces' i.e., on the length of the muscle fibres. This simple formula serves to explain the whole behaviour of the isolated mammalian heart,—its movement, powers of adaptation to varying demands made upon it, its behaviour to fatigue and the influence of its nerves or chemical agencies such as acid ions or adrenalin." (Author's italics.)

The basic idea underlying Starling's law of the heart, namely, that myocardial response is determined basically by the degree to which fibers are stretched, has been supported, with one exception, by all subsequent investigators. However, attention may be directed to the fact that all investigators have assumed the existence of a linear relation between presystolic ventricular capacity and length of fibers, and between presystolic intracardiac pressure and initial tension on muscle fibers. The validity of this assumption for the mammalian ventricles composed of complicated superimposed muscle bands arranged to pull in different directions has never been adequately established.

In 1922, Katz and I restudied the mechanism of adaptation to increasing venous return by means of cardiometric technic in a controlled circulation preparation. The preparation, as progressively improved in subsequent researches, is diagrammatized in figure 1. The heart of a lightly anesthetized dog is exposed under artificial respiration just enough for the animal to retain natural diaphragmatic movements. This offers a simple indication that blood gases remain essentially normal. The cardiac nerves are severed. The heart rate is controllable within..."
wide ranges; it is reduced to 40 or 50 per minute by clamping the sinus node and then driving the heart by electric shocks applied to the right atrium. Venous return can be decreased through graded compression of the inferior vena cava or increased by an infusion of warm saline into a jugular vein. The reduction in blood viscosity which accompanies such infusion is advantageous dynamically, for it has proved just about sufficient to maintain a constant diastolic pressure despite increasing stroke volumes. Arterial resistance can be controlled by tightening or loosening an adjustable clamp placed around the lowest portion of the thoracic aorta.

Volume curves of the ventricle are recorded optically together with arterial pressure pulses as described elsewhere.5, 22 Typical curves are shown in figure 2. The volume tracings descend with diminution of ventricular volume during systole and rise during diastolic filling. Changes in slope (1–9) indicate changes in the rate of ventricular emptying and filling. During the phase of isometric contraction (2–3), the curves either rise or fall slightly. These variations are unavoidable artefacts created by slight shift of the cardiac base with respect to the rubber diaphragm. During systolic ejection (3–7) several changes in rate of emptying corresponding to inflections of the aortic pressure curve are indicated by vertical lines. The rapid ejection rate from 3–6 and the marked reduction from 6–7 are particularly noteworthy. Systole ceases at 7 and the interval 7–8 demarcates the isometric relaxation phase of the ventricles. Ventricular filling occurs rapidly at first (8–9) and then more gradually (9–1), dividing the filling into phases of rapid inflow and diastasis. This is followed by atrial systole (1–2).

The results obtained by Katz and myself22 in the main confirmed those of Starling and his group, but some amplification and certain differences were found:

1. During the compensatory stage of increased venous return (compare curves A and B in fig. 3) ventricular filling proceeded more rapidly throughout diastole, that is, during the successive periods of rapid inflow, diastasis and atrial contraction, and the larger systolic discharge was accomplished by a greater velocity of ejection, a prolongation of the ejection period (compare A and B), and occasionally even more complete emptying. It is obvious at a glance that such curves are not superimposable as regards either their systolic or diastolic limbs. Optical pressure curves from the right ventricle (lower series, fig. 3) demonstrated that the presystolic intraventricular pressure (initial

![Fig. 1. Diagram illustrating the "controlled circulation preparation" for studying separate determinants of ventricular response. Discussion in text.](image1)

![Fig. 2. Simultaneously recorded volume curve of ventricles (upper) and aortic pressure (lower) showing corresponding inflections during phases of ejection and division of systole and diastole into commonly accepted phases: (1–2) atrial systole, (2–3) isometric contraction, (3–5) period of maximal systolic ejection, (5–7) period of reduced systolic ejection, (7) end of systole, (7–8) isometric relaxation, (8–9) rapid diastolic filling, (9–1) retarded diastolic inflow (diastasis).](image2)
tension) increased steadily, the gradient of pressure before ejection (isometric phase) was steeper, and the curves reached higher peaks. The larger volumes ejected by the right ventricle under higher pressure necessarily caused an elevation of left atrial pressure. Contrary to Starling’s observations, Opdyke and his associates8 have recently demonstrated that the increase in pressure was much larger in the left than in the right atrium, owing to a lesser distensibility of the left atrium and its tributary veins.

![Diagram of ventricular volume curves](http://circ.ahajournals.org/)

**Fig. 3.** Changes in configuration of ventricular volume curves (upper series) and right ventricular pressure pulses (lower series) during progressive increase in rate of venous return. All curves matched at beginning of ventricular systole; a, b, c denote ends of systole and illustrate changes in relative durations of systoles. (A) control, (B) during compensatory stage, (C) during decompensatory stage.

2. Contrary to interpretations by Starling and his associates, we found that reduction in stroke volume with excessive rates of venous inflow was not conditioned by the fact that the ventricles had reached their distention limits; decompensation developed while the process of diastolic distention was actually accelerating (fig. 3B, C). In other words, it appears that beyond a critical degree of stretch, additional extension either has a reversed effect on the release of mechanical energy or contraction is hindered by the greatly increasing diastolic tension. This also accords with O. Frank’s observations on frog hearts8 and with those of Lundin44 on stretched moieties of ventricular muscle. Analysis of volume and right ventricular pressure curves (fig. 3C) indicated that despite a large increase in diastolic size and in initial tension, the mechanism of discharge changed, the ventricles emptied themselves less forcibly and completely; indeed, the systolic size was sometimes smaller than the normal diastolic size. An enormous increase in residual volume was apparent (see a and c, curves A and C), indicating that a considerable effective volume of blood stagnated in the heart during progressive decompensation. The systolic pressures in the right ventricle and pulmonary artery decreased and, consonant with Starling’s results, pressure in the left atrium fell.

3. With constant venous return and right atrial pressures, the cardiac output was found to be far from constant at different heart rates, as the British investigators claimed. Under carefully controlled atrial pressure the alterations in stroke volume with progressive acceleration followed the predictions of Y. Henderson rather than the experimental results of Starling and his group. However, unless arterial and venous pressures were readjusted with every change in heart rate, the beats were not superimposable and accurate predictions as to the relation of cardiac output to heart rate could not be made.

The reasons for the variable effects of heart rate changes on stroke volume and cardiac output per minute have gradually become clearer from the study of a large number of ventricular volume curves. The integration of a large number of physical and physiologic determinants on ventricular filling are involved. An attempt is made to dissociate the chain of events with the aid of the diagram in figure 4. The heavy curve (N) represents a ventricular volume curve under normal conditions at a heart rate of 75 per minute. The record is taken in such a manner that ventricular emptying is indicated by the downstroke and filling by the upstroke. The residual volume is indicated without ordinate values. The phases of systole and diastole for this beat are numbered as in figure 2.

An acceleration of the heart approximately
to 120 per minute would, according to Y. Henderson's scheme, merely cut into the filling curve as indicated by the arc A. This, however, is an oversimplification of changes that actually take place. In the first place, despite constancy in returning blood volumes, such acceleration very quickly reduces the pressure and volume of blood in the atria in a mechanical way. Simply stated, more blood is pumped per minute than is received. As a result, the rate of the increment becomes somewhat greater as indicated in the wave Y which may restore the systolic stroke C approximately to that of stroke A. Necessarily the diastolic filling curves are not superimposable, but the net effect on stroke volume approximates Henderson's predictions. If, in addition, the increase in heart rate is induced by activation of the accelerator mechanism and release of the vagus mechanism, the force of atrial systole may be increased.

![Diagram](image)

**Fig. 4.** Heavy curve (N) typical volume curve for heart cycle, 0.8 second (75 per minute). Numerals same as in figure 2. Assembly of superimposed ventricular volume curves illustrate variable factors that may influence stroke volume when heart rate increases to 120 per minute. (A) Abridgment of natural filling and reduction of stroke volume, according to Henderson. (B) Further reduction in systolic discharge owing to coincident reduction in atrial pressure and reduced filling rate shown at F, and diminished force of atrial systole at X. (C) Restoration of stroke volume to control of curve A by greater effectiveness of an atrial systole (Y) which supervenes immediately after or during rapid inflow. (D) Increase in stroke volume to that of a beat with long cycle (N) as a result of accelerator nerve action or adrenergic humoral effects which increase force of atrial contraction Z, and more completely empties the ventricles (reduction of residual volume). (E) Further augmentation of systolic discharge through simultaneous increase in venous return and more rapid filling as in exercise. Lines on right (N-E) indicate at a glance comparative stroke volumes for corresponding volume curves.

filling during the rapid inflow phase tends to become more gradual, as in the curve labeled F. Since the atria start their contractions at a shorter initial length the vigor of their contractions would be diminished, and it might be expected that their contribution to ventricular filling would be reduced, as indicated in the wave X. However, this diminishing effect of atrial contraction appears to be offset by the fact that atrial contractions coming at the time of incomplete ventricular filling are more effective than those that occur after a long diastasis, as in the solid line curve. As a result, significantly and the contribution to ventricular filling may be represented by wave Z. Under such hypothetic conditions the stroke volume D may almost equal that of the control beat X, for the accelerator mechanism also acts directly on the ventricles to reduce their residual volumes.

Such an approximate proportionality of cardiac output to heart rate can obviously be maintained only as long as the volume of venous return equals the cardiac output. If as a result of many conditions—hemorrhage and shock, for example—this is not accomplished,
these compensatory reactions cannot be maintained. If, on the other hand, venous return augments at the same time that the heart accelerates, as in exercise, the stroke volumes can definitely exceed the normal, as illustrated in curve E. This analysis of the many coefficients which affect ventricular filling explains why investigators have differed (a) as to the contribution of atrial systole to ventricular filling, and (b) as to the effect of heart rate changes on cardiac output per minute.

It seems apparent now that the constant cardiac outputs obtained by Starling and his associates over wide ranges of heart rates were due to a fortuitous balance between these variable factors. The British investigators failed to recognize that the available supply and pressure of blood in the right atrium is determined as much by changes in cycle length as by the pressure head in a venous reservoir. Furthermore, as Krayer has pointed out, these investigators altered heart rate through changes of temperature of the inflowing blood which is certainly not without influence on the inherent contractility of the ventricles.

Intrinsic Cardiac Factors. Our analysis of the relationship between atrial volumes and pressures, duration of the inflow periods and force of atrial contractions on the one hand, and systolic discharge and cardiac output per minute on the other, accord basically with the law of initial length. The resultant effect of filling pressure, atrial activity, and the available filling time regulate the degree of ventricular distention (initial length) realized at any given cycle length, and this in turn determines the velocity, volume, and duration of the systolic discharges. However, this is only a first approximation to reactions of the heart muscle at a given initial length in the body. As Starling and his group pointed out, at equivalent initial lengths a heart in good condition responds with a larger stroke volume than a fatigued heart. Also as Katz and I pointed out the pattern of ventricular emptying is not solely governed by presystolic filling, but it is also affected by reduction in coronary flow.

Hearts stimulated or depressed by drugs, chemical changes in the blood, or through nerve actions show similar variations. In a study of the dynamics of drug actions I pointed out in 1927 that the vigor and pattern of ventricular contraction and consequently its systolic discharge can be influenced (a) by agents which primarily affect the contractility of the myocardium as well as (b) by those which secondarily affect contractility through changes in initial tension or length such as are induced by alterations in venous return, arterial resistance, and heart rate. To the latter may be added hydrodynamic effects produced by such pathologic conditions as coronary insufficiency, valvular lesions, anomalous cardiovascular circuits, pulmonary vascular changes, and pericardial effusions. In short, the ventricles do not obey the “law of all or nothing” at any given degree of fiber stretch; their magnitude of response depends on the physiologic state of myocardial reactivity. Starling was certainly aware of the importance of the “condition of the heart muscle” but did not include this in phrasing the law of the heart. I would suggest therefore that in order to avoid ambiguity or misinterpretation the law of the heart be amended somewhat as follows:

“The law of the heart is thus the same as the law of muscular tissue generally, that the energy of contraction, however measured, is a function of the length of the muscle fiber” under equivalent states of responsiveness. Within recent years the operation of the law of initial length has seriously been questioned on the basis of studies of the human heart by catheterization techniques. We may predict with confidence that when we are able to overcome the technical difficulties that still impair the accuracy of pressure determinations in catheterization studies, a careful evaluation of results will demonstrate the validity of the law of cardiac performance. However, I predict that complete assessment of the regulation of cardiac performance is not likely to succeed from analyses of hemodynamic data during health and disease alone, because innumerable variables are bound to be concerned. The multiple factors which can separately influence the response of the myocardium at equivalent initial lengths must be submitted to intensive experimental studies of a basic sort. A wide new field awaits exploration. Nothing would give
me greater pleasure than to attack the many facets of this interesting problem. However, since I am approaching the end of my experimental career I can perhaps best serve the cause of cardiac research in exhorting a new generation of investigators to accept the challenge of their execution.

**Summary**

Three classic discoveries—by Bowditch in 1869, by Howell and Donaldson in 1884, and by O. Frank in 1895—laid the foundation for the basic laws which govern the regulation of ventricular responses. Years of further experimentation have not only shown that the mammalian heart operates according to these basic laws, but have also elucidated the many variables which sometimes obscure the evidence that these basic laws are important under normal and pathologic conditions.

In 1906, Y. Henderson evolved a law of uniformity of cardiac behavior which offered a geometric plan for roughly evaluating the relation of ventricular filling at different cycle lengths to systolic discharge and cardiac output; but his conclusion that the systolic discharge at any given heart rate cannot be increased above its normal value has not been supported by further studies.

In 1914 Straub and the writer independently reported experiments on mammalian hearts which appeared to show that the reactions of the mammalian ventricles to changes in venous return and arterial resistance harmonized with laws derived by Frank from studies on frogs' hearts. These experiments, like those of O. Frank, were unable to determine whether changes in presystolic pressure (initial tension) or volume (initial length) fundamentally regulate the degree of responsiveness, however measured. Shortly after the publication of these researches, Starling and his associates, on the basis of experiments on the heart-lung preparation which were highly suggestive but not quite conclusive, concluded that in the reaction of the heart to increased inflow and increased resistance, the only factor which constantly varies with the response of the ventricles is the volume of the heart, that is, the length of its muscle fibers. The law of the heart was thus reduced to the formula that "the mechanical energy set free on passage from the resting to the constricted state depends on the area of 'chemically active surfaces,' i.e., on the length of the muscle fibers." This basic concept has subsequently been validated by nearly all investigators.

In 1922 the writer and Katz delineated the detailed changes in the patterns of ventricular filling and emptying occasioned by alterations in venous return, arterial resistance and heart rate, and analyzed their relation to presystolic ventricular volume. It was concluded that Starling's interpretations required some modification. For instance, the rate and degree of ventricular filling are a resultant of the atrioventricular pressure gradient, the variable effect of atrial systole, and the time interval available for ventricular filling. Furthermore, these and subsequent studies by the writer have revealed that while the mode, duration, and extent of ventricular emptying are in a measure determined by the presystolic state of the myocardium, the initial contractile state is of great importance. These include such factors as coronary blood supply, humoral agents, and nervous actions on the ventricular muscle.

It is suggested that the operation of the law of initial length will also be found valid in the human heart under equivalent states of myocardial responsiveness.

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