STUDIES ON STARLING'S LAW OF THE HEART. III. OBSERVATIONS IN PATIENTS WITH MITRAL STENOSIS AND ATRIAL FIBRILLATION ON THE RELATIONSHIPS BETWEEN LEFT VENTRICULAR END-DIASTOLIC SEGMENT LENGTH, FILLING PRESSURE, AND THE CHARACTERISTICS OF VENTRICULAR CONTRACTION *

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Although 45 years have now elapsed since Starling's Linacre lecture on the "Law of the Heart Beat" (1), considerable controversy is still centered around the question of the applicability of this fundamental principle to the human heart. In several investigations the Starling concept has been examined by attempts to reproduce in man those experiments on the Starling heart-lung preparation in which its responses to acute changes in venous return were studied (2–6). In most of these investigations no consistent relationship between the filling pressure on the right side of the heart and the cardiac output was apparent. In experiments on the intact dog (7), Rushmer, Smith and Franklin have shown that the augmentation of cardiac work which accompanies muscular exercise is not associated with an increase in left ventricular dimensions. These experiments, when taken together with the observations on man (2–6), have cast considerable doubt on the hypothesis that the Frank-Starling mechanism is involved in the regulation of cardiac performance.

In the present investigation, portions of which have been presented in preliminary form elsewhere (8), attempts were made to examine, in a critical manner, the applicability of Starling's law of the heart to man. To accomplish this, it appeared necessary to relate the end-diastolic fiber length and the end-diastolic filling pressure to the characteristics of ventricular contraction under conditions in which substantial changes in ventricular filling take place. It also seemed desirable to make such observations with the heart functioning with a relatively constant level of circulating catecholamines and of sympathetic stimulation, in view of the importance of these factors on myocardial performance (9).

When the inflow of blood into the left ventricle is not impeded, most of the filling of this chamber occurs during the first portion of diastole, i.e., during the so-called rapid filling phase (10). When the heart rate is slow, this phase of the cardiac cycle is not encroached upon, diastasis is present (11, 12), and changes in the duration of diastole do not profoundly modify ventricular filling. In patients with mitral stenosis, the obstruction to left atrial emptying prevents the left ventricle from filling rapidly during early diastole (12). Accordingly, it might be anticipated that in patients with mitral stenosis, and irregular ventricular rates due to atrial fibrillation, at any given left atrial pressure, beat-to-beat variations in the filling of the left ventricle take place due to alterations in the duration of the filling period. It was considered that if Starling's law of the heart operated in patients with mitral stenosis, the characteristics of each left ventricular contraction should appear to be a function of the previous end-diastolic fiber length or end-diastolic pressure, i.e., beats evidencing a relatively great force of ventricular contraction should be preceded by greater end-diastolic fiber lengths and filling pressures than beats evidencing a relatively smaller force of ventricular contraction. On the other hand, if Starling's law did not operate in these patients, then no clear relationship should be evident between ventricular end-diastolic fiber length or end-diastolic pressure and the characteristics of the subsequent contraction.

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METHOD

A total of 30 adult patients with atrial fibrillation who had rheumatic mitral stenosis of sufficient severity to require mitral valvulotomy were studied. In 26 patients observations were made in the course of the operation, which was carried out under nitrous oxide-oxygen anesthesia after induction with thiopental. In 13 patients the length of a segment of left ventricular muscle was continuously recorded by means of the mercury-filled resistance gauge described by Whitney (13) (Figure 1); this gauge has been extensively employed by Rushmer for the measurement of ventricular dimensions in the dog (14), and its physical properties have been described in detail by Lawton and Collins (15). After the chest had been opened, and prior to the valvulotomy, the gauge was sewn to the surface of the left ventricle between its apex and base in such a manner that the sutures avoided the coronary arteries and their main branches (Figure 1). After these recordings had been obtained the gauges were removed from the heart and calibrated by determining the deflection which resulted from known changes in the length of the gauge. In several instances the absolute length of the mercury column could not be measured and only the effects of changes in the length of the gauge were determined.

Alterations in the length of the segment of myocardium to which the two ends of the gauge were sewn modified the length of the rubber tubing and therefore of the column of mercury, thereby changing the electrical resistance offered by the gauge. Thus, the gauge could be utilized to record continuously the length of the segment of myocardium to which its two ends were sewn. Although it is now well established that the contours of the recordings of various dimensions in any given ventricle obtained simultaneously are not identical (16–18), any directional change in one end-diastolic dimension is generally accompanied by a similar directional change in other dimensions of the same ventricle (16, 17).

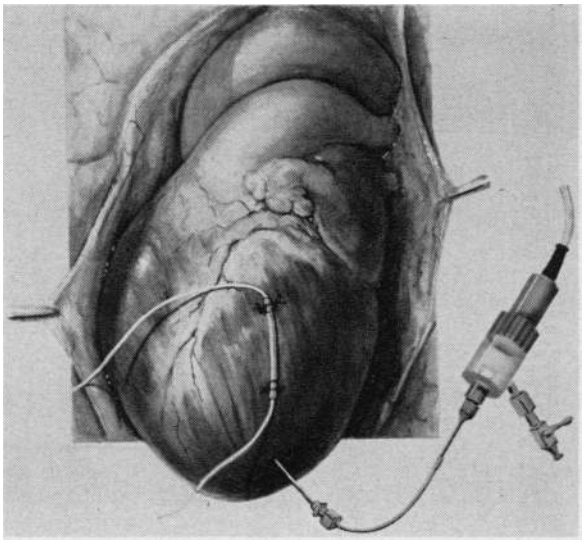

FIG. 1. DRAWING OF THE HEART AS VIEWED IN THE COURSE OF A LEFT THORACOTOMY. The mercury resistance gauge has been sewn to the surface of the left ventricle and left ventricular pressure is measured by means of direct ventricular puncture.

Left ventricular pressures were recorded simultaneously with the segment length in 13 patients (Figure 2) and were obtained without the segment length in an additional 13 patients. The left ventricular pressure was measured by direct puncture with a no. 20 gauge needle which was attached either directly or through a wide-bore nylon connecting tube to a Statham P23D pressure transducer (Figure 1); the baseline for these pressure measurements was the level of the left ventricle and, since the

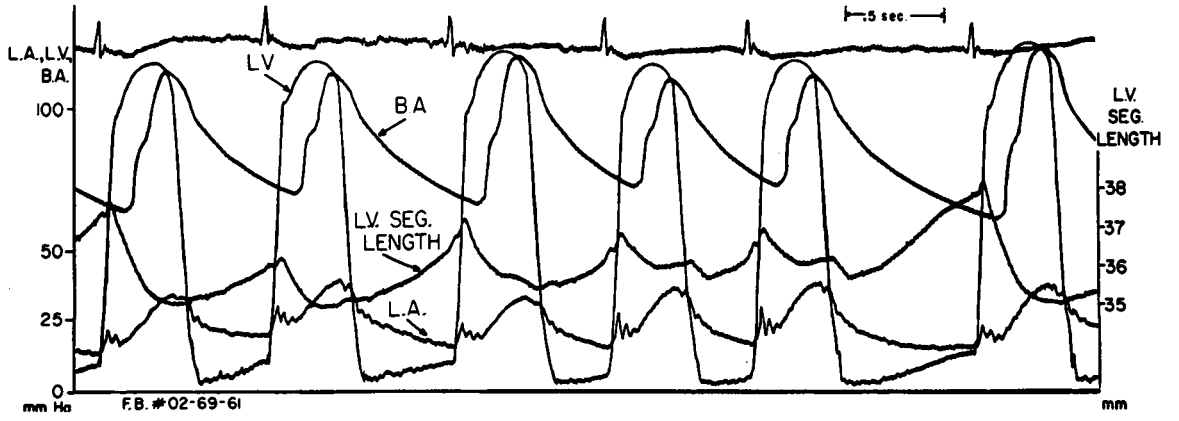

FIG. 2. TYPICAL SIMULTANEOUS RECORDING OF THE ELECTROCARDIOGRAM, LEFT VENTRICULAR (LV), BRACHIAL ARTERIAL (BA) AND LEFT ATRIAL (LA) PRESSURE PULSES AS WELL AS OF LEFT VENTRICULAR SEGMENT LENGTH (LV SEG. LENGTH). It is evident from inspection that the last beat of this tracing is characterized by a greater end-diastolic pressure and segment length than are the preceding beats, and that the peak systolic ventricular pressure, the brachial artery pulse pressure, the duration of systole, and the area beneath the systolic pressure curve are all also greater than in the other beats.

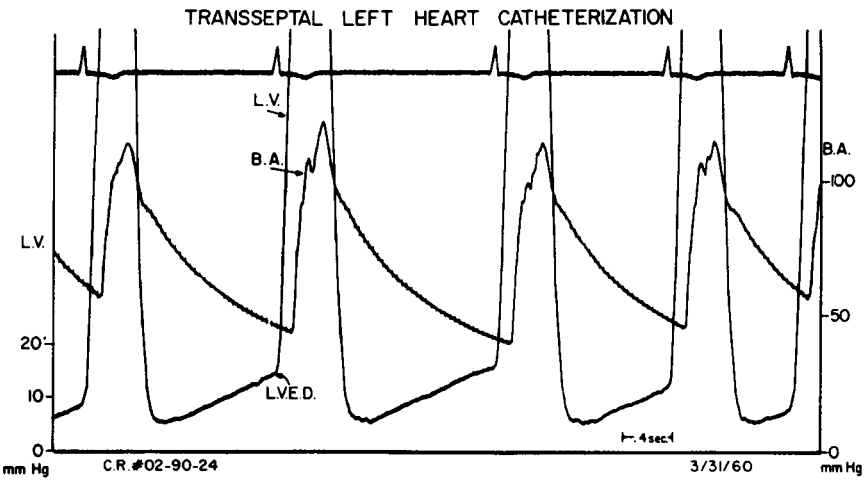

FIG. 3. SIMULTANEOUS LEFT VENTRICULAR (LV) AND BRACHIAL ARTERIAL (BA) PRESSURE PULSES IN A PATIENT WITH PREDOMINANT MITRAL STENOSIS AND ASSOCIATED AORTIC REGURGITATION. These pressure tracings were obtained at left heart catheterization during a time interval when the breath was held. The LV pressure tracing has been amplified in order to increase the accuracy of the measurement of left ventricular end-diastolic pressure (LVED).

pleural cavity and pericardium were open, the recorded pressure is taken as the "effective" left ventricular pressure.

Observations were also carried out on four patients with mitral stenosis and atrial fibrillation who were unanesthetized and intact (Figure 3). Left ventricular pressure was measured through a polyethylene catheter (PE no. 50) at the time of transseptal left heart catheterization (19). In order to avoid the interfering effects of respiration on the "effective" left ventricular pressure, observations were made only on a series of beats which were recorded while the breath was held. The baseline

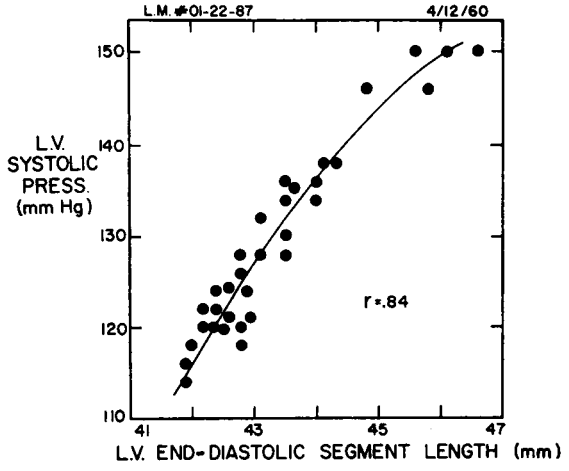

FIG. 4. GRAPH DEPICTING A REPRESENTATIVE RELATIONSHIP BETWEEN THE LEFT VENTRICULAR (LV) END-DIASTOLIC SEGMENT LENGTH AND THE SYSTOLIC PRESSURE OF THE SUBSEQUENT BEAT. Each point represents a single beat.

for these pressures was 5 cm below the sternal angle and although the pressure recorded in this fashion undoubtedly differs slightly from the true "effective" or transmural left ventricular pressure, any *changes* in the latter are reflected accurately in the recorded pressure.

In all 30 patients, systemic artery pressure was recorded from the brachial artery through an indwelling needle attached to a Statham P23D transducer through a nylon connecting tube. All recordings were made on a multi-channel photographic recorder.

Each ventricular contraction was assessed by making four measurements. First, the peak systolic ventricular pressure, a measurement utilized to provide an index of the peak tension developed by the left ventricle, was recorded. Second, the area beneath the entire systolic portion of each left ventricular pressure pulse was obtained by planimetric integration; this permitted calculation of the tension-time index (TTI) for each beat as described elsewhere (20). In these previous studies, the TTI, which is related to the total tension developed by the left ventricle, had been shown to be the hemodynamic determinant of myocardial oxygen consumption. Third, the duration of the tension state was determined by measuring the time interval between the onset of the isometric contraction of the left ventricle and the closure of the aortic valve. Fourth, the brachial artery pulse pressure was determined; changes in this parameter were considered to indicate directional changes in stroke volume (21, 22) and, therefore, directional changes in the extent of shortening of the myocardial fibers.

RESULTS

Analysis of a series of consecutive beats revealed that in any given patient a significant cor-

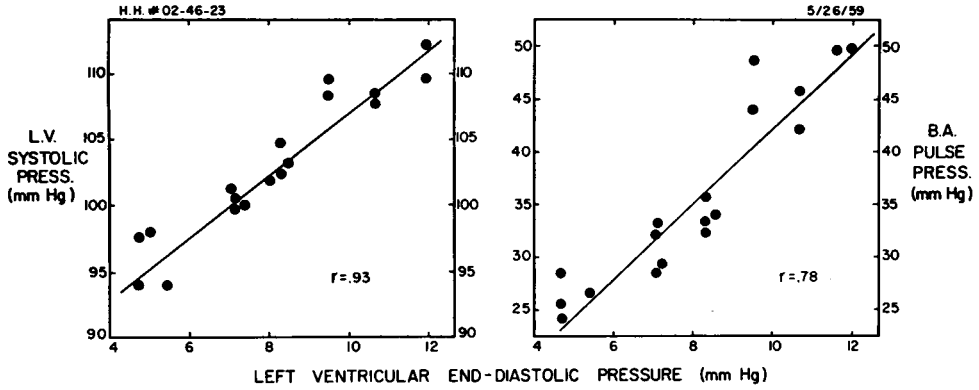

FIG. 5. A REPRESENTATIVE RELATIONSHIP BETWEEN LEFT VENTRICULAR END-DIASTOLIC PRESSURE AND THE SYSTOLIC PRESSURE (LEFT PANEL) AND ARTERIAL PULSE PRESSURE (RIGHT PANEL) OF THE SUBSEQUENT BEAT. Data obtained at the time of operation. Each point represents a single beat and the same series of beats are plotted on both panels.

relation was evident between both the left ventricular end-diastolic segment length (LVEDSL) and left ventricular end-diastolic pressure (LVEDP) and the peak pressure developed by the left ventricle during its next contraction (Figures 4 and 5). Similar correlations between LVEDSL and LVEDP and the TTI (Figure 6), the duration of systole (Figure 7), and the systemic arterial pulse pressure (Figures 5 and 8) of the following beat were also evident. The correlations between the four parameters utilized to characterize ventricular contraction and the LVEDSL, which are illustrated in Figures 4, 6, 7 and 8, are similar to those noted in all 13 patients so studied. The correlations illustrated in Figures 5, 6 and 7 are typical of those observed between LVEDP and the characteristics of ventricular contraction in all but one (Figure 9) of the 26 patients studied at operation. The close correlations between LVEDP and the characteristics of the subsequent contraction, which were evident in the tracings obtained from patients studied at operation, were also present in all four patients studied at the time of transseptal left heart catheterization (Figures 10 and 11).

Since all four parameters of the pressure pulses which were utilized to assess the strength of left ventricular contraction correlated well with both

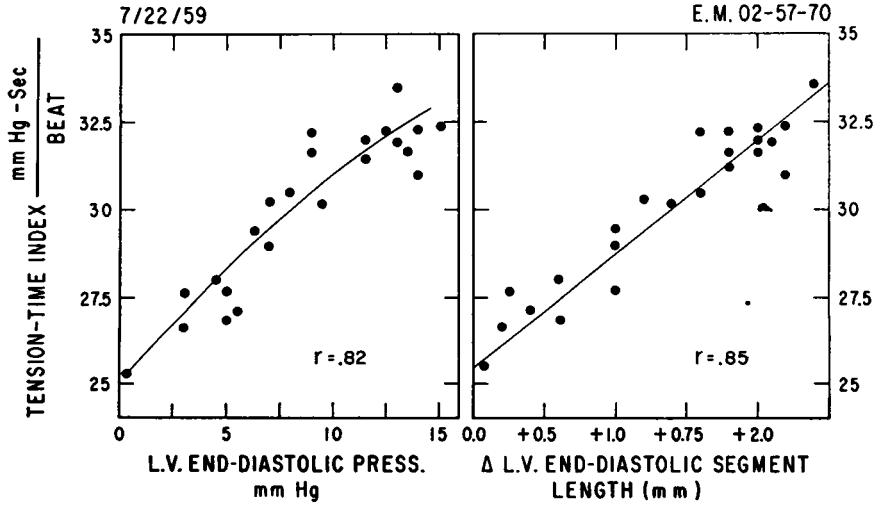

FIG. 6. A REPRESENTATIVE RELATIONSHIP BETWEEN THE TENSION-TIME INDEX AND THE LV END-DIASTOLIC PRESSURE (LEFT PANEL) AND CHANGES IN THE LV END-DIASTOLIC SEGMENT LENGTH (RIGHT PANEL).

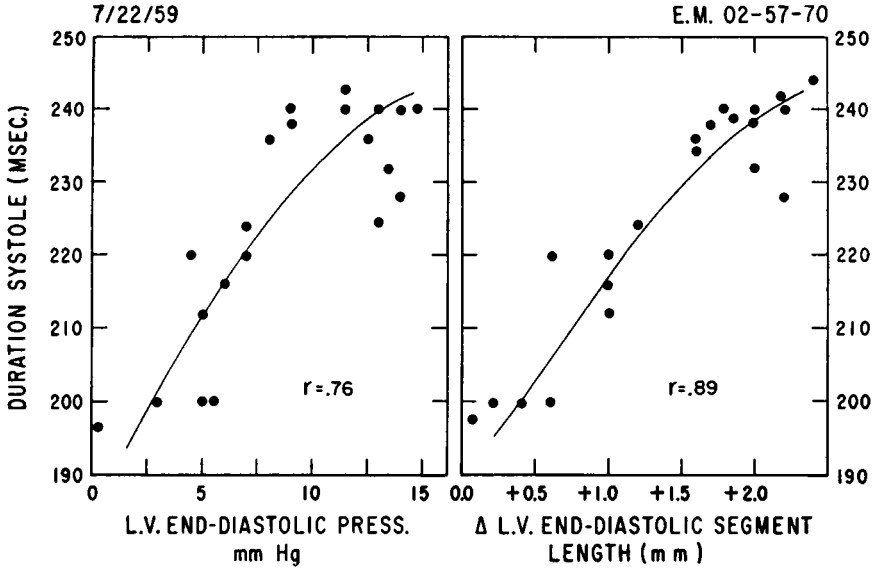

FIG. 7. A REPRESENTATIVE RELATIONSHIP BETWEEN THE DURATION OF SYSTOLE AND LV END-DIASTOLIC PRESSURE (LEFT PANEL) AND CHANGES IN LV END-DIASTOLIC SEGMENT LENGTH (RIGHT PANEL).

the preceding LVEDSL and the LVEDP, it was anticipated that the LVEDSL and LVEDP would, in turn, correlate well with each other. This indeed was the case (Figure 12) in all but one patient (M.L.), in whom unusually large variations in the duration of the ventricular filling period occurred, with some beats following a very brief ventricular filling phase. In this patient it was observed that at any given level of EDP the EDSL was shorter when the duration of filling was less than 0.23 second than when the duration of filling exceeded 0.23 second (Figure 9). In five other patients occasional beats followed filling periods less than 0.20 second; in these beats the EDSL which was observed was shorter than would be anticipated, for the EDP which obtained.

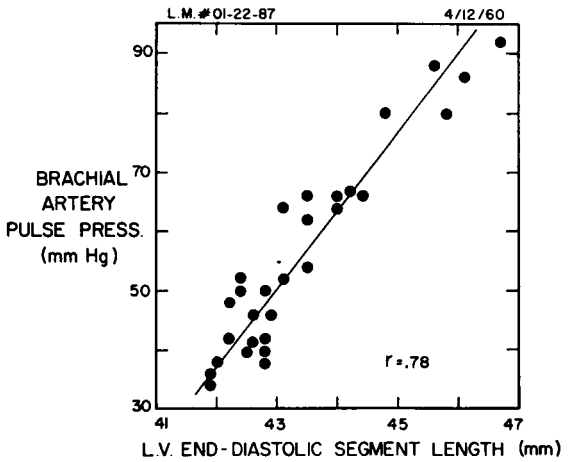

FIG. 8. TYPICAL RELATIONSHIP BETWEEN LV END-DIASTOLIC SEGMENT LENGTH AND THE PULSE PRESSURE OF THE SUBSEQUENT BEAT.

The inconstant relationship between EDSL and EDP in Patient M.L. made it possible to determine which of these two parameters was more closely related to the characteristics of the subsequent contraction. On the left panel of Figure 13 is shown the relationship between LVEDSL and left ventricular systolic pressure in four beats, all of which originated from the same LVEDP (7.5 mm Hg). On the right panel of Figure 13, is shown the relationship between EDP and left ventricular systolic pressure in four beats, all of which originated from the same LVEDSL. It is apparent that alterations in LVEDSL at a constant LVEDP modified the subsequent left ventricular systolic pressure, while changes in LVEDP at a constant LVEDSL did not appear to alter the subsequent left ventricular systolic pressure.

DISCUSSION

The mechanism responsible for the variations in the amplitude of the systolic pressure which occur in atrial fibrillation has been a subject of interest since the description of this arrhythmia

(23). In 1915, Einthoven and Korteweg analyzed the indirect carotid pulse tracings obtained from patients with atrial fibrillation and noted that the height of the systolic deflections varied directly with the duration of the preceding cardiac cycle, and inversely with the height of the previous diastolic pressure. They concluded that the lower diastolic pressure associated with a longer diastolic interval permits the subsequent ventricular contraction to be more forceful than the higher diastolic pressure associated with a shorter interval (24). In the same year, in a study carried out on dogs with experimentally produced atrial fibrillation, Wiggers found that those ventricular contractions which followed preceding beats by a relatively short time interval were characterized by a lower systolic pressure and a more gradual systolic rise than those contractions which followed longer diastolic intervals (25). Katz and Feil, in a study of indirect carotid pulse tracings obtained from patients with atrial fibrillation, observed that both the height of each pulse as well as its duration are functions of the length of the preceding diastole (26). These studies were later extended by Buchbinder and Sugarman who recorded systemic arterial pressure pulses directly (27), and correlated the peak systolic arterial pressure, the pulse pressure, and the duration of ejection with the duration of the preceding cardiac cycle.

More recently, Dodge, Kirkham and King carried out a comprehensive study of ventricular dynamics in patients with atrial fibrillation, and pointed out that the arterial pulse pressure and systolic pressure are functions of the duration of the preceding R-R interval, and of the amplitude of the preceding pulse (28). Utilizing electrokymographic recordings to indicate changes in

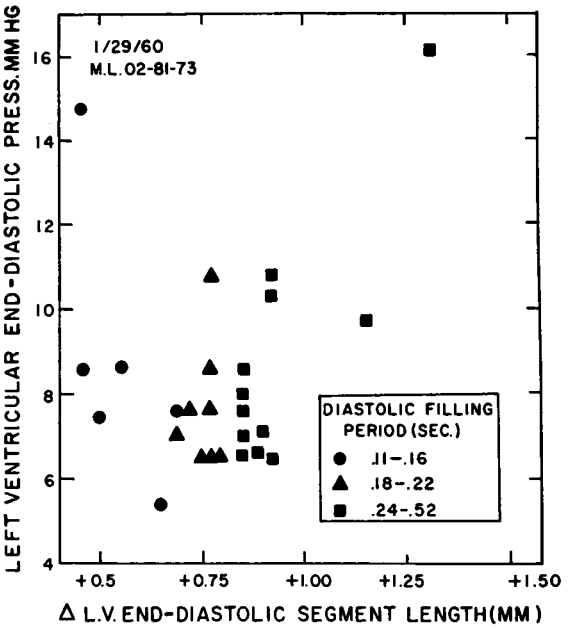

FIG. 9. RELATIONSHIP BETWEEN LV END-DIASTOLIC PRESSURE AND CHANGES IN END-DIASTOLIC SEGMENT LENGTH IN THE ONE PATIENT WITH SOME VERY BRIEF DIASTOLIC FILLING PERIODS.

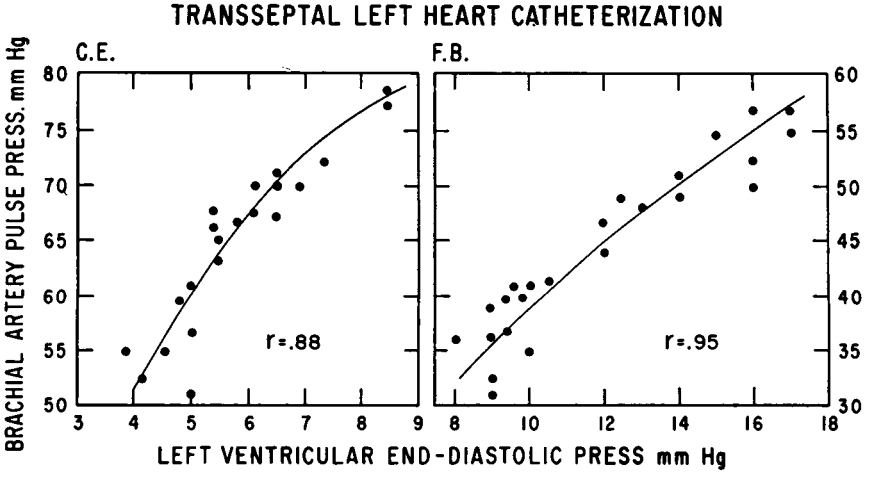

FIG. 10. TYPICAL RELATIONSHIP BETWEEN LV END-DIASTOLIC PRESSURE AND THE BRACHIAL ARTERY PULSE PRESSURE IN TWO PATIENTS STUDIED BY TRANSSEPTAL LEFT HEART CATHETERIZATION.

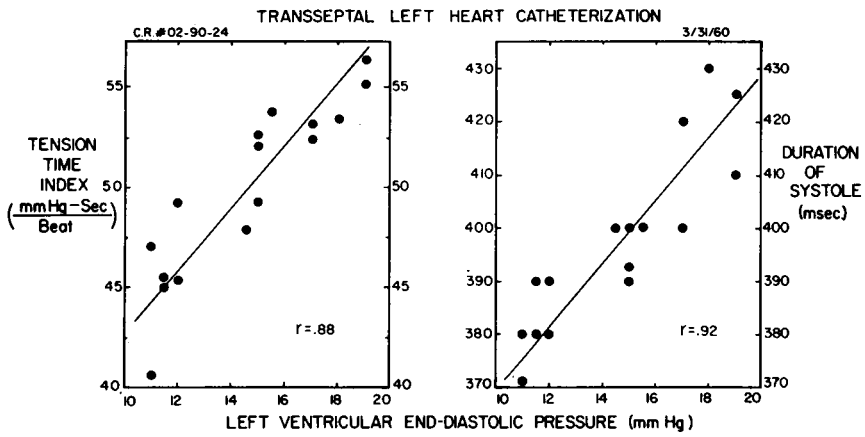

FIG. 11. TYPICAL RELATIONSHIP BETWEEN LV END-DIASTOLIC PRESSURE AND THE TENSION-TIME INDEX (LEFT PANEL) AND THE DURATION OF SYSTOLE (RIGHT PANEL). Data obtained at transseptal left heart catheterization.

ventricular volume, they confirmed the observations of Buchbinder and Sugarman (*27*) and also found an inverse correlation of the end-systolic "volume" with the height of the succeeding pressure pulse. Thus, a more forceful contraction resulted in a smaller end-systolic volume from which ventricular filling was initiated during the following diastole. These studies also provided evidence in support of the view that Starling's law of the heart operates in man.

In the present investigation, carried out on patients with mitral stenosis and atrial fibrillation, attention was focused on the relationship between the characteristics of each individual ventricular contraction and the segment length and pressure from which the contraction was initiated. It was evident from the studies carried out at the time of operation, that regardless of the manner in which the characteristics of ventricular contractions were assessed, *the left ventricular end-diastolic fiber length, as reflected by the left ventricular end-diastolic segment length, appeared to be a fundamental determinant of ventricular contraction.* Observations were then carried out on patients in the course of transseptal left heart catheterizations, in order to determine whether the close correlations between the characteristics of ventricular contraction and LVEDP, which were evident in the open-chest, anesthetized patients studied at operation, also exist in intact, closed-chest unanesthetized patients. The correlations between LVEDP and the characteristics of the subsequent ventricular contraction in the intact patients were similar to those observed in the patients studied at operation. Lauson, Bloomfield and Cournand have also demonstrated the essential features of Starling's law in patients in whom intrapleural and right ventricular pressures were recorded simultaneously (*29*). Although a regular cardiac rhythm was present in their patients, right ventricular filling was altered by respiration. A linear relationship was demonstrated between "effective" right ventricular end-diastolic pressure and the right ventricular systolic pressure of the subsequent beat.

Sarnoff and Berglund found no evidence of a descending limb in the ventricular function curves of open-chest dogs in which ventricular function

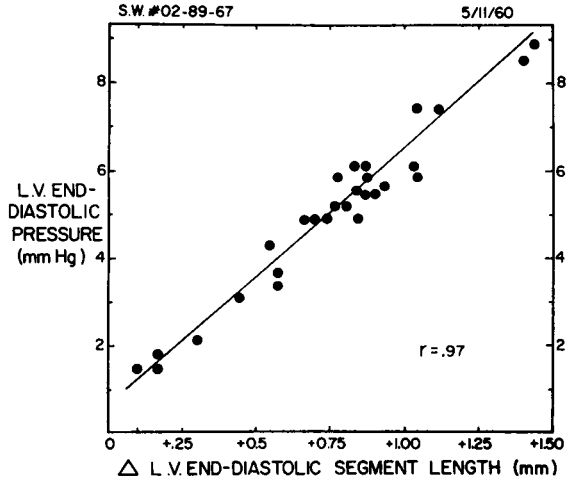

FIG. 12. TYPICAL RELATIONSHIP BETWEEN LV END-DIASTOLIC PRESSURE AND CHANGES IN END-DIASTOLIC SEGMENT LENGTH. Each point represents a single beat.

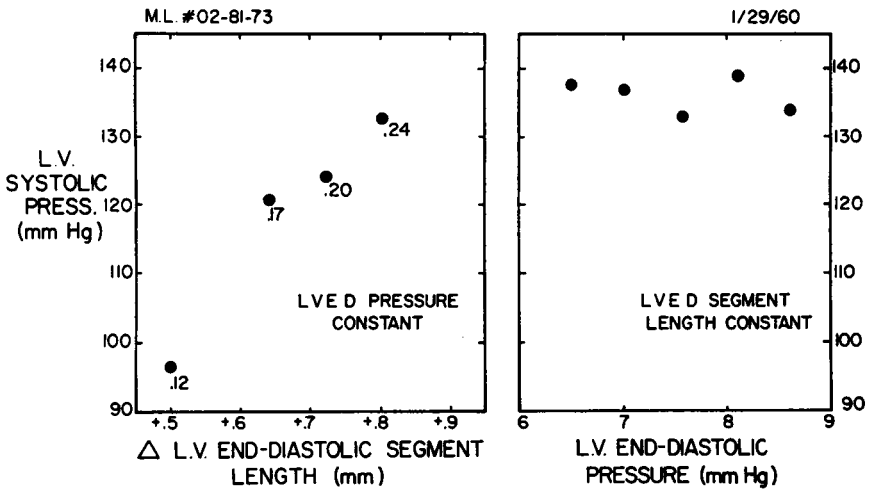

FIG. 13. DATA OBTAINED FROM THE SAME PATIENT WHOSE LV END-DIASTOLIC PRESSURE-SEGMENT LENGTH RELATIONSHIP IS PLOTTED IN FIGURE 9. The left panel illustrates the relationship between changes in LV end-diastolic segment length and LV systolic pressure in 4 beats, all of which had the same LV end-diastolic pressure. The figures to the right of each point represent the duration of the diastolic filling period in seconds preceding each beat. The right panel illustrates 5 other beats recorded from the same patient and depicts the relationship between LV end-diastolic pressure and LV systolic pressure. The LV end-diastolic segment length was identical in all 5 of these beats.

was not depressed (30). Similarly, in the present study, carried out in patients in whom left ventricular function was considered to be unimpaired, there was no instance of a descending limb of the curve relating LVEDSL or LVEDP and the four parameters utilized to characterize left ventricular contraction. It is possible that a descending limb would be evident if LVEDSL and LVEDP were elevated by an infusion. However, it is clear that at least within the range of end-diastolic pressures which obtain in the intact patient in the basal state, or in the anesthetized patient at the time of thoracotomy, the left ventricle appears to operate only on the ascending limb of its Starling curve.

The conclusion that the characteristics of each ventricular contraction are influenced by the preceding LVEDSL and LVEDP is based on a series of correlations which, of course, cannot prove the existence of a causal connection between LVEDSL or LVEDP and the characteristics of the subsequent contraction. The possibility that some other parameter which is the true determinant of ventricular contraction always correlates closely with LVEDSL or LVEDP cannot be excluded from these studies, nor from any of the classic observations which have led to the view that the length and tension existing in a muscle at the onset of contraction are important determinants of the character of the contraction (30–33). It is unlikely that the duration of the preceding diastole, per se, is the determinant of the characteristics of the subsequent ventricular contraction, since experiments performed on isolated cardiac muscle preparations indicate that the force of muscular contraction actually varies inversely with the duration of diastole (34, 35).

In the present investigation carried out on anesthetized, open-chest patients with mitral stenosis and atrial fibrillation, a linear relationship between LVEDP and LVEDSL was usually evident in the range through which these two parameters varied (Figure 12). It would therefore seem that under these conditions and in this range, the changes in effective EDP which occur in the course of a single series of beats may be used as an index of changes in end-diastolic segment length. However, it has long been suspected that changes in heart rate may alter the ventricular end-diastolic pressure-volume relationship (36). Indeed, in a recent study on the determinants of the left ventricular end-diastolic pressure-circumference relationship in the open-chest dog, it was observed

that at any given left ventricular end-diastolic circumference, the LVEDP was higher at rapid than at slower rates (37). When atrial fibrillation was induced, beats which were preceded by very brief R-R intervals were characterized by a greater EDP for any given end-diastolic circumference, than beats preceded by longer R-R intervals. These observations on the effects of heart rate, and similar ones on the effects of hypothermia, were thought to indicate that at the end of an abbreviated diastole ventricular relaxation may be incomplete, resulting in a greater LVEDP at any given left ventricular end-diastolic circumference (37). The data presented in Figure 9, on the one patient encountered in this investigation in whom the duration of diastole was sometimes strikingly abbreviated, confirm these experimental observations and extend them to man. It is of interest that in the present study, evidence was obtained in support of the view that the EDSL correlated better with the various indices of ventricular contraction than did the EDP (Figure 13), a position shared by Dodge and co-workers (28).

The observations reported herein were carried out on a series of consecutive beats which occurred in the course of less than 1 minute. It is possible that as a consequence of the beat-to-beat variations in baroreceptor stimulation, slight reflex alterations in myocardial contractility occurred (38), even during this short time period. It is possible that these alterations in contractility are responsible for the slight scatter which was observed between the LVEDSL or the LVEDP and the characteristics of the subsequent ventricular contraction. On the other hand, it would seem likely that substantial reflexly or humorally induced alterations in myocardial contractility occurred in those experiments in which infusions were utilized to study the applicability of Starling's law of the heart to man (2–6); these changes in contractility might well have obscured the underlying relationship between ventricular filling pressure and ventricular performance.

In a study recently carried out in this laboratory, the observation that the cardiac output and ventricular work fail to rise following the rapid transfusion of large volumes of blood into human subjects was confirmed (39); it was also demonstrated that the hypervolemia which was induced acutely was not accompanied by an augmentation of central blood volume. However, when the activity of the autonomic nervous system was reduced by means of ganglionic blockade with Arfonad (trimethaphan camphorsulfonate), augmentation of the total blood volume resulted in a substantial elevation of central blood volume as well as of cardiac output and ventricular work. It was suggested that in previous investigations on the effects of expansions of the blood volume, the applicability of Starling's law had not been tested adequately, since the presence of an intact autonomic nervous system may have actually prevented significant increases in the venous return to the heart. In other transfusion experiments, carried out on subjects under the influence of ganglionic blockade, it has been observed that ventricular stroke work varies directly with effective EDP (40). In this manner it has been possible to plot ventricular function curves (30) or "modified Starling" curves in man. In addition, the observations described in the present report indicate that under the conditions in which these observations were made and in which large changes in myocardial contractility do not occur, the characteristics of each individual ventricular contraction are closely related to the LVEDSL and LVEDP. Thus, both of these types of observations are consonant with the view that Starling's law operates in the human heart and is one of the important mechanisms which controls its function.

SUMMARY

The present investigation was designed to determine whether left ventricular end-diastolic segment length and end-diastolic pressure are important determinants of ventricular contraction. Systemic arterial pressure and effective end-diastolic pressure were measured at operation in 26 adult patients with rheumatic mitral valve disease and atrial fibrillation. Continuous alterations of the length of a segment of left ventricular muscle were recorded simultaneously in 13 of these patients by means of a mercury-filled resistance gauge sutured to the surface of the left ventricle. The variability of the duration of diastole resulted in beat-to-beat alterations of ventricular filling which resulted in variations of end-diastolic segment length and pressure. For each individual

beat the peak systolic ventricular pressure was utilized as an index of maximum tension developed; the area beneath the left ventricular pressure curve (tension-time index) was employed as a measure of the total tension developed. The systolic period indicated the duration of the tension state, and the systemic arterial pulse pressure was utilized to indicate relative changes in stroke volume. In every patient alterations in end-diastolic segment length correlated closely with all four parameters utilized to characterize ventricular function. In order to determine whether these relationships also exist in intact unanesthetized subjects, left ventricular end-diastolic pressure was determined by means of transseptal left heart catheterization in four patients. The correlations of end-diastolic pressure with systolic pressure, tension-time index, duration of systole, and arterial pulse pressure were similar to those obtained in the patients studied at operation. These results are consistent with the view that Starling's law of the heart operates in patients with mitral stenosis and atrial fibrillation on a beat-to-beat basis, and that end-diastolic segment length and end-diastolic pressure are important determinants of the characteristics of the subsequent ventricular contraction.

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