Instantaneous Pressure-Volume Relationships and Their Ratio in the Excised, Supported Canine Left Ventricle

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ABSTRACT

We have previously shown in the normally ejecting canine left ventricle that $E(t)$, the time-varying ratio of instantaneous pressure, $P(t)$, to instantaneous volume, $V(t)$, is little affected by end-diastolic volume or aortic pressure. The present study on an excised, supported canine heart preparation indicates that the thesis on $E(t)$ is also valid for either totally isovolumic or auxobaric beats. Intraventricular volume was measured more accurately than it was in the previous study by a new volumetric system. Regression analysis of the data showed that the instantaneous pressure-volume relationship could be approximated by the equation $P(t) = E(t) \cdot (V(t) - V_a)$, where $V_a$ is an empirical constant, over a wide range of intraventricular volume. Similar $E(t)$ curves were obtained from both isovolumic and auxobaric beats for a given contractile state. When the contractile state of the preparation was enhanced by a constant-rate infusion (0.2 $\mu$g/min) of norepinephrine or isoproterenol into the coronary artery, the peak magnitude of $E(t)$ increased 63% from 3.6 mm Hg/ml and the time to peak $E(t)$ shortened 10% from 175 msec. We conclude that the present investigation substantiates our earlier study which established a link between $E(t)$ and the contractile state of the heart.

KEY WORDS

- pressure-volume diagram
- instantaneous elasticity
- cardiac mechanics
- ventricular elastance
- index of contractility
- ventricular volume
- ventricular compliance
- volume transducer

In a description of the ventricle as a contracting chamber, instantaneous blood volume and instantaneous pressure constitute the most fundamental variables. In the in situ canine left ventricle contracting in the natural mode, i.e., an isovolumic contraction followed by ejection, we have found that the instantaneous ventricular pressure can be correlated with the concomitant ventricular blood volume in a simple, direct manner (1). We have shown that the magnitude and the time course of the time-varying ratio of pressure to volume, $E(t)$, is independent of end-diastolic volume and arterial pressure within their physiological ranges, whereas $E(t)$ is affected specifically and sensitively by inotropic interventions (1). However, whether these same features of the time-varying pressure-volume ratio characterize totally isovolumic and auxobaric contractions, which represent the two extremes of loading in natural heart beats, has not been fully examined.

In the present study, we thoroughly investigated the pressure-volume relationships obtained at various times during either a totally isovolumic contraction or an auxobaric contraction. Furthermore, we used an excised, supported canine heart preparation, because in this preparation the absolute internal volume of the left ventricle could be measured, by a newly devised volume-transducer system, more accurately than was possible with the plethysmographic method used in the previous study (1). In addition, we could ensure the absence of neurogenically induced changes in the contractile state.

Methods

HEART PREPARATION

Twelve canine hearts (left ventricular weight 112 ± 20 g) were excised from mongrel dogs which weighed 22 ± 3 kg. In each experiment, a pair of dogs was anesthetized with sodium pentobarbital (30 mg/kg, iv). The larger dog (28 ± 4 kg) of the pair was used to support the heart preparation.

After the chest of the smaller dog had been opened under artificial respiration, the left subclavian artery and the right ventricle were cannulated and connected to the support dog’s femoral arteries and veins, respectively. A heart-lung preparation was instituted by ligat-
ing the descending aorta, the brachiocephalic artery, the superior and inferior caval veins, and the aygos vein. The pulmonary hili were ligated, and perfusion of the heart preparation was started. No period of interruption of coronary blood flow occurred. The heart thus supported was then excised from the chest and suspended in a cup that was filled with blood and situated over a funnel (Fig. 1). The right ventricular cannula was removed and connected to the bottom of the funnel. The coronary venous blood was drained through the right ventricular incision, collected by the funnel, and returned to the support dog.

The left atrium was opened, and all the chordae tendineae were freed from the mitral valves. A thin latex balloon with an unstressed volume of about 70 ml was placed within the left ventricle via the mitral annulus. A miniature pressure transducer (Konigsberg, P-21) was placed inside the balloon, and its connection wire was pulled out through a stab incision at the apex. The opening of the balloon was fixed to a rigid connecting tube (12 mm, i.d., 30 mm long), and the roots of the mitral valves were tied around the opening with a purse-string suture. An appropriately shaped flange protruding from the end of the connecting tube attached to the balloon was positioned so as to prevent bulging of the balloon into the aorta.

The space between the balloon and the endocardium was maintained at a minimum by applying continuous suction through a catheter with multiple sideholes placed between the balloon and the ventricle; the catheter drained out the thebesian flow. Since the balloon’s membrane was flabby and its unstretched volume was larger than the intraventricular volume, we assumed that the balloon wall could go into most of the indentations among the trabeculae carneae.

The excised heart preparation and the support dog were placed on the same level. No pump was used for the coronary perfusion. The coronary perfusion pressure (the support dog’s arterial pressure minus some hydrostatic pressure difference) was 95.6 ± 15.0 mm Hg; it remained nearly constant throughout each experiment. Dextran solution (6% Macrodex 70) was infused as needed to maintain the support dog’s arterial pressure. The support dog inhaled 95% O₂-5% CO₂.

**VOLUME MEASUREMENT**

Figure 1 illustrates the system used to measure absolute intraventricular volume. The system consisted of (1) a plastic cylinder (35 mm, i.d., 200 mm long) fitted with a pair of precisely parallel electrodes (stainless steel wires 2 mm in diameter set 20 mm apart), (2) a Wheatstone bridge circuit (arm resistor 30 ohms, 1 w), and (3) a carrier amplifier (Brush 13-4212-02C13). The bottom orifice of the cylinder was connected via a semirigid tube (12 mm, i.d.) to the connector of the intraventricular balloon. The cylinder and the balloon were filled with ordinary tap water. To avoid thermal drift of the measuring device, the water was maintained at 37°C by a heat exchange coil wrapped around the cylinder. Changes in the volume of water in the cylinder were measured by changes in the electrical impedance across the electrodes. The total volume of water in the system was kept constant throughout each experiment. The ventricle ejected water into the cylinder during systole and was filled with water from the cylinder during diastole. The changes in the volume of water in the balloon were exactly the same as those in the cylinder. Therefore, the volume changes measured in the cylinder were equal to the actual volume changes in the ventricle.

The calibration for zero water volume within the balloon was determined by sucking all the water from the balloon into the cylinder by applying negative air pressure to the water column in the cylinder. After this calibration, the instantaneous output of the volume transducer yielded the absolute instantaneous water volume within the balloon.

The calibration for positive water volume within the balloon was determined by forcing all the water from the cylinder into the balloon by applying positive air pressure to the water column in the cylinder. After this calibration, the instantaneous output of the volume transducer could be used to determine the absolute instantaneous water volume within the balloon.

The overall error was 0.5 ml over a 100-ml volume change. The time derivative of the output of the volume transducer was identical to the flow signal measured by an electromagnetic flow probe placed between the volume transducer and a flow generator up to a volume change of 150 ml/sec. Since the electromagnetic flowmeter could measure only the time derivative of a ventricular volume change, we could not use it to measure the absolute intraventricular volume.
VENTRICULAR PRESSURE-VOLUME RATIO

PRESSURE MEASUREMENT
To measure left ventricular transmural pressure, the suspended ventricle was immersed in blood up to the level of the atrioventricular groove (Fig. 1). The hydrostatic pressure gradient thus produced outside the ventricle counteracted the same gradient inside the ventricle to give such a transmural pressure. A low-volume displacement pressure transducer (Statham P23BV) was appropriately calibrated and connected via a short side tube to the intraventricular balloon at the atrioventricular groove. While the ventricle was contracting isovolumically, the miniature pressure transducer was calibrated to give an output identical to that of the second pressure transducer.

LOADING CONDITIONS
The end-diastolic intraventricular volume was controlled by adjusting the amount of air in the air space of the volumetric system. As shown in Figure 1, an air chamber was connected to the air space of the volumetric cylinder. Increasing the amount of the air increased the end-diastolic volume of the ventricle. When the system was set up as is in the figure, the ventricle contracted auxobarically, i.e., it ejected throughout systole. An isovolumic contraction was obtained by completely closing the connecting tube between the balloon and the cylinder after the end-diastolic volume had been set at the desired level.

The size of the air chamber used throughout the experiment was about 100 ml. This size was chosen because it maximized the stroke volume from a midrange end-diastolic volume (about 40 ml) in most hearts. The ejection fraction for an auxobaric contraction was 29.8 ± 7.1% during the control contractile state and 37.7 ± 7.4% during the enhanced contractile state.

EXPERIMENTAL PROTOCOL
The instantaneous pressure-volume relationship was studied during a control contractile state and with an enhanced inotropic background. We defined the contractile state as that of the excised heart perfused by the support dog without any inotropic intervention. The contractile state was enhanced by a constant-rate infusion (0.2 μg/min) of either norepinephrine or isoproterenol into the coronary artery.

During both the control and the enhanced contractile state, end-diastolic volume was changed in steps to about five different levels within the physiological range (15 to 60 ml), which corresponded to an end-diastolic pressure range of 0 to 20 mm Hg. At each end-diastolic volume, contraction was set alternately to the isovolumic or the auxobaric mode. The volume was increased and then decreased at least once to cover the entire range under each contractile state.

DATA ANALYSIS
Intraventricular pressure and volume were traced on a strip chart and recorded on a magnetic tape. The data on the tape were reproduced on an x-y recorder to obtain pressure-volume loop diagrams. The tape was also used to digitize the data (sampling time 5 msec) for computer processing. For a manual analysis of the data, the onset of systole was determined on the strip-chart record as the time at which a clear rise in ventricular pressure was discernible.

To analyze the pressure-volume relationship, we first collected from variously preloaded beats a large number of pressure-volume data points at a specific point in time after the onset of systole. From this set of pressure-volume data, we obtained a best-fit straight line by linear regression analysis. A composite of such regression lines was developed from similar data sets collected every 20 msec after the onset of systole. We then analyzed the time-dependent movement of these lines on the pressure-volume plane. For the computer analysis of the E(t) curve, a different scheme was used which will be described in Results. Throughout this report, variation of the data is indicated in terms of one standard deviation of the mean.

Results
TRANSIENT VERSUS STEADY-STATE RESPONSES
We limited the present analysis to steady-state data after a step change in end-diastolic volume or a change in contraction mode. A step change in volume was associated with an instant change in peak ventricular pressure which then kept changing over the following 0.5–2 minutes and became constant thereafter. This phenomenon was commonly observed in both isovolumic and auxobaric modes of contraction. When the volume was increased, the transient pressure change was a gradual increase to a steady level. A gradual decrease in pressure followed the initial pressure decrease induced by a step decrease in volume. Arrhythmia was occasionally observed during the transient phase. The ratio of the magnitude of the transient change to that of the steady-state change in pressure was 17.3 ± 8.9%. This value is comparable to values found by other investigators for a similar phenomenon (3, 4). Once the steady state was reached, there was little variation in the peak pressure among consecutive beats.

STABILITY OF CONTRACTILE STATE
For an exact determination of the inotropic effects, we attempted to critically assess the constancy of the contractile state of a given ventricle under a given inotropic condition. For this purpose, we used the accepted thesis that a change in the peak isovolumic pressure despite the same intraventricular volume indicates a change in contractile state of the ventricle (5).

The ventricular volume was increased in steps of about 5 ml from a midrange volume of about 30 ml to 60 ml, decreased in steps to 15 ml, and finally increased back to the initial volume. This procedure was carried out at least once in each heart contracting isovolumically under each contractile
state. From these isovolumic beats at various volumes, we plotted peak systolic pressures against volumes. At least two pressure plots were obtained at each volume in each preparation under each contractile state to examine the difference in peak pressure at identical volumes. The difference between two such pressure plots was small in most preparations but considerably larger in some.

We arbitrarily adopted the following criterion for the stability of the control and the enhanced contractile state. When the maximum deviation of the pressure-volume relationship curve was within ±15% of the mean of the peak pressure values at the corresponding volume, we considered the preparation to be reasonably stable. Only pressure and volume data obtained under such stable conditions were subjected to analysis. For the control contractile state, ten preparations were stable and the remaining two were not. For the enhanced contractile state, nine preparations were stable. In the ten stable preparations under control conditions, the peak isovolumic pressure at a volume of 29.1 ± 1.5 ml was 77.0 ± 13.9 mm Hg. In the nine stable preparations given a norepinephrine or an isoproterenol infusion, the peak isovolumic pressure at the same volume was 120.7 ± 23.0 mm Hg. This finding indicates that the contractile state increased 56.2 ± 22.7% (P < 0.001) in terms of peak isovolumic pressure in response to drug infusion.

**RELATIONSHIP BETWEEN END-SYSTOLIC PRESSURE AND VOLUME**

For a given contractile state, peak isovolumic pressure was linearly related to volume over the investigated range of ventricular volume. The top of Figure 2 shows such linear relationships for all of the stable preparations under the control contractile condition. A statistical analysis confirmed that the regression of peak isovolumic pressure on volume was linear; the correlation coefficient was 0.989 ± 0.011. The sample standard deviation from regression (6) was only 5.25 ± 2.64 mm Hg. The mean linear regression for the control beats, shown by the solid line in the bottom of Figure 2 had a slope of 3.86 ± 0.55 mm Hg/ml and a volume-axis intercept of 8.2 ± 3.3 ml.

The slope of the peak isovolumic pressure-volume regression line became significantly (P < 0.005) steeper during the enhanced contractile state (5.18 ± 1.28 mm Hg/ml with norepinephrine and 5.95 ± 0.93 mm Hg/ml with isoproterenol). However, the volume-axis intercept was not significantly (P > 0.6) affected by the inotropic intervention (6.7 ± 5.0 ml with norepinephrine and 8.2 ± 4.9 ml with isoproterenol). These regression lines are shown by the broken and dotted lines, respectively, in the bottom of Figure 2. We assigned the symbol \( V_d \) to the volume-axis intercept.

The end-systolic part of auxobaric pressure-volume loops reached the linear regression line of the peak isovolumic pressure-volume data obtained under the same contractile state. This finding is exemplified in Figure 3 by the data from one heart. The top of Figure 3 depicts a family of isovolumic pressure-volume diagrams, and the upper broken line is the peak isovolumic pressure-volume regression line. It was transcribed in the bottom of the figure where the auxobaric pressure-volume loops are traced. It is evident that the end-systolic pressure-volume relationship curve is
common to both the isovolumic and the auxobaric contractions for the same contractile state. This phenomenon was consistently observed for either the control or the enhanced inotropic condition.

INSTANTANEOUS PRESSURE-VOLUME RELATIONSHIP

As explained briefly in Methods, we took an approach to the characterization of the instantaneous pressure-volume relationship different from and more fundamental than that used in the previous study (1). We first applied regression analysis to a large number of pressure-volume data points collected at 20-msec intervals from the onset of systole. The data were collected for a given contractile state from many beats of a single ventricle contracting in either mode from various end-diastolic volumes. Figure 4 illustrates this manner of data acquisition and regression analysis on a particular set of data points collected 100 msec after the onset of systole. Two samples of pressure-volume loops are illustrated; a single data point (open square) from each loop 100 msec after the onset of systole was taken and used with other similar data points (solid circles) to obtain the rectilinear regression line specified at 100 msec.

Each section of Figure 5 shows a family of such regression lines at 20-msec intervals between 40 and 280 msec after the onset of systole. The two left sections are the data from an isovolumically contracting ventricle, and the two right sections are the data from the same ventricle contracting auxobarically. In either mode of contraction, pressure and volume values at a specified time were highly linearly correlated with each other (correlation coefficient 0.974 ± 0.021). The sample standard deviation from regression (6) was only 7.33 ± 1.80 mm Hg. The slope of the instantaneous regression line increased with time during systole and decreased with time during diastole. Moreover, the systolic regression lines seem to converge closely on the $V_d$ point determined by the peak isovolumic pressure-volume regression analysis. Therefore, it is a reasonable approximation to describe the time-dependent movement of the regression line in systole as a counterclockwise rotation around the $V_d$ point.

Comparison of the two top sections of Figure 5 also indicates that the systolic set of regression lines of the instantaneous pressure-volume relationship in the isovolumic mode (left) was approximately the same as that in the auxobaric mode (right). This absence of an effect of the contraction mode was consistently observed in all of the preparations with a stable contractile state. The pressure-volume relationship in diastole was slightly affected by the mode of contraction, as seen in the bottom sections of Figure 5. The pressure-volume regression line in the auxobaric mode returned to the resting level (shown by the broken line) faster than did the isovolumic regression line.

Figure 6 shows that the end-systolic pressure-volume regression line obtained from both isovolumically and auxobarically ejecting hearts was highly linearly correlated with each other (correlation coefficient 0.974 ± 0.021). The sample standard deviation from regression (6) was only 7.33 ± 1.80 mm Hg. The slope of the instantaneous regression line increased with time during systole and decreased with time during diastole. Moreover, the systolic regression lines seem to converge closely on the $V_d$ point determined by the peak isovolumic pressure-volume regression analysis. Therefore, it is a reasonable approximation to describe the time-dependent movement of the regression line in systole as a counterclockwise rotation around the $V_d$ point.

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Left ventricular pressure-volume regression lines at 20-msec intervals after the onset of systole in one heart for the control contractile state. The broken lines show the end-diastolic pressure-volume curve; the dotted lines are the linear extrapolation of the instantaneous pressure-volume regression lines. \( V_d \) is the volume-axis intercept of the peak isovolumic pressure-volume regression line obtained in the same heart.

Ventricular and auxobaric contractions for the enhanced contractile state was markedly shifted to the left and upward and had a steeper slope than that for the control state. Also at any comparable time in systole, the instantaneous pressure-volume regression line for the enhanced contractile state was markedly steeper than that for the control state. The end of systole was reached faster during the enhanced contractile state. However, all of the systolic pressure-volume regression lines for the enhanced state converged closely on the same \( V_d \) that was obtained for the control contractile state.

The regression analysis indicates that the instantaneous pressure-volume relationship at any specified time, \( t \), can be formulated by the following equation.

\[
P(t) = E(t) \cdot \left[ V(t) - V_d \right].
\]

where \( P(t) \) and \( V(t) \) are the ventricular pressure and volume, respectively, at \( t \), \( E(t) \) is the slope of the pressure-volume regression line at \( t \), and \( V_d \) is the volume-axis intercept of the same regression line at \( t \).

There was only an insignificant (\( P > 0.2 \)) difference between \( V_d \) and \( V_{d,i} \) during systole (except in its very early phase) and during early diastole. Therefore, we substituted \( V_d \) for \( V_{d,i} \) in Eq. 1.

\[
P(t_i) = E(t_i) \cdot \left[ V(t_i) - V_d \right].
\]

Previously we called \( E(t) \) the time-varying pressure-volume ratio (1), since it is the ratio of instantaneous pressure to instantaneous volume.

The regression analysis suggests that, if we calculated the pressure-volume ratio as it is defined by Eq. 3 in a given contraction, its time course would represent an instantaneous pressure-volume relationship of the ventricle essentially the same as that determined by regression analysis of multiple beats. To verify this idea, we calculated the pressure-volume ratio curves in individual isovolumic and auxobaric contractions and compared them with each other and with the pressure-volume ratio curves obtained in the previous study (1). We used a computer technique which handled a larger set of data. These results are described in the following section.
VENTRICULAR PRESSURE-VOLUME RATIO

TIME-VARYING PRESSURE-VOLUME RATIO

The computer calculated the mean $E(t)$ curve and the standard deviation from a set of five to ten consecutive beats under each loading condition for each contractile state. This output was recorded on an x-y plotter. The pressure-volume ratio curves obtained for a given contractile state were similar in contour and magnitude regardless of the drastic difference in the loading conditions. The top of Figure 7 shows examples of the computer-produced mean $E(t)$ curves, one from isovolumic beats and the other from auxobaric beats. The bottom of the figure shows examples of the means of the mean $E(t)$ curves acquired under the different loading conditions and a constant contractile state in one heart. As the curves indicate, there was little difference between the isovolumic and auxobaric $E(t)$ curves at any time in systole. The diastolic phase of the curve in auxobaric contractions was situated slightly lower than that in isovolumic ones. Statistical analysis showed that the peak value of the pressure-volume ratio curve, $E_{\text{max}}$, was unaffected by the changes in loading condition (standard deviation of the mean $E_{\text{max}}$ in a given preparation was 3-4%). Moreover, the time to $E_{\text{max}}$ from the onset of systole, $T_{\text{max}}$, was not affected by the changes in end-diastolic volume (standard deviation of the mean $T_{\text{max}}$ in a given ventricle was about 6%). $T_{\text{max}}$, however, was slightly prolonged (by $15.2 \pm 12.8$ msec, 9.2%) with the change of the contraction mode from isovolumic to auxobaric. These findings were common to both the control and the enhanced contractile state.

By contrast, inotropic interventions significantly affected the pressure-volume ratio curve. Two examples of the inotropic effects are shown in Figure 8. With the infusion of isoproterenol or norepinephrine, contractile state was markedly enhanced as reflected by a mean increase of 56% in peak isovolumic ventricular pressure. The mean increase in $E_{\text{max}}$ for all nine hearts was 63%. Mean $T_{\text{max}}$ was shortened by 10%. The statistical data for $E_{\text{max}}$ and $T_{\text{max}}$ are given in Table 1. Similar changes occurred whether or not heart rate was kept constant by artificial pacing.

An increase in heart rate by atrial pacing affected the steady-state value of $E_{\text{max}}$ only slightly in a given heart and inconsistently in different hearts. On an average, the change in $E_{\text{max}}$ was insignificant ($P > 0.1, 0.54 \pm 0.84$ mm Hg/ml or $16.9 \pm 26.3\%$ per 100-beats/min increase in paced heart rate). However, $T_{\text{max}}$ shortened consistently and significantly ($P < 0.025$) at a rate of $71.2 \pm 35.5$ msec or $40.7 \pm 20.3\%$ per 100-beats/min increase. In the nonpaced hearts, the decrease in $T_{\text{max}}$ associated with the enhanced contractile state was $63.6 \pm 34.8$ msec or $36.2 \pm 19.8\%$ per 100-beats/min increase in heart rate. This value is not significantly different from the shortening rate of $T_{\text{max}}$ resulting from the pure change in heart rate induced by pacing. However, in two paced ventricles, $T_{\text{max}}$ shortened $10.0 \pm 3.2\%$ when the contractile state was enhanced without any change in heart rate.

UNIFORMITY OF $E(t)$ CURVES

Regardless of the considerable changes in $E_{\text{max}}$ and $T_{\text{max}}$ associated with the changes in contractile state, the basic shape of the systolic part of the pressure-volume ratio curve appeared to be unaffected by the inotropic intervention (Fig. 8). To examine this impression more rigorously, we normalized the size of the $E(t)$ curves, disregarding loading conditions or contractile state, so that their $E_{\text{max}}$ and $T_{\text{max}}$ values would both be unity. There was only an insignificant variation in the systolic part of the normalized $E(t)$ curve among the 103
Two examples of superimposed tracings of the time-varying pressure-volume ratio, $E(t)$, of the left ventricle for the control contractile state (C) and the enhanced contractile state induced by norepinephrine (NE) infusion. **Left:** Mean $E(t)$ curves each from six consecutive auxobaric beats at a given end-diastolic volume and contractile state in one heart. The original pressure and volume curves are shown in the insert. **Right:** Mean $E(t)$ curves each representing the mean of five mean $E(t)$ curves from differently loaded beats under one of the specified contractile states in one preparation from another dog. The vertical bars indicate ± SD.

sets of beats for the different contractile states and the different modes of contraction (Fig. 9). Also, there was little variation in the normalized curves among different preparations. Only the diastolic phase of the normalized $E(t)$ curve was moderately affected, primarily by the change in contraction mode.

### Discussion

The results of the present study reaffirmed that the time-varying pressure-volume ratio, $E(t)$,

### Table 1

**Effects of Enhanced Inotropism on $E_{\text{max}}$ and $T_{\text{max}}$.**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Enhanced inotropism</th>
<th>$p^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>119 ± 20</td>
<td>124 ± 37</td>
<td></td>
</tr>
<tr>
<td>$E_{\text{max}}$ (mm Hg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>3.65 ± 0.54</td>
<td>6.12 ± 0.82</td>
<td>0.001</td>
</tr>
<tr>
<td>A</td>
<td>3.58 ± 0.73</td>
<td>5.95 ± 1.05</td>
<td>0.001</td>
</tr>
<tr>
<td>$P^*$</td>
<td>0.9</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>$T_{\text{max}}$ (msec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>167 ± 15</td>
<td>152 ± 17</td>
<td>0.02</td>
</tr>
<tr>
<td>A</td>
<td>184 ± 28</td>
<td>171 ± 26</td>
<td>0.02</td>
</tr>
<tr>
<td>$P^*$</td>
<td>0.01</td>
<td>0.005</td>
<td></td>
</tr>
</tbody>
</table>

Enhanced inotropism was induced by infusing isoproterenol or norepinephrine (0.2 µg/min) into the coronary artery. I isovolumic mode and A – auxobaric mode.

* t-Test comparison between the control and the enhancement data.

* t-Test comparison between the isovolumic and the auxobaric data in the same ventricle.

adequately represents the instantaneous pressure-volume relationship of the left ventricle in systole irrespective of the mode of contraction. The load-independence and the similarity of the basic shape of the $E(t)$ curve seem to be fundamental features of ventricular contraction whatever the underlying mechanism might be.

The unique basic shape of the normalized $E(t)$ curve (Fig. 9) is approximately the same as that obtained from the naturally ejecting ventricle in our previous study (1). Therefore, any given $E(t)$ curve, particularly its systolic portion, can be fully represented by two parameters, $E_{\text{max}}$ and $T_{\text{max}}$, and the normalized $E(t)$ curve. We cannot explain at this time the difference in the diastolic portion of the $E(t)$ curve between isovolumic beats and auxobarically ejecting beats (Fig. 7). The volumetransducer system imposes certain inertial and compliance loads but little resistive load on the ventricle. When it is coupled with the ventricle, the entire system can induce an oscillatory motion of water under some conditions (e.g., in diastole with a large amount of air in the transducer system). It is possible, but of doubtful value, to assess the mechanical behavior of the whole system (such as its natural frequency and damping factor) from the present results; however, the ventricle constitutes a nonlinear, time-varying component of the system even during diastole. More important

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than the mild discrepancy of diastolic $E(t)$ is the fact that, for a constant contractile state, the systolic portions of the $E(t)$ curves superimpose despite the two artificial, drastically different load conditions. In our previous study (1) on naturally beating hearts, the diastolic portion of the $E(t)$ curve had a much greater dispersion than did the systolic portion. This finding suggests that the mechanical properties of the volume-transducer system did not contribute importantly to the diastolic discrepancy of the $E(t)$ curve.

There is much supportive evidence in earlier publications for the load-independence of $E_{\text{max}}$, or the end-systolic pressure-volume relationship as discussed previously (1). The steady-state pressure-volume loop (or force-length loop of myocardium) in an ejecting contraction mode reaches the isovolumic end-systolic pressure-volume relationship curve (or isometric maximum force-length curve) determined for the same contractile state. Although Taylor (7) reported that the force-length loop did not reach the isometric force-length relationship curve had a much greater dispersion than did the systolic portion. This finding suggests that the inverse force-velocity relationship determined for the same contractile state.

The relatively small effect of heart rate on $E_{\text{max}}$ also has supportive evidence. Many investigators (10-14) have shown that the peak isovolumic ventricular pressure (or peak force of in situ myocardium) and the end-systolic pressure-volume relationship are little affected by changes in heart rate. The shortening of $T_{\text{max}}$ with an increase in heart rate is also consistent with their observations. The rate of shortening of $T_{\text{max}}$, per given change in heart rate in the present study is similar to that observed previously (1).

The concept of the time-varying pressure-volume ratio is consistent with the pressure-volume relationship synthesized in a model ventricle based on myocardial contractile properties (15). A similar concept of time-varying elastance or reciprocal compliance has often been used by modelers of the circulatory system in simulating the ventricular pump performance (16-20); the present findings give a firm physiological basis to their intuition. Earlier, Suga (21) showed mathematically that $E_{\text{max}}$ determines stroke volume when preload and afterload are given, whereas the time course of $E(t)$ during systole affects the time course of ejec-

Therefore, the $E_{\text{max}}$ parameter serves as a useful predictor of flow-generating capacity of the ventricle under a given end-diastolic volume and pressure afterload as well as an index of its contractile state.

Another mathematical analysis of ours (22) indicated that the inverse force-velocity relationship can be obtained from $E(t)$; myocardial force is proportional to $E_{\text{max}}$ and shortening velocity is proportional to the reciprocal of $T_{\text{max}}$. These results lend support to our concept that $E(t)$ is a manifestation at the ventricular chamber level of the basic nature of myocardial contraction.

One interpretation of the time-varying pressure-volume relationship is that the ventricular wall has a time-varying elasticity. At a given time in systole, the ventricle can be considered to have an actively augmented elasticity which is represented by the slope of the pressure-volume relationship curve at that time. The magnitude of this elasticity is then considered to increase and decrease with time in proportion to the rotation of the pressure-volume relationship curve on the pressure-volume plane. $E(t)$, which represents the time course of the changing slope of the pressure-volume relationship curve in this study, therefore represents the time-varying elasticity of the ventricular wall. This interpretation is supported by the demonstration of time-varying stiffness in both the ventricle ($\Delta P/\Delta V$) and papillary muscle ($\Delta \text{force}/\Delta \text{length}$) by Templeton et al. (23, 24). However, their time-varying stiffness should not be immediately identified with the present $E(t)$, because the stiffness was obtained with a sinusoidal change in volume or length of a relatively high frequency (10-30 Hz) whereas $E(t)$ is concerned with the naturally existing absolute pressure and absolute volume of the ventricle.

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