Studies on Starling’s Law of the Heart
Determinants of the Relationship Between Left Ventricular End-Diastolic Pressure and Circumference

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In experiments on the dog heart-lung preparation which led to the formulation of the well-known “Law of the Heart,”1 Patterson, Piper and Starling2 observed that when cardiac work was augmented, ventricular volume sometimes increased in the face of a constant left ventricular end-diastolic pressure. These investigators concluded that the strength of myocardial contraction was a function of end-diastolic fiber length.1,2 Although this view is supported by the experiments of Kozawa,3 other investigators have concluded that the initial intraventricular tension4-10 or both the end-diastolic fiber length and the initial tension7-9 are responsible for the characteristics of the subsequent contraction.

In view of these divergent experimental results and the importance of a clear understanding of the operation of the Frank-Starling mechanism,10 a study was undertaken in the dog with a complete circulation of the relationship between the left ventricular end-diastolic fiber length, as reflected in left ventricular end-diastolic circumference, and left ventricular end-diastolic pressure. The investigations reported herein were designed to determine whether this relationship is always a constant one or whether it may be modified by alterations in heart rate, temperature, myocardial contractility, cardiac output and arterial pressure. These parameters were chosen for examination because with the exception of temperature they are frequently altered in situ, and it was therefore of interest to determine whether or not changes in these factors can influence the end-diastolic pressure-circumference relationship. The effects of changes in temperature were studied because, as indicated below, they helped to elucidate one of the mechanisms controlling the end-diastolic pressure-circumference relationship.

Recent observations have indicated that the area beneath the ventricular pressure curve, i.e., the tension-time index, is the hemodynamic determinant of myocardial oxygen consumption.11 Accordingly, the present experiments were also designed to permit examination of the relationship between the tension-time index and the left ventricular end-diastolic circumference. Preliminary reports of portions of this study have been presented previously.12-18

Methods

Twenty-seven experiments were performed on adult mongrel dogs, weighing 13 to 24 Kg. with an average weight of 17.8 Kg. Anesthesia was provided by a combination of morphine, chloralose, and urethane in a manner described previously.14 A left thoracotomy was performed, utilizing positive pressure respiration with 100 per cent oxygen. The heart was exposed through a left thoracotomy, and the pericardium was opened widely. Left ventricular pressure was measured by means of a large-bore (1.5 mm. I.D.) cannula, 7 mm. in length, which was introduced into the left ventricular cavity through the ventricular apex and attached directly to a Statham P23D pressure transducer.* The left ventricular pressure pulse recording was amplified, and usually only the diastolic pressure was recorded, permitting precise measurement of left ventricular end-diastolic pressure.

Left ventricular circumference was recorded continuously by means of the mercury-filled re-
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The gages provided measurements of the external circumference of that portion of left ventricular muscle which they surrounded, and they have been employed extensively by Rushmer for such measurement of left ventricular circumference.10 The gages were sewn around the base of the left ventricle, the right ventricle being excluded by placement of the gage within the cavity of the right ventricle next to the interventricular septum.16

At the completion of each experiment, the gage was excised and calibrated by recording the deflection resulting from stretching it to various known lengths. The physical characteristics and frequency response of these gages were recently described in detail by Lawton and Collins;17 in the present experiments their use was confined to the range in which they are linear. Aortic pressure, an electrocardiographic lead, left ventricular pressure, left ventricular circumference, and in 6 experiments systemic blood flow were recorded on a multichannel oscillograph (fig. 1).

To prevent coagulation an initial dose of 500 mg. of Mepesulfate and approximately 250 mg. per hour thereafter were administered. In 6 experiments bilateral cervical vagotomy was carried out. In 24 experiments heart rate was held constant or varied by means of a stimulating electrode sewn to the right atrium or right ventricle.

In 21 experiments central aortic pressure was measured by means of a catheter introduced via the femoral artery; in these experiments cardiac output was not recorded. Left ventricular end-diastolic pressure and circumference were altered by rapid infusions of 100 to 200 ml. of whole blood into the femoral vein or by bleeding similar amounts from the femoral artery. The blood was obtained from donor dogs and was thoroughly mixed with that of the experimental animal prior to the experimental period.

In 6 experiments a preparation similar to one described previously was utilized;18 this preparation permitted independent control of cardiac output and arterial pressure (fig. 2). The aorta was divided distal to the left subclavian artery and wide-bore cannulas were inserted into each segment. The blood flow was then diverted through an air-filled Starling resistance and a Shipley-Wilson recording rotameter10 into an open reservoir. The blood delivered into the reservoir was returned to the cannulated descending aorta and common carotid arteries by means of a roller-pump. The brachiocephalic and left subclavian arteries were then ligated. The recording rotameter thus measured total left ventricular output with the exception of coronary blood flow. Left ventricular output could be varied stepwise by modifying the output of the pump, which determined the rate of blood flow into the arterial tree and thereby the return of blood to the heart. Arterial pressure was controlled by varying the degree of inflation of the Starling resistance. Hypothermia and rewarming of the dog were accomplished by refrigeration or heating of a water bath surrounding the reservoir. The blood temperature was monitored by means of a thermistor probe inserted through a jugular vein into the superior vena cava.

Each point plotted on figures 3 and 5 to 9 represents the average of 6 consecutive values of left ventricular end-diastolic pressure and of circumference. Each experimental point represents the conditions which existed when the dog was in a steady or equilibrium state at least 1 minute after any given hemodynamic intervention. When after an intervention the left ventricular end-diastolic pressure rose at every level of end-diastolic circumference which was examined, the curve or line relating end-diastolic pressure to end-diastolic circumference was shifted toward the pressure axis. The tension-time index in mm. Hg seconds per minute was calculated from the area under the systolic portion of the left ventricular pressure curve, as described previously.11

Results

Heart Rate

The effect of changes in heart rate on the relationship between left ventricular end-diastolic pressure and end-diastolic circumference was examined in 13 dogs. Vagotomy had been performed in 3 of these dogs, and heart rate was controlled by means of an electric pacemaker sewn to the right atrium.
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Results of a typical experiment illustrating the relationship between left ventricular end-diastolic pressure and circumference for individual beats in an experiment in which atrial fibrillation had been produced. R-R refers to the time interval between consecutive R waves of the electrocardiogram.

In one of these 5 experiments the relationship between left ventricular end-diastolic pressure and end-diastolic circumference remained constant when the heart rate was permitted to slow spontaneously from 130/min. to 80/min. as the temperature was lowered from 35.0°C to 28.4°C. However, when the heart rate was re-elevated to 130/min. at 28.4°C, the left ventricular end-diastolic pressure was higher at any given end-diastolic circumference than it had been at 35.0°C.

In a sixth experiment the relationship between left ventricular end-diastolic pressure and end-diastolic circumference remained constant when the heart rate was permitted to slow from 177 to 75/min. as the temperature was lowered from 34.8 to 28.0°C.

Acute "Heart Failure"

In 6 dogs left ventricular contractility became impaired as the experiment was continued for several hours. This state of impaired contractility was characterized by progressive dilatation, i.e., an increased left ventricular end-diastolic circumference was required in order to maintain any given systemic arterial blood pressure. It was observed consistently that this form of myocardial failure was accompanied by a lower left ventricular end-diastolic pressure for any given level of end-diastolic circumference. A representative experiment is illustrated in figure 6.

Alterations in Arterial Pressure and Cardiac Output

In the 6 experiments in which systemic flow and arterial pressure could be controlled independently, the effect of alterations in arterial pressure and of cardiac output on the relationship between left ventricular end-diastolic pressure and end-diastolic circumference was studied. Cardiac output was first augmented at each of various levels of mean aortic pressure, and aortic pressure was then progressively elevated at a constant cardiac output. The dogs were vagotomized in 3 of the 6 experiments, but this maneuver did not
Results of a typical experiment illustrating the relationship between left ventricular end-diastolic pressure and circumference, first at the beginning of the experiment ("control") and after myocardial contractility declined several hours later ("failure").

It was observed in each experiment that the relationship between left ventricular end-diastolic pressure and end-diastolic circumference was not modified either by changes of aortic pressure or of cardiac output, i.e., changes in aortic pressure and cardiac output did not result in displacement of the points relating end-diastolic pressure to end-diastolic circumference. The results of a representative experiment are shown in figure 7.

In 4 experiments left ventricular end-diastolic circumference was held constant while aortic pressure and cardiac output were varied in opposite directions. End-diastolic pressure remained relatively constant and showed no systematic change (fig. 8).

Relationship Between Tension-Time Index and Left Ventricular End-Diastolic Circumference

In 3 experiments aortic pressure and cardiac output were varied in opposite directions. The magnitude of these changes was such that both left ventricular end-diastolic circumference and end-diastolic pressure changed in the same direction as the cardiac output. In each instance the changes in the end-diastolic circumference were directionally opposite to the changes in the tension-time index. The results of a representative experiment are reproduced in figure 9.

Discussion

The experiments reported herein were performed in the anesthetized dog with an open chest after some operative interventions. Although it is realized that the results of experiments performed under these conditions are not always identical to those obtained in...
the intact organism, the manipulations were necessary to provide precise control of each hemodynamic variable.

It was found that the elevation of heart rate above a critical level was associated with a higher left ventricular end-diastolic pressure for any given end-diastolic circumference. These observations on the effects of changes in heart rate are in agreement with the views of Katz,10 as well as with the findings of Ullrich, Riecker and Kramer21 on the ventricle contracting isometrically. These workers demonstrated a progressive elevation of end-diastolic pressure at any given end-diastolic volume as heart rate was increased. Our findings are also consonant with those of Buckley, Ogden, Linton and Sidky who demonstrated an augmentation of impedance to ventricular filling when the heart rate was increased.22,23 As has been indicated by Mitchell, Linden and Sarnoff,24 the inertia and viscosity of the myocardium during ventricular filling are capable of modifying the pressure-length relationships of ventricular fibers. It is clear that tachycardia abbreviates diastole significantly,25 and it would seem possible, as suggested by Möck,26 that at very rapid heart rates ventricular relaxation may not be complete at the onset of ventricular contraction; this could result in a change in the ventricular pressure-volume relationship with a greater end-diastolic pressure at any given end-diastolic circumference. The ob-

Figure 8
Results of a typical experiment in which mean aortic pressure and stroke volume were altered in opposite directions, while end-diastolic circumference (EDC) was held constant. EDP refers to end-diastolic pressure. Heart rate was constant at 146/min.

Figure 9
Results of a typical experiment in which mean aortic pressure and stroke volume were altered in opposite directions. T.T.I. refers to the tension-time index, EDC to end-diastolic circumference and EDP to end-diastolic pressure.

Circulation Research, Volume VIII, November 1960
to note that under both of these experimental conditions the left ventricular end-diastolic pressure increased at any given end-diastolic circumference. However, the left ventricular end-diastolic pressure-end-diastolic circumference relationship was not altered in the 2 experiments on hypothermia in which the heart rate was permitted to slow and in which the abbreviation of diastole was prevented. However, it is also possible that factors other than the mechanical one resulting from changes in the duration of diastole may modify the left ventricular end-diastolic pressure-end-diastolic circumference relationship when changes in heart rate or temperature are induced.

A number of the earlier investigators indicated that the resistance to ventricular ejection may modify the ventricular filling pressure-fiber length relationship. In addition to Patterson, Piper and Starling, Mansfeld and Hecht also observed that an increase in aortic pressure results in an augmentation of ventricular end-diastolic volume without any change in end-diastolic pressure. Kiese and Garan found that for any given increment of diastolic volume both left and right atrial pressures increased more when aortic pressure was elevated than when the stroke volume was increased. In contrast, Gollwitzer-Meier and Krüger reported that a smaller elevation of atrial pressure occurred when any given increment in diastolic volume was brought about by elevating aortic pressure than when the stroke volume was increased. However, in the present study no alteration of the left ventricular end-diastolic pressure-end-diastolic circumference relationship was noted when both aortic pressure and cardiac output were varied over wide ranges. When cardiac output was altered by varying the output of the pump, the perfusion pressure to which the carotid sinuses were subjected was also changed. Since it has been shown by Mitchell, Linden and Sarnoff that stimulation of the vagi and of the cardiac sympathetic does not modify the ventricular end-diastolic pressure-length relationship, it would appear unlikely that these alterations in carotid sinus perfusion pressure modified the results reported herein.

The difference in our results from those obtained by others may be related to the fact that the earlier workers measured the combined volume of both ventricles, while increased resistance to ejection was applied only to the left ventricle. The augmented coronary flow which this maneuver undoubtedly produced may well have resulted in a substantial, but unrecognized, increase in the stroke and end-diastolic volumes of both ventricles. In contrast, in the present study the circumference of only the left ventricle was measured. It should also be noted that the earlier investigators worked with heart-lung preparations rather than with animals with complete circulations. The heart-lung preparation always exhibits varying degrees of heart failure; the application of data derived under such conditions to the heart supported by its humoral and neurogenic stimuli has been questioned, and the alterations in the left ventricular end-diastolic pressure-volume relationships which the earlier investigators observed may perhaps be related to progressive failure of the heart. The results obtained from the preparation employed for the experiments reported herein cannot be considered to be representative of those obtained from an intact, unanesthetized dog. However, the hearts were stable for periods which exceeded 6 hours during which times they were capable of performing without dilatation levels of external work similar to those achieved by the resting intact dog.

In the present investigation an increased left ventricular end-diastolic circumference at any given end-diastolic pressure was demonstrated in the presence of a depression of myocardial contractility which occurred in the course of a single experiment. Similar conclusions have been derived from experiments in which skeletal muscle and the frog ventricle were subject to repeated stress. Kabat and Visscher also reported that when the tortoise ventricle fails spontaneously or when it is asphyxiated, it develops an increased fiber length for any given filling pressure. Our findings, however, are not consonant with those of Buckley and Zeig, who observed that when the dog's left ventricle fails acutely,
its compliance during diastole falls, while its impedance to filling is augmented.\textsuperscript{37} If, as in the acute experiments reported by others\textsuperscript{34-36,38} and those presented herein, an increase in ventricular extensibility occurs in clinical heart failure, the patient could actually benefit therefrom since the altered left ventricular end-diastolic pressure-volume relationship would tend to lower the ventricular filling pressure and, therefore, the atrial pressure which would occur at any given ventricular diastolic volume. Many of the clinical features of heart failure result from elevated atrial pressures, and any process which lowers these pressures would tend to ameliorate those manifestations. It has been shown that chronic heart failure may be associated with changes either in the structure\textsuperscript{39} or quantity\textsuperscript{40} of the contractile proteins, and it is also of interest that the physical properties of the ventricle are modified by acute depression of myocardial contractility.

In an extension of earlier studies on the relationship between ventricular end-diastolic volume and the strength of ventricular contraction,\textsuperscript{2} Starling and Visscher found that under all conditions which they examined, myocardial oxygen consumption ($\text{VO}_2$) was a function of diastolic volume.\textsuperscript{41} They also confirmed the findings of Anrep\textsuperscript{42} that when the heart was functioning well, its diastolic volume and therefore its $\text{VO}_2$ depended not on arterial pressure or on cardiac output but on the product of these 2 parameters, i.e., the external work. Thus, Starling and Visscher related myocardial $\text{VO}_2$ not only to diastolic fiber length, but also to the external work performed, provided cardiac function was well maintained. However, in contrast with this view a number of investigators\textsuperscript{31, 32, 43, 44} have shown that a given increase in the work of the heart produced by raising aortic pressure while maintaining cardiac output constant results in a greater increment of $\text{VO}_2$ than a similar increase in work achieved by raising cardiac output, i.e., the external mechanical efficiency rises significantly when cardiac output is increased but shows little change or even declines when aortic pressure is augmented.

These observations have recently been extended with the demonstration that myocardial $\text{VO}_2$ is not determined by the external work of the heart per se but that the primary hemodynamic determinant is the area beneath the systolic pressure curve, i.e., the tension-time index.\textsuperscript{11} In other studies\textsuperscript{18} it was shown that $\text{VO}_2$ is not dependent on ventricular end-diastolic pressure. Indeed, significant changes in $\text{VO}_2$ were observed at a constant left ventricular end-diastolic pressure, and it was suggested that if large changes in the ventricular end-diastolic pressure-volume relationship do not occur as a result of alterations in arterial pressure and flow, the observed data were not consonant with the view that myocardial $\text{VO}_2$ is determined by the end-diastolic volume.\textsuperscript{18} Thus, the finding, that (1) large changes both in arterial pressure and cardiac output do not modify the left ventricular end-diastolic pressure-end-diastolic circumference relationship (fig. 7) and (2) myocardial $\text{VO}_2$ is independent of left ventricular end-diastolic pressure,\textsuperscript{18} would not appear to be compatible with classic views.\textsuperscript{41}

Finally, since the tension-time index is determined primarily by the arterial pressure and is modified only slightly by the stroke volume,\textsuperscript{11} while the left ventricular end-diastolic circumference is a function both of arterial pressure and stroke volume, it might be predicted that there would be no consistent relationship between the tension-time-index and the end-diastolic circumference. This view is supported by those experiments in which arterial pressure and cardiac output were manipulated so that the tension-time index and the end-diastolic circumference actually varied in opposite directions (fig. 9). Thus, when these observations are viewed in the light of the constant relationship between the tension-time index and myocardial $\text{VO}_2$,\textsuperscript{11} they also appear to be inconsistent with the belief that myocardial $\text{VO}_2$ is a function of end-diastolic volume.

**Summary**

The relationship between left ventricular end-diastolic pressure and circumference was studied in 27 open-chest dogs, utilizing a mercury-resistance gage to measure left ventricle-
lar end-diastolic circumference. In 6 experiments aortic pressure, cardiac output and heart rate were varied independently. Tachycardia above a rate critical for each heart elevated left ventricular end-diastolic pressure for any given end-diastolic circumference. Hypothermia at a constant heart rate had a similar effect. The altered left ventricular end-diastolic pressure-end-diastolic circumference relationships resulting from tachycardia and hypothermia are believed to be related to the incomplete ventricular relaxation which occurs as the duration of diastole is enercoached upon. Acute, spontaneous heart failure was accompanied by an augmented left ventricular end-diastolic circumference for any given end-diastolic pressure, an effect which may be considered to reflect an increase in myocardial extensibility. The relationship between left ventricular end-diastolic pressure and end-diastolic circumference was not modified either by changes of aortic pressure or of cardiac output. There was no constant relationship between the left ventricular end-diastolic circumference and the tension-time index. Indeed, it was possible to manipulate aortic pressure and cardiac output so that these 2 parameters moved in opposite directions. These observations are not consonant with the view that myocardial oxygen consumption is primarily dependent on end-diastolic fiber length.

Summario in Interlingua
Le relation inter le tension termino-diastolico sinistro-ventricular e le circumference esseva studiate in 27 canes a thorace aperte, utilizante le calibrator a resistenza de mercuro pro mesurar le circumference termino-diastolico sinistro-ventricular. In 6 experimentos, le tension aorta, le rendimento cardiac, e le frequentia del corde esseva variate independentemente. Tachycardia in ultra de un limite eriti pro omne corde individual elevava le tension termino-diastolico sinistro-ventricular pro omne circumference termino-diastolico particular. Hypothermia con constant del frequentia cardiac habeva le mesmo effetto. Es opinate que le alterate relations inter le tension termino-diastolico sinistro-ventricular e le circumference termino-diastolico que resulta de tachycardia e de hypothermia es relacionate al incomplete relaxation ventricular occorrente in tanto que le duration del diastole es compromittite. Acute, spontane disfallimento cardiac esseva accompagnate de un augmento del circumference termino-diastolico sinistro-ventricular pro omne tension termino-diastolico particular. Il pare justificate considerar isto effetto como reflectente un augmento del extensibilitate myocardial. Le relation inter le tension termino-diastolico sinistro-ventricular e le circumference termino-diastolico non esseva modificate per alterationes del tension aortal e non per alterationes del rendimento cardiac. Esses trovate nelle constant relation inter le circumference termino-diastolico sinistro-ventricular e le indice de tension e tempore. De facto, il esseva possibile manipule le tension aortal e le rendimento cardiac de maniera quod isto duo parameetros se movera in direzione contrario. Iste constatationes non es in congruentia con le theese quod le consumption myocardial de oxygen depende primarimente del longor termino-diastolico del fibras.

References
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_Circ Res._ 1960;8:1254-1263
doi: 10.1161/01.RES.8.6.1254

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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/content/8/6/1254