A n important recent finding in the study of cardiac energetics is that the left ventricular systolic pressure-volume area (PVA) is closely correlated with myocardial oxygen consumption (MVO) under a wide range of loading conditions.\(^1\)\(^-\)\(^4\) PVA is defined as a specific area in the pressure-volume (P-V) diagram circumscribed by the end-systolic P-V relation line, the end-diastolic P-V relation line, and the systolic segment of the P-V trajectory for a contraction. This area corresponds to the myocardial energy expenditure derived theoretically from a time-varying elastance model of the ventricle,\(^1\) which describes the mechanical behavior of the ventricle in terms of a P-V relation that changes as a function of time.\(^7\)\(^8\) Thus, PVA is interesting not simply because it is closely correlated with MVO, but also because the close correlation of PVA with MVO lends validity to the time-varying elastance model in terms of energetics.

The purpose of the present study was to determine whether the PVA concept obtains in an isolated, linear muscle preparation: that is, whether the close correlation of PVA with MVO on the ventricular level reflects a basic property of cardiac muscle. This overall question was addressed for two specific reasons. First, a compelling impetus for this study was provided by experimental data suggesting that the PVA concept and the time-varying elastance model on which the PVA concept is based do not obtain in isolated muscle. From a mechanical point of view, the time to end-systole for the cat trabecular preparation varies greatly as a function of changing loading conditions.\(^9\) Although the PVA concept itself does not require the constancy of time to end-systole,\(^10\) this variability suggests that there is a major difference between the mechanical behavior of a ventricle and that of isolated muscle in terms of the time-varying elastance model. From an energetic point of view, quick release after end-systole during the isometric contraction has been shown to curtail MVO,\(^3\)\(^-\)\(^9\)\(^-\)\(^12\) although it should not affect MVO, according to the time-varying elastance model and the definition of PVA.\(^1\)\(^-\)\(^3\) These data suggest that the time-varying elastance model and the PVA concept may not obtain in a linear muscle preparation, or at least they suggest that the mechanical and energetic behavior of the ventricle cannot be considered to be a simple analogy of a muscle in terms of the time-varying elastance model. Thus, the close correlation of PVA with MVO, as well as the time-varying elastance property of the ventricle, may arise not from a basic property of cardiac muscle but instead may depend on some specific property of the ventricle.
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such as its complex structure. It is important, therefore, to examine the PVA concept in an isolated cardiac muscle preparation having simple, linear geometry.

Apart from addressing this basic question, a second reason for this study was a matter of practical interest because the PVA concept on the level of linear muscle may be used to estimate the regional energy expenditure of a linear muscle segment of the ventricular wall. However, before such an application is possible, the PVA concept must be validated on the linear muscle level. Furthermore, it is preferable to determine which index is the best predictor of MVO₂ in linear muscle. Thus, the second goal of this study was to determine the best mechanical index of MVO₂ for a linear cardiac muscle preparation. The ideal characteristics of a mechanical index of MVO₂ would be 1) close correlation with MVO₂, 2) independence of the relationship with MVO₂ on the type of contraction, 3) ease of calculation, and 4) simple relation to a corresponding index on the level of the ventricle. Therefore, PVA has been compared with other widely used mechanical indexes of MVO₂ with respect to these characteristics.

Materials and Methods

Experimental Apparatus

Oxygen consumption of the papillary muscle was measured by a modification, which is illustrated elsewhere, of the flow respirometer reported previously. Briefly, it consists of a muscle bath, an oxygen electrode, platinum stimulation electrodes, and a water jacket for heat exchange. A modified Krebs-Henseleit solution at 29°C equilibrated with 95% O₂-5% CO₂ is passed through the upper part of the muscle bath at a rate of 3.5 ml/min. The atmosphere above the bath is displaced by a continuous flow of 95% O₂-5% CO₂ to prevent desaturation of the solution. A small portion of the Krebs-Henseleit solution enters the lower part of the muscle bath at a flow rate of 5.2 ml/hr and superfuses the muscle specimen, which is located at the bottom of the bath. This superfusate is then passed through a sampling capillary, on the side wall of which the cathode of the oxygen electrode is located.

The oxygen electrode is of the Clark type, consisting of a platinum cathode 1.5 mm in diameter and a silver-silver chloride anode reference. The electrode is filled with a solution of Na₂HPO₄ 33 mM, NaOH 35 mM, and KCl 100 mM. The cathodal tip of the electrode is covered with 0.5-mil Teflon, and a polarizing voltage of -0.9 to -0.95 V is applied. The electrode solution and polarizing voltage were selected so as to improve the linearity of the electrode. The linearity of the electrode is shown in Figure 1. The electrode was calibrated after each experiment using 95% O₂-5% CO₂ and 90% O₂-5% CO₂-5% N₂.

MVO₂ was calculated using the output of the oxygen electrode, the flow rate of the solution through the sampling capillary, and the solubility of O₂ in the solution.

To measure muscle force, the mural end of the muscle was mounted on a stainless steel rod terminating in a C-shaped metal clip. The rod, passing through a mercury seal at the bottom of the muscle bath, was screwed directly onto a stiff semiconductor strain gauge. The chordal end of the muscle was tied to a stainless steel hook, and the hook was hung from the arm of a muscle length controller, consisting of a penmotor and an associated control circuit. The penmotor has a built-in displacement sensor, and the arm moves in a feedback control mode in response to a command signal. The command signal was supplied by the associated circuit. To obtain a shortening contraction, the command signal was adjusted so that the arm moved downward at a given interval after each muscle stimulation. By changing this interval and the speed and extent of the downward movement, the various types of shortening contractions, to be described later, were obtained. After the muscle contraction was complete, the arm was moved upward to the initial position. The position signal generated by the displacement sensor was used as the source of the recorded length signal. The actual positional change of the penmotor arm, when measured by a microscope, was linearly correlated (r = 1.00) with the length signal over the experimental range.

Both the signal from the force transducer and the signal from the penmotor displacement sensor were fed to a storage oscilloscope to obtain the force-length trajectory, as well as to an A/D converter connected to a computer. The A/D conversion was done every 1 msec with 12 bits resolution.

Muscle Preparation

Rapid cardectomy was performed on adult male ferrets (0.74–1.99 kg) after full surgical anesthesia had been induced with sodium pentobarbital (50–70 mg/kg i.p.). Fifteen right ventricular papillary muscles, ranging from 2.15 to 5.82 mm in length (4.07 ± 0.31 mm, mean ± SEM) and from 0.36 to 1.03 mm² in cross-sectional area (0.62 ± 0.06 mm²) at Lₘₐₓ, were excised and mounted in the flow respirometer. The metabolism of muscles of these dimensions has been shown not to be diffusion-limited under similar experimental conditions.

After being mounted in the respirometer, each muscle was lightly preloaded and stimulated at a frequency of 12/min for approximately 2 hours until a
stable mechanical response was obtained. Field stimuli approximately 10% above threshold and of alternating polarity were employed. The muscle was then stretched to determine $L_{\text{max}}$. At $L_{\text{max}}$, the developed tension was 57.0 \pm 4.9 \text{ mN/mm}^2$, and the ratio of resting tension to total tension (developed plus resting) was 12 \pm 1%.

After each experiment, muscle length was measured by a micrometer with a known preload attached to the muscle. This length, along with the resting force-length relationship, allowed calculation of muscle length at $L_{\text{max}}$. The wet weight of the muscle was measured with an analytic balance. The cross-sectional area of the muscle was calculated by dividing the wet weight by muscle length at $L_{\text{max}}$, assuming a specific gravity of 1.0 and uniformity of the cross-sectional area.

The composition of the modified Krebs-Henseleit solution was as follows (mM/l): NaCl 98.0, KCl 4.7, KH$_2$PO$_4$ 1.1, NaHCO$_3$ 24.0, MgSO$_4$ 1.2, CaCl$_2$ 2.5, glucose 10.0, and Na acetate 20.0. Ten units of zinc-insulin were added per liter. This solution had a pH of 7.4 when bubbled with a 95% O$_2$-5% CO$_2$ gas mixture and maintained at 29°C.

**Experimental Protocol**

Each experimental protocol was conducted as follows: after measuring the oxygen consumption of the quiescent muscle at a slack length, the muscle was stimulated at a frequency of 12/min and subjected to one of the test loadings described below. After both the mechanical response and the oxygen electrode output reached steady states, the force and length signals for one beat were A/D converted and stored in the computer. Stimulation was then discontinued, and the muscle was returned to the slack length. After oxygen consumption returned to the quiescent level, the next experimental protocol was begun. MV$_0$ under each loading condition was expressed with respect to the quiescent state.

A variety of shortening contractions, as well as isometric contractions, were examined. In 5 of the 15 muscles, isometric contractions (I) and shortening contractions with differing preloads but with a constant amount of shortening (S1) were examined. In another 5 muscles, I and shortening contractions with differing amounts of shortening but with a fixed preload (S2) were examined. In the last 5 muscles, I and shortening contractions with differing times of onset of shortening (S3) were examined; a fixed amount of shortening and 2 preloads were employed for S3. These shortening contractions, S1, S2, and S3, are illustrated in force-length diagrams (Figures 3A, 4A, and 5A).

**Force-Length Area**

Force-length area (FLA), the analog of PVA for a linear muscle, was employed in this study. Figure 2A illustrates the PVA of a ventricle in the P-V diagram. Similarly, Figure 2B illustrates the FLA of a linear muscle in the force-length (F-L) diagram. The end-systolic P-V or F-L line and the end-diastolic P-V or F-L line are indicated as ESL and EDL, respectively. The thick loop with arrowheads represents the P-V or F-L trajectory for contraction; closed circle at upper left corner of loop represents end-systolic P-V or F-L point. Both PVA and FLA have two components: external work (EW) and potential energy (PE). EW is defined as the area within the P-V or F-L trajectory of one contraction and indicates net work done by ventricle or muscle during that contraction. PE is defined as area circumscribed by end-systolic P-V or F-L line, end-diastolic P-V or F-L line, and diastolic segment of P-V or F-L trajectory. This area corresponds to elastic energy which is assumed to be stored in ventricle or muscle at time of end-systole according to time-varying elastance model. Thus, sum of external work and potential energy, i.e., PVA or FLA, represents total mechanical energy in terms of time-varying elastance model. As is seen in figure, end-systolic P-V relationship may be represented by straight line, while end-systolic F-L relationship is curvilinear. Differing shapes of two relations may be explained by fact that volume of ventricle is proportional to segmental length to third power, while intraventricular pressure is function not only of wall tension but also of ventricular geometry as in law of Laplace.

**FIGURE 2.** Graphic representation of pressure-volume area (PVA) and force-length area (FLA). A, PVA in pressure-volume (P-V) diagram. B, FLA in force-length (F-L) diagram. ESL, end-systolic P-V or F-L line; EDL, end-diastolic P-V or F-L line. Thick loop with arrowheads represents P-V or F-L trajectory for contraction; closed circle at upper left corner of loop represents end-systolic P-V or F-L point. Both PVA and FLA have two components: external work (EW) and potential energy (PE).
assumed to be equivalent to a spring for which the F-L relationship is the same as the end-systolic F-L line of that muscle. Therefore, as in the calculation of energy stored in a stretched spring, the energy stored in the muscle at end-systole is the area under the end-systolic F-L line. The area under the end-diastolic P-V line is then subtracted to calculate the net increase in elastic energy because this part of the elastic energy exists even at end-diastole and is considered not to be supplied actively by muscle contraction. The resultant area, i.e., PE in Figure 2B, corresponds to the elastic energy increment. In a ventricle, similar considerations obtain. It is worth noting that this definition of PE is different from the classic internal work assumed to be done on series elasticity.

The sum of EW and PE, that is, PVA or FLA, represents the total mechanical energy of the ventricle or muscle in terms of the time-varying elastance model. In the isovolumic or isometric contraction, PE is the only component of PVA or FLA since EW is zero. As is seen in Figure 2A, PVA can be defined as the area circumscribed by the end-diastolic P-V line, the end-systolic P-V line, and the systolic segment of the P-V trajectory for each beat. Similarly, FLA may be defined as the area circumscribed by the end-diastolic F-L line, the end-systolic F-L line, and the systolic segment of the F-L trajectory for each beat (Figure 2B).

The method used in this study to calculate FLA is as follows. First, the end-diastolic F-L line was determined from the diastolic lengthening segments of F-L trajectories of shortening contractions as well as from the end-diastolic F-L points of isometric contractions. Second, the end-systolic F-L line was determined. The end-systole of each contraction is assumed to be the time corresponding to the left upper corner of the F-L trajectory. This corresponds to the time of peak tension in an isometric contraction. To obtain the end-systolic F-L line, the end-systolic points, i.e., the peak force points for isometric contractions with differing preloads, were displayed on the CRT terminal, and the end-systolic F-L line was traced manually from these points and input to the computer. This manual approach was necessary because, as is seen in Figure 2B, the end-systolic F-L relation was curvilinear, especially at shorter muscle lengths, and could not be approximated by a straight line as is usually done for the end-systolic P-V relationship of a ventricle.

The end-systolic F-L point of an individual beat often did not fall exactly on this manually traced end-systolic F-L line. Thus, the end-systolic F-L line for each beat was assumed to pass through the end-systolic F-L point of that beat and to have force values proportional to the force values of the manually traced end-systolic F-L line for all muscle lengths. This method is analogous to the calculation of the PVA of a ventricle where the end-systolic P-V line of an individual beat is assumed to be the straight line connecting the end-systolic P-V point of that beat with the volume intercept of the end-systolic P-V line obtained from isovolumic end-systolic P-V points.

FLA for each contraction was calculated by the computer as the area circumscribed by these end-diastolic and end-systolic F-L lines and by the systolic segment of each F-L trajectory.

**Force-Time Integral and Peak Force**

Mechanical indexes of MVO, other than FLA were also measured in this study. Force-time integral, as well as pressure-time integral, has been used widely as indexes of myocardial oxygen consumption. However, there are variations in the definitions of these terms. First, muscle force during contraction can be defined in three ways. The simplest of these definitions is total force. Here, no correction is made for the diastolic or passive force. Another definition of contractile force is total force minus end-diastolic force for that beat. Although this seems to be reasonable for the isometric contraction, it has little meaning for the active shortening phase of a shortening contraction.

The third definition of contractile force is total force minus diastolic force at the same muscle length. Because we studied shortening contractions as well as isometric contractions, the third definition seemed reasonable and was used in this study.

Another variable to be considered when using the force-time integral is the time span over which the force is integrated. Two time spans were used; the first was the time for the whole contraction, and the second was the time between stimulation and end-systole. To represent these two methods, FTI was used to indicate the force-time integral for the whole contraction and FTIES to indicate the force-time integral through end-systole.

Peak force (PF) was also tested as a mechanical index of MVO. In a manner analogous to the three definitions of force used for the calculation of the force-time integral, the force value in the PF term may be defined in three ways: first, as total force; second, as total force minus end-diastolic force for that beat; and third, as total force minus resting force at the same muscle length. Because the third definition again seemed to be reasonable for both isometric and shortening contractions, it was used herein. Thus, PF was measured as total force minus resting force at the same muscle length when this value was maximum.

**Results**

**Correlation of Force-Length Area With MVO**

Figures 3, 4, and 5 show representative results of protocols I and S1, protocols I and S2, and protocols I and S3, respectively. In each figure, Panel A shows the F-L diagram, and Panel B is a scatter diagram of FLA-MVO, data. In Panel B, the linear regression line obtained by the least squares method, the 95% confidence limit of this regression line (inner pair of dashed curves), and the 95% confidence limit of the sampled data points (outer pair of dotted curves) are also shown. The regression line and the confidence limits are for isometric and shortening contractions admixed. In each of the three protocols, FLA was closely correlated with MVO, as is seen in Panel B in each
FIGURE 3. Representative results for muscle in which isometric contractions (I) and shortening contractions with differing preloads and fixed shortening amount (S1) were examined. A, Force-length (F-L) diagram. Solid lines represent isometric contractions; dotted lines represent shortening contractions. Manually traced F-L curve is shown by dotted line. Muscle length is shown with reference to Lmax. B, Scatter diagram of FLA-MVO2 data. Closed circles represent isometric contractions; open circles represent shortening contractions. Linear regression line, 95% confidence limit of regression line (inner pair of dashed curves), and 95% confidence limit of sampled data points (outer pair of dotted curves) are also shown. C, Regression lines calculated from either isometric contractions only or shortening contractions only. D, E, and F, Scatter diagrams of PF-MVO2 data, FTI-MVO2 data, and FTIES-MVO2 data, respectively. Linear regression lines, the 95% confidence limits of these regression lines, and 95% confidence limits of sampled data points are also shown.

FIGURE 4. Representative results for muscle in which isometric contractions (I) and shortening contractions with fixed preload and differing shortening amounts (S2) were examined. See legend of Figure 3 for explanation of each panel.
instance. The correlation coefficients were comparable to those of MVO$_2$ vs. PVA for canine left ventricles.²⁻⁴

Panel C in Figures 3, 4, and 5 shows regression lines that are calculated either from isometric contractions only or from shortening contractions only. In each case, these two lines corresponded closely, and as will be discussed later, there was no statistically significant difference between these two regression lines.

Correlation coefficients and estimated regression lines for isometric contractions only, for shortening contractions only, and for isometric and shortening contractions admixed in all muscles are summarized in Table 1.

**Comparison of Force-Length Area With Other Mechanical Indexes of MVO$_2$**

Panels D, E, and F of Figures 3, 4, and 5 show the relation of three other mechanical indexes with MVO$_2$. In each figure, Panel D shows a scatter diagram of PF-MVO$_2$ data, Panel E a scatter diagram of FTI-MVO$_2$ data, and Panel F a scatter diagram of FTIES-MVO$_2$ data. Again, in these panels, for isometric contractions and shortening contractions admixed, the linear regression line obtained by the least squares method, the 95% confidence limit of this regression line (inner pair of dashed curves), and the 95% confidence limit of the sampled data points (outer pair of dotted curves) are shown. As is seen in these figures, the correlation in each case was worse than that between MVO$_2$ and FLA.

Mean ± SEM of correlation coefficients between the mechanical indexes and measured MVO$_2$ for all muscles are shown in Table 2. In isometric contractions, correlation coefficients for FLA, PF, FTI, and FTIES were all near unity. However, if we consider a wide range of contraction types, i.e., shortening contractions and isometric contractions admixed, the correlation coefficient for FLA is the best overall.

Because the distributions of correlation coefficients were not normal, two-way analysis of variance could not be used directly to compare correlation coefficients for FLA with those for other mechanical indexes. Thus,

**Table 1. Regression of MVO$_2$ on Force-Length Area**

<table>
<thead>
<tr>
<th>Mode of contraction</th>
<th>Regression Equation</th>
<th>SD from regression</th>
<th>Correlation coefficient</th>
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<tr>
<td>A/muscle weight nL/beat/mg</td>
<td>B nL/beat/erg</td>
<td>Syx (nL/beat)</td>
<td>r</td>
</tr>
<tr>
<td>I</td>
<td>A + (B \times FLA)</td>
<td>0.237 ± 0.028</td>
<td>0.965 ± 0.005</td>
</tr>
<tr>
<td>S</td>
<td>0.367 ± 0.013</td>
<td>±0.028 ± 0.005</td>
<td>±0.005 ± 0.005</td>
</tr>
<tr>
<td>± 0.050 ± 0.002</td>
<td>0.012 ± 0.001</td>
<td>0.021 ± 0.015</td>
<td>0.953 ± 0.004</td>
</tr>
<tr>
<td>± 0.013 ± 0.001</td>
<td>0.217 ± 0.017</td>
<td>0.017 ± 0.004</td>
<td>0.959 ± 0.004</td>
</tr>
<tr>
<td>S + S</td>
<td>0.385 ± 0.013</td>
<td>±0.017 ± 0.004</td>
<td>0.959 ± 0.004</td>
</tr>
</tbody>
</table>

Regressions of myocardial oxygen consumption (MVO$_2$) on force-length area (FLA) in 15 papillary muscles. A, MVO$_2$ axis intercept of regression line. B, regression coefficient. Because intercept A is theoretically proportional to muscle weight, value of A/muscle weight is shown. SD from regression (Syx), sample standard deviation from regression line. I, regression calculated using isometric contraction data only in each muscle. S, regression calculated using shortening contraction data only in each muscle. The three different protocols for shortening contractions, S1 (differing preloads, fixed shortening amount), S2 (differing shortening amounts, fixed preload), and S3 (differing times of onset of shortening) are included. I + S, regression calculated using isometric and shortening data admixed in each muscle; again, the three different protocols for shortening contractions, S1, S2, and S3, are included. All values are mean ± SEM.
Table 2. Correlation Coefficients for MVO₂ vs. Mechanical Indexes

<table>
<thead>
<tr>
<th>Mode of contraction</th>
<th>Mechanical indexes of MVO₂</th>
<th>FLA</th>
<th>PF</th>
<th>FTI</th>
<th>FTIES</th>
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<tbody>
<tr>
<td>I</td>
<td></td>
<td>0.965 ± 0.005</td>
<td>0.952 ± 0.012</td>
<td>0.970 ± 0.006</td>
<td>0.961 ± 0.008</td>
</tr>
<tr>
<td>S</td>
<td></td>
<td>0.953 ± 0.015</td>
<td>0.915 ± 0.022</td>
<td>0.937 ± 0.024</td>
<td>0.915 ± 0.024</td>
</tr>
<tr>
<td>I + S</td>
<td></td>
<td>0.959 ± 0.004*</td>
<td>0.903 ± 0.013</td>
<td>0.879 ± 0.014</td>
<td>0.925 ± 0.012</td>
</tr>
</tbody>
</table>

Data shown are mean ± SEM of correlation coefficients for 15 muscles. MVO₂, myocardial oxygen consumption; FLA, force-length area; PF, peak force; FTI, force-time integral for entire contraction; FTIES, force-time integral through end-systole; I, correlation coefficient calculated using isometric contraction data only in each muscle; S, correlation coefficients calculated using shortening contraction data only in each muscle. The three different protocols for shortening contractions, S1 (differing preloads, fixed shortening amount), S2 (differing shortening amounts, fixed preload), and S3 (differing times of onset of shortening) are included. I + S, correlation coefficients calculated using isometric and shortening data admixed in each muscle; again, the three different protocols for shortening contractions are included. For comparison of correlation coefficients for I + S, two-way analysis of variance and Fisher’s protected least significant difference method were used after Fisher’s z-conversion and division by standard deviation of z to obtain normal distribution with standard deviation of 1. Analyses revealed statistically significant differences between correlation coefficient for FLA (*) and for each of other three mechanical indexes at level of p < 0.01.

On the other hand, for PF and FTI, there were definite differences in the heights of the regression lines. In addition, differences between the slopes of the regression lines were detected for FTI and FTIES. These differences between the regression lines for isometric contractions and those for shortening contractions are probably the principal reason why the correlations of MVO₂ with PF, FTI, and FTIES were worse than those with FLA when considering isometric and shortening contractions together.

Table 3. Comparison of Regression Lines for Isometric Contractions With Those for Shortening Contractions

<table>
<thead>
<tr>
<th>Mechanical indexes</th>
<th>Comparison of slopes</th>
<th>Comparison of location</th>
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</thead>
<tbody>
<tr>
<td>FLA</td>
<td>0/15</td>
<td>0/15</td>
</tr>
<tr>
<td>PF</td>
<td>0/15</td>
<td>Ns/Nt p&lt;0.05</td>
</tr>
<tr>
<td>FTI</td>
<td>3/15</td>
<td>13/15* p&lt;10⁻⁴</td>
</tr>
<tr>
<td>FTIES</td>
<td>4/15</td>
<td>0/15</td>
</tr>
</tbody>
</table>

FLA, force-length area; PF, peak force; FTI, force-time integral for entire contraction; FTIES, force-time integral through end-systole. Comparisons of slopes of regression lines were made in each muscle using t test for parallelism (two-tailed test). Locations of regression lines were compared by comparing Y values of regression lines at center of range for each mechanical index using t test for common intercept (two-tailed test). Ns, number of muscles in which significant difference was shown at p < 0.05 level; Nt, total number of muscles tested. *In all muscles where significant differences were detected, heights of regression lines for shortening contractions were greater than those for isometric contractions. In all muscles where significant differences were detected, slopes of regression lines for shortening contractions were less than those for isometric contractions. In all muscles where significant differences were detected, slopes of regression lines for shortening contractions were smaller than those for isometric contractions. Because t test was done independently in each muscle, the probability (P) that under null hypothesis, number of muscles in which significant differences are erroneously detected at p < 0.05 level would be equal to or greater than Ns following binomial distribution calculated as follows:

\[ P = \sum_{i=Ns}^{Nt} \binom{Nt}{i} (0.05)^i (0.95)^{Nt-i} \]

where \( \binom{Nt}{i} \) is number of combinations of i letters out of Nt letters.

after Fisher’s z-conversion²⁵ and division by the standard deviation of z, or \( \frac{1}{n(\alpha - 3)^{1/2}} \), to get a normal distribution with a standard deviation of 1, two-way analysis of variance and Fisher’s protected least significant difference method²⁶ were used. These analyses showed statistically significant differences between the correlation coefficients for FLA and those for the other three indexes for isometric and shortening contractions admixed (F ratio in two-way analysis of variance, \( p < 0.01 \); differences between FLA and PF, between FLA and FTI, and between FLA and FTIES, \( p < 0.01 \)).

As discussed before, the regression lines of MVO₂ on FLA for shortening contractions correspond closely to those for isometric contractions (Panel C in Figures 3, 4, and 5). This finding is explained by the fact that the FLA-MVO₂ data points for shortening contractions are located close to those for isometric contractions as is seen in Panel B in each figure. On the other hand, for the other mechanical indexes, there was a general tendency for the points representing shortening contractions to segregate from the points representing isometric contractions (Panels D, E, and F in each figure).

To examine this tendency, the difference between the regression line for shortening contractions alone and that for isometric contractions alone was analyzed for each mechanical index in each muscle. Slopes of these two regression lines were compared by the t test for parallelism.²⁶ The heights, or positions, on the ordinate of the regression lines were compared in terms of the Y values of regression lines at the center of the range for each mechanical index using the t test for intercept.²⁶ Table 3 summarizes the results of the statistical tests for each mechanical index. The number of muscles where statistical differences (\( p < 0.05 \)) were detected (Ns) and the total number of muscles tested are listed. Because the comparisons were done independently in each muscle, the probability that Ns would be equal to or greater than the actual Ns under the null hypothesis using a binomial distribution was calculated.

For FLA, no difference in slope or height of the regression lines was detected in any of the 15 muscles.
Time to End-Systole

As discussed in the introduction, the change in elastance and, therefore, the time to end-systole (TES) is assumed to be load-independent in the original time-varying elastance model.\textsuperscript{1,2} However, in cat trabeculae, TES has been shown to be load-dependent.\textsuperscript{3} Although the PVA concept itself does not require a constant TES,\textsuperscript{4,5} this disparity suggests a difference between the mechanical behavior of an isolated muscle and that of a ventricle in terms of the time-varying elastance model. Because of this disparity and because the present experiment was done in ferret papillary muscles, the load dependency of TES was examined in the same 15 ferret papillary muscles used for the preceding portion of this study. Figure 6 shows an example of the load dependency of TES in a representative muscle, the same muscle as that shown in Figure 3. In this figure, TES is plotted against muscle length at end-systole. TES was load-dependent in two ways. First, TES was related to muscle length at end-systole, as shown by the two regression lines in Figure 6, which are either for isometric contraction data or for shortening contraction data. The correlation coefficient for isometric contractions was 0.929 (p < 0.01). The correlation coefficient for shortening contractions was 0.875, although the correlation is statistically insignificant. Second, shortening contractions have a longer TES than isometric contractions with a corresponding end-systolic muscle length. This was shown statistically by the fact that the height of the regression line for isometric contractions and that for shortening contractions were significantly different (p < 0.01) from each other by the t test for intercept.\textsuperscript{6,7} Similar results were found for all muscles. The shortest TES was as short as 53-68% (60 ± 1%, mean ± SEM) of the longest TES in each of these 15 muscles.

Effect of Load Change After End-Systole on MVO$_2$

It was previously reported by one of us that quick release of a papillary muscle after end-systole curtails MVO$_2$.\textsuperscript{1,11,12} This result seems to be at variance with the PVA or FLA concept as discussed later. However, these experiments were done in cat papillary muscles, while the present experiments, where FLA was shown to be closely correlated with MVO$_2$, were done in ferret papillary muscles. Therefore, similar quick release experiments were done in 5 additional ferret muscles.

The protocol of the experiments was as follows: the muscle was allowed to contract isometrically at L$_{max}$. After both the mechanical response and the oxygen electrode output reached steady states, a quick release was imposed, where the muscle was released at a rate of about 5 L$_{max}$/sec to its slack length just after end-systole, i.e., the time of peak force. Quick release was then imposed during each succeeding contraction until steady states of mechanical performance and oxygen electrode output were reached.

Figure 7 shows a representative result of these release experiments. The upper left and upper right panels show, respectively, force and length recordings of an isometric contraction and of a released contraction. As is seen in the figure, MVO$_2$ for the released contraction decreased by 35% when compared with that for the full isometric contraction despite a slight increase in peak developed force. Similar decreases in MVO$_2$ (36 ± 4%, mean ± SEM) were found consistently in each of a total of 5 muscles. The amount of decrease in MVO$_2$ found here is comparable to that found earlier in cat papillary muscles.\textsuperscript{11}

Discussion

Correlation Between Force-Length Area and MVO$_2$

This study has shown that the concept of pressure-
volume area, which was originally described in the left ventricle, obtains as force-length area in a linear muscle preparation under variable conditions of preload and afterload. This result indicates that the close correlation of PVA with MVO₂ on the ventricular level arises from a basic property of cardiac muscle and not from some specific characteristic of the ventricle, such as its complex structure.

It has also been shown that FLA has a better correlation with MVO₂ than with other mechanical indexes when a wide range of loading conditions was examined. Furthermore, the relationship between FLA and MVO₂ is not dependent on the mode of contraction, while the regression lines of MVO₂ on other mechanical indexes for shortening contractions differ significantly from those for isometric contractions.

An interesting application of mechanical indexes of MVO₂ for a linear muscle is the calculation of energy expenditure by a linear ventricular segment. Beyar and Sideman have employed the FLA concept successfully to calculate regional oxygen demand in the ventricular wall. The present results not only validate their usage of the FLA concept but also suggest that FLA is the preferred index for such an application both because of its optimal correlation with MVO₂ and because of the independence of the relationship between MVO₂ and FLA on the mode of contraction.

The disadvantage of the FLA index is the complexity of its measurement. To calculate FLA, it is necessary to measure both muscle force and length, while other indexes, such as peak force and force-time integral, require only force measurement. Furthermore, the use of FLA necessitates the determination of the end-systolic F-L line. These requirements for the measurement of FLA are not troublesome for experiments on isolated muscle, where the end-systolic F-L line can be determined easily, and for a simulation approach such as that mentioned before, where the end-systolic F-L line is assumed. However, if an attempt is made to estimate regional energy expenditure by calculating the stress and strain of a specific part of the ventricle, using pressure and geometric data from an actual ventricle, this complexity can be a problem. The nonlinearity of the end-systolic F-L relationship may also increase the difficulty.

Relationship Between Force-Length Area and Pressure-Volume Area

In addition to its optimal correlation with MVO₂ and the independence of this relationship with MVO₂ on the mode of contraction, FLA has another major advantage over other indexes. Because it is theoretically derived from the time-varying elastance model, FLA is an quantity of energy. Furthermore, FLA has a simple relationship with the corresponding mechanical index on the ventricular level, i.e., PVA. It has been found that the sum of FLAs for the individual muscle fibers that constitute a ventricle theoretically becomes the PVA of that ventricle and that this relationship of FLA with PVA is completely independent of ventricular geometry, fiber orientation, and stress-strain distribution (data not shown). This equivalence of FLA and PVA is quite attractive in that the energy expenditure as well as the oxygen consumption by a ventricle is the sum of these data from the individual muscle fibers that comprise that ventricle. This provides a good reason to consider that the close correlation of PVA with MVO₂ on the level of the ventricle results from the close correlation of FLA with MVO₂ on the level of a linear muscle.

In addition to their relatively poor correlation with MVO₂, such other indexes as PF, FTI, and FTIES have a disadvantage in that they are not quantities of energy and do not have a simple relationship with the corresponding indexes of ventricular contraction. That is, for any of these indexes, the sum of contributions from each muscle fiber constituting the ventricle does not become the corresponding index for the entire ventricle as does the sum of FLAs for the muscle fibers comprising a ventricle. To relate PF to the peak pressure of a ventricle, FTI to the pressure-time integral, and FTIES to the pressure-time integral through end-systole, assumptions must be made about ventricular geometry, fiber orientation, and stress and strain distribution.

It is reasonable to consider that the load on a linear muscle is the final determinant of energy expenditure. Thus, even in experiments employing ventricles, many investigators have tried to convert the pressure and geometric data to linear muscle indexes, such as peak force and force-time integral. For this calculation, the assumptions mentioned before are required. Furthermore, the values of the indexes are usually calculated only at the level of the ventricular equator. On the other hand, using the PVA and FLA concepts, this conversion is no longer necessary. PVA can be considered to represent the total of the FLA loads on the linear muscle level because the sum of FLAs for all muscle segments constituting the ventricle is equal to the PVA. In this sense, in a ventricular experiment, PVA can be used without any conversion as a measure of load at the level of linear muscle.

Validity of the Time-Varying Elastance Model

It is necessary to consider the validity of the FLA concept in relation to the time-varying elastance model. Just as the PVA concept was derived from a time-varying elastance model of the ventricle, the FLA concept can be derived theoretically from a time-varying elastance model of a linear muscle. The fact that FLA is highly correlated with MVO₂ supports the time-varying elastance model of a linear muscle in terms of energetics.

However, in the present study using the ferret papillary muscle preparation, as shown previously by Elzinga and Westerhof in cat trabeculae, TES differs greatly as a function of loading conditions (Figure 6). The change in time-varying elasstance and, therefore, TES are both load-independent in the original time-varying elastance model from which PVA was first derived. Thus, this type of time-varying elastance model, where the elastance change is only a function of time, may not obtain in linear muscle. However, the PVA concept itself does not require the load...
independency of the elastance change. In other words, even in a time-varying elastance model in which elastance change has load dependency, PVA represents the total mechanical energy. Thus, the load dependency of TES does not invalidate the time-varying elastance concept for the papillary muscle.

However, the results of the release experiment shown in Figure 7 may be inconsistent with the time-varying elastance model. Mechanical events after end-systole should not affect energy expenditure in terms of the definition of PVA or FLA, which does not include the diastolic, or post-end-systolic, segment of the P-V or F-L trajectory. This observation implies that the time-varying elastance model assumes that a muscle converts chemical energy to mechanical energy (i.e., external work and elastic potential energy) only before end-systole or at least that the energy utilization after end-systole is load-independent.

This assumption in the time-varying elastance model that the energy expenditure is independent of any load change after end-systole is definitely different from but may be analogous to the assumption in the classic “new elastic body” theory where energy expenditure depends only on initial conditions and any change in mechanical conditions after the onset of contraction should not affect muscle energy expenditure. The Fenn effect, where load changes after the onset of contraction affect the total energy expenditure of the muscle, contradicts the classic “new elastic body” theory of a muscle. Although it must be clearly noted that the Fenn effect itself does not contradict the time-varying elastance model in that the time-varying elastance can explain the change of energy expenditure due to the afterload change after end-systole, it is of interest to determine whether a load change after end-systole affects MVO.

The effects of load changes after end-systole on MVO have been studied in both ventricular and isolated muscle preparations. In the ventricle, volume changes after end-systole have little effect on MVO. These results support the PVA concept and the time-varying elastance model, on which PVA is based, in the ventricle. On the other hand, in isolated ferret papillary muscles, the present results indicate that quick release after end-systole during an isometric contraction greatly reduces MVO. This result was shown previously in the cat papillary muscle preparation for all phases of the isometric contraction. The finding that mechanical events after end-systole affect MVO would appear to be inconsistent with the time-varying elastance model.

A basis for the difference between the results in the ventricle and those in the papillary muscle is available in further recent data where the effect of quick release on the MVO of papillary muscles was shown to be dependent on the mode of contraction. Quick release imposed on an isometric contraction at any moment in the contraction decreases MVO. Quick release before shortening begins in an isometric contraction effectively terminates MVO, but quick release during the later phases of an isometric contraction, after shortening has begun, does not have a major effect on MVO unless there is a large afterload. The latter result may be due to shortening deactivation. That is, normally occurring shortening during an isotonic contraction may cause deactivation of the muscle and thus terminate oxygen consumption. Because ejection occurred in both of the ventricular experiments mentioned above before the quick volume change was imposed, shortening deactivation may well explain the results.

Thus, from this point of view, while the time-varying elastance model is not a complete description of the energy expenditure of cardiac muscle during isometric contractions, it may be able to describe more completely the energy expenditure during shortening contractions.

To explain the finding that a load change after end-systole affects energy expenditure in terms of the time-varying elastance model, it would be necessary to consider the possible recoupling of potential energy (and Figure 2B) into chemical energy. However, this possibility cannot be examined as yet because the time course of energy expenditure during the course of a contraction cannot be measured. The ultimate validity of the time-varying elastance model in terms of energetics remains to be tested using such a measurement.

The present study has shown that FLA is closely and linearly related to MVO in the papillary muscle preparation under a wide range of loading conditions, indicating that the linear correlation of PVA with MVO, in a ventricle results from a basic property of cardiac muscle. This study has also shown that the correlation of FLA with MVO is better than that for other mechanical indexes and that the relationship of FLA with MVO is not dependent on the mode of contraction, while the relationships of other mechanical indexes with MVO are dependent on the mode of contraction. In addition, FLA has a simple relationship to PVA, in that the sum of the FLAs of all muscle segments constituting a ventricle is equal to the PVA for that ventricle. From both of these points of view, FLA can be said to be the optimal index of MVO, for a linear muscle. However, because quick release after end-systole affects MVO in isometric contractions, as does quick release before end-systole, the time-varying elastance model for a muscle, on which FLA is based, cannot be considered a complete description of myocardial energetics, especially for contractions in which muscle shortening is minimal.

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