Effect of Positive Inotropic Agents on the Relation between Oxygen Consumption and Systolic Pressure Volume Area in Canine Left Ventricle

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SUMMARY. We analyzed the effect of positive inotropic agents on the relation between left ventricular oxygen consumption and the systolic pressure-volume area. Pressure-volume area is a measure of total mechanical energy for ventricular contraction, and is a specific area in the ventricular pressure-volume diagram circumscribed by the end-systolic and end-diastolic pressure-volume relation curves and the systolic segment of the pressure-volume trajectory. Either epinephrine (1 μg/kg per min, iv) or calcium ion (0.03 mEq/kg per min, iv) was administered to canine excised cross-circulated hearts. These agents increased an index of ventricular contractility, E_max, or the slope of the end-systolic pressure-volume line, by 70%. The regression lines of ventricular oxygen consumption on pressure-volume area in control and in enhanced contractile states were of the same formula: ventricular oxygen consumption (ml O_2/beat per 100 g) equals A times pressure-volume area (mm Hg ml/beat per 100 g) plus a constant B. Coefficient A remained unchanged at 1.8 X 10^-5 ml oxygen/(mm Hg ml), but constant B increased from 0.03 ml oxygen/beat per 100 g by more than 50% with either agent. The reciprocal of A reflects the energy conversion efficiency for the total mechanical energy, and this efficiency remained near 36%. The increase in B was equal to the directly measured increment in ventricular oxygen consumption for mechanically unloaded contraction. The basal metabolism remained unchanged.

We conclude that the augmented oxygen consumption under the acutely enhanced contractile state with either epinephrine or calcium was caused primarily by an increased energy utilization associated with the excitation-contraction coupling. (Circ Res 53: 306-318, 1983)

ENHANCEMENT of cardiac contractile state with an acutely administered positive inotropic agent is generally associated with an increase in cardiac energy utilization and oxygen consumption (Braunwald, 1969; Gibbs and Chapman, 1979). The increment in energy utilization for a given measure of mechanical contraction has been called oxygen-wasting effect of the positive inotropic agent (Chandler et al., 1968; Rooke and Feigl, 1982). Although quantitative relations between the augmented energetics and the enhanced contraction have been analyzed (Sonnenblick et al., 1965; Gibbs, 1978), the mechanism of the oxygen-wasting effect has not been fully elucidated, and has been ascribed either to the enhancement of contractile state in terms of the increase in the shortening velocity (V_max) of myocardium (Sonnenblick et al., 1965, Braunwald, 1969) or to the increased generation of force-independent heat associated with augmented calcium release and retrieval in the enhanced contractile state (Gibbs and Gibson, 1972; Gibbs, 1978). In addition, the effect of the positive inotropic agent on energy conversion efficiency for mechanical contraction has not been analyzed explicitly in relation to the oxygen-wasting effect. One major reason for this situation seems to be that the mechanical parameters (force, force-time integral, etc) to be correlated with the energy utilization are not energy quantities (Braunwald, 1969; Gibbs, 1978).

In the present study, we investigated the relation between cardiac oxygen consumption and mechanical contraction acutely augmented by epinephrine and calcium, two representative agents that enhance myocardial contractile state by different pharmacological mechanisms. To this end, we utilized a new measure of total mechanical energy for ventricular contraction. This measure is called the left ventricular systolic pressure-volume area (PVA). PVA is the specific area in the pressure-volume (P-V) diagram that is circumscribed by the end-systolic and end-diastolic P-V relation curves and the systolic segment of the P-V loop trajectory (Suga, 1979a). PVA has been shown to represent the total mechanical energy required for each contraction by the ventricle (Suga, 1979b). In fact, PVA is closely correlated with cardiac oxygen consumption per beat (VO_2) over wide ranges of end-diastolic volume and systolic pressure in a stable canine left ventricle preparation (Suga et al., 1981a, 1981b). In addition, the correlation between VO_2 and PVA is significantly better than the correlations between VO_2 and ventricular pressure, wall tension, and pressure-time integral (Suga et al., 1981c). Taking advantage of these characteristics of PVA, we have investigated.
the effect of the acutely enhanced contractile state on the relationship between the agumented cardiac mechanics and energetics.

Methods

Heart Preparation

In each experiment, two mongrel dogs (9–20 kg in body weight) were anesthetized with sodium pentobarbital (30 mg/kg, iv). Blood was heparinized in both dogs (750 U/kg). The details of the surgical preparation have been described previously (Suga et al., 1981c). Briefly, the heart lung section was isolated in a smaller dog [12 ± 2 (so) kg], and the left subclavian artery and the right ventricle were connected via the cross-circulation tubings to the common carotid arteries and the external jugular vein, respectively, of the other dog (14 ± 3 kg). The cross-circulation was started after ligation of the pulmonary hili and removal of the lung lobes. The supported beating heart was excised from the chest. The left atrium was opened and the left ventricular chordae tendineae were cut. A thin rubber balloon with an unstretched volume of 60 ml, tied on a balloon-to-pump connector, was placed in the left ventricle, and its mouth was secured at the mitral annulus. The electrical cable of a miniature pressure gauge (Konigsberg, P-7), placed inside the apical end of the balloon, was pulled out of the ventricular apex through a stab incision.

The balloon was connected to the volume servo pump that was identical with our most recent version (Suga et al., 1983). The strain gauge compliance of the water housing of the double Bellofram cylinder (Fujikura Rubber Works, custom-made model BFDA-KRJK-70-50D) was 0.3 ml/300 mm Hg. With this volume servo pump, we were able to control precisely and measure accurately the instantaneous absolute left ventricular volume.

The arterial blood pressure of the support dog served as the coronary perfusion pressure of the heart preparation. The mean level of this pressure was relatively constant throughout each experiment, but varied among preparations. It was 90 ± 7 (so) mm Hg (range: 75–130 mm Hg) in the control run (see Experimental Protocol). It remained unchanged in the calcium run (see Experimental Protocol), but increased by 18 ± 4 mm Hg in the epinephrine run, except in experiments 8 and 9 in which epinephrine or calcium infusion until mechanical contractions. We waited for 5-10 minutes after the start of each change in cardiac mechanics and energetics.

Pressure-Volume Area

PVA, an abbreviation of the left ventricular systolic pressure-volume area, is the specific area in the P-V diagram (Fig. 1A) that is circumscribed by the end-systolic (ES) and end-diastolic (ED) P-V curves and the systolic segment of the P-V trajectory (TJ). PVA was determined on line with a digital computer (PDP 11/60 with LPA-11K A/D converter) by the method that we devised recently (Suga et al., 1982a). We used this method instead of the manual planimetry of the area (Suga et al., 1980b, 1981a, 1981b, 1981c, 1982a) because of the higher reproducibility and reliability of the measured PVA data by the computer method.

Briefly, both left ventricular pressure P and volume V signals of chosen steady state contractions in each run were digitized at 2-msec intervals and stored in computer memories. The ventricular volume (Vd) at which peak...

Oxygen Consumption

We used the same method of measurement of left ventricular oxygen consumption per beat, VO2 (ml O2/beat), as described in detail previously (Suga et al., 1981a, 1981c). Briefly, the total effective coronary perfusion flow was measured with an electromagnetic flowmeter in the middle of the coronary venous tubing that hydrostatically drained out all coronary venous blood returning to the right heart. The right ventricle was maintained collapsed by this drainage, so that it consumed oxygen at a negligibly small constant rate. The thebesian coronary venous return to the left ventricle was only a few percent of the total coronary flow and, therefore, was not included in the coronary flow measurement.

The oxyhemoglobin percent saturations of the coronary arterial and venous bloods were continuously measured with two oximeters of the same model (Waters Instrument, model O-600A) which were cross-calibrated to each other. Their readings were converted into oxygen contents in vol% with a saturation-to-content conversion factor obtained in each experiment by determining oxygen contents of arterial blood samples of known oxyhemoglobin saturations with a galvanometric oxygen content analyzer (Lexington Instruments, model Lex O2 Con-TL). On the average, arterial oxygen content was 14 ± 2.5 (so) vol% and its oxyhemoglobin percent saturation as 97.5 ± 2.4%, both being constant in each experiment.

The product of total coronary flow in milliliters per minute and coronary arteriovenous oxygen content difference in vol% gave oxygen consumption rate per minute. This quantity was divided by heart rate to yield oxygen consumption per beat, VO2, in ml O2/beat. It was normalized with respect to the left ventricular weight to give VO2 in ml O2/beat per 100 g of left ventricle (LV).

Because both coronary flow and venous oxygen saturation gradually changed to their new levels after changes in ventricular load, as described by Weber and Janicki (1977), we made measurements when they were reasonably stabilized 1–3 minutes after each change in cardiac conditions. We waited for 5–10 minutes after the start of epinephrine or calcium infusion until mechanical contraction, coronary flow and coronary venous saturation were reasonably stabilized.
isovolumic pressure was zero (Suga and Sagawa, 1974) was directly determined by reducing ventricular volume, and stored in a computer memory before each run. Vd was reproducible with a variability less than ±1 ml in each left ventricle regardless of contractile state. Vd was 7 ± 1 (so) ml.

PVA is equal to the area in the P-V diagram that is swept by a rotating line segment (L) connecting Vd and the instantaneous P-V data point over the systolic period from end diastole to end systole (Fig. 1A). PVA was therefore calculated as the sum of all the individual narrow triangular areas (delta PVA) during systole, each area being swept by the moving line segment pivoting on Vd within each 2-msec sampling period. The individual triangular area (delta PVA) can be considered equivalent to the mechanical energy generated in the ventricle within the 2-msec interval (Fig. 1B). Given P(I), V(I), P(I + 1), and V(I + 1) for ventricular pressure and volume at a sampling time (t) and at the next sampling time (t + 2 msec). Then, the lengths S1 and S2 of the two sides of the narrow triangle are

\[
|V(I) - Vd|^2 + P(I)^2|^{1/2}
\]

and

\[
|V(I + 1) - Vd|^2 + P(I + 1)^2|^{1/2}.\]

The interior angle \( \theta \) at Vd of the narrow triangle is given by the difference between arctan \( P(I + 1)/V(I + 1) - Vd) \) and arctan \( P(I)/V(I) - Vd). Therefore, the area of this narrow triangle is given as S1 S2 \( \theta/2 \). PVA was calculated by summing all S1 S2 \( \theta/2 \) for all 2-msec periods from end diastole to end systole. End diastole was identified as the time of R wave of ECG. End systole was identified as the time at which the pressure-volume ratio, i.e., \( E(t) = P(t)/V(t) - Vd) \), reached maximum value, \( E_{max} \) (Suga et al., 1973; Suga and Sagawa, 1974).

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An additional part of PVA to be computed is the area between the straight line connecting Vd and the end-diastolic P-V point \( [V(0), P(0)] \) and the actual nonlinear end-diastolic P-V relation curve (dark area in Fig. 1B). This area was given by

\[
P(0)V(0) - Vd)/4
\]

because we could reasonably approximate the end-diastolic P-V relation curve in the normal working range by a third power of \( [V(0) - Vd) \) instead of the conventionally used exponential relation (Suga et al. 1982a).

Possible errors in the computed PVA seem to be due to the following two factors. One is a slight variability of Vd. As mentioned above, Vd was reproducible with a variability less than ±0.1 ml in each left ventricle, regardless of the contractile state. This variability of Vd may correspond to a variability of PVA less than ±5%. The other factor is the approximation of PVA by the sum of the small triangular areas. We estimated the magnitude of the computation error of PVA by replacing both pressure and volume signals with standard electric signals of known magnitudes so that we could compare the computed PVA with the theoretically determined PVA. The magnitude of the error was found not greater than ±2.5% of PVA. These magnitudes of PVA errors are relatively small, and therefore we considered that the present method of PVA computation was acceptable for the purpose of the present study.

Although the end-diastolic P-V relation curve ran slightly into the negative pressure region as ventricular volume approached Vd, as schematically shown in Figure 1 as well as in Figure 2 in the study by Ross et al. (1966), we did not include any area below the volume axis in the computed PVA. The area between the end-systolic and end-diastolic P-V relation curves in the negative pressure region may be a part of PVA. However, the physiological significance of the area in the negative pressure region remains to be known. Fortunately, this area was not greater than 100 mm Hg-ml, or 5% of the midrange of PVA. Even if we added this area to PVA, the Vo2-PVA data points in the scatter diagram as shown in Figure 2 would be only slightly shifted to the right along the PVA axis in both control and the enhanced contractile states. Therefore, we consider that the exclusion of this negative area from PVA have not essentially affected the results of the present study.

The dimensions of PVA are mm Hg-ml. PVA was normalized with respect to left ventricular weight and expressed in mm Hg-ml/beats per 100 g LV. PVA was always obtained in steady state contractions.

We also computed external mechanical work (EW) of those steady state contractions as the area within the P-V trajectory loop. PVA minus this EW is what we call the end-systolic potential energy (PE) (Suga, 1979a; Suga et al., 1981c). These values for both EW and PE were used to study the relative contributions of these two parts of PVA to Vo2 in control and in the enhanced contractile states.

**Contractility**

The level of ventricular contractile state was assessed in terms of an index of ventricular contractile state, \( E_{max} \) (Suga et al., 1973; Suga and Sagawa, 1974). \( E_{max} \) is the maximal or end-systolic value for the ratio \( P(t)/V(t) - Vd) \), where \( P(t) \) and \( V(t) \) are left ventricular instantaneous pressure and volume and Vd is the ventricular volume at which peak isovolumic pressure is zero. We decided to
The contractile state of the cross-circulated heart preparation without any intentional inotropic interventions was called control. Heart rate in the control run was fixed by pacing at a rate of 177 ± 24 (so) beats/min before epinephrine and 154 ± 18 before calcium. The higher pacing rate in the epinephrine run than in the calcium run was inevitable because any lower pacing rate was exceeded by the positive chronotropic effect of epinephrine. We considered that the difference in the heart rate between the epinephrine and calcium runs did not significantly affect the results of the present study, because our previous study had shown that the relation between VO2 per beat and PVA was not affected by heart rate changes under a constant inotropic background (Suga et al., 1983).

In a first group of nine experiments, the contractile state was enhanced by a continuous infusion of epinephrine at a rate of 1.0 ± 0.4 (sd) µg/min per kg of support dog, iv, in experiments 1–7, and at 2 µg/min directly into the coronary arterial tubing in experiments 8 and 9.

In a second group of nine preparations, the contractile state was enhanced by a continuous infusion of calcium chloride at a rate of 0.03 ± 0.01 mEq/min per kg, iv, in experiments 3 through 9 and by a single shot of calcium of 0.4 mEq/kg, iv, in experiments 1 and 2. Hearts 6 and 8 in the calcium group were identical with hearts 8 and 9, respectively, in the epinephrine group. In each heart, an average of 11 (4–17) different loading conditions were imposed on each left ventricle to cover a wide range of PVA in the control contractile state. A similar number of loads were imposed on the same heart in the enhanced contractile state at the identical paced heart rate. Both isovolumic and ejecting contractions were produced at about a one-to-one ratio. Stroke volume in ejecting contractions ranged from 5 to 25 ml. Each of the control, epinephrine, and calcium runs took 10–30 minutes, depending on the number of loads in each run and the duration of the transient responses to the load changes. Each experiment was over within 3–4 hours after the onset of the cross-circulation.

In each steady state, we obtained VO2, PVA, and E∞, and subjected them to analyses. To minimize the possibility of anaerobic conditions, we avoided pacing each heart so rapidly that pulsus alternans would appear, according to the observations of Weber et al. (1980). We also used moderate doses of epinephrine and calcium to minimize the likelihood of anaerobic conditions.

In some experiments (1, 8, 9 in the epinephrine group and 6 in the calcium group), we repeated the control run after the epinephrine or calcium infusion was stopped to examine whether the changes in the VO2-PVA relation by the inotropic agents were reversible, as seen in Tables 1 and 2. This run was called the second control. In experiment 3 in the epinephrine group and experiment 2 in the calcium group, a second set of control and positive inotropic runs was carried out at a different heart rate, as seen in Tables 1 and 2.

In five hearts of the epinephrine group and five other hearts of the calcium group, we arrested heart beat by continuously infusing potassium chloride (0.5–1 ml/min of 300 mEq/liter) directly into the coronary circulation to determine VO2 for basal metabolism. Although the coronary venous blood containing potassium chloride returned to the support dog, there were no observable responses within the first 10 minutes in the support dog's systemic arterial pressure, probably because the potassium chloride was considerably diluted in the support dog's circulating blood.

We compared VO2 of the KCl-arrested unloaded heart before and during either epinephrine (2 µg/min) or calcium chloride (0.04 mEq/min) infusion directly into the coronary circulation to study the effect of these agents on the basal metabolism.
Therefore, we can convert V02 in ml O2/beat per 100 g LV (Suga, 1979a). Under normal aerobic conditions, 1 ml of oxygen consumed by myocardium is approximately equivalent to 20 J (Gibbs, 1978; Gibbs and Chapman, 1979). Therefore, we can convert VO2 in ml O2/beat per 100 g LV and PVA in mm Hg·ml/beat per 100 g LV to VO2 and PVA both in the same unit of energy of J/beat per 100 g LV. Then, the ratio of PVA to VO2 both in J/beat per 100 g LV, namely, PVA/VO2, indicates the efficiency of energy conversion from VO2 to PVA.

We assumed that the ratio of PVA to VO2 in excess of VO2 for unloaded contraction, namely, PVA/(VO2 — un-

### Table 1: Effects of Epinephrine on Ventricular Mechanics and Energetics

<table>
<thead>
<tr>
<th>Exp no.</th>
<th>HR (beats/min)</th>
<th>Emax [mm Hg/ml (ml per 100 g)]</th>
<th>n</th>
<th>r</th>
<th>Slope ± SD [ml O2/(mm Hg·ml)]</th>
<th>Intcp</th>
<th>so from reg (ml O2/beat per 100 g)</th>
<th>Covar F test</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>188C</td>
<td>6.6</td>
<td>5</td>
<td>0.990</td>
<td>1.49 ± 0.13</td>
<td>44.7</td>
<td>0.020</td>
<td>0.0026</td>
</tr>
<tr>
<td></td>
<td>188E</td>
<td>11.2</td>
<td>5</td>
<td>0.996</td>
<td>2.21 ± 0.12</td>
<td>30.2</td>
<td>0.026</td>
<td>0.0017</td>
</tr>
<tr>
<td></td>
<td>188C</td>
<td>6.6</td>
<td>6</td>
<td>0.989</td>
<td>1.31 ± 0.10</td>
<td>50.9</td>
<td>0.020</td>
<td>0.0021</td>
</tr>
<tr>
<td>2</td>
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<td>4</td>
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<td>1.89 ± 0.24</td>
<td>35.3</td>
<td>0.025</td>
<td>0.0028</td>
</tr>
<tr>
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<td>6</td>
<td>0.911</td>
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<td>0.962</td>
<td>1.93 ± 0.31</td>
<td>34.5</td>
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<td>0.0051</td>
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<td>11.0</td>
<td>5</td>
<td>0.966</td>
<td>2.38 ± 0.12</td>
<td>28.0</td>
<td>0.058</td>
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<td>5.5</td>
<td>5</td>
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<td>1.98 ± 0.32</td>
<td>33.7</td>
<td>0.032</td>
<td>0.0050</td>
</tr>
<tr>
<td></td>
<td>178E</td>
<td>10.0</td>
<td>5</td>
<td>0.970</td>
<td>2.35 ± 0.34</td>
<td>28.4</td>
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<tr>
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<td>2.08 ± 0.09</td>
<td>32.0</td>
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<td>0.0017</td>
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<tr>
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<td>0.993</td>
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<tr>
<td>6</td>
<td>171C</td>
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<td>1.49 ± 0.13</td>
<td>44.7</td>
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<tr>
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<td>1.61 ± 0.07</td>
<td>41.4</td>
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<td>8</td>
<td>0.983</td>
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<td>41.1</td>
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</tr>
<tr>
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<td>181C</td>
<td>4.9</td>
<td>16</td>
<td>0.983</td>
<td>2.08 ± 0.10</td>
<td>32.0</td>
<td>0.019</td>
<td>0.0031</td>
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<tr>
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<td>0.991</td>
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<td>0.994</td>
<td>1.88 ± 0.07</td>
<td>35.5</td>
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<td>0.0012</td>
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<tr>
<td>9</td>
<td>166C</td>
<td>9.3</td>
<td>17</td>
<td>0.978</td>
<td>1.69 ± 0.09</td>
<td>39.4</td>
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<td>0.953</td>
<td>1.81 ± 0.22</td>
<td>36.8</td>
<td>0.027</td>
<td>0.0061</td>
</tr>
</tbody>
</table>

Control (n = 13)

| M | 170 | 6.3 | 0.982 | 1.75 ± 0.15 | 38.8 | 0.025 | 0.0030 |
| SD | 17 | 1.4 | 0.014 | 0.25 ± 0.09 | 5.9 | 0.008 | 0.0016 |

Enhanced (n = 10)

| M | 170 | 11.3 | 0.975 | 2.04 ± 0.20 | 34.0 | 0.044 | 0.0033 |
| SD | 17 | 1.6 | 0.025 | 0.44 ± 0.13 | 6.5 | 0.014 | 0.0018 |

Paired t-test

* NS ns NS ns * NS

Exp no. = experiment number, in chronological order. HR = heart rate fixed by pacing. C and E following HR data indicate control (C) and enhanced contractility by epinephrine (E). C before E is the first control and C after E is the second control. Emax = slope of the end-systolic pressure-volume relation line, normalized with respect to left ventricular weight of 100 g. n = number of different loading conditions under which steady state data were obtained. r = correlation coefficient between VO2 and PVA. Slope ± SD = the regression coefficient of VO2 on PVA and its standard deviation. Eff = efficiency of energy conversion from VO2 in excess of that for unloaded contraction to PVA (for details, see text). Intcp = VO2-axis intercept of the regression line (ml O2/beat per 100 g LV), equal to PVA for unloaded contraction with zero PVA. so from reg = standard deviation of sampled VO2-PVA data from the regression line (ml O2/beat per 100 g LV). Analysis of covariance (Covar) was applied to the comparison between the control and enhanced contractile state regression lines. Differences of the slope (sl) and the elevation (el) of the regression lines were tested by F test. Control row at the bottom shows mean (M) ± standard deviation (SD) of all the control data of each heart. Enhanced data row at the bottom shows mean ± so of all the epinephrine data of each heart. Paired t-test row at the bottom shows the significance level of the difference between the first control and enhanced data. NS = statistically insignificant at P > 0.1 ns = statistically insignificant at 0.1 > P > 0.05 * = statistically significant at P < 0.05.

### Energy Conversion Efficiency

Physically, 1 mm Hg·ml of PVA is equal to $1.33 \times 10^{-4}$ J (Suga, 1979a). Under normal aerobic conditions, 1 ml of oxygen consumed by myocardium is approximately equivalent to 20 J (Gibbs, 1978; Gibbs and Chapman, 1979). Therefore, we can convert VO2 in ml O2/beat per 100 g LV and PVA in mm Hg·ml/beat per 100 g LV to VO2 and PVA both in the same unit of energy of J/beat per 100 g LV. Then, the ratio of PVA to VO2 both in J/beat per 100 g LV, namely, PVA/VO2, indicates the efficiency of energy conversion from VO2 to PVA.

We assumed that the ratio of PVA to VO2 in excess of VO2 for unloaded contraction, namely, PVA/(VO2 — un-
flow and arteriovenous oxygen content difference increased, and VO₂ increased in proportion to PVA in either control or the enhanced contractile state. With epinephrine or calcium, both coronary flow and arteriovenous oxygen content difference increased, and VO₂ for a comparable PVA increased markedly.

Figure 2 shows an example set of the scatter diagrams plotting VO₂ on the ordinate against PVA on the abscissa in control (part A) and in the enhanced contractile state with epinephrine (part B), and in control (part C) and in the enhanced contractile state with calcium (part D). The solid circles indicate isovolumic contractions, and the open circles ejecting contractions. The correlation between VO₂ and PVA was always very high and linear, and

**Table 2**

<table>
<thead>
<tr>
<th>Exp no.</th>
<th>Exp</th>
<th>HR (beats/min)</th>
<th>E_max [mm Hg/ml per 100 g]</th>
<th>Slope ± SD ( \times 10^{-5} ) [ml O₂/beat (mm Hg ml)]</th>
<th>EH (%)</th>
<th>Intcp (ml O₂/beat per 100 g)</th>
<th>SD from reg (ml O₂/beat per 100 g)</th>
<th>Covar</th>
<th>F test</th>
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Control (n = 11)

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<th>Slope ± SD ( \times 10^{-5} ) [ml O₂/beat (mm Hg ml)]</th>
<th>EH (%)</th>
<th>Intcp (ml O₂/beat per 100 g)</th>
<th>SD from reg (ml O₂/beat per 100 g)</th>
<th>Covar</th>
<th>F test</th>
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<tr>
<td>SD</td>
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Enhanced (n = 10)

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<th>E_max [mm Hg/ml per 100 g]</th>
<th>Slope ± SD ( \times 10^{-5} ) [ml O₂/beat (mm Hg ml)]</th>
<th>EH (%)</th>
<th>Intcp (ml O₂/beat per 100 g)</th>
<th>SD from reg (ml O₂/beat per 100 g)</th>
<th>Covar</th>
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<tr>
<td>SD</td>
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<td>4.9</td>
<td>0.018</td>
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<td>9.1</td>
<td>0.013</td>
<td>0.0017</td>
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</table>

Paired t-test

* NS NS NS NS * NS

Exp no = experiment number in chronological order. Experiments 6 and 8 in the calcium run used the same heart preparations as experiments 8 and 9, respectively, in Table 1. HR = constant paced heart rate. C and Ca after HR data indicate control (C) and enhanced contractile state with calcium (Ca). C before Ca is the first control and C after Ca is the second control. As for the explanations of the other symbols, see the footnote of Table 1. Enhanced data row at the bottom shows mean ± SD of all the calcium data of each heart.
the VO₂-PVA relation was closely fitted by a linear regression line. As indicated by the 95% confidence zones of both the regression line and the sampled data, the scatter of the data points from the regression line was little. All the other hearts showed similar results.

The statistical data of the correlation and regression analyses in all the hearts are listed in Tables 1 and 2. All the hearts in both control and enhanced contractile states showed high correlation coefficients (r) between VO₂ and PVA and small standard deviations of the sampled data from the linear regression line of VO₂ on PVA. These results indicate that VO₂ was always highly linearly correlated with PVA in either the control or the enhanced contractile state, whether the positive inotropic agent was epinephrine or calcium. Square of the correlation coefficient (r²) indicates the proportion of the variance of VO₂ values that can be attributed to its linear regression on PVA values (Snedecor and Cochran, 1971). The mean values for r² were 0.957 ± 0.036 (range: 0.83–0.99) in the control, epinephrine, and calcium runs. This indicates that as high as 83–99% of the variance of VO₂ can be attributed to the intentionally changed PVA in either control or enhanced contractile state.

The VO₂-PVA regression lines in the enhanced contractile states were considerably higher than those in control as seen in Figure 2, parts B and D. The upward shift with either epinephrine or calcium was primarily a parallel shift. Tables 1 and 2 list the values for the VO₂ axis intercept of the VO₂-PVA regression lines. We compared the elevations of the regression lines in the control and the enhanced contractile states by the analysis of covariance (Snedecor and Cochran, 1971). The statistical results show that the increase in the elevation of the regression line with either epinephrine or calcium was always statistically significant (P < 0.05 by the F test).

The upward shift of the VO₂ axis intercept with either epinephrine or calcium was statistically significant by the paired t-test (P < 0.05), as shown in the VO₂ intercept panels of Figure 3. The increase in the VO₂ axis intercept, calculated from the pooled mean data in Tables 1 and 2, amounted to 76% of control with epinephrine and 53% with calcium. The VO₂ axis intercept was almost identical with the directly measured VO₂ of the mechanically unloaded contraction with zero PVA in both control and enhanced contractile states, as seen in Figure 2. The directly measured VO₂ of the unloaded contraction was also significantly increased with either epinephrine or calcium in all the hearts (P < 0.05 by the
paired (t-test), as seen in the unloaded \( \text{Vo}_2 \) panels of Figure 3. This increase amounted to an average value of 67% of control with epinephrine and 52% with calcium.

In contrast to the shift of the \( \text{Vo}_2 \) axis intercept, the slope of the \( \text{Vo}_2 \)-PVA regression line was not significantly affected by epinephrine and calcium. The change in the slope of the \( \text{Vo}_2 \)-PVA regression line in each heart was statistically insignificant in all hearts \((P > 0.05)\) with epinephrine and calcium by the analysis of covariance, except in heart 1 with epinephrine. The average change in the slope coefficient between the control and the enhanced contractile states, 17% with epinephrine and 4% with calcium, was statistically insignificant \((P > 0.05)\), as seen with slope panels of Figure 3. These results indicate that the \( \text{Vo}_2 \)-PVA relation was shifted in the enhanced contractile state such that \( \text{Vo}_2 \) for any given PVA was increased approximately by the same amount as the increase in \( \text{Vo}_2 \) for the unloaded contraction with zero PVA.

Tables 1 and 2 also list \( E_{\text{max}} \) in control and the enhanced contractile states. \( E_{\text{max}} \) always increased with epinephrine and calcium. An average increase in \( E_{\text{max}} \) was 79% with epinephrine and 72% with calcium, both statistically significant \((P < 0.05)\), as seen in the \( E_{\text{max}} \) panels of Figure 3. These percent increases are comparable to the percent increases in either \( \text{Vo}_2 \) for unloaded contraction or the \( \text{Vo}_2 \) axis intercept of the \( \text{Vo}_2 \)-PVA relation line, as seen in Figure 3.

The ratios of \( E_{\text{max}} \), \( \text{Vo}_2 \) for unloaded contraction, and \( \text{Vo}_2 \) axis intercept and slope of the \( \text{Vo}_2 \)-PVA regression line in the enhanced contractile states over their control values, calculated from the individual data in Tables 1 and 2, are 1.84 ± 0.34 (SD), 1.67 ± 0.25, 1.67 ± 0.22, and 1.15 ± 0.22 with epinephrine, and 1.68 ± 0.45, 1.63 ± 0.46, 1.56 ± 0.39, and 1.04 ± 0.12 with calcium, respectively. The first three ratios in either epinephrine or calcium run are significantly greater than 1 \((P < 0.001)\), whereas the last ratio for the slope change was not significantly different from 1 in either run \((P > 0.05)\). These results also indicate that the enhanced contractile states, which augmented \( E_{\text{max}} \), primarily increased the \( \text{Vo}_2 \) axis intercept of the \( \text{Vo}_2 \)-PVA regression line, but had little effect on the slope of the regression line whether the positive inotropic agent was epinephrine or calcium.

In the second control run after epinephrine in experiments 1, 8, and 9 and after calcium in experiment 6, we observed that the \( \text{Vo}_2 \)-PVA regression line parallel shifted downward close to the first control position from its elevated position reached in the enhanced contractile state. This confirmed that the parallel upward shift of the \( \text{Vo}_2 \)-PVA relation was characteristically associated with the positive inotropic intervention.

The effect of epinephrine and calcium on the basal metabolic \( \text{Vo}_2 \) was studied by comparing \( \text{Vo}_2 \) values of the unloaded KCl-arrested heart before and during the positive inotropic interventions. The unloaded beating heart before the arrest had a \( \text{Vo}_2 \) of 5.24 ± 1.38 (SD) ml O\(_2\)/min or 0.0381 ml O\(_2\)/beat per 100 g LV. After 3 minutes of arrest, \( \text{Vo}_2 \) decreased to 1.47 ± 0.54 ml O\(_2\)/min per 100 g LV. We assumed that the basal metabolic rate per minute remained unchanged in both contracting (regardless of heart rate) and KCl-arrested heart under a given inotropic background, according to the observations of Gibbs et al. (1980). Then, the above \( \text{Vo}_2 \) value was considered to be equivalent to 0.0108 ± 0.0034 ml O\(_2\)/beat per 100 g LV when divided by the heart rate before arrest. We then infused epinephrine \((2 \mu\text{g}/\text{min})\) or calcium \((0.04 \text{mEq}/\text{min})\) directly into the coronary circulation of the arrested heart. These doses, if given to a beating left ventricle, were to increase \( E_{\text{max}} \) by more than 50%. We found that \( \text{Vo}_2 \) was 1.57 ± 0.17 ml O\(_2\)/min per 100 g LV with epinephrine and 1.57 ± 0.33 ml O\(_2\)/min per 100 g LV with calcium. This \( \text{Vo}_2 \) was considered to be equivalent to 0.0113 ± 0.0012 ml O\(_2\)/beat per 100 g LV with epinephrine and 0.0103 ± 0.0021 ml O\(_2\)/beat per 100 g LV with calcium when divided by the heart rate before arrest. Thus, \( \text{Vo}_2 \) of the arrested heart, or the basal metabolic \( \text{Vo}_2 \), was about 30% of the \( \text{Vo}_2 \) for the unloaded beating heart and was not affected by epinephrine and calcium, as can be seen in Figure 4.

Figure 5A shows two \( \text{Vo}_2 \)-PVA regression lines in the control and the enhanced contractile state by epinephrine. In this figure, both \( \text{Vo}_2 \) and PVA coordinates were converted to the common unit of energy, J. This conversion had already been explained in Methods. Superimposed on these \( \text{Vo}_2 \)-PVA lines are a family of the iso-efficiency lines that indicate various efficiencies of energy conversion.

**Figure 4.** Histograms comparing \( \text{Vo}_2 \) for unloaded contraction in control (leftmost), \( \text{Vo}_2 \) of KCl arrested heart in control (2nd from left), and \( \text{Vo}_2 \) of KCl-arrested heart administered epinephrine (EPI) (3rd from left) and calcium (Ca) (rightmost). The ordinate is \( \text{Vo}_2 \) per minute, different from \( \text{Vo}_2 \) per beat elsewhere. The vertical bars indicate ± SD. **•** = statistically significant difference \((P < 0.05)\) between the unloaded \( \text{Vo}_2 \) and KCl arrest \( \text{Vo}_2 \). NS = insignificant difference \((P > 0.1)\) between the KCl arrest \( \text{Vo}_2 \)'s in control and either with epinephrine (EPI) or calcium (Ca) and between EPI and Ca.
FIGURE 5. The relationship between VO\(_2\) and PVA both in the common energy unit of J. The solid circles are control data and the open circles epinephrine data. In panel A, VO\(_2\) coordinate indicates total VO\(_2\), whereas, in panel B, VO\(_2\) coordinate indicates excess VO\(_2\), i.e., total VO\(_2\) – VO\(_2\) for unloaded contraction. The heavy solid lines diverging from the origins are the iso-efficiency lines of energy conversion from VO\(_2\) (total VO\(_2\) in panel A and excess VO\(_2\) in panel B) to PVA.

from VO\(_2\) to PVA (Suga et al., 1981a). For example, the 50% iso-efficiency line indicates that 50% of VO\(_2\) is to be converted to PVA.

The results as shown in Figure 5A indicated that the efficiency of energy conversion from VO\(_2\) to PVA increased from zero in unloaded contractions with zero PVA to as high as 25% with increases in PVA. Maximal values for this efficiency in the individual left ventricles were 30–40% in the present study. Similar results were obtained with calcium. The efficiency of energy conversion from VO\(_2\) to a given PVA decreased with the enhancement of contractile state due to the parallel upward shift of the VO\(_2\)-PVA relation line. Thus, this energy conversion efficiency from total VO\(_2\) to PVA depends both on ventricular loading conditions and on contractile state as to whether it was enhanced by epinephrine or calcium.

In Figure 5B, the part of VO\(_2\) in excess of that for the unloaded contraction, which we hereafter call excess VO\(_2\), was plotted against PVA in both the control and the enhanced contractile state by epinephrine. These excess VO\(_2\)-PVA lines are parallel to the corresponding total VO\(_2\)-PVA lines in Figure 5A. The excess VO\(_2\)-PVA lines were superimposed on the iso-efficiency lines. These iso-efficiency lines are now considered to indicate the efficiencies of energy conversion from the excess VO\(_2\) to PVA.

We found that the excess VO\(_2\)-PVA lines in both control and the enhanced contractile states, either by epinephrine or calcium, were on or near a certain iso-efficiency line. This indicates that the efficiency from the excess VO\(_2\) to PVA was constant, regardless of loading conditions in a given ventricle, and that this constant efficiency of energy conversion from the excess VO\(_2\) to PVA was not significantly altered by the enhancement of contractile state with either epinephrine or calcium. This efficiency was approximately 40% in the left ventricle (shown in Fig. 5B), regardless of the loading conditions and of the change in contractile state.

As shown in Tables 1 and 2, the efficiency from the excess VO\(_2\) to PVA was 37–39% on an average in the control contractile state and 34–36% on an average in the enhanced contractile states with epinephrine and calcium. The change in this efficiency with the inotropic interventions was statistically insignificant (P > 0.05), as shown in the rightmost panels of Figure 3.

We finally examined whether the two parts of PVA, i.e., external mechanical work (EW) and end-systolic potential energy (PE), contributed equally to the determination of VO\(_2\) in both the control and the enhanced contractile state. The method of analysis used was identical with that described previously (Suga et al., 1980b). Briefly, we computed correlation coefficients between VO\(_2\) and EW + k PE [i.e., the sum of EW and a variable coefficient (k) times PE] while varying k by a step of 0.01 from 0 to infinity, using data in control and the enhanced contractile states, separately.

Figure 6 shows how the correlation coefficient varied with k in control and the enhanced contractile state in one heart. The correlation coefficient increased as k increased from 0, reached a peak when k was close to 1, and then decreased as k further increased. Similar results were obtained in all the other hearts.

The value for k that maximized the correlation coefficient between VO\(_2\) and EW + k PE, which we called optimal k, was determined in all the hearts. The optimal k was 1.05 ± 0.07 (SD) in control, 0.98 ± 0.10 with epinephrine, and 1.08 ± 0.05 with calcium. There was no statistically significant difference between these mean values. These values were
close to 1. These results indicate that the contribution of the end-systolic potential energy (PE) to VO₂ was always equal to that of the external mechanical work (EW) regardless of the contractile states.

Discussion

Using the left ventricular systolic pressure volume area (PVA) as a measure of the total mechanical energy of ventricular contraction, we have analyzed the effect of two representative positive inotropic agents, epinephrine and calcium, on the relation between energetics and mechanics of the canine left ventricle. Taking advantage of the characteristics of PVA, we have obtained several new findings on the effect of the enhanced contractile state on cardiac energetics. Based on these findings, we are able to present possible mechanisms underlying the observed results.

The parallel upward shift of the regression line of VO₂ on PVA with the enhancement of contractile state (Fig. 2) appears to be similar to the upward shifts of the regression lines and curves of VO₂ on myocardial force and force-time integral reported by Coleman (1967), Graham et al. (1968), Gibbs and Gibson (1972), Gibbs (1978), and Gibbs and Chapman (1979). Their results indicate that the enhanced contractile state is accompanied by an augmented energetics for a given level of myocardial force or force-time integral.

The incremented energy utilization for a given level of mechanical performance under the enhanced contractile state has been known as the oxygen-wasting effect of the inotropic agents (Chandler et al., 1968; Rooke and Feigl, 1982). This oxygen-wasting effect has been shown to result from the enhancement of contractile state in terms of the increased shortening velocity, V max, of myocardium (Sonnenblick et al., 1965; Graham et al., 1968). However, Gibbs and Gibson (1972) ascribed the same effect to the augmented energetics for force-independent heat generation associated with calcium release and retrieval in the excitation-contraction coupling. The present upward shift of the VO₂-PVA line appears to be ascribed to the oxygen-wasting effect of epinephrine and calcium. However, the use of PVA instead of myocardial force and force-time integral allows us to look into the mechanisms of the augmented energetics by the positive inotropic agents differently than did the previous investigators.

The parallel upward shift of the VO₂-PVA regression line indicates that VO₂ for a given PVA increases by an approximately constant amount over the normal range of PVA. This constant increment in VO₂ is equal to the increment in VO₂ for the unloaded contraction (Fig. 2). VO₂ of the unloaded beating heart is considered to be used for the basal metabolism, electrical activation, and excitation-contraction coupling involving calcium release and uptake (Braunwald, 1969; Gibbs et al., 1980). The basal metabolism measured as VO₂ of the unloaded arrested heart is about 1.5 ml/min in this study. This value is comparable with the data of other investigators (Braunwald, 1969; Gibbs et al., 1980).

The independence of the basal metabolism from the contractile state observed in the present study is consistent with previous findings (Klocke et al., 1965). The energy for the electrical activation is known to be negligible in VO₂ for unloaded contraction (Klocke et al., 1966). Therefore, we consider the upward parallel shift of the VO₂-PVA line with either epinephrine or calcium to indicate that the increase in energy utilization for the excitation-contraction coupling is associated with the enhancement of contractile state.

In fact, the excitation-contraction coupling is known to require a large amount of energy at the sarcoplasmic reticulum, and epinephrine and calcium are known to augment both the calcium uptake by sarcoplasmic reticulum and energy expenditure for it, although by different pharmacological mechanisms (Tada et al., 1978). We therefore consider that the increment in VO₂ for the unloaded contraction is probably a result of a marked increase in the energy utilization for the augmented excitation-contraction coupling by the positive inotropic agents. This consideration is consistent with Gibbs and Gibson's (1972) contention. We assume that this augmented energetics for the nonmechanical activity of myocardium always exists in all contractions with various PVA's under epinephrine and calcium. We speculate that this mechanism is most likely responsible for the parallel upward shift of the VO₂-PVA relation in the enhanced contractile state, either by epinephrine or calcium.

There seems to be some residual mechanical contraction in the unloaded beating left ventricle because a slight shape change was observed even when the empty ventricle was not generating any positive end-systolic pressure. In our previous study (Suga, 1979c), the amount of internal work performed within the left ventricular wall during systole was actually determined in the canine heart. It was about 200 mm Hg·ml when the end-systolic pressure was 100 mm Hg and was proportional to the end-systolic pressure. We therefore assumed that the residual mechanical work in the unloaded beating left ventricle was considerably smaller than the above 200 mm Hg·ml, and it did not significantly affect the present results. This assumption seems reasonable because the wall force of the unloaded ventricle is very small according to the Laplace law. Therefore even if the ventricle is deformed by the residual contraction, the mechanical work probably is very small.

We can discuss the efficiency of conversion of energy from VO₂ to PVA if we assume that PVA is equivalent to the total mechanical energy for ventricular contraction (Suga, 1979a). One mm Hg·ml of PVA is physically equal to 1.33 × 10⁻⁶ J. VO₂ is known to be equivalent to the total energy utilized by myocardium and 1 ml O₂ is approximately equal
to 20 J under normal aerobic conditions (Gibbs, 1978). In the Results, the energy conversion efficiency from total Vo2 to PVA has been shown to depend on PVA, and the efficiency for a given PVA is reduced by epinephrine and calcium, as well (Fig. 5A). These results can be accounted for by the increment in Vo2 for the unloaded contraction with epinephrine and calcium, as seen in Figure 5.

However, the energy conversion efficiency from the excess Vo2 (= total Vo2 − Vo2 for unloaded contraction) to PVA is independent of PVA as well as the change in contractile state with epinephrine and calcium (Fig. 5B). We consider that the excess Vo2 represents the energy that is primarily used by the mechanical contraction. Then, the calculated constant efficiency seems to indicate that the efficiency of the energy conversion in the contractile machinery is constant, regardless of the ventricular loading conditions, and regardless of the ventricular contractile state.

This constant efficiency of energy conversion from the excess Vo2 to PVA may be correlated with the molecular mechanism of muscle contraction as follows. The mechanical energy-conversion system in myocardium is considered to be the myosin cross-bridges with their ATPase activity (Huxley, 1974). Although contractile state is enhanced by epinephrine and calcium, the myosin ATPase activity is known to be uninfluenced by them in their normal ranges (Katz, 1967; Braunwald et al., 1976). In addition, the energy conversion efficiency of muscle is known to be inversely related to the myosin ATPase activity (Alpert et al., 1977). Therefore, the constant energy conversion efficiency from the excess Vo2 to PVA, despite the enhanced contractile state, may be a manifestation of the independence of the myosin ATPase activity from such positive inotropic agents as epinephrine and calcium.

The conclusion we draw from the present findings can be illustrated in Figure 7. Three panels in Figure 7 have Vo2, or the total energy input utilized by the left ventricle, on the ordinates, and PVA, or the total mechanical energy output, on the abscissas, both in the same unit of energy, J. The diagonal lines (solid and dashed) in panels A and B indicate the relationships between the total energy utilization and the total mechanical energy in control and an enhanced contractile state, respectively.

The total energy input comprises (1) the nonmechanical activity consisting primarily of the basal metabolism and the excitation-contraction coupling metabolism and (2) the mechanical activity associated with cross-bridge turnover. The energy utilization for this nonmechanical activity may be assumed to be independent of the energy utilization for the mechanical activity of myocardium in either contractile state (Monroe and French, 1960). The energy utilization for excitation-contraction coupling is greater in the enhanced contractile state, whereas the basal metabolism remains the same at a given heart rate, and, as a result, the energy utilization for the nonmechanical activity is greater in the enhanced contractile state. The relation between the energy utilization in excess of that for the nonmechanical activities and the total mechanical energy output is unchanged in spite of the enhancement of contractile state, as shown in panel C. Therefore, the relation line between the total energy utilization and the total mechanical energy in the enhanced contractile state is shifted upward, as in panel B, but is parallel to the control line in panel A. The balance of the total energy input minus the total mechanical energy output may be converted into heat (Gibbs, 1978).

Because the external mechanical work is a variable fraction of the total mechanical energy (Suga et al., 1980b, 1981a, 1981b), the conventional mechanical efficiency of the heart is different from the energy conversion efficiencies that we have discussed above. The conventional mechanical efficiency of the heart is the efficiency from either total or excess Vo2 to the actual external mechanical work, which is equal to PVA minus end-systolic potential energy. The conventional efficiency is therefore a variable fraction of the efficiency from Vo2 to PVA. For this reason, the effect of epinephrine and calcium on the conventional efficiency of the heart may vary with the accompanying changes in preload and afterload. This mechanism seems to be responsible for the variable mechanical efficiencies calculated on the basis of external mechanical work documented in literature (Gibbs, 1978).

Both epinephrine and calcium have produced apparently the same effect on the V02-PVA relation. These two representative positive inotropic agents are known to augment mechanical contraction of...
myocardium by increasing myoplasmic calcium ion concentration by different pharmacological mechanisms. An increased concentration of extracellular calcium ion raises myoplasmic calcium ion concentration by an increased calcium influx through cell membrane during the plateau phase of the membrane action potential and an increased calcium release from the sarcoplasmic reticulum (Harris and Opie, 1971). In contrast, epinephrine stimulates the \( \beta \)-adrenergic receptor in the cell membrane where more cAMP is synthesized. cAMP activates specific protein kinase, leading to phosphorylation of phosphorylamban, which in turn activates Ca-dependent ATPase and enhances calcium uptake by the sarcoplasmic reticulum (Tada et al., 1978). Epinephrine also increases the transmembrane calcium influx. Epinephrine thus increases myoplasmic calcium ion concentration. Therefore, the increased energy utilization for the augmented excitation-contraction coupling by these mechanisms very likely is responsible for the augmented energetics of the left ventricle subjected to the two representative positive inotropic agents, epinephrine and calcium.

We have discussed the present results assuming that the left ventricular contraction can be simulated by the simple time-varying elastic chamber (Suga et al., 1973; Suga and Sagawa, 1974). This assumption seems to hold reasonably well for describing the pressure-volume relationship of cardiac ventricles pumping within the physiological ranges of preload and afterload (Sunagawa and Sagawa, 1982). In this respect, Elzinga and Westerhof (1981) could not find in papillary muscle a time-varying elasticity similar to that observed in the ventricle and suggested that the ventricular time-varying elastance may be related to the complex organization of myocardial fibers in the wall, rather than to basic myocardial properties. Based on these results, they concluded that viscoelastic models are untenable for heart muscle as was shown long ago for skeletal muscle (Fenn, 1923), casting a doubt on the validity of the time-varying elastance model of the left ventricle.

However, their results [seen in Fig. 5 of Elzinga and Westerhof (1981)] did show the existence of a time-variant force-length relationship in myocardium; their instantaneous pressure-volume relation of a theoretical ventricle constructed from their myocardial force-length relation data shifted upward to the left in a parallel manner during systole rather than rotating counterclockwise around a pivot of an unstressed length, and the end-systolic relation was reached at a varying end-systolic time. Although such a time-varying pressure-volume relation could be modeled by the viscoelastic model that was found not applicable to skeletal muscle (Fenn, 1923), it can alternatively be modeled by a nonlinear time-varying elastance. In the time-varying elastance model, a gradual shift of the instantaneous pressure-volume relation, regardless of whether it is linear or not and regardless of the type of shift, is theoretically associated with a gradual increment in elastic potential energy (Suga, 1979a). Although the time-varying elastance model and the viscoelastic model may appear similar in structure, there is a marked difference in the behavior of the elasticity in the two models.

The simple time-varying elastance model has a single elastic element whose elastance gradually increases with contraction. In contrast, the viscoelastic model consists of an elastic element and a viscous element to damp the elastic element. The elastance of this elastic element increments stepwise rather than gradually at the onset of contraction, and the viscous element damps what would otherwise be a step force increment. This difference in the mechanical behavior of the two models results in a significant difference in their energetic properties.

In the time-varying elastance model, the total mechanical energy generated by each contraction depends on the time course of the P-V trajectory, as explained in detail (Suga, 1979a). In other words, even when the ventricular contraction starts with the same end-diastolic volume, the total mechanical energy generated in each contraction is not constant, but becomes smaller as a greater ejection occurs against a lower afterload pressure. In contrast, in the classical viscoelastic model, the total mechanical energy is instantaneously generated on the rapid increment in the elastance, and its amount is constant and, hence, independent of the time course of the shortening from a given initial length. However, the amount of external mechanical work depends on the time course of the shortening. The difference between the constant total mechanical energy minus the variable external mechanical work is dissipated as heat in the viscous element. This particular source of heat production does not arise in the simple time-varying elastance model because it has no viscosity. Even when the time-varying elastance is partially damped by a viscous element (Suga et al., 1980a), the slightly damped time-varying elastance model is still completely different from the viscoelastic model in terms of energetics, as long as the systolic increment in the elastance remains gradual. Consequently, we consider that the time-varying elastance model reasonably simulates the mechanics and energetics of the left ventricle as a whole.

In conclusion, enhancement of the contractile state is accompanied by an augmented energy utilization in the canine left ventricle in an acute experimental setting. The augmented energetics is caused by an increased energy utilization for the nonmechanical activity of myocardium, in which the basal metabolism remains unchanged and the energy associated with the excitation-contraction coupling is significantly increased. The efficiency of energy conversion into the total mechanical energy, as measured by the ventricular systolic pressure-volume area (PVA), remains constant under both control and acutely enhanced contractile state conditions. Epinephrine and calcium affect the \( \text{VO}_2 \)-PVA relation in a similar manner, in spite of the different
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