The performance of the heart has been described traditionally in terms of relations between the end diastolic volume or filling pressure of the ventricles and their stroke volume or stroke work, the latter relationship having been extended to include a family of "ventricular function curves." While these measurements provide considerable insight into the level of cardiac performance, recent studies on the mechanics of contraction of isolated heart muscle have suggested that these concepts can be extended. It has now been shown that the contractile state of the papillary muscle, like that of skeletal muscle, can be characterized best in terms of the relation between instantaneous force, velocity, and length, and that, unlike skeletal muscle, isolated heart muscle has the ability to alter its force-velocity relation.

Recently, an important contribution has been made by Fry et al., and Levine and Britman, who described an inverse relation between myocardial wall tension and the shortening velocity of the muscle fibers, or the contractile elements, in the canine left ventricle. In some of these experiments, alterations in the tension of the myocardial wall were produced by varying the ventricular end diastolic volume and aortic pressure simultaneously, tension and velocity being measured at isovelocity points during ejection. It has been shown recently in isolated cardiac muscle that the instantaneous velocity of shortening diminishes progressively as muscle shortening occurs during isotonic contraction; hence, this factor could have played an important role in the latter studies. It seems likely, therefore, that the results of previous studies in the intact heart were influenced significantly by two factors other than force and velocity, i.e., level of active state relative to time, and instantaneous muscle length.

The present investigations were undertaken, first, to define the basic force-velocity relation in the intact canine left ventricle in a manner analogous to that employed in isolated muscle, i.e., by serial, reproducible variations in the afterload alone. Since the relation between force and velocity was examined only during the first beat after each of a series of sudden diastolic alterations in the afterload, the effects of variations in the end diastolic fiber length were avoided. Moreover, the instantaneous relation between force and velocity was measured with the ventricle at the same volume during ejection, thus minimizing effects due to differences in fiber length during contraction. Secondly, the experiments were designed to determine whether or not, in a

From the Cardiology Branch, National Heart Institute, Bethesda, Maryland.
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given ventricle, acute heart failure and positive inotropic influences alter the basic force-velocity relation. Finally, attention was directed toward analyzing the time course of contractile element velocity during single auxotonic contractions, as well as the force-velocity relation during single, isovolumic beats. It is suggested from these studies that the application of such analyses to the assessment of ventricular performance adds an additional dimension to definitions of the myocardial contractile state. Portions of this study have been presented previously in preliminary form.20

Methods
Ten dogs, weighing between 21.8 and 32.3 kg, were studied with morphine premedication (3 mg/kg), and chloralose anesthesia (80 to 100 mg/kg). The trachea was intubated, and ventilation with 100% oxygen was provided by a Harvard respiratory pump. The experimental preparation, shown schematically in figure 1, consisted essentially of a right heart bypass circuit, and a system that permitted a sudden, controlled increase or decrease in the aortic pressure during diastole.

A bilateral thoracotomy was performed, the heart was suspended in a pericardial cradle, and bypass of the right heart was accomplished as described previously21 (fig. 1). The first portion of the descending aorta was divided and cannulated with glass tubing which led through a three-way valve and thence back to the descending aorta. One arm of the valve was attached to a large reservoir bottle within which pressure was

FIGURE 1
Diagram of the experimental preparation. Blood drains by gravity from the venae cavae (SVC, IVC) and right ventricle (RV) to a reservoir, from which it is returned by a pump to the pulmonary artery (PA). The probe of an electromagnetic flowmeter (E.M.F.) is placed around the aorta and strain gauge pressure transducers (SG) are attached to metal cannulae inserted into the aorta and left ventricle (LV). The descending aorta (des. aorta) is cannulated and blood is diverted through a three-way valve (see insert) which directs blood either to the reservoir bottle or to the distal descending aorta. Pressure in the reservoir bottle is regulated by a compressed air (compr. air) circuit.
regulated by a compressed air circuit. The three-way valve, which directed blood either into the bottle or into the descending aorta, had a plastic core of one-half inch bore, seated in a stainless steel housing* (fig. 1, insert). The core was attached to a heavy spring which turned the stopcock rapidly when released. A metal plunger moved by a solenoid accomplished the release, the solenoid in turn being triggered by an electrical circuit that inserted a variable time delay after the electrical impulse that paced the heart. The time required to actuate the valve was approximately 50 msec, and with an appropriate additional delay it was possible to fill or empty the aorta during a single diastolic interval.

A flow probe was placed about the ascending aorta, and the rate of left ventricular ejection, minus systolic coronary blood flow, was measured with a gated sine wave electromagnetic flowmeter.† The dynamic accuracy of this instrument was assessed by an electronic method.22, 23 At the two levels of electronic damping used in the present studies, the time delays were found to be 8.5 and 11.6 msec; these delays remained constant up to 60 cycles/sec. Appropriate corrections for time were therefore made in the data presented. The amplitude attenuation was 5% at 20 cycles/sec, and no correction for this factor was made. Small pressure gradients across the flowmeter probe were evident, and during the control periods the peak systolic gradients averaged 10 mm Hg; in five experiments the gradients were 6 mm Hg or less, and the largest pressure gradient was 21 mm Hg.

Left ventricular pressure was measured through a metal cannula (bore, 5 mm), inserted through the ventricular apex and attached directly to a Statham P23D transducer. The first derivative of the left ventricular pressure (dp/dt) was determined with a linear R-C differentiating circuit. This circuit exhibited a phase shift of 90° ± 1° from 0 to 35 cycles/sec. Pressure in the aortic arch was also measured with a metal cannula-transducer system, and all determinations were recorded with the electrocardiogram on a multichannel oscillograph‡ at a paper speed of 100 mm/sec.

The heart rate was controlled by crushing the sino-atrial node and driving the right atrium with a stimulator.* A reservoir bottle was attached to the femoral arteries for regulation of systemic arterial pressure during control periods. In the first four experiments, the brachiocephalic artery was ligated and perfused from the femoral artery; however, this procedure resulted in modification of the phasic aortic flow pattern, as well as in more rapid deterioration of the contractile state of the heart. Thus, in the remaining six experiments, this vessel remained patent.

The units presented in the present study are those of tension rather than force, as described below, although the more familiar term "force-velocity relation" will be retained for purposes of discussion. A force-velocity (F-V) relation was determined by imposing a series of 6 to 10 sudden diastolic alterations in the afterload, which may be defined as the pressure encountered at the time the aortic valve opens. The left ventricular end diastolic pressure (LVEDP) was held constant, and ordinarily no alteration in the output of the pump was necessary to maintain the LVEDP stable during a series of afterloaded beats. The pressures produced in the aorta during diastole ranged from approximately 25 mm Hg to that pressure necessary to induce a completely isovolumic beat. Lower pressures were usually not attainable, since the aortic wall tended to break contact with the flowmeter probe. Following each afterloaded beat, the three-way valve was turned manually, restoring flow to the descending aorta, and control conditions were permitted to recur.

The relation between instantaneous velocity of shortening and wall tension (see section on calculations) was determined at the same systolic ventricular volume during each of the beats comprising a given F-V relation, and at an identical or closely similar volume in the same ventricle when the F-V relation was again determined during alterations in the contractile state. The point of isovolume, determined from the end diastolic volume (see below) and the integrated flowmeter tracing, was chosen so that it occurred not earlier than 10 msec before, or 30 msec after, peak aortic flow. In seven experiments, after determination of the control F-V relation, norepinephrine 0.048 to 0.196 µg/kg/min was infused, and a second series of afterloaded contractions was induced. The output of the pump was increased during the infusion to maintain the LVEDP equal to that of the control period. In three experiments, the effect of repetitive delivery of paired stimuli, as described in detail previously,24 on the F-V relation was also determined. In four experiments, the effects of acute heart failure

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*The valve was constructed by the Instrument Fabrication Section, National Institutes of Health; the core was machined from Kel-F, Minnesota Mining and Mfg. Company, Minneapolis, Minnesota.
†Biotronex Laboratory, Inc., Silver Spring, Maryland, model no. 310.
‡Sanborn Company, Waltham, Massachusetts, model no. 350.

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on the F-V relation were examined. These studies were performed late in the course of an experiment, and in two dogs the ventricle was further depressed by the rapid administration of pentobarbital sodium 15 mg/kg. In these experiments, in order to maintain the LVEDP at a level comparable to that of the control period, the output of the pump was reduced. Mean aortic pressure was regulated during these interventions, varying by no more than 5 mm Hg (avg = 3 mm Hg) before and during norepinephrine infusion and paired stimulation, and by no more than 8 mm Hg (avg = 5 mm Hg) in three of four studies of acute heart failure; in one experiment (dog no. 9), mean aortic pressure dropped from 100 to 63 mm Hg following pentobarbital infusion.

In some experiments the shortening velocity of the circumferential fibers \( V_{CF} \) and the contractile elements \( V_{CE} \), and the myocardial wall tension, were calculated in single beats at 10 msec intervals throughout isovolumic contraction and ejection (see section on calculations). These contractions were analyzed at varying degrees of afterload and at a constant LVEDP. In some studies, \( V_{CB} \) and the tension were computed at 10 msec intervals during isovolumic beats, and the resulting F-V curve was plotted commencing at maximum \( V_{GB} \). The latter curves were also examined during alterations in the ventricular contractile state induced by norepinephrine infusion and acute heart failure, and following changes in the left ventricular end diastolic volume.

DETERMINATION OF THE DIASTOLIC VOLUME OF THE VENTRICLE

The diastolic pressure-volume relationship of each ventricle was determined directly in situ. After each experiment, the ventricle was immediately arrested with 25% KCl solution mixed with blood. This was introduced into the left ventricle as the aorta was occluded. Following arrest, the left atrium was cross-clamped close to the mitral annulus, and the aorta was reoccluded at the coronary ostia. A large bore needle was inserted into the midportion of the ventricular cavity, the chamber was emptied completely by aspiration and then filled with 2 ml increments of saline using a spring-loaded 2 ml syringe, left ventricular pressure being recorded continuously (fig. 2). If leakage from the ventricular cavity occurred during this procedure, a fall in pressure after each 2 ml increment was apparent, and, in addition, all of the injectate could not be regained. If leakage was noted within the range of pressures used in the experiment, the clamps were reapplied until the leak was corrected. Following arrest of the heart, reproducible pressure-volume curves could be obtained for many minutes with this technique, and from three to five curves were recorded for each ventricle (fig. 2C). The mean ventricular volumes, measured at a pressure of 7 mm Hg in the 10 ventricles studied ranged from 21 to 48 ml/100 g of left ventricular weight. The maximum deviation in absolute volume from the mean volume at 7 mm Hg in the group of curves for any given ventricle was 2.67 ml, and the maximum deviations in all 10 ventricles averaged 1.27 ml.

CALCULATION OF MYOCARDIAL WALL TENSION

The ventricle was considered to be a sphere, and the end diastolic volume for each beat was determined from the pressure-volume curve described above. The instantaneous systolic volume (\( V_s \)) was obtained by subtracting from the end diastolic volume the quantity of blood ejected up to the point of measurement, obtained by manual integration of the electromagnetic flowmeter tracing. The instantaneous radius could then be calculated by solving for \( r \) the formula: 
\[
V_s = \frac{4}{3} \pi r^3, \quad r = \text{the radius of the ventricle at the endocardial surface.}
\]
The total tension in grams developed by the myocardium at the equator was calculated from the formula \( T = P \cdot \pi r^2 \). In addition, in some experiments, radius at the midpont of the LV wall was also determined, wall thickness being estimated from the difference between intracavitary ventricular volume and ventricular weight; one-half of this additional radius was then added to the radius at the endocardium. The tension per unit length of circumference and per unit of wall thickness was calculated using the formula:
\[
T^* = \frac{P \cdot r'}{2 \delta}, \quad \text{where} \quad T^* = \text{wall tension in grams per cm}^2, \quad P = \text{intraventricular pressure in g/cm}^2, \quad r' = \text{midwall radius in cm}, \quad \delta = \text{instantaneous ventricular wall thickness in cm.}
\]
The shape of the basic force-velocity relation, and its alteration by inotropic influences were similar, regardless of the method used for calculating tension (fig. 6A and B).

CALCULATION OF \( V_{CF} \) AND \( V_{CE} \)

The instantaneous shortening rate of the circumferential fibers comprising the inner equator of the ventricle \( V_{CF} \) was calculated in the manner described by Levine and Britman. Thus, differentiation of the equation for a sphere yields
\[
dv/dt = 4 \pi r^2 \ \text{d}r/dt, \quad \text{and since} \quad V_{CF} = 2 \pi r^2 \ \text{d}r/dt, \quad \text{by substitution,} \quad V_{CF} = \text{aortic flow rate}/2 \ r^2.
\]
To calculate the shortening velocity of the contractile elements \( V_{CE} \), it was necessary first to derive the rate of lengthening of the nonlinear series elastic component (SE) of Hill’s 3-component system. The rate of tension development \( (dT/dt) \) is related both to the stiffness of the SE \( (dT/dl) \) and the rate at which the SE

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lengthens \((dl/dt)\). This relation,

\[
dT/dt = (dT/dl) (dl/dt),
\]

may be rearranged\(^{10}\) to:

\[
dl/dt = \frac{dT/dl}{dT/dl}.
\]

The relation between the stiffness of the SE and the load has been calculated recently for the cat papillary muscle and shown\(^{25}\) to be:

\[
dp/dl = k \cdot p
\]

where \(p\) = load in g. Since it was considered likely that factors such as ballooning of valves would tend to increase systolic ventricular compliance, and because the papillary muscle may become stiffer after excision,\(^{25}\) the lowest value for \(k\) observed in the isolated papillary muscle was selected. Thus, for use in the intact heart, \(k = 28\) (corrected for a muscle of 1 cm\(^3\) dimensions). The stiffness of the SE, \(dT/dl\) (\(T = \) tension per cm of circumference), could then be calculated as \(28T\).

\(dT/dt\) was calculated from the measured \(dp/dt\). Having calculated \(dT/dl\) and \(dT/dt\), it was then

\[
\frac{dT}{dt} = \frac{r^2}{A} \frac{dp}{dt} - p \cdot \frac{V_{CF}}{4 \pi A}.
\]

---

**FIGURE 2**

Left ventricular diastolic pressure-volume relations. Top two panels show pressure tracings obtained at slow (panel A) and more rapid paper speeds (panel B) as 2 ml increments of saline were introduced into the arrested, empty ventricle during inscription of two separate pressure-volume curves. Pressure recorded at a volume (Vol.) of 48 ml is shown at arrows. In panel C are plotted pressures and volumes measured during four injections of saline in the left ventricle of dog no. 10; a number of the points are superimposed.
Tracings showing effects of sudden progressive elevations of aortic pressure (Ao. Pr.) during diastole. Control conditions, shown by first beat in each panel, were allowed to recur between each pressure change, second beat in each panel is the contraction against altered afterload. Moment of pressure change (Pr. A), which occurred with actuation of the three-way valve, is indicated by arrow in first panel. Ao. Flow: blood flow in ascending aorta, S: driving stimulus on electrocardiogram (ECG), S.A. (arrows): stimulus artifact on flowmeter tracing. Left ventricular (L.V.Pr.) and left ventricular end diastolic pressure (LVED Pr.) are recorded at low and high sensitivities, respectively. dp/dt: rate of change of L.V. pressure.

Results

THE BASIC FORCE-VELOCITY RELATION

As shown in figure 3, with progressive increases in the afterload from a constant LVEDP, an inverse relation was observed between the left ventricular systolic pressure and the velocity of ejection. As the aortic pressure was increased, the peak ejection rate, the stroke volume and the duration of ejection diminished progressively.

In figure 4B, the changes in ejection velocity in the aorta, the LV pressure, and LV dp/dt are plotted against time during three individual contractions, selected from a series of beats in which the left ventricle was subjected to varying afterloads. Also shown (panel 4A) are the calculated tensions, the Vof, and the Vcb during these three contractions. In two beats ejection occurred, and in the third contraction was completely isovolumic. The time during the two auxotonic contractions at which isovolume point calculations were made are indicated by the vertical arrows in the middle panel (see below). In considering the time course of Vcb, it is apparent that the maximum Vcb for each beat did not occur.

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FIGURE 4

Time course of events occurring during three single contractions, one being isovolumic (open squares), one against a relatively high afterload (control, open triangles), and one against a lower afterload (unloaded, closed circles). Panel A shows data calculated at 10-msec intervals from information in panel B, the latter being obtained directly from tracings.

In panel A, tension = total myocardial wall tension in grams at the ventricular equator (T = P • r • r, see text); velocity of fibers = shortening velocity of circumferential fibers at the equator (VCF); velocity of C.E. = shortening velocity of the contractile elements (VCE).

Upward pointing arrows in middle figure of panel A indicate points of isovolumic used when calculating the F-V relation from multiple beats at varying afterloads. In panel A, top figure, the dotted line represents VCF, from adjacent panel below, superimposed on VCB.

HU: heart rate. Other abbreviations as in figure 3.

until approximately 40 msec had elapsed from the onset of ventricular pressure rise, and that the maximum levels were comparable in the three contractions. The subsequent time course of the VCF for each beat was then similar until the onset of ejection. The latter event was associated consistently with an increase in VCB, the VCE then reaching a higher level in the contraction in which the aortic pressure was lower. During ejection, the VCF and the VCE tended to approach the same level, becoming equal at maximum tension (dT/dt = zero).

When VCF and, in some experiments, VCE were plotted against myocardial wall tension at isovolume points in many beats subjected to a range of afterloads, an inverse linear relation between tension and velocity was shown clearly in all 10 dogs. The maximum and minimum levels of VCF and VCE and the corresponding tensions are summarized in table 1, and representative examples of the tension-velocity relation are shown in the control curves, figure 7. In figure 6A, both VCF and VCE were plotted simultaneously against myocardial wall tension. The relation between tension and VCE exhibited a slightly greater slope, since the difference between VCF and VCE was larger in unloaded beats (fig. 4); however, the basic reciprocal relation between force and velocity remained clearly apparent with either method of analysis. The differences between VCF and VCE in the control F-V rela-
TABLE 1

Relations Between Myocardial Wall Tension and the Velocity of Shortening in Variably Afterloaded Beats

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<th>Expt. no.</th>
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<th>Tension</th>
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<th>V\textsubscript{CE}</th>
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For each experiment, the relations between tension and velocity of shortening of the circumferential fibers (V\textsubscript{CF}) and contractile elements (V\textsubscript{CE}) are shown at the highest (top line) and the lowest imposed afterloads (lower line). V\textsubscript{CF} and V\textsubscript{CE} are also shown corrected for ventricular circumference (cm/sec/cm). HR: heart rate and MAP: mean aortic pressure during the control period prior to sudden alteration in the afterload. Tension in the myocardial wall is presented in two units: in the first column, tension in g (grams) represents total tension at the internal equator; in the second column, tension in g/cm\textsuperscript{2} represents tension corrected for unit wall thickness and circumference (see text). In experiments no. 1 and 6 \textit{dp/dt} was not recorded.

Velocity of shortening of circumferential fibers (V\textsubscript{CF}) plotted against myocardial wall tension at isovolume points in beats facing a range of aortic pressures. Tension in grams was calculated as in figure 4. Control tension-velocity relations in all three panels are represented by solid circles. Relation is shifted downward and to the left by acute heart failure (panel A, open triangles), and upward and to the right by norepinephrine (panel B, open triangles) and paired stimulation (panel C, open triangles).
Panel A: comparison of tension-velocity relations when shortening of both circumferential fibers ($V_{CP}$, circles) and contractile elements ($V_{CE}$, triangles) are plotted. Control relations are represented by open symbols and relations during norepinephrine infusion are represented by solid symbols. Tension in grams calculated as in figure 4. Panel B: relative position of tension-velocity relation when tension is calculated in terms of muscle length and wall thickness ($T' = \frac{P \cdot r}{2 \delta}$, see text). This panel may be compared with panel A, in which tension is calculated as total tension at the equator.

Velocity of contractile elements ($V_{CE}$) plotted against tension during single, isovolumic contractions. Control beats in both panels A and B are represented by open circles. In panel A, left ventricular end diastolic pressure ($LVEDP$) was constant at 5 mm Hg, and norepinephrine infusion (open triangles) resulted in a shift of the curve upward and to the right. In panel B, $LVEDP$ was constant at 4.5 mm Hg, and acute heart failure (open triangles) caused a shift of the curve downward and to the left. Tension was calculated as in figure 4.
tions are summarized in table 1. At the highest tensions, $V_{CE}$ exceeded $V_{CF}$ by an average of 7% (range 0 to 27%), and at the lowest tensions $V_{CE}$ exceeded $V_{CF}$ by an average of 21% (range 1 to 61%).

ALTERATIONS IN THE FORCE-VELOCITY (F-V) RELATION

After determination of the basic F-V relation, a positive inotropic influence was exerted either by the infusion of norepinephrine, or by paired electrical stimulation. The F-V relation was always shifted upwards and to the right by norepinephrine (figs. 5B, 6A, and B), and an even more striking shift in the same direction was apparent during paired electrical stimulation (fig. 5C), increases being evident both in the maximum tension developed, and in the maximum velocity, estimated by straight-line extrapolation to zero tension.

During acute heart failure, the F-V relation was shifted downward and to the left of the control determination (fig. 5A). The maximum tension developed was reduced and the maximum velocity estimated by extrapolation of the F-V relation to zero tension was lower.

$V_{CE}$ DURING SINGLE, COMPLETELY ISOVOLUMIC BEATS

An example of a completely isovolumic left ventricular contraction is shown in the final beat of the sequence reproduced in figure 3. During such contractions, an inverse and usually curvilinear relation between $V_{CE}$ and wall tension was evident (fig. 7A and B). In all experiments in which the output of the pump was varied to yield steady-state changes in ventricular end diastolic volume, inotropic background and heart rate remaining constant, the maximum tension developed was increased, but no obvious change was apparent in maximum velocity at zero tension, obtained by extrapolation (fig. 8). During norepinephrine administration (fig. 7A), the curve was shifted upwards and to the right, with increases both in maximum tension and maximum velocity, while during acute ventricular failure (fig. 7B), the relation was shifted downwards and to the left, both maximum tension and velocity being reduced.

Discussion

The present studies indicate that in the intact, canine left ventricle in which ventricular end diastolic volume is constant, stepwise increases in the afterload alone result in progressive decrements in the velocity of ejection, and that an inverse relation can be clearly demonstrated between the calculated wall tension and fiber or contractile element velocity.

In previous studies concerned with force-velocity relations in the intact heart, an inverse relation between wall tension and contraction velocity was also demonstrated; however, as mentioned earlier and as recognized by these authors, factors other than the force-velocity relation probably contributed to the scatter observed in these studies. Thus, when the F-V
relation is determined using velocities measured at peak tension, it is influenced by variations in muscle length. In addition, $V_{CB}$ measured at this point may be affected by a beginning decline in active state, since peak tension can occur late in ejection (fig. 4); moreover, the duration of the active state is shortened by many positive inotropic influences. In the studies by Fry and his co-workers, velocity was determined at a single muscle length, and while end diastolic volume was not constant, these authors deduced that in contractions originating from different resting fiber lengths, $V_{CB}$ should become identical at a given muscle length, an assumption which appears to apply within limits to skeletal muscle as well as to isolated heart muscle. However, isolument points occur at different times in beats that originate from various muscle lengths. Thus, variations in $V_{CB}$ can occur early in ejection (fig. 4), or result from termination of the active state. In the present experiments, isovolume points were taken as close in time as possible to peak flow (fig. 4), while ventricular end diastolic volume was constant. Although with high afterloads, isovolume points were of necessity slightly later in time, nevertheless they always occurred well before peak tension, and it is likely that inconsistencies resulting from variations in active state and muscle length were thereby minimized.

When $V_{CE}$ was plotted against time during single contractions, a delay in achieving maximum $V_{CE}$ was always evident (fig. 4). As pointed out earlier, the onset of active state in isolated cardiac muscle is relatively slow. In addition, in the intact ventricle, the time required for electrical activation, for effective synchronization of contractions, and for closure of the atrioventricular valves would further delay the time at which maximum $V_{CE}$ is measured. A secondary rise in $V_{CE}$ at the onset of ejection was observed consistently (fig. 4). In the papillary muscle, a rise and then a plateau in $V_{CE}$ are also observed regularly during external shortening, although the rise is sometimes less striking (fig. 9). The reason for this second increase in $V_{CE}$ is un-

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studies, a delay in achieving peak $V_{CB}$ was not observed, problems in determining $dp/dt$ by means of a cardiac catheter apparently precluding measurement of $V_{CB}$ early in contraction; and secondly, during early ejection they noted a fall rather than a rise in $V_{CB}$. The reason for the latter difference is not apparent, although it could be related in part to the aortic obstruction which these authors induced.10

While the curvilinear, inverse relation between force and velocity during single auxotonic contractions described by Levine and Britman16 thus was not apparent in the present studies, such a relation did occur during the isovolumic phase of such contractions, and during single isovolumic beats. It should be appreciated that the latter relation does not represent a true force-velocity curve, since shortening of the contractile elements, as well as unknown changes in the level of active state occur throughout the beat. However, internal shortening also occurs in determinations of the force-velocity relation in isolated papillary muscle, and the findings in the present studies suggest that determination of force-velocity curves during single isovolumic beats provides considerable insight into the level of contractile state. Thus, with positive inotropic influences, both $P_n$ and the extrapolation to $V_{max}$ increased, while with acute heart failure they diminished (fig. 7). Moreover, with this technique, the influence of changes in resting fiber length on the F-V relation could be analyzed, and was found to resemble the effect observed in the papillary muscle7 (fig. 8). The latter effect was difficult to determine using the technique of analyzing beats at various afterloads, since with steady-state increases in end diastolic volume, only those beats which ejected a substantial stroke volume could be compared at isovolume points with beats originating from a lower end diastolic volume. The method of analyzing isovolumic beats thus appears useful, and further investigations concerning its general applicability seem warranted since it offers the obvious advantages of eliminating the measurement of aortic blood flow and requiring relatively uncomplicated calculations.

Several problems concerned with the methods used in these experiments deserve comment. Heart rate, blood pressure, and stroke volume were, of necessity, controlled in this preparation, and the use of anesthesia and bypass of the right heart probably resulted in some depression of ventricular performance, particularly when perfusion of the head and neurogenic support of the heart were inadequate. However, in later experiments, the LVED pressures were low (10 mm Hg or less), and the cardiac outputs were relatively normal (averaging 81 ml/min/kg), suggesting that ventricular performance was not significantly compromised. The dynamics of ejection into the aortic root may have been modified somewhat in this preparation by cannulation of the descending aorta and by the small resistance imposed by the flowmeter probe. In addition, since aortic pressure was varied over a wide range, some alteration in the distensibility of the vascular segment faced by the left ventricle must also have occurred. To minimize this effect, a large reservoir bottle was used, which contained a small, constant volume of blood. With increases or decreases in afterload provided by this system, external shortening began only when pressure developed by the ventricle equalled that in the aorta.

Imperial et al. and Wilcken et al., using sudden alterations in resistance, demonstrated an inverse relation between resistance to ventricular ejection, and stroke volume and peak flow rate.20-27 However, use of the present technique, by which blood is actively introduced or removed from the aorta during diastole, offers advantages over methods in which resistance alone is altered, since in the latter case, ejection commences at a diastolic pressure close to that of the previous beat, and external fiber shortening must occur before pressure can attain the new level.

It is recognized that uncertainties exist in regard to the technique for determining ventricular end diastolic volume. Acute changes in ventricular distensibility could have fol-
lowed cardiac arrest, although against this possibility are the reproducibility of the pressure volume curves for many minutes, and previous observations indicating that rigor develops in acutely excised mammalian hearts only after periods of approximately 50 to 80 minutes. Most available data indicate that acute changes in inotropic state do not alter diastolic compliance in isolated muscle or in intact ventricles, although there is some evidence to the contrary. Finally, it is possible that some diminution in the volume of the empty ventricle resulted from application of the clamp near the mitral annulus. However, such an effect would produce identical errors in all of the volume measurements during an experiment and, therefore, should not affect the magnitudes of the shifts in the F-V relations that were demonstrated. In addition, indirect evidence that the end diastolic volumes were appropriate in magnitude is provided by the ratios of stroke volumes, measured with the flowmeter, to the end diastolic volumes. Thus, the average ratio of 50% observed in the later experiments in the present studies is comparable to that found in various species by the indicator dilution technique. While the possible limitations discussed above may apply to the method described, significant technical difficulties and inaccuracies are also inherent in all other techniques currently available for measurement of ventricular end diastolic volume.

Lastly, as mentioned earlier, the factor for series elastic stiffness was selected from data obtained in isolated cardiac muscle. Since this factor was a constant, its magnitude should not have influenced shifts in $V_{CE}$ which occurred during induced changes in contractile state. Moreover, it is of interest that the maximum values for $V_{CE}$ calculated using this factor (table 1) are of a similar order of magnitude as those reported by Fry et al. using an entirely different approach.

In conclusion, it is proposed that with the present analyses, basic changes in the contractile state of the myocardium can be identified. In isolated papillary muscle, the velocity that can be achieved with zero load ($V_{max}$) has been shown to increase with positive inotropic influences, such as norepinephrine and paired stimulation, suggesting that these interventions accelerate the basic processes controlling the rate of force generation. Maximum tension ($P_o$) is markedly influenced by resting muscle length in the papillary muscle, while positive inotropic influences may or may not vary $P_o$. It would appear from these considerations that $V_{max}$ provides the most reliable indication of the level of myocardial contractile state in isolated muscle. In the intact heart, recent studies from this laboratory on sustained postextrasystolic potentiation have pointed out limitations of the ventricular function curve in describing alterations in the contractile state, particularly when they are evidenced primarily through effects on speed of contraction. While analysis of the rate of change of the ventricular pressure $(dp/dt)$ gives additional insight into the level of contractile state, it cannot provide direct information regarding $V_{max}$ and $P_o$, and the precise nature of its correlation with the force-velocity relation awaits further clarification. It is suggested, therefore, that the methods described for relating tension and velocity extend previous measures of the ventricular contractile state by providing an estimate of maximum speed of contraction, as well as maximum strength relative to instantaneous muscle length.

**Summary**

Relations between tension and the velocity of shortening in the intact left ventricle of the dog were examined in a manner analogous to that employed in isolated muscle, i.e., by serial, reproducible variations in the afterload alone, from a constant end diastolic volume. Sudden increases or decreases in the aortic pressure during diastole were produced, and ejection rate was measured with an electromagnetic flowmeter; LV wall tension and the shortening velocities of the myocardial fibers and the contractile elements were then calculated. By analyzing isovolume points early in ejection, effects resulting from two other determinants of shortening velocity, duration of active state and instantaneous muscle length.
length, were minimized. Shifts in the basic force-velocity relation with alterations in $V_{\text{max}}$ obtained by extrapolation, and maximum tension were clearly demonstrated. Norepinephrine and paired electrical stimulation caused a shift in this relation to the right, with increases in velocity at any tension, and acute heart failure produced a shift to the left, with decreases in velocity at any tension. Similar shifts were also apparent in curves relating tension to velocity, calculated during single isovolumic contractions. It was suggested that determination of these relations expands traditional definitions of ventricular performance, and that estimation of changes in maximum velocity as well as maximum strength relative to muscle length provides direct information concerning alterations in the contractile state of the intact heart.

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Contractile State of the Heart Characterized by Force-Velocity Relations in Variably Afterloaded and Isovolumic Beats
John Ross, Jr., James W. Covell, Edmund H. Sonnenblick and Eugene Braunwald

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