Myocardial Oxygen Consumption in Acute Experimental Cardiac Depression

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ABSTRACT

Myocardial oxygen consumption (M\(\text{Vo}_2\)) during drug-induced cardiac depression was measured in 8 anesthetized, open chest dogs in which myocardial wall tension was controlled. The right side of the heart was bypassed and myocardial contractility was reduced with procaine HCl, propranolol, or pronethalol. M\(\text{Vo}_2\) consistently fell during cardiac depression (avg = 1.52 ml/min per 100 g left ventricle or — 11.6%). These reductions occurred despite small increases in developed tension. Changes in the tension-time index, contractile element work, and contractile element power did not correlate invariably with ΔM\(\text{Vo}_2\), while reductions in velocity of the contractile elements at isotension, maximum left ventricular dp/dt, and the extent of shortening of the contractile elements and circumferential fibers were associated in every experiment with the reductions in M\(\text{Vo}_2\). The finding that negative inotropic influences are associated with a reduction in myocardial energy utilization, when considered with earlier observations showing that positive inotropic influences induce an augmentation of M\(\text{Vo}_2\), provides evidence that the inotropic state and its mechanical correlates are coupled with myocardial energy utilization by a mechanism that is independent of tension development.

ADDITIONAL KEY WORDS

heart failure propranolol myocardial metabolism procaine pronethalol anesthetized dogs

Knowledge of the mechanical determinants of the energy used by the heart is fundamental to an understanding of normal and abnormal cardiac function. Since the studies of Rohde in 1912 (1) and Evans and Matsuoka in 1915 (2), a direct correlation has been recognized between the myocardial oxygen consumption (M\(\text{Vo}_2\)) and the pressure developed by the ventricles. Consideration of the time of pressure maintenance per minute, either through direct measurement of the area under the systolic pressure curve (the "tension-time index") (3), or indirectly from the product of peak ventricular pressure and heart rate (the cardiac effort index) (4), subsequently was shown to provide excellent correlation with the M\(\text{Vo}_2\) under controlled experimental conditions. That the tension\(^1\) in the myocardial wall, rather than the pressure

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\(^1\)Used herein in a broad sense to indicate either total force, as commonly applied in isolated muscle physiology, or tensile stress (force per unit cross sectional area).
developed by the heart, might prove a more definitive determinant of myocardial energy utilization has been recognized by many investigators, and studies over the past few years have supported this view (5-9).

It has also been appreciated that the increase in M\(\text{Vo}_2\) associated with muscular exercise or administration of catecholamines is often disproportionate to the changes in myocardial wall tension or heart rate which may occur, and that other factors must affect the M\(\text{Vo}_2\) (10, 11). Recent studies have established that M\(\text{Vo}_2\) increases substantially during a variety of positive inotropic influences when the stroke volume and arterial pressure are controlled (12), and this effect also has been demonstrated when wall tension is maintained relatively constant (9, 13). Although the mechanism responsible for this augmentation of M\(\text{Vo}_2\) has not yet been described, it has been suggested that it may be related to the positive inotropic effects of these interventions, as reflected in a more rapid intrinsic velocity of the muscle (\(V_{\text{max}}\)) or a greater extent of muscle shortening (9, 11-13).

While it is clear that an increase in M\(\text{Vo}_2\) accompanies positive inotropic influences, whether the reciprocal relation also holds true, that is, whether M\(\text{Vo}_2\) is reduced during negative inotropic influences, has not been ascertained. Such a relation should have particular pertinence to the problem of myocardial energetics in heart failure, where evidence concerning the energy requirements of the myocardium has been conflicting (14-17). The analysis of M\(\text{Vo}_2\) during acute cardiac depression, or heart failure, is complicated by the cardiac dilatation and accompanying increase in wall tension that usually occur. Therefore, in the present investigation the energetic concomitants of depressed myocardial contractility were examined under conditions where wall tension was controlled and maintained relatively constant. The data were analyzed in terms of the mechanics of the ventricular muscle, which permitted correlation of changes in energy utilization with alterations in the velocity of shortening, the extent of shortening, the power, and the work of the contractile elements.

**Methods**

**EXPERIMENTAL PREPARATION**

Experiments were performed on 8 mongrel dogs weighing from 17.7 to 23.6 kg. The animals were anesthetized with pentobarbital sodium (35 mg/kg). A bilateral thoracotomy was performed and ventilation was supplied with a positive pressure pump. The right heart bypass preparation depicted schematically in Figure 1 was used. Systemic and coronary venous return (excluding left Thebesian flow) were drained separately by gravity into a reservoir and thence through a disc oxygenator supplied with either 100% O\(_2\) or a mixture of 97% O\(_2\) and 3% CO\(_2\). The oxygenated blood was pumped through a heat exchanger and into the pulmonary artery with a variable speed occlusive roller pump. Control of aortic pressure was achieved with a blood reservoir and shunt system (Fig. 1).
CARDIAC DEPRESSION AND OXYGEN CONSUMPTION

Aortic pressure (0 = 200 mm Hg) and left ventricular pressure (0 to 40 mm Hg and 0 to 200 mm Hg) were measured with wide bore (0.5-mm i.d.) cannulas attached directly to Statham P23Db transducers. The first derivative of left ventricular pressure with respect to time (LV dp/dt) was measured with an electronic differentiator (18). Phasic aortic flow was measured with a gated sine wave electromagnetic flowmeter placed around the ascending aorta. The dynamic characteristics of this instrument have been described previously (19).

After bypass of the right side of the heart had been achieved, cardiac output was established with the calibrated roller pump at a level sufficient to maintain mean aortic pressure between 80 and 100 mm Hg and was not varied during the remainder of the experiment. Flow rates ranged from 1730 to 2820 ml/min and averaged 98.3 ml/min per kg of body weight. After crush of the sinus node, the heart rate was maintained constant; therefore, during each experiment the stroke volume remained unchanged. The right atrium alone was stimulated (5 dogs), or the right atrium and the right ventricle were stimulated sequentially with a stimulus interval of 50 to 100 msec (3 dogs). Heart rates for the separate experiments ranged from 133 to 158 with a mean of 145 beat/min.

Coronary blood flow (minus left Thebesian flow) was measured by timed collection of the right ventricular drainage. The coronary arteriovenous oxygen difference (ΔA-Vo₂) was monitored continuously with a Guyton analyzer (20) to provide indication of steady-state conditions, and arterial and coronary venous blood samples were analyzed in duplicate for oxygen content by the method of Van Slyke and Neill (21). ΔMVo₂ was calculated as the product of the coronary blood flow and the A-Vo₂. The right ventricle was vented and maintained in a collapsed state, and ΔMVo₂ was expressed as ml/min per 100 g left ventricle. In 2 experiments, the right coronary artery was ligated at the initiation of the experiment, and the changes in ΔMVo₂ were similar in all respects to those without right coronary ligation.

Myocardial wall tension was monitored with an analog computer, as described below. The tension, electrocardiogram, ΔA-Vo₂, aortic flow, LV dp/dt, left ventricular pressure, and aortic pressure were recorded on a multichannel oscillograph, paper speeds of 100 mm/sec being used for all measurements from which calculations of force, velocity, work, and power were performed.

EXPERIMENTAL PROTOCOL

In each experiment, control hemodynamic conditions were established, and when coronary blood flow and A-Vo₂ were stable, the ΔMVo₂ was measured. Thereafter, one of three pharmacologic agents, procaine HCl (5 to 10 mg/ml), propranolol (1 mg/ml), or pronethalol (10 mg/ml), was infused into the pulmonary artery at a rate sufficient to depress myocardial performance. The averaged cumulative doses were: procaine HCl, 46 mg/kg; propranolol, 2.6 mg/kg; and pronethalol, 14.6 mg/kg. During myocardial depression, left ventricular pressure was decreased to maintain calculated tension at a level similar to that of the control state by opening the shunt between the femoral arteries and the reservoir. In all experiments, mean aortic pressure was maintained above 70 mm Hg in the depressed condition, and for this reason the tensions could not be matched precisely. When hemodynamic conditions, coronary blood flow, and ΔA-Vo₂ had again stabilized, ΔMVo₂ was redetermined.

At the conclusion of each experiment the heart was rapidly arrested with 15% potassium chloride solution, the mitral and aortic valves were occluded, and the passive pressure-volume relationship of the left ventricle was determined by injecting 2-ml increments of saline, as outlined in detail previously (19). The end-diastolic volumes for each experimental point were then determined directly from the passive pressure-volume curve.

CALCULATIONS

A. Interaexperimental Estimation of Wall Tension

An estimate of myocardial wall tension for the purpose of matching tensions during the experiment was derived in the following manner. Data for left ventricular pressure (0 to 200 mm Hg) and phasic aortic blood flow were fed into the analog computer after appropriate scaling. The ventricular end-diastolic volume was obtained by reference to a passive pressure-volume curve normalized for body weight. This curve was constructed from previous experiments on potassium chloride-arrested dogs hearts using the method described. Instantaneous ventricular volume during ejection was derived by integration of the phasic aortic blood flow and subtraction of the ejected volume from the end-diastolic volume. Internal radius was calculated by assuming a spherical left ventricle, and tension in grams was

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5Model #350 from Sanborn Company.
6Kindly supplied as Inderal by Ayerst Laboratories.
7Kindly supplied as Nethalide by Imperial Chemical Industries Limited.
computed as \( P \pi r_1^2 \) where \( P = \) left ventricular pressure in grams per square centimeter and \( r_1 = \) internal left ventricular radius in centimeters. This value was recorded with a delay of approximately 1 sec. This estimate of tension was used for monitoring the experiment. A more accurate estimate of wall force normalized for wall thickness (stress) was calculated at the conclusion of each experiment.

The reported experimental data were calculated using a digital computer; the left ventricular pressure, LV \( \frac{dp}{dt} \), end-diastolic ventricular volume, left ventricular muscle volume, and aortic flow were converted manually to digital form. With the digital computer, it was feasible to employ formulas for the calculation of force and velocity that included a variable wall thickness during ejection. Force, velocity, work, and power were calculated at 10-msec intervals throughout representative contractions during each hemodynamic condition.

### B. Mean Wall Stress

The wall thickness was first calculated as follows. The instantaneous internal volume was determined from the end-diastolic volume and the phasic aortic blood flow, the ventricular end-diastolic volume for each beat being obtained from the resting pressure-volume relation for each ventricle measured at the conclusion of the experiment. Left ventricular muscle volume was determined from the weight of the left ventricle (assuming a specific gravity for muscle of 1.0). Internal volume plus muscle volume equalled external volume; external radius (\( r_2 \)) could then be calculated, and external radius minus internal radius equalled wall thickness (\( h \)). Using this calculation, it is apparent that the instantaneous \( h \) during ejection increases progressively. During isovolumic ventricular contraction and relaxation \( h \) was assumed to be constant.

Mean wall stress per unit cross-sectional area in g/cm\(^2\) was calculated as \( \frac{Pr_1}{2h} \). A square wave distribution of stress across the myocardial wall was assumed, and this formulation therefore provided an index of mean wall stress. Hereafter, tension will be used as a synonym for stress to denote \( Pr_1 \), unless otherwise stated.

Resting tension was defined as tension at end diastole, peak tension as the highest total tension during systole, and peak developed tension as peak tension minus one half of the resting tension. The latter definition of peak developed tension was designed to provide some consideration of the progressive unloading of the parallel elastic components (PEC) during fiber shortening that is predicted by the three-component muscle model (22). Since in this model resting tension is borne partially or entirely by the PEC, during shortening, resting tension must be transferred progressively to the contractile elements (CE) and series elastic components (SEC). In cardiac muscle when resting tensions are high, the magnitude of this transfer of load during systole can be quite large (23). Since in the intact heart the PEC stiffness and the distribution of resting tension between PEC and SEC are unknown, the assumption was made that at peak tension one-half of the resting tension had been transferred to the contractile system. Developed tension area (the area under the developed tension-time curve) was calculated as

\[
\int_a^b (tension) dt - \left( \frac{\text{resting tension}}{2} \right) n,
\]

where \( a = \) end diastole, \( b = \) the point at which tension falls to the level of resting tension, and \( n = \) number of 10-msec intervals over which the integration was performed.

### C. Velocity and Shortening

1. **Shortening Rate of Circumferential Fiber (V\(_{CF} \))**

The instantaneous shortening rate of the midwall circumferential fibers (V\(_{CF} \)) was calculated by a modification of the method of Fry, Griggs and Greenfield (24). A spherical model was used, and for any radius (\( r \)), \( \frac{dv}{dt} \) (aortic flow rate or \( Q \)) = \( 4\pi r^2 \frac{dr}{dt} \). Rearrangement of the equation gives \( \frac{dr}{dt} = \frac{Q}{4\pi r^2} \) and integrating this function from internal to external radius and dividing by wall thickness yields average radial shortening velocity. This function was multiplied by \( 2\pi \) which then yields average circumferential shortening velocity (V\(_{CF} \)), which is equal to

\[
\frac{Q}{2r_1r_2}.
\]

2. **Lengthening Velocity (V\(_{SE} \)) of the Series Elastic Component.**

The rate of series elastic lengthening was calculated in a manner similar to that previously described (19), except that \( V_{SE} \) was calculated for the midwall circumference and changing wall thickness was included in the formulation. \( V_{SE} \) (dl/dt) was equal to \( \frac{dT}{dt} \frac{r_1r_2}{2T} \),

where \( \frac{dT}{dt} = \) the rate of stress development and \( \frac{dl}{dT} = \) the stiffness of the SEC. The value of 28T (19) was used for \( \frac{dl}{dT} \) and \( \frac{dT}{dt} \) was calculated by differentiation of the equation for
stress \( \frac{dT}{dt} \). In the form \( \frac{dT}{dt} \), \( V_SE \) is given in muscle lengths or circumferences per second; this value was converted to centimeters per second for calculations of contractile element power by multiplying by instantaneous midwall circumference.

3. Velocity (\( V_CE \)) of the Contractile Element. Contractile element velocity was equal to the rate of SEC lengthening (\( V_SE \)) during isovolumic contraction and was equal to the sum of \( V_SE \) and \( V_{CP} \) during ejection.

4. Extent of Shortening of the Circumferential Fiber. The extent of CE and CF shortening and extent of SEC lengthening were calculated as

\[
\int_c^d \left( \text{Vel} \right) \, dt,
\]

where \( c = \) onset of shortening of the CE and CF and onset of lengthening of the SEC, and \( d = \) point at which velocity reaches zero.

D. Work and Power

Contractile element work (\( W_CE \)) (25) was calculated as \( W_CE/\text{beat} \) equal to \( \int_a^e (\text{tension} \cdot V_CE) \, dt \), where \( a = \) onset of contraction and \( e = \) point at which \( V_CE \) becomes negative. Series elastic work, \( (W_{SE}) \), which is the work expended in stretching the SEC to peak tension, was calculated as \( W_{SE}/\text{beat} = \int_f^h (\text{tension} \cdot V_SE) \, dt \), where \( f = \) peak tension. Fiber shortening work \( (W_{FS}) \), the work done by the midwall circumferential fibers, was calculated as \( W_{FS}/\text{beat} = \int_g^h (\text{tension} \cdot V_{CF}) \, dt \), where \( g = \) onset of ejection and \( h = \) end-ejection. This definition of \( W_{FS} \) includes the work done by the recoiling SEC on the circumferential fibers. All work variables were expressed as gram-meters per beat (g-m/beat).

Contractile element work was calculated by Britman and Levine (25) as \( \int_a^e (\text{tension} \cdot V_CE) \, dt \) with tension equal to \( \text{Pmr}^2 \), and velocity referenced to the internal ventricular circumference. In the present study, a thick-walled ventricular model was used, tension was calculated as \( \text{Pmr}^2 \), and mean velocity referenced to midwall.

For purposes of comparison, \( W_CE \), \( W_{SE} \), and \( W_{FS} \) were calculated using both of these formulations.

Mean contractile element power per beat (CEP) was calculated as \( \frac{W_CE}{\text{beat}} \) divided by the duration of systole and expressed as gram-meters per systolic second per beat.

E. Efficiency

Three different forms of the general efficiency equation were used. Contractile element efficiency was calculated as:

\[
\text{CE efficiency} = \frac{W_CE/\text{beat} \cdot \text{heart rate} \cdot 10^{-3}}{\left( \text{CF} \cdot \Delta \text{MV}O_2 \right) - (1.50) \left( \frac{100}{\text{left vent. wt}} \right) 2.06},
\]

where 1.50 is the \( \text{MV}O_2 \) of the arrested dog heart in milliliters per minute per 100 grams of left ventricle and 2.06 is the work equivalent of \( \text{MV}O_2 \) in kilogram-meters per milliliter of \( O_2 \) consumed. (27) Fiber shortening efficiency and stroke work efficiency were calculated using the same equation, with \( W_{FS} \) and \( SW \) being substituted respectively for \( W_CE \) in the above formula.

The tension-time index (TTI) (3) was calculated as mean ventricular pressure during ejection multiplied by the duration of ejection. Stroke work per beat (SW) was calculated as mean ventricular pressure during ejection multiplied by the stroke volume.

The results represent data from 16 observations in 8 animals. Four experiments were eliminated from consideration due to undersaturation of the arterial blood. In 5 additional dogs, there was a considerable widening of the QRS during the experiment, due either to a change from atrial to ventricular pacing necessitated by drug-induced atrioventricular block or to drug-induced slowing of intraventricular conduction or both. Although the results in this group were similar to those of the 8 remaining animals, interpretation of the calculated values for force and velocity is uncertain probably because of an alteration in the effective series elasticity resulting from delayed, sequential activation of the ventricular muscle. These five experiments, therefore, have not been included in the results.

Results

Mean values for hemodynamic, tension-velocity-length and energetic data are presented in Table 1. Despite small but significant increases in peak developed tension (stress) and developed tension area \( (P < .001) \), \( \text{MV}O_2 \) always decreased \( (P < .001) \) during acute cardiac depression, the values for \( \text{MV}O_2 \) averaging 13.13 ± 0.30 ml/min per 100 g of left
**TABLE 1**

**Left Ventricular Dynamics and Myocardial Oxygen Consumption during Acute Cardiac Depression (N = 8)**

<table>
<thead>
<tr>
<th></th>
<th>Control (Mean ± SEM)</th>
<th>Depression (Mean ± SEM)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDP (mm Hg)</td>
<td>5.2 ± 0.1</td>
<td>10.2 ± 0.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SV/EDV</td>
<td>.457 ± 0.016</td>
<td>.320 ± 0.015</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>88.9 ± 1.3</td>
<td>70.0 ± 1.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Max dp/dt (mm Hg/sec)</td>
<td>2014 ± 57</td>
<td>1285 ± 39</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SW (g-m/beat)</td>
<td>20.9 ± 1.1</td>
<td>15.8 ± 0.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TTI (mm Hg-sec/beat)</td>
<td>18.5 ± 1.0</td>
<td>17.0 ± 0.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Peak tension (g/cm²)</td>
<td>132 ± 13</td>
<td>143 ± 15</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Peak developed tension (g/cm²)</td>
<td>129 ± 13</td>
<td>135 ± 14</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Peak tension—resting tension (g/cm²)</td>
<td>125 ± 13</td>
<td>128 ± 13</td>
<td>N.S.</td>
</tr>
<tr>
<td>Developed tension area (g-sec/cm²)</td>
<td>20.3 ± 1.4</td>
<td>24.4 ± 1.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>VCE at isotension (cm/beat)</td>
<td>1.26 ± .03</td>
<td>1.02 ± .04</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Extent of shortening of CE (cm/beat)</td>
<td>2.53 ± .04</td>
<td>2.07 ± .05</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Extent of shortening of CF (cm/beat)</td>
<td>1.31 ± .09</td>
<td>1.07 ± .08</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CBF (ml/min per 100 g LV)</td>
<td>128 ± 14</td>
<td>114 ± 11</td>
<td>&lt;.003</td>
</tr>
<tr>
<td>MVo2 (ml/min per 100 g LV)</td>
<td>13.13 ± 0.30</td>
<td>11.61 ± 0.26</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Student’s t-test for paired differences. N.S. = not significant. LVEDP = left ventricular end-diastolic pressure; SV/EDV = stroke volume/end-diastolic volume; MAP = mean aortic pressure; Max dp/dt = maximum positive value of first derivative of left ventricular pressure with respect to time; SW = stroke work; TTI = tension-time index; peak tension = peak tension-1/2 resting tension (see text); developed tension area = area under developed tension time curve per beat; VCE at isotension = contractile element velocity at an isotension point during isovolumic contraction (see Fig. 3); extent of shortening of CE = contractile element shortening per beat; extent of shortening of CF = circumferential fiber shortening per beat; CBF = coronary blood flow; and MVo2 = myocardial oxygen consumption.

ventricle during the control period and 11.61 ± 0.26 during cardiac depression.

Figure 2 is an experimental record in which myocardial function was depressed with pronethalol. Left ventricular end-diastolic pressure increased from 4.5 to 10 mm Hg, and maximum dp/dt decreased from 2050 to 1194 mm Hg/sec. Despite a slight increase in developed tension, MVo2 decreased from 12.89 to 10.43 ml/min per 100 g of left ventricle.

Figure 3 shows the contractile element force-velocity relations in the left ventricle in another experiment before and after pronethalol administration. Following the initial phase of contraction (symbols on lower left) in which tension and velocity progressively increase with onset of the active state (19), both curves describe an inverse relation between force and velocity until the onset of ejection, when changing fiber length complicates this relationship (19). Although these relatively short isovolumic segments of auxotonic beats cannot be extrapolated with accuracy to the y-axis to quantify Vmax, there is a clear separation of the two curves when VCE is compared during isovolumic systole at a point of isostress (dotted line, Fig. 3). A similar depression of VCE at isostress points during the isovolumic contraction phase was found in all 8 experiments (Table 1).

Figure 4 shows stress and velocity plotted against time during the control state and during pronethalol-induced cardiac depression. The rise in resting and peak stress with drug infusion is evident; developed stress (broken line) is changed to a lesser degree. The velocity-time plots illustrate the reductions in VCE, VSE, and VCF, and the areas under the respective curves show the decreases in the extent of shortening of the CE.
The effect of pronethalol infusion on hemodynamic variables and $A-VO_2$ difference. $P_{w}$ = wall tension where $P$ = left ventricular pressure, $r_i$ = internal radius of the left ventricle, $\Delta AV_{O_2}$ = arterial-coronary venous oxygen difference, $AF$ = aortic flow rate, $dp/dt$ = first derivative of left ventricular pressure with respect to time, $LVP$ = left ventricular pressure, $LVEDP$ = left ventricular end-diastolic pressure, and $AP$ = aortic pressure. (The notch on the downslope of the tension tracing is an artifact due to cessation of computer integration of aortic flow when flow reaches zero. Since tension was computed on line only for the purpose of controlling peak developed tension, the artifact does not enter into any calculations.)

In Figure 5, $\Delta MVO_2$ is plotted as a function of the changes in peak developed tension and tension-time index accompanying cardiac depression. The lack of a consistent correlation between these variables and energy utilization is evident. In Figure 6, $\Delta MVO_2$ is plotted against changes in $W_{CE}$ calculated with two different formulas. A dissociation of $W_{CE}$ and $MVO_2$ can be seen with either method of calculation. Although the directional changes in $W_{CE}$, using either $Pr_{T}$ and midwall velocity ($panel A$) or $Pr_{T}$ and velocity at the internal radius ($panel B$), were similar in six of eight experiments, the absolute values were quite different and these differences bear on the efficiency calculations reported below.

Changes in contractile element power and...
Tension-velocity relationship before and after myocardial depression induced by pronethalol.

$V_{CE} = \text{contractile element velocity. Stress} = \frac{P \cdot r_1}{2h}$ where $h = \text{wall thickness and } \Delta V_{CE} = \text{decrease in velocity at an isotension point with depression. Arrows mark the onset of ejection.}$

In fiber shortening work from control to failure using either formulation were similar to the $W_{CE}$ changes, and did not always correlate with $\Delta M\text{Vo}_2$. Stroke work did not invariably follow changes in $W_{FS}$ but was decreased during depression in all experiments since stroke volume was held constant, and mean aortic pressure was lowered.

Stroke work efficiency consistently decreased from an average of 12.3 to 10.7% ($P < .001$). Contractile element efficiency, when $W_{CE}$ was calculated using $P \cdot r_1^2$ and internal velocity, increased in three of eight experiments with mean values not significantly different; it increased in seven of eight experiments ($P < .001$) when $\frac{P \cdot r_1}{2h}$ and midwall velocity were used. Changes in fiber shortening efficiency paralleled those in the CE efficiency.

Figure 7 shows that the decreases in $M\text{Vo}_2$ were associated in every instance with reductions in $V_{CE}$ at isotension, maximum dp/dt, and the extent of shortening of the CE and CF.

Mean changes in $M\text{Vo}_2$ are plotted as a function of mean changes in peak LV dp/dt in Figure 8 both for the negative inotropic agents in this experiment and for positive inotropic agents in previously reported experiments (9, 12, 13) to contrast the reciprocal changes in these variables with different inotropic interventions.

**Discussion**

The present study demonstrates that when peak developed tension is maintained relatively constant, a depression of myocardial contractile state is associated with a reduction in myocardial energy utilization, reflected in a diminution of the $M\text{Vo}_2$. These results extend to negative inotropic influences (previous observations indicating that positive inotropic influences are associated with increased $M\text{Vo}_2$).
Stress and velocity as functions of time before and after myocardial depression induced by pronethalol. Stress $= \frac{F \cdot r}{2h}$. Developed stress = total stress-(1/2) resting stress (see text).

Velocity plots: $V_{CE}$ = contractile element velocity, $V_{SE}$ = series elastic velocity, $V_{CF}$ = midwall circumferential fiber velocity. Area A + B = extent of shortening of CE, area B + C = extent of shortening of CF. $V_{SE}$ during tension development is plotted on a negative axis to indicate it is a lengthening velocity in contrast to the shortening velocities of the CE and CF during this period. The stippled area encompassing parts of areas B and C is that portion of CF shortening contributed by the recoiling SE.

$MV \text{O}_2$ (9-13), and suggest that a coupling exists between inotropic state and its mechanical correlates, and the energy utilization of the heart. Added significance is attached to the present data because the peak developed tension actually increased in five of eight experiments, and the developed tension area increased in all experiments during...
cardiac depression. These changes in tension undoubtedly tended to minimize the observed reductions in $\text{MV}_\text{O}_2$. The decreases in the peak LV $dp/dt$ and in the $\text{MV}_\text{O}_2$ observed in the present study are placed in perspective relative to the increases in LV $dp/dt$ and $\text{MV}_\text{O}_2$ produced in previous studies by a variety of positive inotropic influences in Figure 8.

The concomitants of the negative inotropic state produced in these experiments in terms of muscle mechanics are decreased velocity of shortening during isovolumic contraction and ejection, and a decreased extent of shortening. In addition, it has been shown recently that acute cardiac failure induced by pronethalol or pentobarbital at a constant or increased end-diastolic volume is characterized by a decrease in $V_{\text{max}}$ (29).

The decrease in $\text{MV}_\text{O}_2$ was always accompanied by a reduction in the speed of contraction when compared at isotension points (Fig. 7). The peak $dp/dt$ was consistently reduced (avg = 729 mm Hg/sec or -36%), and the velocity of shortening of the contractile elements during the isovolumic phase of contraction was always reduced (avg = 0.24

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**Figure 5**

A, change in $\text{MV}_\text{O}_2$ as a function of change in peak developed stress times heart rate with cardiac depression; and B, as a function of change in tension-time index.

**Figure 6**

A, change in $\text{MV}_\text{O}_2$ as a function of change in contractile element work (CEW) with $\text{CEW} = \int \left( \frac{P_v}{2h} \cdot V_{CE} \right) \cdot dt$ with $V_{DB}$ = midwall velocity; and B, as a function of change in contractile element work (CEW) with $\text{CEW} = \int \left( \frac{P_v}{2h} \cdot V_{CB} \right) \cdot dt$ with $V_{DB}$ = internal wall velocity.
CARDIAC DEPRESSION AND OXYGEN CONSUMPTION

A, decrease in $MV_o$ as a function of decrease in contractile element velocity at isotension with cardiac depression (see Fig. 3); B, as a function of decrease in maximum dp/dt; C, as a function of decrease in extent of contractile element shortening; and D, as a function of decrease in extent of shortening of the midwall circumferential fibers.

Changes in $MV_o$ as a function of changes in maximum dp/dt with both positive and negative inotropic influences. AS = acetylstrophanthidin (19), NE = norepinephrine (12), Ca++ = calcium chloride (12), PS = paired stimulation (12), MJ = MJ 1988 (6, 7-dimethoxy-4 ethylquinazoline, kindly supplied by Mean Johnson and Company). Each point represents mean ± SEM. Numbers in parentheses are references from which data was obtained. Data on MJ 1988 obtained during the course of these experiments.
muscle length/sec or −19%). This decrease occurred despite an elevation of ventricular end-diastolic volume, and hence reflected a decreased contractile state of the ventricle (19, 29). The observed reductions of $\text{MV}_{\text{O}_2}$ were also associated with a decreased extent of shortening of the contractile elements and the circumferential fibers. The oxygen cost of fiber shortening appears to be load-dependent, being very low in lightly loaded contractions (6) and somewhat higher with larger afterloads (30), and therefore proportional to work. However, the decreases in the extent of fiber shortening induced by cardiac depression in these experiments (avg = −0.24 cm/beat or −18%) were small relative to those observed in other experiments to be associated with a similar reduction in $\text{MV}_{\text{O}_2}$ (30).

One experiment is of interest in regard to the relative importance of shortening extent, and the contractile state of the myocardium as determinants of $\text{MV}_{\text{O}_2}$. In experiment 4, a total dose of 1.1 mg/kg of propranolol was given, and myocardial contractility was depressed, as reflected in reductions in maximum $\text{dp/dt}$ and $V_C\text{E}$ at isotension. In addition, in this experiment an analysis of single isovolumic beats induced by aortic occlusion (19) showed reductions both in maximum isovolumic tension and the extrapolation to $V_{max}$. These changes occurred with only a small increase in left ventricular end-diastolic pressure (from 3.5 to 5.0 mm Hg), and the extent of CE and CF shortening decreased by only 4 and 2.3% respectively; peak developed tension remained constant. Under these conditions, $\text{MV}_{\text{O}_2}$ fell from 11.57 to 9.98 ml/min per 100 g of left ventricle, and in this experiment energy utilization appeared to be directly related to the inotropic state or its mechanical reflection in the velocity of contraction or both. Although the energy cost of the intrinsic velocity of the contractile elements or the contractile state relative to the costs of tension and shortening extent has not yet been defined, from this and earlier studies it would appear that the expense is substantial (Fig. 8), and may approach that of tension.

In these experiments, the possibility of a metabolic action of the pharmacologic agents, independent of their effects on the mechanics of contraction must be considered and for this reason different myocardial depressants were used. Wollenberger has shown that procaine HCl does not depress the oxidative metabolism of muscle slices from the dog heart at concentrations similar to those used in the present experiments (31). Although information concerning direct metabolic effects of toxic doses of propranolol or pronethalol is not available, the results with these agents did not differ from those obtained with procaine HCl. The possibility that the depressant effects were due to withdrawal of sympathetic tone alone was investigated in several animals. Propranolol and pronethalol in the doses usually employed to produce $\beta$-adrenergic receptor block, however, caused only minimal decreases in contractility. In addition, procaine HCl in toxic doses does not abolish the positive inotropic effects of exogenous norepinephrine. In this connection, it should be emphasized that the mechanisms by which the agents employed produced cardiac depression are unknown, and that other modes of inducing depression exist that may affect the heart in a fundamentally different manner. Thus, whether or not the depression in cardiac function produced by hypoxia, for example, also is accompanied by a reduced $\text{MV}_{\text{O}_2}$ remains to be established.

Certain limitations concerning the methods used herein have been discussed previously (19, 29); however, several points concerning the volume and tension determinations deserve emphasis. The use of the passive pressure-volume relationship after cardiac arrest with KCl for estimation of end-diastolic volume seems justified, since this agent does not appear to induce detectable changes in ventricular diastolic compliance when coronary flow is maintained (26). In addition, since each dog served as its own control, comparisons between control and cardiac depression should have been valid, provided no systematic error in volume was induced between the control and the depressed state. Since the passive pressure-volume relationship, without
coronary blood flow, was used to represent the in vivo curve, we have investigated this assumption by performing pressure-volume curves with and without coronary flow. A small decrease in passive stiffness usually occurs when there is no coronary flow; however, this effect would have altered estimated volumes by only 2 to 3 ml when a maximal change in coronary flow was induced, i.e., from normal to zero flow. Because instantaneous coronary blood flow at end diastole was unknown and because the alterations in it between control and failure were minor (avg = 128 and 114 ml/min per 100 g of left ventricle, respectively), this effect was neglected. The possibility that the agents used affected the passive pressure-volume relation was also considered. This hypothesis was tested using the cat papillary muscle and, as with inotropic agents (32), large doses of pronethalol did not alter the diastolic compliance. Within the reported range of left ventricular end-diastolic pressure (3.5 to 14 mm Hg), appreciable stress relaxation is not observed in the passive pressure-volume curves, and a compliance change on this basis should not have been a major factor during these experiments. Changes in diastolic compliance induced by alterations in systolic tension (32) should not have occurred, since aortic pressure was lowered concomitantly with drug depression, and peak developed tension was relatively constant.

The tension calculations assumed a spherical left ventricular model for both the control and depressed conditions. At equal volumes, total tension, calculated as pressure times internal surface area, is 8% greater for an ellipsoid than a sphere (33). It is probable that, in the transition from the control to the failure state, the ventricle became more spherical. Therefore, while the spherical model might apply accurately to the failing heart, it is possible that the tensions in the more ellipsoidal heart of the control state were actually somewhat higher than those calculated. This effect, if large, could even have resulted in a higher tension in the control state than during failure. To explore this possibility, the magnitude of shape changes and their possible effect on the results were investigated by measuring major to minor left ventricular semiaxis ratios in 2 dogs, from cineangiograms obtained before and after increases in end-diastolic volumes had been produced with blood infusions. The largest change in semiaxis ratios at end diastole was from 2.1/1 to 1.4/1 when left ventricular end-diastolic pressure was increased from 1.4 to 12.6 mm Hg. This change was applied to the present data assuming an ellipsoidal model with a 2.1-1 ratio during control and a 1.4-1 ratio (more spherical) during failure. This correction resulted in an 8% higher tension in the control state and a 3% higher tension during failure than the tensions calculated with a spherical model. This small difference could not alter the interpretation of our data, since even with this maximum correction, peak tension and developed tension area were both still significantly increased, and peak developed tension was not significantly changed during cardiac depression.

In these experiments, peak developed tension was defined as peak tension minus one-half of resting tension to provide consideration of the progressive transfer of load from the parallel elastic components to the contractile elements during fiber shortening (see Methods). This approximation does not alter the directional changes of the results, however, since peak tension, total developed tension area, and peak tension minus end-diastolic resting tension were all either increased or not significantly different during depression (Table 1).

A value of 28 was used for k in calculating series elastic component velocity (see Methods). This constant was derived from cat papillary muscle data, but recent studies using a quick release method in dogs have shown a similar value, which was not changed by noradrenaline infusion (34). It would appear from recent studies in isolated cardiac muscle that series elasticity increases slightly with increasing preload (23). Although the applicability of this observation to the intact heart has not yet been shown, if such a change...
did occur from control to failure in the present investigations, calculated contractile element velocity during cardiac depression would have been even further decreased.

The relation between WCE and energy utilization has proved meaningful in isolated cardiac muscle (35), and Britman and Levine have shown a close correlation between MVo2 and WCE in closed chest dogs (25). It is apparent, however, that the complex geometry of the heart makes characterization of the total contractile effort of the heart difficult. Contractile element work would be most meaningful were it a true measure of average CE shortening distance multiplied by the average tension against which the shortening was performed. Furthermore, there should be some means of normalization for the number of sarcomeres performing this work under different hemodynamic conditions. Such a formulation has not yet been derived, and in this study WCE was calculated by two different methods, to illustrate possible approaches to the problem. The failure to find a consistently positive correlation between WCE and MVo2 with either method further supports the view that factors in addition to force and CE shortening extent may be of importance in determining the heart's energy requirements. Since WCE may not account explicitly for the inotropic state and its reflection in the intrinsic speed of contraction, the possibility was considered that the estimation of mean contraction element power (CEP) might enhance the correlation between MVo2 and WCE; however, the changes in CEP in all cases were directionally similar to the changes in WCE, and thus the correlation was not improved. It must be recognized, however, that variable transfer of resting tension from the PEC to the contractile elements during systole, and the lack of a precise knowledge concerning possible changes in series elasticity when diastolic tension is increased in the intact dog heart, provide potential sources of error in these calculations of CEP and WCE.

Studies on experimentally induced cardiac failure in animals and the failing human heart have produced conflicting results in regard to energy utilization, as reflected in the MVo2 (14-17). Blain and his associate (14) found no significant difference in the MVo2 of patients with clinical heart failure and those without failure, while Levine and Wagman (15) and Messer and Neill (16) have observed considerably greater MVo2 in patients with congestive failure than in control groups. A recent study in which acute drug-induced cardiac failure was produced in dogs at a constant cardiac output, heart rate, and mean aortic pressure showed no changes in MVo2 (36). It seems likely that at least some of the variability in these studies can be explained by the large differences in tension that probably existed and the metabolic cost of this augmented tension. The present study illustrates that cardiac depression at a relatively constant level of developed tension results in a reduction of MVo2.

The somewhat divergent changes in CE and fiber shortening efficiency found with the two different work formulas emphasize the difficulties in assessment of the efficiency of the total cardiac effort at the present time. Nevertheless, the fact that these calculated efficiencies sometimes increased during heart failure may prove significant when considering the energetics of cardiac failure. It is recognized that major differences exist between clinical congestive heart failure and acute cardiac depression; nevertheless, as discussed in detail elsewhere (29), there are marked similarities between the experimental model and clinical cardiac failure in terms of the alterations that occur in force, shortening extent, and fiber shortening velocity (37).

The mechanism through which the MVo2 is altered by positive and negative inotropic influences remains uncertain. Clearly, however, the effect is not dependent upon alterations in tension. The precise energy requirements of mechanical correlates of contractility other than tension (i.e., velocity and extent of shortening) remain to be defined, and the efficiency of other events in the translation of chemical to mechanical energy, such as the process of activation, could also be affected by inotropic influences. The demon-
inotropic influences are associated with an inotropic state and its mechanistic correlates are closely linked to myocardial energy utilization, in a manner that is independent of the energy cost of tension development.

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