Comparison of the Force-Velocity Relation and the Ventricular Function Curve as Measures of the Contractile State of the Intact Heart

By James W. Covell, M.D., John Ross, Jr., M.D., Edmund H. Sonnenblick, M.D., and Eugene Braunwald, M.D.

ABSTRACT

The contractile state of the intact canine left ventricle was investigated by determining the instantaneous relations between tension and contractile element velocity (VCE) during the course of single, isovolumic beats produced by balloon occlusion of the aorta. The relative sensitivity of this relation was compared with that of the ventricular function curve (VFC) by exerting small inotropic influences. In seven experiments, low doses of norepinephrine always shifted the isovolumic force-velocity (FV) relation, increases occurring in maximum VCE (32.7%) and maximum tension (P0) (16.9%). The VFC was unchanged in four of the seven dogs. Moderate hypothermia (average 30.8°C) in four dogs increased P0 (average 28%), with no change, or a fall, in maximum VCE; the VFC during hypothermia was shifted upward and to the left in two experiments and unchanged in two. Moderate increases in heart rate always produced increases in maximum VCE (average 13.5%) but no change in the VFC was observed. Thus, the isovolumic FV relation proved more sensitive than the VFC in detecting changes in myocardial contractile state and allowed more complete definition of these alterations by providing separation of changes in shortening velocity from alterations in the strength of myocardial contraction.

ADDITIONAL KEY WORDS left ventricular performance mechanics of cardiac muscle end-diastolic volume cardiac wall tension cardiac output heart rate hypothermia norepinephrine cardiac contractility anesthetized dogs

- The contractile state of isolated cardiac muscle can be described in terms of the instantaneous relations between the force of contraction and the velocity of shortening.1,2 Recently, it has been demonstrated that an inverse relation between force and velocity also applies to the intact canine left ventricle,3-5 and that when ventricular volume and time are considered, the position of the curve describing this relation reflects the contractile state of the ventricle.5 Studies in this laboratory have shown that a single isovolumic contraction can be induced in the intact heart by sudden elevation of the resistance to left ventricular ejection during diastole; analysis of the relation between the force of contraction and the velocity of the contractile elements (VCE) during the course of such an isovolumic beat also provides an indication of the level of contractile state.5,6

The present investigation was designed to determine the usefulness of this type of analysis in the detection of changes in the contractile state of the intact left ventricle and to compare its sensitivity with that of the ventricular function curve. Relatively small inotropic influences were exerted by low doses of norepinephrine, mild hypothermia, or moderate increases in the rate of ventricular contraction. The relative sensitivity of the force-
velocity (FV) relation during isovolumic contractions was then compared with that of two standard techniques for assessing ventricular performance: the relations between the left ventricular end-diastolic pressure and stroke work\(^7\)\(^8\) and stroke volume\(^9\).

**Methods**

Fifteen mongrel dogs weighing between 14.5 and 23.6 kg were anesthetized with sodium pentobarbital (average dose 40 mg/kg). The trachea was intubated and ventilation with 100% oxygen was provided with a Harvard respiratory pump. The experimental preparation, shown schematically in figure 1, consisted of a right heart bypass preparation, and a device for rapidly occluding the aortic root during diastole. A bilateral thoracotomy was performed, the heart was suspended in a pericardial cradle, and bypass of the right heart was carried out as described previously\(^10\). Large-bore metal cannulae were inserted into the femoral arteries pointing toward the aorta and systemic arterial pressure was regulated by means of a reservoir attached to a compressed air circuit. The sinoatrial node was crushed and heart rate was maintained constant or, in some experiments, was increased by pacing the right atrium or right ventricle with an electronic stimulator.* Left ventricular and aortic pressures were measured through large-bore (5 mm) metal cannulae inserted through the left ventricular apex and the left subclavian artery and connected directly to Statham P23Db transducers. The first derivative of the left ventricular pressure pulse (LV dp/dt) was obtained with an analog differentiating circuit.† This circuit exhibited a phase shift of \(90^\circ \pm 1^\circ\) to a sine wave input from 0 to 160 cps, and amplitude was a linear function of frequency. A flow transducer was placed around the ascending aorta, and the flow was monitored with a gated sine wave electromagnetic flowmeter‡ to confirm that ejection was absent during the isovolumic contractions. The dynamic characteristics of this instrument have been described previously.\(^8\) All determinations were recorded together with the electrocardiogram on a multichannel oscillograph§ at a paper speed of 100 mm/sec.

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*American Electronic Laboratories, Inc., Colmar, Pa., Model No. 104A.
†Assembled by Electronic Gear Inc., Valley Stream, N. Y., from a Philbrick #P65AU operational amplifier.
‡Biotronex Laboratories, Inc., Silver Spring, Maryland.
§Sanborn Model 350.

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Sudden occlusion of the aortic root was accomplished by rapid inflation of a rubber balloon attached to the tip of a metal cannula. The cannula was inserted through the right subclavian artery so that the balloon was positioned in the ascending aorta just above the aortic valve (fig. 1). The tip of the cannula was placed in the left
sinus of Valsalva, so that when the balloon was inflated, it interfered with aortic valve opening; systolic coronary blood flow was thereby minimized and the contraction was essentially isovolumic. A power syringell was employed to inflate the balloon, and the syringe was triggered by the electrocardiogram to fire at a selected time during diastole.

Left ventricular function curves, i.e., the relations between left ventricular end-diastolic pressure (LVEDP) and stroke work⁷,⁸ were determined by altering the output of the occlusive pump and maintaining mean arterial pressure constant. It should be emphasized that with the right heart bypass preparation, in contrast to the isolated supported heart,⁷,⁸ relatively high flow rates, in the neighborhood of 170 ml/min/kg, are required to achieve LVEDP's of 20 cm H₂O. At higher flow rates, pulmonary hemorrhage frequently ensues, apparently as a result of the nonphysiologic pattern of pulmonary arterial perfusion. However, the flow rates employed were sufficient to produce at least a threefold increase in the LVEDP; LVEDP averaged 5.4 cm H₂O in the control state, and the physiologic range was thus encompassed.

Stroke work (SW) in g-mm was calculated as the product of the mean left ventricular pressure during ejection, determined by planimetric integration (mean LV), and stroke volume (SV), using the following formula:

\[ SW = \frac{(\text{mean LV} - \text{LVED}) \times (1.36) \times (SV)}{100} \]

In some experiments, SW was also calculated using mean aortic pressure, and no differences in the results were apparent. SV was determined from the output of the calibrated occlusive pump and the heart rate. Stroke power was calculated by dividing stroke work by the ejection time.

Isovolumic contractions of the left ventricle, induced by sudden occlusion of the aorta by the balloon in early diastole (fig. 1), were analyzed only when no evidence of ventricular ejection appeared in the aortic pressure or aortic flow tracings. The diastolic pressure-volume curve of the left ventricle was determined at the end of each experiment using a method described in detail previously⁵; in brief, the heart was arrested with 25% KCl, the mitral and aortic valves occluded, and the cavity filled with 2-ml increments of fluid. The left ventricular end-diastolic volume of each beat was then determined directly from the pressure-volume curve.

Myocardial wall tension in isovolumic beats was calculated at 10 msec intervals from the Laplace relation, as described previously⁶, \( T = \frac{P \pi r^2}{2}, \) where \( T = \) wall tension in grams, \( P = \) intraventricular pressure in g/cm² and \( r = \) internal left ventricular radius. \( r \) was calculated from the end-diastolic volume by assuming a spherical left ventricular model and solving the equation \( V = \frac{4}{3} \pi r^3, \) for \( r. \)

Contractile element velocity (Vₐₑ) during the isovolumic beats was considered equal to the rate of lengthening (dl/dt) of the series elastic component, dl/dt being directly proportional to the rate of tension development (dT/dt) and inversely proportional to the stiffness of the series elastic component (dT/dl)¹¹; thus, \( V_{CE} = \frac{dT/dt}{dl/dt}. \)

In analyzing the instantaneous relations between force and velocity, a slow rise in Vₐₑ has been found during the initial 20 to 30 msec of contraction, which necessitates considerable estimation in constructing the extrapolation of the force-velocity curve to zero tension (Vₐₑ). Therefore, the maximum Vₐₑ reported herein represents the greatest measured velocity on the FV curve following this slow increase in Vₐₑ. Comparisons between the maximum Vₐₑ before and after an intervention were always made at the same tensions. The tension developed during each beat when Vₐₑ was zero, i.e., the maximum tension, is referred to as F₀.

After determining the force-velocity relation and the ventricular function curve during the control state, the following interventions were employed: (1) infusion of norepinephrine, in doses ranging from 0.03 to 0.36 μg/kg/min, and averaging 0.16 μg/kg/min (7 experiments); (2) increases in heart rate of 17 to 42 beats per minute and averaging 32 beats per minute (four experiments); (3) hypothermia, induced by blood cooling with the heat exchanger (fig. 1), to levels of 30.3° to 31.4°, and averaging

*The stiffness of the series elastic component has been shown to be a linear function of tension in cardiac muscle: \( dT/dl = KT + al \), as described previously, this factor corrected for 1 cm³ of muscle becomes: \( dT/dl = 28T. \) For the calculation of \( dT/dl, \) tension is expressed per unit circumference, assuming a constant wall thickness of 1 cm: \( T = \frac{Pr}{2}. \) Differentiation of this equation yields: \( dT/dl = \frac{r}{(r \sqrt{P^2 - D^2})}, \) where \( r \) is zero in isovolumic beats, \( dT/dl = \frac{r}{(r \sqrt{P^2 - D^2})}, \) and the final form of the equation \( V_{CE} = \frac{dT/dt}{dl/dt} \) then becomes:

\[ V_{CE} = \frac{(2\pi r)}{28} \frac{dP/dt}{dP/dt} = \frac{\pi r dP/dt}{14P} \]

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30.8°C (four experiments). During a steady state following any of these interventions, the isovolumic FV relation was again determined, the LVEDP being maintained at a level identical to that during the control period by altering the output of the pump (fig. 1). The ventricular function curve was also determined again at the same mean aortic pressure and heart rate (except in experiments in which the effects of changing this variable were studied); ordinarily, the FV relation was determined before and after each ventricular function curve. The mean aortic pressure in these studies ranged from 79 to 130 mm Hg and averaged 98 mm Hg. In some experiments, sequential, paired measurements of the isovolumic FV relation were made during a steady state. The interval between these paired analyses was 2 to 4 minutes, and the reproducibility of the technique was determined from a comparison of these curves.

Results

1. Reproducibility of FV curves. A curvilinear, inverse relation between force and velocity was always obtained during isovolumic contractions plotted from maximum \( V_{CE} \) to peak tension (\( P_o \)). Representative tracings are shown in figure 2 and examples of this relation obtained during the control state and during various interventions are shown in figures 3 to 5.

The reproducibility of these curves was examined by determining the differences between maximum \( V_{CE} \) and \( P_o \) in 14 pairs of isovolumic beats. The differences between paired determinations of maximum \( V_{CE} \) averaged 3.4% (range 0 to 10.8%, \( \text{SD} = \pm 3.44\% \)) and of \( P_o \), 2.4% (range 0.4 to 5.9%, \( \text{SD} = \pm 2.0\% \)). In absolute terms, the \( \text{SD} \) of the differences

![Figure 2](image-url) - Recordings of auxotonic and isovolumic beats at 35.8°C (control) and 30.8°C (hypothermia). Mean aortic pressure (Ao. Press.) is 75 mm Hg during both control and hypothermia. The arrows indicate the onset of inflation of the balloon in the aortic root, producing an isovolumic contraction in the following beat.

![Figure 3](image-url) - Isovolumic force-velocity curves and ventricular function curves obtained prior to (dots) and during (triangles) the infusion of norepinephrine (0.03 \( \mu \)g/kg/min). The force-velocity relation is shifted upward and to the right during norepinephrine infusion, while the relations between left ventricular end-diastolic pressure (LVEDP) and stroke work and stroke volume show no change.

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of the values for maximum $V_{CE}$ and $P_o$ during the control state was $\pm 0.38$ cm/sec and $\pm 34.8$ g, respectively.

2. Effects of norepinephrine. In the seven experiments in which norepinephrine was infused, $P_o$ always increased; these increases ranged from 20.4% to 45.1%, and averaged 32.7%. In addition, maximum $V_{CE}$ was always augmented, the increases ranging from 14% to 29% and averaging 16.9%. In contrast, in four of the seven experiments, the relations between LVEDP and the SW or SV showed no detectable alteration from the control state during the infusion of norepinephrine; curves representative of those showing no discernible change are shown in figure 3. In the remaining three experiments, the shift of the FV relation was accompanied by a shift in the relation between LVEDP and SW upwards and to the left. In only one of the seven experiments was there a clear-cut shift of the relation between LVEDP and SV upwards and to the left. Stroke power at any given LVEDP was increased in five of the seven experiments, and LV dp/dt increased in all experiments.

3. Effects of hypothermia. In the four experiments in which moderate hypothermia was induced, $P_o$ was always increased, the increases ranging from 22% to 40% and averaging 28%. In three experiments, maximum $V_{CE}$ was unchanged (fig. 4, bottom), while in one experiment it appeared to be slightly decreased (fig. 4, top). The relations between LVEDP and both SV and SW were shifted upwards and to the left in two experiments (fig. 4, bottom) and were unchanged in two (fig. 4, top). Stroke power and LV dp/dt were slightly decreased in all experiments.

4. Effects of increases in heart rate. In four experiments, moderate increases in heart rate were induced. These increases averaged 32 beats per minute above control, and maximum levels of 163/min (154 to 171) were reached. In all four experiments maximum $V_{CE}$ increased by 10 to 18%, average 13.5% (fig. 5). Although $P_o$ was slightly increased in all four experiments (1 to 8%, average 3.5%), in three of them this change was less than 2 SD of the differences between $P_o$ in paired control beats. The increase in heart rate did not alter the relations between LVEDP and SV or SW. Stroke power and LV dp/dt were slightly greater at the higher heart rates.

Discussion

It has been shown previously that when the LVEDP and the instantaneous relations between muscle length and time are controlled, the force-velocity relation reflects the contractile state of the intact left ventricle. In the present study, the usefulness and sensitivity of the relation between wall tension and the velocity of the contractile elements during
the course of single isovolumic left ventricular contractions, which has also been shown to reflect alterations in contractile state, was examined using a less complicated preparation. This experimental technique entails sudden occlusion of the ascending aorta with a balloon, and has the advantages of technical simplicity and of being potentially applicable to the closed-chest animal; moreover, since external shortening does not occur, the calculations are simplified.

The force-velocity (FV) relation calculated during isovolumic beats consistently detected relatively minor alterations in the contractile state of the intact left ventricle. Thus, in seven experiments in which small doses of norepinephrine were infused, both maximum VE and Pp always increased. These effects on the FV relation were qualitatively similar to those produced by norepinephrine in isolated cardiac muscle, and by larger doses of norepinephrine in the intact canine left ventricle. In contrast, the effects of these doses of norepinephrine on the ventricular function curve were inconsistent, and in four of the seven experiments these curves showed no detectable change from control; the relation between LVEDP and SW was shifted in only one experiment. Thus, although it is clear that large doses of norepinephrine can shift the relation between LVEDP and SW upwards and to the left, the isovolumic FV relation proved to be more sensitive in describing the alterations in the contractile state induced by smaller doses of this agent. The increases in Pp and maximum VE were sizeable and averaged 20.1% and 33.7% of control, respectively, in the four experiments in which no detectable shift in the ventricular function curve occurred.

During hypothermia, the isovolumic FV relation was also consistently altered, Pp being increased in all four experiments, and maximum VE being unchanged in three and slightly depressed in one. The ventricular function curves were not shifted in two experiments and were shifted upward and to the left in two. It has been shown in isolated cardiac muscle that hypothermia diminishes Vmax. It is possible that the finding of a diminution of maximum VE in only one of the present experiments is related to the fact that they were performed at considerably higher temperatures than those in the isolated muscle. It has also been shown in isolated cardiac muscle that hypothermia causes an increase in Pp, and that in the isovolumically or auxotonically contracting left ventricle an increase in peak LV pressure, or in LV contractile force measured with a strain gauge arch, occurs during hypothermia. The consistent increases in Pp in the present studies, with a shift of the ventricular function curve in only two of the experiments, indicate that the isovolumic FV relation was again more sensitive than the ventricular function curve in detecting alterations in the strength of left ventricular contraction. Moreover, the FV relation permitted more complete definition of the effects of hypothermia on left ventricular performance than the ventricular function curve, since, despite increases in Pp, the maximum velocity of contraction was unchanged or reduced.

In the present study, moderate increases in heart rate always resulted in an increase in maximum VE. The effect of heart rate on Pp was slight, this variable being significantly
increased in only one experiment. In all four experiments the ventricular function curves showed no change from control at the increased contraction rates. In the isolated cat papillary muscle, increasing the frequency of contraction increases $V_{\text{max}}$, with a small increase in $P_o$, the latter becoming negligible at higher frequencies of stimulation. An increase in force has been observed in the isovolumic dog left ventricle as heart rate is elevated up to 148/min and in the isolated right ventricle of the dog at rates up to 240/min. Mitchell and his co-workers have also shown that the speed of contraction, reflected in stroke power and LV dp/dt, is increased by increasing heart rate, while stroke work may remain unchanged. In the present study, the increases in maximum $V_{\text{CE}}$ at higher heart rates, in the absence of alteration in the ventricular function curve, demonstrate directly the inability of the latter to assess alterations in contractile state that are reflected primarily in changes in the velocity of contraction, a conclusion suggested from previous observations in this laboratory.

It is evident that determination of the FV relation during the course of single isovolumic contractions by the present method presents certain theoretical problems. First, changes in the level of active state with time may affect the instantaneous relation between force and velocity. However, in isolated cardiac muscle, active state (defined as the time course of contractile element velocity at constant load and length) has been shown to be rather slow in onset, to reach a plateau, and then to decline at about the time peak tension is reached. Thus it is likely that when the FV relation is measured only between maximum measured velocity and peak tension, the effect of variations in the level of active state is relatively minor. The effects of fiber bundle slippage, and the compliance of the short segment of aorta between the balloon and the left ventricular outflow tract, while probably small, would tend to make the calculated contractile element velocities too low. Finally, in cardiac muscle, true $P_o$ as measured in skeletal muscle cannot be determined because of inability to tetanize cardiac muscle. In this connection it is of interest that the higher $P_o$ during hypothermia may be related solely to the increased duration of active state; thus, it is possible that in the hypothermic heart, the observed $P_o$ approaches true $P_o$. It is apparent, then, from the above considerations that in general the two extremes of the FV curve during single isovolumic contractions, can provide only estimates of the true $V_{\text{max}}$ and $P_o$.

All of the comparisons between isovolumic beats were made in contractions originating from the same LVEDP, and any errors in absolute volume would apply therefore during both the control state and the intervention. Moreover, although there are some suggestions to the contrary, the bulk of evidence suggests that norepinephrine, moderate changes in heart rate, or mild hypothermia do not affect diastolic compliance, and the assumption that a single diastolic pressure-volume curve is applicable therefore appears justified. Recent experiments in isolated papillary muscle in this laboratory have further supported the concept that the interventions employed in the present studies have no direct effect on diastolic compliance; thus norepinephrine, mild hypothermia, and changes in heart rate were found to have no influence on resting length or tension under conditions of isotonic contraction, although when large increases in isometrically developed tension were permitted to occur, stress relaxation of a series viscous component resulted in small reductions in resting tension. It should be emphasized that in the present experiments, the systolic tensions before and during the interventions were maintained quite constant. While it is recognized that apparent changes in diastolic ventricular compliance can result from incomplete relaxation of the myocardium during tachycardia and hypothermia, the heart rates employed were selected to avoid this problem. Thus, the maximum heart rates were below those which shift the diastolic pressure-volume relations both at normal temperature and during mild hypothermia (154 to 177, and 92 to 106, respectively).
Several factors may play a role in the greater sensitivity of the FV relation compared to the ventricular function curve in detecting small increases in the velocity and force of myocardial contraction under the present experimental conditions. Most importantly, it is clear that the relation between LVEDP and stroke work provides no direct information concerning the speed of myocardial contraction, while the FV relation permits comparison of instantaneous velocities at comparable tensions, as well as estimation of changes in $V_{\text{max}}$. Since positive inotropic influences are generally accompanied by increased shortening of muscle fiber and elevation in the ratio of stroke volume to end-diastolic volume, these influences usually augment the stroke work from the same ventricular end-diastolic pressure and at a constant mean aortic pressure; the ventricular function curve is then shifted upwards, revealing the directional alteration in the extent of muscle fiber shortening. However, the ventricular function curve appears to be less sensitive than the FV relation in detecting alterations in the force of contraction. An explanation for the finding that in many experiments no increase in the stroke work was apparent when positive inotropic influences were exerted, while the FV curve was displaced, probably lies in the complexity of the instantaneous relations between preload, afterload, and length, as well as in the varying level and duration of the active state. All of these factors are reflected in the isovolumic tension-velocity curve, while the relation between mean systemic arterial pressure, stroke volume, and the LVEDP appears to provide an indirect and less insensitive measure of actual tensions in the ventricular wall, and the extent of myocardial fiber shortening.

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