Left Ventricular Performance at High End-Diastolic Pressures in Isolated, Perfused Dog Hearts

By R. G. Monroe, M.D., W. J. Gamble, M.D., C. G. LaFarge, M.D., A. Edalji Kumar, M.D., and F. J. Manasek, D.M.D.

ABSTRACT

In the isolated, blood-perfused heart of the dog, left ventricular developed pressure and developed mean wall stress were observed while the ventricle contracted at a constant, nearly isovolumic afterload and while end-diastolic pressure was raised to levels exceeding 100 mm Hg. Coronary perfusion pressure was maintained at the level of the peak systolic pressure. Dilatation of the mitral ring and consequent mitral regurgitation were avoided by left atrial plication. Normalized graphs of percent of peak developed pressure against end-diastolic pressure showed that developed pressure rose abruptly with diastolic pressure, peaked at a diastolic pressure of approximately 30 mm Hg, and declined 14.7% (±0.9 SE) at an end-diastolic pressure of 100 mm Hg. Likewise, developed mean wall stress rose abruptly with diastolic pressure, peaked at a higher diastolic pressure of approximately 50 mm Hg, and declined only 7.5% (±0.8 SE) from this peak at an end-diastolic pressure of 100 mm Hg. Similar findings were observed in hearts acutely depressed with propranolol. Electron micrographs showed sarcomere length to average 2.275 μm and 2.300 μm in ventricles fixed in diastole while subjected to pressures of 61 and 100 mm Hg, respectively, after potassium arrest, confirming the findings illustrated by the normalized graphs. These observations imply that in the isolated heart of the dog there is no loss of ventricular performance attributable to a descending limb of the Frank-Starling mechanism until the end-diastolic pressure exceeds 60 mm Hg and that this loss is minimal at diastolic pressures as high as 100 mm Hg.

ADDITIONAL KEY WORDS

sarcomere length supported heart
propranolol Frank-Starling developed pressure descending limb
isovolumic contraction mean wall stress ventricular circumference
developed tension

It is generally accepted that the tension developed by striated muscle during the active state is a direct function of its resting length up to a point at which a further increase in resting length is accompanied by a decrease in developed tension. Recent observers have shown both for cardiac and skeletal muscle strips that an increase in resting length is accompanied by a decrease in developed tension when the sarcomere is stretched beyond 2.2 μm and the H band appears (1-4).

In contrast to muscle strips, evidence for a descending limb of ventricular performance in the intact ventricle has been less consistent. Some observers have not been able to find a descending limb at left ventricular end-diastolic pressures far exceeding the physiological range (5-7). In addition, arguments have been presented which imply that the cardiovascular system can support the instability inherent in a descending limb for only a very short period of time and that such a
prolonged clinical state can hardly occur (8). Others have reported descending limbs of ventricular function at high but physiological end-diastolic pressures (9, 10). Still others have observed descending limbs of ventricular function with anemia, coronary constriction, absence of the pericardium, excessive myocardial edema, and inadequate coronary perfusion pressure (11-13).

An attempt, therefore, was made to examine the relationship between ventricular performance and end-diastolic pressure in an isolated heart preparation, looking specifically for that level of end-diastolic pressure at which performance was maximal and noting the extent to which performance declined at increasing end-diastolic pressures. When possible, ventricular performance was calculated in terms of mean wall stress so as to reflect the tension developed by the myofibril and, in the face of previously established relationships between developed tension and sarcomere length, incidently allow an ultrastructural confirmation of the physiological data obtained. It was believed that if peak ventricular performance could be reached only at very high end-diastolic pressures that exceeded physiological bounds, it would imply that the loss of ventricular performance normally associated with the descending limb of the Frank-Starling mechanism may well not occur in the healthy left ventricle.

**Methods**

**PREPARATION I—HEARTS WITH PERICARDIUM INTACT**

Hearts with lungs attached were rapidly excised from heparinized healthy mongrel dogs (18 to 25 kg) under chloralose (60 mg/kg) and urethan (900 mg/kg) anesthesia and perfused with blood from the femoral artery of a healthy, heparinized, anesthetized donor dog. The time from excision to perfusion was less than 4 minutes, during which the heart continued to contract. As illustrated schematically in Figure 1, the perfusing blood was directed retrograde into the ascending aorta using two parallel Debakey pumps and a small (20 cm$^3$) air chamber to ensure a relatively nonpulsatile perfusion pressure. A Starling resistance was used to maintain the pressure of the perfusing blood between 90 and 125 mm Hg. Accordingly, the valve shown adjacent to the Starling resistance on Figure 1 was kept open and the pump adjusted to maintain an adequate flow.
While the heart was being perfused, the pulmonary artery was cannulated and both venae cavae ligated so that the coronary sinus blood could be returned to the femoral vein of the donor via the pulmonary artery cannula. Two catheters were introduced into the left ventricle by way of the pulmonary veins so as not to disrupt the integrity of the pericardium. One was attached to a pressure transducer (Sanborn 267B) and allowed the continuous measurement of left ventricular pressure. The other was connected to the output of the perfusing pumps via the upper rotameter shown in Figure 1 and served to supply the ventricular cavity with a small flow of blood (approximately 1 ml/beat) which it ejected into the aorta.

While perfused in this manner the heart contracted at its intrinsic rate. As the donor was 100 cm lower than the heart, the right ventricle, which contained only the coronary venous blood, was kept empty by a continuously negative pressure. The left ventricle, on the other hand, contracted virtually isovolumically: the peak systolic ventricular pressure equalled the perfusion pressure and its end-diastolic pressure was that which the ventricle required in order to develop such a peak pressure.

The heart was immersed to the level of the coronary ostia and maintained at 39°C in a bath of normal saline, which also contained electrodes for recording the electrocardiogram. Perfusion pressure was monitored at the level of the coronary ostia with a pressure transducer (Sanborn 267B). The ECG, perfusion pressure, and ventricular pressure were continuously recorded on a Sanborn polyviso recorder. The surface of the saline in which the heart was immersed was the zero reference level for the pressure transducers.

**Preparation II—measurement of left ventricular circumference**

The preparation of hearts for measurement of left ventricular circumference was similar to that just described, with the following exceptions. After perfusion was established and the pulmonary artery cannulated, the pericardium was removed. Through an incision in the right atrium, the bundle of His and the A-V node were ligated and cauterized to ensure a complete heart block. Leads were sutured to the distal portion of the bundle of His, and ventricular rate was controlled with an electronic pulse generator. Through the right atriotomy, a plastic coated, stranded, stainless steel wire snare was positioned circumferentially around the outside of the left ventricle and septum at its maximum diameter (Fig. 1) and attached to a linear displacement transducer (Hewlett Packard—Linearsys 585 D.T.) capable of measuring 6 cm of linear displacement. Loose sutures were used to maintain the position of the snare, thereby allowing the transducer to monitor the outside diameter of the left ventricle continuously.

The right atrium was subsequently closed, and the left atrium plicated with heavy sutures to reduce its volume as much as possible and to reinforce the mitral ring. The outputs from the linear displacement transducer and the pressure transducers were recorded on the Sanborn polyviso recorder.

**Calculation of Left Ventricular Mean Wall Stress**

The formula used for the calculation of left ventricular mean wall stress was

$$s = \frac{Pr_i}{2h}$$

as applied to thick-walled spheres where $s =$ stress in g/cm$^2$; $P =$ pressure in g/cm$^2$; $r_i =$ ventricular internal radius in cm; $h =$ ventricular wall thickness in cm.

Internal radius ($r_i$) and wall thickness ($h$) were calculated in terms of measurements of circumference made by the snare described earlier using the relationships

$$r_i = \sqrt{\frac{(Cd)^2 - (Ce)^2}{2\pi}}$$

and

$$h = \frac{Cd}{2\pi} - r_i$$

where $Cd$ was the external circumference of the distended ventricle and $Ce$ the external circumference of the empty ventricle in centimeters.

To the extent that the ventricle departed from being a homogeneous, elastic hollow sphere, three assumptions must be discussed in connection with the method.

1. The total wall thickness of the empty ventricle could be measured by the snare when the ventricle was collapsed by a negative pressure.
2. Wall thickness would be evenly distributed as the ventricle was distended.
3. As the ventricle was distended, wall strain was equally distributed in directions tangential to the wall.

To test the validity of the first two assumptions, seven hearts were perfused as described and arrested with 5% potassium citrate. The left ventricle of each heart was then subjected to a pressure of either —20 mm Hg, +20 mm Hg, or +100 mm Hg by the withdrawal or infusion of blood. The hearts were next rapidly frozen by immersion in liquid nitrogen and subsequently sectioned at the equator and from apex to base in three planes roughly at right angles to each other.
Figure 2 is a photograph of the cut surface of three hearts in each of the three planes. The left, middle, and right columns contain photographs of hearts arrested and frozen, respectively, at —20 mm Hg, +20 mm Hg, and +100 mm Hg left ventricular intracavitary pressure. The photographs in the left column are offered as evidence that the ventricular cavity could be virtually obliterated by subjecting it to a negative pressure of —20 mm Hg, as implied in the first assumption, permitting the snare to measure the total wall thickness at the equator. The middle and right columns of the figure are offered as evidence supporting the second assumption that wall thickness is fairly evenly distributed as the ventricle is distended with intracavitary pressures exceeding +20 mm Hg. This assumption is hazardous, however, if the ventricle is distended...
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at lower pressures as may be inferred by a comparison of the left and middle columns of the figure.

The third assumption, that as the ventricle was distended, wall strain was equally distributed in directions tangential to the wall, was examined in seven perfused hearts. Four adjacent points on the ventricular epicardium were marked with black sutures (Fig. 3) and photographed during diastole as the end-diastolic pressure was increased from —20 to +100 mm Hg and while the hearts were contracting as described earlier. By comparing the distance between the horizontally and vertically aligned suture points and plotting this as a ratio \((H/V, \text{Fig. 3})\) against end-diastolic pressure, it was apparent that the ventricle expanded more horizontally than vertically when the end-diastolic pressure was increased from —20 mm Hg to +20 mm Hg. As the ventricle was distended with an end-diastolic pressure exceeding +20 mm Hg, however, it appeared to expand as a sphere, in that strain was equal in the two directions measured, thereby validating the third assumption within the stated limits. Greater credence, therefore, was placed on stress values obtained when the end-diastolic pressure exceeded +20 mm Hg in the studies subsequently described.

The relationship \(s = \frac{Pr^3}{2h}\) has been used previously in estimations of mean wall stress \((14, 15)\). This is a simplification of the relationship

\[ s = \frac{Pr^3}{r_0^3 - r_1^3} \left(1 + \frac{r_0^5}{2r_1^5}\right) \]

as applied by Sandler and Dodge in estimating the wall stress of thick-walled spheres \((16)\). As documented by the latter authors the percent error in the simplified relationship is small when the ratio \(h/r\) is small, a ratio that decreases with distention of the ventricle (Fig. 2). As the data here presented deal specifically with high end-diastolic pressure far exceeding the physiological range it was believed that the error caused by using the simplified relationship was small. Furthermore, as the stress values presented here were developed stress (systolic minus diastolic stress) the error would be even less.

PREPARATION OF THE MYOCARDIUM FOR ELECTRON MICROSCOPY

As a parallel study, an attempt was made to correlate the data obtained in estimates of mean wall stress with the ultrastructure of the sarcomere. For this, the heart was arrested with a perfusion of 5% potassium citrate while the selected ventricular pressure was maintained. From each heart, small (0.5 mm) cubic blocks of ventricular tissue were removed from the middle of the left ventricular wall beneath the snare at the level of its maximum circumference. These were rinsed in ice-cold 0.1M cacodylate buffer (pH 7.4) for 30 minutes, and immersed in ice-cold 1.0% osmium tetroxide in .05M cacodylate buffer for 90 minutes. The blocks were subsequently dehydrated with increasing concentrations of ice-cold ethyl alcohol for 1 hour and finally raised to room temperature in absolute alcohol. They were then transferred to absolute alcohol 50% saturated with uranyl acetate, given a final brief rinse with fresh absolute alcohol, and immersed in propylene oxide for 2 hours, during which the propylene oxide was changed several times. All blocks of tissue were immediately processed past the propylene oxide stage and stored overnight in a mixture of 3% propylene oxide and 3% Araldite. Within 48 hours the tissue blocks were embedded in Araldite and later sectioned with diamond knives. Sections were mounted on uncoated copper grids, stained with lead citrate, and examined with either a Hitachi HU-11E or RCA EMU-3 electron microscope operated at 50 kv.

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Results

I. VENTRICULAR PERFORMANCE WITH THE PERICARDIUM INTACT

In five hearts, perfusion was arranged for hearts with an intact pericardium as described under Methods. For a short period of stabilization (10 to 20 minutes) the left ventricle was allowed to contract virtually isovolumically while the perfusion pressure was maintained between 80 and 100 mm Hg and the ventricle developed an equivalent systolic pressure. Periodically during this time, the ventricle was evacuated with a syringe through the catheter used for recording pressure. Invariably after doing so, it was found that when the end-diastolic pressure was made distinctly negative, the systolic pressure was likewise negative. This is illustrated in Figure 4, which shows a recording of ventricular pressure as the ventricle is slowly filling after having been evacuated.

Further observations were confined to the study of ventricular performance at positive end-diastolic pressures. By closing the valve adjacent to the Starling resistance illustrated in Figure 1 and increasing the capacity of the pump, the perfusion pressure as well as the end-diastolic and systolic pressure gradually increased while the ventricle continued to contract almost isovolumically, ejecting approximately 1 ml/beat. As soon as the end-diastolic pressure exceeded 100 mm Hg, the valve adjacent to the Starling resistance in Figure 1 was opened and the ventricle decompressed. An example of the ventricular and perfusion pressure recordings obtained during this maneuver may be found in the second and third panels of Figure 5.

Using data from high speed recordings of the ventricular pressure as shown in the second panel of Figure 6, the pressure developed by the ventricle (systolic minus end-diastolic) could be plotted against end-diastolic pressure when the perfusion pressure was increased in the manner described above. An example of such a graph of developed pressure against end-diastolic pressure may be found in Figure 7, together with stress graphs described subsequently.

Seventeen graphs of developed pressure against end-diastolic pressure were obtained in the five hearts studied with intact pericardia. These were normalized by plotting the percent of peak developed pressure at various end-diastolic pressures against end-diastolic pressure, as shown in Figure 8. In all these hearts, as illustrated in Figure 4, the developed pressure was zero when the end-diastolic pressure was zero or slightly negative.

From the curve shown in Figure 8, it is evident that the pressure developed by ventricles with intact pericardia increased rapidly from an end-diastolic pressure of zero and reached its maximum, on the average, at an end-diastolic pressure of approximately 60 mm Hg. As the end-diastolic pressure was increased from 60 to 100 mm Hg there was only a very slight decrease from the maximal developed pressure that averaged 5.2% (±1.3 SE).

II. VENTRICULAR PERFORMANCE AFTER REMOVAL OF THE PERICARDIUM

Twelve hearts were studied without pericardia to determine the extent to which the pericardium might restrain an enlarging ventricle and thereby avert a decrease in develop

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**Figure 4**

Recording of left ventricular and perfusion pressures of isolated heart following evacuation of ventricle. Base-line ventricular pressure (left) is recorded while ventricle is evacuated through catheter recording pressure. Ventricle gradually fills through arterioluminal channels until systolic pressure equals perfusion pressure. Note negative systolic pressure when diastolic pressure is negative and, subsequently, positive systolic pressure when diastolic pressure is positive. Baseline time marker indicates seconds.
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In this series the hearts were prepared as described in preparation II under Methods. A short period of stabilization was again allowed as for hearts with intact pericardia. Furthermore, upon evacuation of the ventricle with a syringe, the same findings were observed as illustrated in Figure 4—the systolic pressure was zero when the diastolic pressure was zero or slightly negative and the ventricle developed a negative pressure at more negative end-diastolic pressures.

Using the same technique of increasing the perfusion pressure used in hearts with intact pericardia, 66 graphs were made of developed pressure against end-diastolic pressure in the 12 hearts. These were normalized as before, by plotting percent of peak developed pressure against end-diastolic pressure, as shown in Figure 9. Here it can be seen that the pressure developed by ventricles without pericardia peaked at approximately 30 mm Hg end-diastolic pressure and, with further increases in diastolic pressure, declined at a steeper rate than ventricles with intact pericardia. In the hearts without pericardia, the pressure developed by the ventricle declined 14.7% (±0.9 se) from its peak when distended with an end-diastolic pressure of 100 mm Hg.

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studied in the previous section, where the relationship between developed pressure and end-diastolic pressure was examined, and graphs were drawn of systolic stress, diastolic stress, and developed stress against end-diastolic pressure. Figure 7 is an example of such a graph, where the diastolic stress and systolic stress rise fairly steadily with the end-diastolic pressure while developed stress rises rapidly at low end-diastolic pressure and tends to flatten at the high end-diastolic pressures. As in the previous section, a composite curve describing the relationship between developed stress and end-diastolic pressure in all these studies was obtained by plotting percent of peak developed stress against end-diastolic pressure (Fig. 9). In this figure, where percent of peak developed pressure and stress are plotted and compared, the curve obtained for stress had a somewhat less abrupt rise than that for developed pressure and less of a descending limb. As seen in the figure, the developed stress curve peaked at an end-diastolic pressure of approximately 50 mm Hg and thereafter declined only 7.5% (± 0.8 SE) of its peak value when the ventricle was distended with an end-diastolic pressure of 100 mm Hg.

**IV. LEFT VENTRICULAR MEAN WALL STRESS IN ACUTELY DEPRESSED HEARTS**

Six additional hearts were prepared for the measurement of mean wall stress (preparation II) and subjected to the sequential increases in perfusion pressure described previously while left ventricular pressure and circumference were continuously recorded. Sufficient data were obtained to plot 17 graphs of developed pressure, systolic stress, diastolic...
stress, and developed stress against end-diastolic pressure both before and after the infusion of propranolol. After the control data were obtained, propranolol was infused into the coronary circulation at the rate of 0.34 to 2.18 mg/min while the perfusion pressure was maintained constant and the ventricle developed a systolic pressure equal to the perfusion pressure. When the systolic pressure was maintained constant in this manner, a loss of contractility was indicated by an increase in the end-diastolic pressure, as illustrated in Figure 10. In the six hearts, propranolol was infused until the end-diastolic pressure rose 5 to 8 mm Hg. The infusion was then reduced to one-tenth of its rate to insure maintenance of its effect, and the measurements of pressure and estimates of stress were again obtained during the sequential increases in the perfusion pressure. As in the previous studies, curves of percent of peak developed stress plotted against end-diastolic pressure were drawn for the six hearts both before and after the infusion of propranolol.

After the infusion of propranolol the circumferences of the depressed ventricles were not significantly different from their control circumferences when compared at equivalent end-diastolic pressures. At an end-diastolic pressure of 100 mm Hg, evidence of continued depressed performance was indicated by the developed stress of the depressed ventricles, which ranged from 45% to 85% of the control value (average 63.5%).

The control curves obtained by plotting percent of peak developed stress against end-diastolic pressure prior to the infusion of propranolol peaked at an end-diastolic pressure of approximately 60 mm Hg and thereafter declined an average 6.1% (± 0.9 se) at an end-diastolic pressure of 100 mm Hg (Fig. 11). The curves obtained after the hearts were depressed peaked at an end-diastolic pressure of approximately 70 mm Hg and then declined 6.6% (± 5.0 se) at an end-diastolic pressure of 100 mm Hg, implying that after acutely depressing the hearts, the relationship between percent of peak developed stress and end-diastolic pressure was not significantly altered. The relatively larger standard error of the mean found after administration of propranolol was attributed to difficulties in maintaining a steady state in the acutely depressed hearts after the initial infusion.

V. CORRELATION OF LEFT VENTRICULAR MEAN WALL STRESS WITH SARCOMERE LENGTH

In view of the findings discussed in the previous sections, an attempt was made to correlate sarcomere length with end-diastolic pressure in eight experiments. In four of these, each heart was prepared as described under...
Methods (preparation II) and subjected to sequential increases in perfusion pressure until the end-diastolic pressure reached 100 mm Hg while ventricular pressure and circumference were recorded, as described under section II of Results. The hearts were then arrested with 5% potassium citrate and fixed with 3.3% glutaraldehyde at an end-diastolic pressure of 61 mm Hg (± 1) as described under Methods. Four additional hearts were fixed at an end-diastolic pressure 100 mm Hg (± 1) after first being studied during the sequential increases in the perfusion pressure. After fixation, blocks of tissue were obtained from the midwall of each ventricle at its maximal circumference, the portion underlying the snare. The tissue was further processed as described in Methods, and electron micrographs were obtained to permit measurement of sarcomere length.

Sarcomeres were measured from properly aligned sections, assuming the width of the A band to be 1.5μ throughout, thereby automatically correcting for the small error induced when the plane of section was not completely parallel to the sarcomere. A total of 1,487 sarcomeres were measured from the four

![Graph of frequency of distribution against sarcomere length in left ventricular myocardium of two groups of hearts fixed at indicated pressures. Solid vertical lines represent means and dashed lines, ± 1. Note average length of sarcomeres from ventricles fixed at 61 and 100 mm Hg is 2.275μ and 2.300μ, respectively.](http://circres.ahajournals.org/)

**TABLE 1**

<table>
<thead>
<tr>
<th>Experiment no.</th>
<th>Fixation pressure (mm Hg)</th>
<th>Sarcomeres measured</th>
<th>Mean sarcomere length (μ)</th>
<th>S.D.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Ventricles Fixed at 61 mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>428</td>
<td>61</td>
<td>258</td>
<td>2.259</td>
<td>0.091</td>
</tr>
<tr>
<td>430</td>
<td>61</td>
<td>390</td>
<td>2.295</td>
<td>0.122</td>
</tr>
<tr>
<td>432</td>
<td>61</td>
<td>332</td>
<td>2.287</td>
<td>0.094</td>
</tr>
<tr>
<td>429</td>
<td>61</td>
<td>507</td>
<td>2.261</td>
<td>0.077</td>
</tr>
<tr>
<td>Average</td>
<td>61</td>
<td>(total 1487)</td>
<td>2.275</td>
<td>0.098</td>
</tr>
<tr>
<td></td>
<td>Ventricles Fixed at 100 mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>424</td>
<td>100</td>
<td>618</td>
<td>2.299</td>
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<td>236</td>
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<tr>
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<td>2.324</td>
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<tr>
<td>431</td>
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<td>415</td>
<td>2.321</td>
<td>0.067</td>
</tr>
<tr>
<td>Average</td>
<td>100</td>
<td>(total 1782)</td>
<td>2.300</td>
<td>0.116</td>
</tr>
</tbody>
</table>

The mean sarcomere lengths of 2.275μ at a fixation pressure of 61 mm Hg and 2.300μ at a fixation pressure of 100 mm Hg are significantly different (P < .001) by the paired t-test. The small difference in mean sarcomere length might be even of less importance, since by analysis of variance each group is heterogeneous, and in fact, the heart with the smallest mean sarcomere length was fixed at 100 mm Hg diastolic pressure.
ventricles distended with a pressure of 61 mm Hg and 1,782 sarcomeres measured from the four ventricles distended with a pressure of 100 mm Hg. The measurements made from all eight hearts are presented in Table 1.

Figure 12 is a frequency distribution graph of frequency of sarcomere length against sarcomere length for both groups of hearts. The sarcomeres of those ventricles distended with a pressure of 61 mm Hg ranged from 2.2μ to 2.6μ in length and averaged 2.275μ (± 0.098 SD). The sarcomeres of those ventricles distended with a pressure of 100 mm Hg ranged from 1.9 to 2.7μ in length, and averaged 2.300μ (± .116 SD).

Discussion

The isolated heart preparation used in this study has both hazards and advantages which merit discussion and must be understood to interpret the data. The assumptions made for the calculation of mean wall stress present the greatest interpretive hazard. Here, in essence, it was assumed that the ventricle is distended as a homogeneous, hollow, thick-walled sphere in which strain was equally distributed in all directions tangential to the wall. As indicated by Figures 2 and 3, this is somewhat hard to justify when the ventricle is distended with diastolic pressures below 20 mm Hg. For this reason, the observations in this report were generally confined to the description of ventricular performance at diastolic pressures above this level, where the assumptions were more realistic.

Procedural hazards in the use of the preparation must also be avoided. Strict attention must be paid to the avoidance of hypoxemia, anemia, or any obstruction of the coronary bed of the isolated heart. All of these have been shown to produce descending limbs of ventricular performance at high diastolic pressures (11-13). Further, the ventilation, blood pressures, and the level of anesthesia of the donor dog must be maintained constant. The release of catecholamines that might accompany hypotension of the donor, for instance, could obviously disturb the performance of the isolated heart.

The advantages of the preparation lie primarily in its simplicity and the relatively high success rate in setting up working preparations (94%) in which data relating to ventricular performance, coronary flow, and incidentally, myocardial oxygen consumption can be obtained. The instrumentation involved is not excessively costly or elaborate. As the heart contracted almost isovolumically, ejecting a stroke volume of about 1 ml/beat, afterload was automatically maintained constant, as was heart rate, factors known to affect the performance of the ventricle or the assessment of its performance (7). The relative simplicity of the surgery has made it possible to use a modified version of the preparation to study ventricular performance and myocardial oxygen consumption in the blood-perfused, isolated, supported heart of the rat. The ease of preparing the heart prior to perfusion opens up the possibility of using such a preparation to study hearts from animals with induced heart disease or even diseased human hearts removed before a transplant.

As shown in Figure 4 and as noted in Section I of Results, the ventricle usually developed a negative systolic pressure when subjected to a negative diastolic pressure and invariably did so if the diastolic pressure was more negative than −3 mm Hg. This was observed when the ventricle was immersed to the level of the coronary ostia in a container of saline, the surface of which was the reference for zero pressure. Although this was not expected, it had been noticed in a previous preparation (6) and serves as evidence that the ventricular geometry is such that the contraction in systole tends to enlarge the ventricular cavity if the diastolic pressure is distinctly negative. The photograph at top left in Figure 2 shows the equatorial plane of a ventricle frozen while subjected to a negative pressure and where the ventricular cavity was reduced to a slit; contraction of such a ventricle might well enlarge the slit. The finding that, in general, the mathematical sign of the diastolic pressure determined the sign of the systolic pressure in the preparation.
described is not, in itself, presented as of physiological importance. In the studies reported, however, it permitted the relationship between developed pressure and diastolic pressure to be extrapolated to the intercept or its immediate vicinity with reasonable confidence.

In the initial studies of hearts with an intact pericardium (Fig. 8), ventricular performance, as reflected in developed pressure alone, increased markedly at low diastolic pressures (below 20 mm Hg) and remained relatively constant at high diastolic pressures. A barely perceptible descending limb of ventricular performance was noted at diastolic pressures as high as 100 mm Hg. This is in keeping with the findings of previous observers, although their observations were limited to lower diastolic pressures (5-7).

These studies raised a question concerning the extent to which the pericardium confined expansion of the ventricle and thereby hid what might otherwise have been an earlier peak and more extensive descending limb when developed pressure was plotted against diastolic pressure. Even with the pericardium removed and the left atrium plicated to avoid mitral regurgitation at high diastolic pressures, the descending limb was imperceptible until the end-diastolic pressure exceeded 30 mm Hg and only ~15% at an end-diastolic pressure of 100 mm Hg (Fig. 9). This led to an attempt to define the relationship between the tension developed by the myofibril and diastolic pressure and to determine that level of end-diastolic pressure required for the sarcomere to contract on the descending limb of the Frank-Starling mechanism. In Figure 9, the diastolic pressure had to be raised to well above 50 mm Hg, on the average, before there was a perceptible decrease in developed stress. Furthermore, the relationship between developed stress and end-diastolic pressure descended only 7.6% from its peak at an end-diastolic pressure of 100 mm Hg.

As the end-diastolic pressure increased above 30 mm Hg, the average developed pressure decreased. With the decrease in developed pressure there was an attending in-
crease in radius and decrease in wall thickness.

In view of the relationship \( s = \frac{P_t}{\frac{2h}{h}} \) discussed in Methods, the total effect of these changes was such that the developed stress remained relatively constant as the end-diastolic pressure increased above this level.

Ventricular performance in the described preparation was less than that found in more intact preparations. In a recent report by Kumar et al., the average systolic pressure developed by the isovolumically contracting ventricle in an intact unanesthetized dog was approximately 215 mm Hg when distended with an end-diastolic pressure of 20 mm Hg (17). From the studies reported here the average left ventricular systolic pressure developed by the isolated pericardectomized heart was only 138 mm Hg (±3.90 se) when distended with an end-diastolic pressure of 20 mm Hg. In general the ventricles of isolated hearts with an intact pericardium in the present studies showed significantly better performance, developing an average systolic pressure of 196.5 mm Hg (±13.8 se) at an end-diastolic pressure of 20 mm Hg (\( P < .001 \)). It appears, therefore, that under the circumstances described, the pericardium served to improve ventricular performance though not quite to the level reported in intact unanesthetized animals. It may well be that sympathetic denervation in nonpericardectomized isolated hearts accounts for this relatively small (10%) discrepancy.

In recent years, various observers have called attention to the positive inotropic effect that accompanies an increase in the pressure developed by the ventricle, termed by some homeometric autoregulation (18, 19). The question therefore arises on the extent to which this phenomenon could have artifici-tiously prevented more of a descending limb than that reported here. However, it is doubtful whether this is a significant factor in these observations, since the sequential increases in end-diastolic pressure were usually completed in less than 30 seconds, far less than the time required for the full homeometric effect referred to above. Furthermore,
many of the sequential increases in diastolic pressure were started when the developed pressure was close to maximal. As this homeometric effect has been reported as a direct function of the change in developed pressure it is unlikely that it significantly distorted the observations here (19).

Likewise, the failure to observe more of a descending limb could not be attributed to an increase in coronary flow as the end-diastolic pressure was increased. In an average of 13 experiments in which coronary flow was observed, at end-diastolic pressure of 100 mm Hg, it was within 4% of that noted at an end-diastolic pressure of 30 mm Hg. As in the experiment in Figure 7, therefore, the average coronary flow remained relatively constant as the ventricle was distended with end-diastolic pressures exceeding 30 mm Hg. Furthermore, in individual experiments, there was no correlation between the extent of a descending limb and the percent change in coronary flow as the ventricle was distended.

The studies of the ultrastructure of the sarcomere at high end-diastolic pressures were consistent with the other data presented. Previous observers have noted that the sarcomere develops its greatest tension when it is stretched to a sarcomere length of 2.2 μ (1-4). In the studies reported here the average sarcomere length of sections taken from ventricles distended with pressures of 61 and 100 mm Hg were fairly consistent (2.275 μ and 2.300 μ, respectively). Although the differences in sarcomere lengths at the two pressures are statistically significant, the average sarcomere length at 100 mm Hg was only 1% greater than that found at 60 mm Hg.

In reporting sarcomere lengths one must be careful because shrinkage of the sarcomeres could have occurred despite all precautions. However, the histological findings are in good agreement with the data illustrated by Figures 9 and 11 where the average developed stress is relatively constant from an end-diastolic pressure of 61 mm Hg to an end-diastolic pressure of 100 mm Hg. From the data of A. F. Huxley showing the developed tension of striated muscle plotted against sarcomere length, the tension developed by sarcomeres stretched to a resting length of 2.30 μ was approximately 6% less than the peak tension developed at 2.20 μ (1). This is remarkably consistent with the extent to which the stress developed by the ventricle decreased from its peak (7.5%) at an end-diastolic pressure of 100 mm Hg in this report.

At the high pressures at which the ventricles were fixed, the average sarcomere length was somewhat shorter than in one other study where the ventricles were similarly fixed at lower pressures (20). A subsequent paper by the same authors (21) reported the average sarcomere length of ventricles distended with an average pressure of 32 mm Hg to be 2.25 μ (±0.051 SD), a figure more consistent with the findings reported here and also with the findings of Anversa et al. (22). This confirms the suggestions by the latter authors that greater ventricular performance at high end-diastolic pressures may well be achieved by a more favorable alignment of the myofibrils rather than by absolute increases in sarcomere length.

The average sarcomere length at a distending pressure of 100 mm Hg was approximately 1% greater than that at an end-diastolic pressure of 61 mm Hg. As indicated in Figures 5 and 6, this was accompanied by a roughly proportional change in ventricular circumference. It might appear, therefore, that at end-diastolic pressures exceeding 60 mm Hg the series elastic element may well be stretched to its limits. This is further substantiated by the rapidly increasing slope of the diastolic ventricular pressure volume curve at high end-diastolic pressures.

With acute depression following the infusion of propranolol, there was essentially no difference in the relationship between end-diastolic pressure and percent of peak developed stress from that noted prior to the infusion. Whether left ventricles in cases of clinical congestive heart failure would show a definite difference is a matter of speculation. However, for both the healthy ventricle and the acutely depressed, there is evidence that the loss of performance normally associated
with the descending limb of the Frank-Starling mechanism is probably never encountered. The end-diastolic pressure required to effect an appreciable descending limb far exceeds the physiological range.

To explain the discrepancy between this report and the reports of those who found descending limbs of ventricular performance at high diastolic pressures (9, 10), the authors are obliged to point out the limits of their observations. It should be remembered that the described preparation was designed to be incapable of indicating a descending limb of ventricular performance due, say, to mitral regurgitation or to the reduction in cardiac output that could be attributed to the large coronary flow noted when the ventricle approached its maximal developed stress. The evidence here supporting the conclusion that a descending limb is probably never encountered applies specifically to the performance of the left ventricular musculature in contrast to the ventricle as an intact organ, where there could be a descending limb of ventricular performance for the reasons mentioned. Only to that extent are the presented observations intended to describe ventricular performance at high diastolic pressures.

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References


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R. G. MONROE, W. J. GAMBLE, C. G. LAFARGE, A. EDALJI KUMAR and F. J. MANASEK

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