ABSTRACT

Instantaneous contractile element velocity was calculated from left ventricular pressure and its first derivative during isovolumic left ventricular contractions produced by sudden balloon occlusion of the ascending aorta during diastole in closed-chest, sedated dogs. Wall tension was derived from ventricular pressure and volume, the latter being obtained from the pressure-volume relation of the arrested ventricle. During isovolumic contractions, there was an inverse curvilinear relation between tension and velocity, except at the onset of contraction and near peak tension. Increasing diastolic ventricular volume shifted the tension-velocity relations to the right, with increase in mean total isovolumic tension from 188 to 471 g/cm², but without an obvious change in extrapolation to maximum velocity, which averaged 3.0 circumferences/sec. End-diastolic pressure-tension and circumference-tension relations indicated that active tension development continued to increase up to the maximum measured end-diastolic pressures of approximately 20 mm Hg. The normalized data, pooled from 15 animals, showed little scatter in the data for tension and velocity. It is concluded that the contractile properties of left ventricular muscle in the intact, sedated dog may be meaningfully described by tension-velocity relations obtained from single isovolumic contractions. The responses of the intact ventricle to increased diastolic volume and digitalis glycosides are analogous to those of isolated cardiac muscle. The small variability in the normalized tension-velocity relations in the normal dog suggests that it will also be possible to characterize abnormal left ventricular function with this approach.

ADDITIONAL KEY WORDS
mechanics of cardiac muscle
ventricular filling
force-velocity relations
left ventricular tension
digitalis glycosides

Cardiac function in the intact animal and man is ordinarily assessed in hemodynamic terms which reflect not only the function of the heart but also the body's metabolic demands and the state of the peripheral circulation. The relations between cardiac filling pressure and the stroke volume, stroke work, or stroke power, which are of considerable value in assessing cardiac function in the controlled circulation (1), are of limited value in the intact animal since they are influenced by the level of aortic pressure (1-3) and do not directly reflect alterations in wall tension and the extent and velocity of muscle fiber shortening. Since the heart is a muscular organ, it would seem more appropriate to describe its function in the latter terms, which better define its characteristics as a muscle.

The contractile properties of isolated skeletal (4-6) and cardiac (7-9) muscle can be characterized, and the contractile state of cardiac muscle defined, in terms of force, velocity, length, and time. In isolated heart
muscle, as in skeletal muscle, there is a hyperbolic relation between force and velocity at any one muscle length, although in a single cardiac muscle twitch this relation may be modified by other factors, notably the delayed onset of active state, the duration of active state, and the fact that cardiac muscle cannot be tetanized (10, 11). In the intact heart, it is of historical interest that as early as 1895, Frank observed an inverse relation between outflow resistance and velocity of blood ejection in the frog heart, and drew an analogy to the behavior of skeletal muscle (12). More recently, an inverse relation between wall tension and the velocity of shortening of muscle fibers or contractile elements in the canine left ventricle has been described (13-16). This relation is influenced by diastolic ventricular filling (13-15) and by the inotropic state of the ventricular muscle (14, 15). In one of the later studies in a controlled circulation (15), tension and velocity were measured at isovolume points in beats originating from the same end-diastolic pressure and fiber length, but facing wide variations in aortic pressure. The inverse tension-velocity relations so obtained were therefore largely independent of changes in time, active state, and muscle length, factors which may have influenced earlier studies (13, 14). It was also found that meaningful relations between contractile element velocity and left ventricular wall tension could be obtained from isovolumic contractions (15), and subsequently these tension-velocity relations were shown to be particularly sensitive to changes in cardiac filling and in inotropic state (17).

The aim of the present study is to describe left ventricular function in the closed-chest, sedated but unanesthetized dog in quantitative, normalized terms of tension and velocity. The tension-velocity relations of the left ventricle were derived from analysis of isovolumic contractions, using certain simplifying assumptions concerning left ventricular geometry. Isovolumic contractions were produced by sudden balloon occlusion of the ascending aorta during diastole (17). There is no external muscle shortening during isometric contractions of isolated muscle or during isovolumic ventricular contraction if shape changes are neglected. However, according to Hill's muscle model (4), the contractile elements shorten to stretch the series elastic elements, with the development of tension. The rate of contractile element shortening may then be derived from the rate of tension development and the stress-strain relation of the series elastic elements. The study indicates that left ventricular function in the closed-chest, unanesthetized dog can be described with these techniques in terms of tension, velocity, length, and time. In addition, the effects of increased ventricular diastolic fiber length and of digitals glycosides on the left ventricular tension-velocity relation in the intact circulation are shown to parallel closely those in isolated cardiac muscle. Finally, the normalization of these mechanical properties of the contraction of ventricular muscle is described. The small variability of the normalized data in these intact animals suggests that this type of approach will allow sensitive detection and characterization of abnormal ventricular muscle function.

Methods

In mongrel dogs weighing between 15.0 and 23.6 kg a median sternotomy was performed under pentobarbital anesthesia (30 mg/kg). The left lateral aspect of the pericardium was opened from apex to base and its lower free edge and apex were sutured to the left chest wall, the upper margin remaining free. This procedure, by carrying the left ventricle closer to the left chest wall, facilitated later percutaneous needle puncture of the left ventricle. The pericardium, cradling the heart, was left widely open. In some experiments a ¼-inch band of Teflon tape was placed around the ascending aorta to provide support during balloon inflations. Electrodes were sutured to the right atrial appendage and the ends of the lead wires were implanted subcutaneously. The chest was closed with drainage. The experimental procedure was undertaken between 2 and 4 weeks later. The animals were sedated with morphine (3 mg/kg), promazine (1.5 mg/kg) and promethazine (1.5 mg/kg) by intramuscular injection. Local anesthesia with lidocaine was used for catheter insertions. Aortic pressure was measured through a polyethylene cannula passed into the thoracic aorta
from a femoral artery; left ventricular pressure was obtained through a short, stiff polyethylene cannula (PE 220) that was inserted by direct percutaneous puncture with a no. 19 spinal needle as a trocar and then attached directly to a pressure transducer. Intraventricular pressure was referred to the level of the mid left ventricular cavity, which was determined directly at the completion of each experiment. The first derivative of left ventricular pressure, LV dp/dt, was obtained with an analog differentiating circuit. Intrapleural pressure was measured through a self-retaining Foley catheter inserted through the right chest wall. Left ventricular transmural pressure was obtained by subtraction of the intrapleural pressure from the measured left ventricular pressure, and was used in all calculations. All pressures were measured with Statham P23Db transducers and were recorded with the electrocardiogram on a multichannel oscillograph at a paper speed of 100 mm/sec. Cardiac output was measured in duplicate by injection of indocyanine-green dye into the superior vena cava, with aortic sampling. The standard deviation of cardiac output by the method of paired measurements was 0.24 liter/min.

A rubber balloon mounted at the tip of a metal cannula was passed through the left carotid artery and placed in the ascending aorta just above the aortic valve. The balloon was rapidly inflated during diastole with 5 to 18 ml of saline by a power injector triggered from the electrocardiogram (17). Beats were analyzed only if they had features characteristic of isovolumic contractions, a smooth left ventricular pressure contour, a steady, uninterrupted fall in LV dp/dt following its peak, and a progressively falling aortic pressure (15). All isovolumic beats used for analysis were obtained during expiration.

DETERMINATION OF VENTRICULAR END-DIASTOLIC VOLUME

The left ventricular end-diastolic volume, from which isovolumic beats originated, was derived from the transmural end-diastolic pressure and the passive pressure-volume relation of the KCl-arrested ventricle, determined after death of the animal (15). Potassium arrest appears to have little influence on left ventricular diastolic pressure-volume relations (18). The pericardium had previously been left widely open so that it would not contribute to the ventricular transmural pressure, and only minor intrathoracic adhesions were noted. The pressure-volume relation was obtained with the heart lying in its pericardial cradle, as in the closed-chest situation, the right ventricle being vented during this procedure.

Distention of either the right or left ventricle is known to influence the passive pressure-volume relation of the other ventricle, making it less distensible (19-21). Therefore, when the right ventricle is empty, a given left ventricular pressure would correspond to a larger left ventricular volume than when the right ventricle is filled, as in the intact circulation. The magnitude of this effect was measured in separate experiments (21) in open-chest dogs, in which the correlation between right and left ventricular filling pressures over a wide range was obtained by blood infusions. The influence on the left ventricular pressure-volume relation of appropriate degrees of right ventricular filling was then determined. The effect varied directly with the degree of filling of the ventricles, being undetectable when left ventricular end-diastolic pressure was less than 3 mm Hg and reaching an average maximum value of 3.9 ± 2.4 (SD) ml, or 7.1 ± 4.7% of left ventricular volume at an end-diastolic pressure of 20 mm Hg. Using these data, the volumes derived in the present experiments from the left ventricular pressure-volume relation obtained with the right ventricle empty were corrected by the appropriate small volume to account for right ventricular filling in the intact circulation.

CALCULATION OF MYOCARDIAL WALL TENSION AND CONTRACTILE ELEMENT VELOCITY

Myocardial wall tension was calculated from the formula $T = \frac{P_t}{2h} g/cm^2$ where $P_t =$ transmural ventricular pressure in grams per square centimeter, $r_i =$ internal radius in centimeters and $h =$ wall thickness in centimeters. The internal radius of the left ventricle was obtained from the cavity volume, assuming a spherical ventricular shape. Wall thickness was calculated by assuming the mass of left ventricular muscle to be evenly distributed around its contents. The mass was determined at the completion of each experiment. The units of $T$, g/cm², are those of stress. The term tension is used interchangeably with the term stress, and is expressed as total tension, end-diastolic tension and the difference between these, active tension.

The derivations of equations currently in use for the calculation of myocardial wall tension are based on the physics of passive elastic bodies (22-24). During systole, the ventricular walls do not passively support an internal pressure but, rather, actively develop tension appropriate to

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1Model S602, Electronic Gear, Inc., Valley Stream, N. Y.
2Model 350, Sanborn Company, Waltham, Massachusetts.
3Cordis Power Injector, Cordis Corp., Miami, Florida.

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the lengths of the muscle fibers within the wall, the orientation of the fibers and the characteristics of their loading. The nature of tension distribution across the ventricular wall must influence the absolute magnitude of the total force developed in the wall, by determining the functional radius. Lack of knowledge of tension distribution has led to differing opinions concerning the calculation of myocardial wall force and tension, Burton (22) considering wall force to be a function of P and mid wall radius \( r_m \), whereas Fry, Griggs and Greenfield (26) held that internal radius \( r_i \) is appropriate. Assuming that the force supported by a wall cross section perpendicular to a plane bisecting a relatively thin walled sphere is a function of pressure \( P \), distributed over a surface area \( \pi r_o^2 \) in the plane of section, then mean wall tension will be
\[
\frac{\pi Pr_i^2}{\pi (r_o^2 - r_i^2)}
\]
where \( r_o \) is the external radius (27, 28). The function \( Pr_i/2h \) represents a simplified version of this expression but will closely approximate it for spheres having a low ratio of \( h \) to \( r_i \) (27), and has been applied by Sandler and Dodge (23) to the calculation of ventricular wall stress. However, in a thick walled sphere, if \( r_i \) is the radius appropriate to the calculation of force, then \( Pr_i/2h \) would overestimate tension by a factor of \( r_m/r_i \). On the other hand, if \( r_o \) is considered appropriate (22), then \( Pr_i/2h \) would underestimate tension by a factor of \( r_m/r_i \). It should be emphasized that there is little experimental evidence to indicate which radius is most appropriate, although Hefner et al. (29), measuring variations in force across a myocardial slit in the left ventricle, found that this force correlated better with \( Pr_i^2/r_o^2 \) than with \( Pr_i r_o^2 \). Therefore, since it is likely that the true functional radius, which is presently unknown, lies somewhere between \( r_i \) and \( r_m \), it would seem reasonable to use the simplified expression \( Pr_i/2h \) to estimate mean wall stress until further information becomes available.

During the isovolumic phase of auxotonic contractions there is shortening of the left ventricular base-to-apex length with an increase in circumference. The function \( P^2/r_0 \), distributed over a surface area \( \pi r_o^2 \) in the plane of section, then mean wall tension will be
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in units of cm/cm per sec, that is, muscle lengths or circumferences per second and therefore requires no further normalization for comparisons between different ventricles. Tension values, expressed in terms of force per unit wall cross-sectional area, or stress, also allow direct comparisons between different ventricles. Tension lengths or circumferences per second and therefore are expressed in units of cm/cm per sec, that is, muscle lengths or circumferences per second and therefore require no further normalization for comparisons between different ventricles. Tension values, expressed in terms of force per unit wall cross-sectional area, or stress, also allow direct comparisons between different ventricles. Tension lengths or circumferences per second and therefore can be regarded as accurate activity to $P_0$ only to within 5 msec.

The time required to reach peak tension was measured from the first appearance of mechanical activity to $P_0$ and can be regarded as accurate only to within 5 msec.

Results were obtained in 15 animals in which the mean arterial oxygen saturation averaged 93% (range 88 to 100%), arterial pH 7.31 (range 7.24 to 7.37) and arterial hematocrit 40% (range 37 to 43%). Rectal temperature ranged from 36°C to 38°C. Control measurements were made with the dogs resting quietly in the supine position. Following these measurements, the dog's blood was exchanged with fresh blood obtained from donor dogs lightly anesthetized with sodium methohexitale. The experimental animal's state of consciousness was not obviously affected by this procedure and in the 5 animals in which tension-velocity relations could be compared at similar heart rates, left ventricular contractility was unchanged in 3, slightly depressed in one and slightly increased in another. The previously implanted right atrial electrode leads were then attached to a stimulator, and heart rate was subsequently controlled at an average level of 150.6 ± 5.6 (SD) beats/min.

A wide range of transmural end-diastolic pressures was obtained by rapid infusion of 50- to 100-ml increments of previously exchanged blood, isovolumic contractions being produced 30 sec after each infusion. In 5 animals, acetylstrophanthidin (0.025 mg/kg) was given intravenously, and isovolumic contractions were obtained 10 min later; 1 animal was studied 30 min after ouabain (0.025 mg/kg) was given.

Results

Control Hemodynamic Measurements.—The initial hemodynamic measurements at the spontaneous heart rates are shown in Table 1.
FIGURE 1
Tracings showing the effects of increasing transmural left ventricular end-diastolic pressure from 4.5 mm Hg (panel A) to 10.0 mm Hg (panel B). Heart rate controlled at 148/min. Arrows indicate points at which balloon has been inflated. Left ventricular pressure (LVP) is recorded on three sensitivities. LV dp/dt = rate of change of LVP. IPP = intrapleural pressure. AP = aortic pressure. ECG = electrocardiogram.

Characteristics of Isovolumic Contractions.
—Subsequent results were obtained following cross-transfusion and control of heart rate.

Figure 1 shows the recorded variables and typical isovolumic contractions before (panel A) and after (panel B) an increase in transmural left ventricular end-diastolic pressure with its accompanying increase in end-diastolic volume and muscle fiber length. Respiratory variations in the intrapleural pressure (IPP) and in the ventricular pressure can be seen in the slow tracing immediately preceding that obtained at a paper speed of 100 mm/sec. In an expiratory phase the aortic balloon was rapidly inflated during diastole (arrow). The subsequent contraction shows the characteristic contour of the left ventricular pressure, the left ventricular (LV) dp/dt and the aortic pressure associated with an isovolumic contraction. After infusion, peak isovolumic pressure increased, with a commensurate increase in maximum dp/dt, the time to peak pressure and tension was essentially unchanged, and the total duration of

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FIGURE 2
Contractile element velocity in circumferences per second ($V_{CE}$) plotted against tension during four isovolumic contractions originating from different transmural end-diastolic pressures (LVEDP). The extrapolations to maximum velocity and maximum tension were derived from Hill's equation.

FIGURE 3
Mean tension-velocity relations derived from grouping the relations obtained in 15 dogs according to the transmural end-diastolic pressure (LVEDP) from which the isovolumic beats originated.

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Relations between left ventricular total isovolumic tension, active tension, end-diastolic tension and transmural end-diastolic pressure (LVEDP). Results from 15 dogs grouped according to the LVEDP from which the isovolumic beats originated.

Tension maintenance was markedly increased. Calculated total isovolumic tension, $P_0$, increased proportionally more than did peak pressure (tension increased from 260 to 455 g/cm², pressure from 188 to 241 mm Hg), since tension depends not only on ventricular pressure, but also on volume, which increased from 39.6 ml to 60.6 ml.

**Tension-Velocity Relations and Diastolic Fiber Length.**—Figure 2 shows the relations between tension and $V_{OE}$ in isovolumic contractions at four different left ventricular end-diastolic pressures (LVEDP) in another experiment. At any one pressure there was an inverse curvilinear relation between tension and $V_{OE}$ after the first 30 to 40 msec of contraction, before which velocity was below the curvilinear relation. Over the 10 to 30 msec before $P_e$ was reached, velocity decreased more rapidly to zero than would have been predicted by extrapolation. Increasing the transmural end-diastolic pressure and hence the end-diastolic volume and muscle fiber length, shifted the tension-velocity relation to the right with an increase in $P_e$. $V_{max}$, the theoretical maximum velocity of the muscle at zero load, obtained by extrapolation, did not appear to be changed.

**Analysis of Pooled Data.**—The results from all experiments were also analyzed collectively. $V_{max}$, obtained by extrapolation in each experiment (Fig. 2), averaged $3.007 \pm 0.07$ (mean ± 1 se) circumferences/sec for the 15 animals and ranged in different animals from 2.7 to 3.5 circumferences/sec. The time to peak pressure and tension, which did not vary by more than 10 msec in any given experiment, averaged $139 \pm 3$ (mean ± 1 se) msec and ranged from 125 to 155 msec.

Figure 3 shows the mean tension-velocity curves obtained when the results from all animals were grouped according to trans-
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Figure 5: Total isovolumic tension plotted against end-diastolic tension. Lines join individual observations made in each animal.

Mural end-diastolic pressure, the mean tensions being calculated at selected velocities. Increasing pressure was accompanied by a progressive shift of the mean curves with an increase in P_o. In an attempt to obtain the V_max appropriate to each level of transmural end-diastolic pressure, the values of tension and V_CE at velocities of 1.5, 1.0 and 0.5 circumferences/sec in each group were substituted into the Hill equation \((P + a)(V + b) = K\), and the simultaneous equations obtained were solved for V_max. Calculated V_max for the groups listed on Figure 3, from the top down, were 3.0, 2.9, 2.8, 3.1, 3.0 and 3.5 circumferences/sec, supporting the conclusion that, at all but the highest end-diastolic pressure, V_max was not changed substantially by alterations in this pressure. The variation in position of the tension-velocity relations among different animals at any given pressure was small relative to the effect of changing the pressure, as indicated by the standard errors on the mean curve of each group (Fig. 3).

Figure 4 shows the mean values of total isovolumic tension, end-diastolic tension and active tension in the same groups of isovolumic contractions. Increasing end-diastolic pressure was accompanied by a progressive increase in total tension and in active tension. The increments in total and active tension became less at higher end-diastolic pressures, but active tension development continued to increase over the range studied, the highest end-diastolic pressure achieved being 23 mm Hg.

In Figure 5, P_o in individual experiments is plotted against end-diastolic tension, which is analogous to the relation between preload or resting tension and the total tension in isolated muscle. Figure 6 illustrates the relations between active tension, end-diastolic tension and normalized end-diastolic internal circumference, i.e. length-tension relations, for all experiments. Active tension increased in an approximately linear manner with increasing circumference, both in individual animals and in the pooled data from all experiments, and there was little if any tendency for this relation to flatten even at higher circumferences, although the increase in developed pressure was small in the higher range. Figure 6 also shows that end-diastolic tension increased more rapidly for a given change in muscle length at greater lengths. Thus, while at greater muscle lengths a given change in length produced a change in tension development similar to that at lesser lengths, this change in muscle length required a greater increment in end-diastolic, resting tension. This finding explains the nonlinear relation of active and total tension to end-diastolic pressure and tension (Figs. 4 and 5).

Tension-Velocity Relations and Cardiac Glycosides—Tracings obtained in experiment 15, before and 10 min after intravenous administration of acetylstrophanthidin (0.025 mg/kg) are reproduced in Figure 7. In panel A, from a transmural end-diastolic pressure of 9.3 mm Hg, peak isovolumic pressure was...
Active tension and end-diastolic tension plotted against normalized end-diastolic internal circumference. Individual observations in each animal are joined by fine lines. The linear correlation of active tension (AT) on normalized circumference (C) is described by the equation:

$$AT = 260.8 \times C - 446; \quad r = 0.835; \quad P < 0.001.$$  

**TABLE 2**

<table>
<thead>
<tr>
<th>Dog</th>
<th>Intervention</th>
<th>Heart Rate (beat/min)</th>
<th>Aortic Pressure (mmHg)</th>
<th>LVEDP (mmHg)</th>
<th>Peak Isovolumic Pressure (mmHg)</th>
<th>Total Isovolumic Tension (g/cm²)</th>
<th>Active Isovolumic Tension (g/cm²)</th>
<th>Time to peak Tension (msec)</th>
<th>Max $V_{CE}$ (circ/sec)</th>
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<td></td>
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<td>145</td>
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<td>192/135</td>
<td>8.9</td>
<td>274</td>
<td>498</td>
<td>482</td>
<td>140</td>
<td>2.09</td>
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$V_{CE} =$ contractile element velocity; ACS = acetylstrophanthin; other abbreviations as in Table 1.
FIGURE 7

Recordings showing the effects of acetylstrophanthidin (0.025 mg/kg iv) on isovolumic contractions originating from a constant transmural end-diastolic pressure. Heart rate controlled at 148/min. Panel A = control; panel B = acetylstrophanthidin. Arrows indicate points at which the balloon has been inflated. Abbreviations as in Figure 1.

210 mm Hg, max dp/dt 2,575 mm Hg/sec, and $P_o$ 377 g/cm². After acetylstrophanthidin, at an end-diastolic pressure of 8.9 mm Hg, peak isovolumic pressure was 274 mm Hg, max dp/dt 4,022 mm Hg/sec, and $P_o$ 498 g/cm². Table 2 shows the results from all 6 animals given a digitalis preparation. Comparisons before and after the intervention were made at closely similar end-diastolic pressures, because of the influence of ventricular filling per se on peak isovolumic pressure and $P_o$. The velocities compared in Table 2 are those at the smallest tension common to the nonextrapolated portions of the tension-velocity curves of the control contraction and of that following the glycoside. The velocity increased an average of 35% (range 10 to 66%), from an average of 1.37 to 1.82 circumferences/sec, while $P_o$ increased an average of 24% (range 9 to 40%), from an average of 233 g/cm² to 297 g/cm². The increase in both tension and velocity follow-
ing the intervention typically resulted in a nearly parallel shift of the tension-velocity curves (Fig. 8). The time to peak tension decreased in 3 experiments (9 to 20 msec) and remained essentially constant in 3 experiments (Table 2).

**Discussion**

The behavior of left ventricular muscle in the unanesthetized closed-chest dog has been described in quantitative terms within a framework of force, velocity, length and time, derived from an analysis of single isovolumic contractions. As detailed earlier, the complexity of left ventricular geometry and lack of knowledge of the characteristics of tension development and shortening of the individual fibers composing the ventricular wall has necessitated certain simplifying assumptions. These assumptions, further discussed below, imply that the tension-velocity relations should be regarded as representative of the entire left ventricle functioning as a single unit. Despite these assumptions, marked similarities were found between the contractile properties of the intact left ventricle and those of isolated cardiac muscle, including the nature of the responses to increased muscle length and to the inotropic effect of digitals glycosides. The findings demonstrate, therefore, that with appropriate techniques it is possible to evaluate changes in contractile state and to derive normalized mechanical data concerning the properties of left ventricular contraction in the intact animal.

The control hemodynamic observations are similar to those made by Bristow, Farrehi and Ueland in sedated dogs (38), but differ from those in unsedated, trained dogs (39), especially in respect to the higher heart rates and smaller stroke volumes observed in the present experiments. The mean left ventricular ejected fraction, SV/EDV, of 0.50 tends to be midway between that found by indicator dilution and by angiocardiographic techniques (40-42). This realistic value of SV/EDV may be taken to support the validity.
of the present ventricular volume measurements.

The isovolumic contractions produced in the present study are identical in contour to isovolumic contractions produced by sudden elevation of aortic pressure to a level that prevented opening of the aortic valve (15). This suggests that rapid inflation of the balloon, suitably placed in the root of the aorta, was successful in completely eliminating ventricular ejection, including the coronary blood flow.

The dependence of isovolumic tension development on muscle fiber length reflects the Frank-Starling mechanism (12, 43), now acknowledged to be important in the intact circulation (44). The present results suggest that in the intact animal the apex of the left ventricular length-active tension curve has not been reached even at filling pressures around 20 mm Hg. A similar conclusion can be drawn from observations in isolated circulations (19, 45, 46). However, above the upper limit of normal transmural end-diastolic pressures of 12 to 15 mm Hg, greater changes in end-diastolic tension and pressure are necessary to produce given changes in ventricular muscle length and hence in tension development. Further, as ventricular volume increases, given increments in tension development are translated into progressively smaller changes in pressure, because of the Laplace effect. Hence, at high transmural end-diastolic pressures, little increment in active pressure development results from further increases in end-diastolic pressure.

If the linear regression of active tension on normalized internal circumference (Fig. 6) is extrapolated, zero active tension is found to correspond to a circumference (L<sub>0</sub>) of 1.71. From the equation C/M<sup>4</sup> = 1.71 (where M<sup>4</sup> = volume in cubic centimeters of the left ventricular muscle to the one-third power, assuming a specific gravity of 1, and C = circumference in centimeters), this figure is found to correspond to a volume of 6.8 ml in an 80-g left ventricle and 10.1 ml in a 120-g ventricle. It is of interest that zero pressure on the passive ventricular pressure-volume curve corresponds to similar volumes. The internal circumference in the upper range of the length-tension relation was as much as twice L<sub>m</sub>, a proportionately greater difference in length than that observed in isolated muscle between L<sub>0</sub> and L<sub>m</sub>, when individual sarcomeres measure 1.5 μ and 2.2 μ, respectively (47). This difference is consistent with infolding of inner portions of the ventricular wall at small volumes and perhaps with slippage of muscle fibers as well, at large volumes.

The inverse curvilinear relation between tension and velocity at any one muscle length shown by the left ventricle in the closed-chest unanesthetized dog is similar to that observed in the left ventricle of a dog with a controlled circulation (15) and in cardiac (7, 8) and skeletal (4) muscle in vitro. The relation became established approximately 40 msec after the first appearance of mechanical activity, a delay similar to that observed in the dog with a controlled circulation (15, 16), indicating that maximum intensity of active state was only approached after this interval. Once established, the relation usually resembled a displaced hyperbola, as originally described by Hill in tetanized frog sartorius muscle (4) and generally discernible in a single cardiac muscle twitch, both in vitro (7-9) and in the intact left ventricle (15). That this is not always so in vitro has been attributed to variable intensity of active state (11), but in the intact left ventricle, in this and other studies (15), decay of active state appears to obscure the relation only during the 10 to 30 msec before P<sub>0</sub> is reached. P<sub>0</sub> falls approximately 10% short of the value predicted had the hyperbolic relation been maintained.

The present results not only confirm the relevance of the Frank-Starling mechanism to the intact circulation of the closed-chest unanesthetized dog but also define it in terms of muscle force, velocity, and time. The response to increased stretch, marked by an increase in P<sub>0</sub>, a shift to the right in the tension-velocity relation, without a definite change in V<sub>max</sub> and time to peak tension,
appears to be characteristic of cardiac muscle, whether it is isolated papillary muscle (7, 8), the left ventricle in a controlled circulation (14, 15), or the left ventricle in an intact circulation. Although the blood infusions used to increase ventricular filling in the present experiments might have been expected to produce some reflex withdrawal of cardiac sympathetic support and a negative inotropic effect, a large component of such a response was presumably countered by keeping the heart rate constant and preventing bradycardia and its associated negative inotropic effect, and no such effect was evident.

Acetylstrophanthidin produced a nearly parallel shift in the force-velocity relation of the intact ventricle. This is contrary to the suggestion that the administration of cardiac glycosides to the intact animal is accompanied by sympathetic withdrawal of such a degree as to negate the inotropic influence of the glycoside per se (48). The nature of the shift in the force-velocity relation, with approximately equivalent increases in \( V_{\text{max}} \) and \( P_{\infty} \), resembles the response of isolated cardiac muscle to acetylstrophanthidin (49) and of the left ventricle in a controlled circulation to norepinephrine and to paired electrical stimulation (15). The small decrease in time to peak tension is also consistent with that produced by acetylstrophanthidin in vitro (49). While these cardiac effects of the digitalis glycosides are not necessarily translated into changes in gross hemodynamic measures in the normal intact animal because of concurrent peripheral vascular effects (50), the present results emphasize that digitalis glycosides have an inotropic effect on the left ventricle in the closed-chest, unanesthetized animal similar to that observed in isolated cardiac muscle.

It should be reemphasized that the tension-velocity relation must be interpreted within the framework of the assumptions made in its derivation (see methods). These assumptions imply that the tension-velocity relations obtained should be considered to characterize the behavior of the whole left ventricular muscle. Calculated tension is considered to adequately represent mean ventricular wall tension; it is not possible with present knowledge and techniques either to calculate or to measure the tension developed by a specific part of the ventricular wall in the intact ventricle. Likewise the estimations of contractile element velocity, \( V_{CE} \), apply to the ventricle as a unit. Although shape changes occur during isovolumic contraction, it has not yet been possible to define the relative degrees of shortening or lengthening of individual fibers or contractile elements within the ventricle. Nevertheless, the fact that tension is developed indicates that overall shortening of the contractile elements must have occurred, and it is this net effect which is represented in the tension-velocity relation of the intact ventricle. In the calculation of \( V_{CE} \) we employed a series elasticity constant, \( K \), initially derived from the cat papillary muscle in vitro (35). However, as pointed out earlier, similar values for \( K \) have now been found in the intact canine left ventricle (36, 37). Further, the importance of any possible error in the selected value of \( K \) is greatly minimized by the fact that the error would be systematic, and relative velocities in the same or different animals would not be influenced, since \( K \) appears to vary little between normal animals (36, 37). Several points concerning the derivation of left ventricular end-diastolic volume from pressure-volume relations in the closed-chest animal should also be emphasized. The pericardium had previously been incised and left widely open to obviate any possible constricting effect and hence any influence on the transmural ventricular pressure. The pericardial and pleural spaces were in free communication, and the measured transmural pressure should therefore have represented the true ventricular distending pressure. Correction was also made for the small effect of right ventricular filling on the left ventricular pressure-volume relation. While these precautions should have overcome the specific difficulties imposed by the closed-chest and intact circulation, the estimation of ventricular volume from passive pressure-volume rela-
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...tions takes no account of myocardial viscous properties. Cardiac muscle shows viscosity as well as elasticity, i.e., the stress-strain relations of the intact ventricle depend on the mechanics of loading (51, 52). However, the effect is considered to be small and not to have introduced an important error in measuring left ventricular volume. Similarly, any possible effect of potassium arrest on the left ventricular diastolic pressure-volume relation has been considered negligible in this context (18).

While the present method of analysis necessitates a number of assumptions and qualifications it also has certain advantages. Only a single isovolumic contraction is necessary to describe left ventricular function at any particular muscle length. Blood infusion was undertaken in the present study to demonstrate the effect of increasing muscle length in the intact animal and to provide normalized data over a range of filling pressures in the normal animal. The present methods allow analysis of left ventricular performance independent of peripheral vascular changes, exemplified by the clear demonstration of the influence of digitalis glycosides on the mechanical properties of left ventricular contraction in the intact animal. Furthermore, it has been shown that wall force and velocity may be normalized and compared in animals with hearts of different sizes. The small variability in the normal dog suggests that this type of approach will permit specific characterization of ventricular muscle function in disease states, when other hemodynamic variables may not accurately reflect the state of the ventricular myocardium.

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Feb. 5. At 4 p.m.
Height of $A = 53$ cm. serum.
Height of $B = 40$ mm. Hg.
Height of $C = 15$ cm. serum. Experiment stopped.
At beginning of experiment $\Delta$ of serum $= -600^\circ \text{C}$.  
$\Delta$ of outer fluid (1-03 % NaCl) $= -630^\circ \text{C}$.  
At end of experiment $\Delta$ of serum $= -635^\circ \text{C}$.  
$\Delta$ of outer fluid $= -635^\circ \text{C}$.  

The serum contained 7-56 % proteids.

The importance of these measurements lies in the fact that, although the osmotic pressure of the proteids of the plasma is so insignificant, it is of an order of magnitude comparable to that of the capillary pressures; and whereas capillary pressure determines transudation, the osmotic pressure of the proteids of the serum determines absorption. Moreover, if we leave the frictional resistance of the capillary wall to the passage of fluid through it out of account, the osmotic attraction of the serum for the extravascular fluid will be proportional to the force expended in the production of this latter, so that, at any given time, there must be a balance between the hydrostatic pressure of the blood in the capillaries and the osmotic attraction of the blood for the surrounding fluids. With increased capillary pressure there must be increased transudation, until equilibrium is established at a somewhat higher point, when there is a more dilute fluid in the tissue-spaces and therefore a higher absorbing force to balance the increased capillary pressure. With diminished capillary pressure there will be an osmotic absorption of salt solution from the extravascular fluid, until this becomes richer in proteids; and the difference between its (proteid) osmotic pressure and that of the intravascular plasma is equal to the diminished capillary pressure.

Here then we have the balance of forces necessary to explain the accurate and speedy regulation of the quantity of circulating fluid. It is evident however that we cannot explain in this way the absorption of serum or other fluids rich in proteids from the serous cavities and connective tissues. I would point out however that we have as yet no sufficient evidence that such fluids are absorbed by the blood vessels. If we inject serum into the pleural cavity we find that it is absorbed very much more slowly than is a similar amount of salt solution. The absorption is indeed so slow that it is impossible to exclude the possibility that the whole of it has taken place through the lymphatics.

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*from Ernest H. Starling*  
*ON THE ABSORPTION OF FLUIDS FROM THE CONNECTIVE TISSUE SPACES*  
*JOURNAL OF PHYSIOLOGY, VOL. 19, PP. 312-326, 1895-96*

Starling's early discussion of the importance of proteins to fluid balance and exchange between capillary blood and tissue.
A Quantitative Analysis of Left Ventricular Myocardial Function in the Intact, Sedated Dog
ROGER R. TAYLOR, JOHN ROSS, Jr., JAMES W. COVELL, EDMUND H. SONNENBLICK
and Robert Lewis

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