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Contractile Element Work: A Major Determinant of Myocardial Oxygen Consumption *

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The study of the determinants of myocardial oxygen consumption during the past fifty years has formed an interesting historical sequence. In 1927 Starling and Visscher proposed that the energy requirement of the heart was determined by its initial fiber length (1), and this observation was confirmed by others (2, 3). Rhode, on the other hand, stated that only ventricular pressure and heart rate determined the oxygen consumption of the heart (4). In an effort to resolve the importance of both fiber length and pressure generated, stroke work was examined but found by a number of workers to correlate poorly with oxygen consumption (1–3, 5–8). As early as 1915, Evans and Matsuoka suggested that myocardial wall tension may be the major determinant of myocardial oxygen consumption (5). This thesis received some support from the work of Fischer, who found that oxygen consumption varied directly with isometric tension in isolated skeletal muscle twitches (9).

In 1958 Sarnoff and associates (7) described a remarkably constant relationship between oxygen consumption and the area under the systolic portion of the arterial pressure curve (tension-time index). This measure of pressure and time (hereafter referred to as pressure-time per minute), however, did not bear a constant relation to oxygen consumption during exercise in normal human subjects (10). As changes in ventricular dimensions during exercise had been reported (11), it was suggested that changes in radius and therefore of wall tension may have been responsible for the observed discrepancy between pressure-time per minute and oxygen consumption (10). Subsequently, oxygen consumption has been related to the product of mean myocardial tensile force and the systolic ejection period (force-time per minute). Despite this consideration, the relationship between force-time per minute and oxygen consumption was not always found to be linear (12).

In terms of basic muscle mechanics, however, the concept of force-time per minute, like the other indexes mentioned, fails to consider the total contractile effort of the heart. It has long been considered that the contractile effort of muscle may be manifested either as fiber shortening or as force generation brought about by the stretching of a series elastic component (13, 14). Since the energy requirement of the muscle must be governed by the contractile element itself, a reasonable assumption is that both manifestations of the contractile process should be represented in a consideration of muscle energetics.

The purpose of this paper is to describe a method for the calculation of total contractile element work in the intact dog heart. We found that over a wide range of altered hemodynamics, contractile element work (CEW) bears a closer relation to myocardial oxygen consumption than does the pressure-time per minute, force-time per minute, or left ventricular work.

Methods

Methods and experimental design. Thirty-four studies were carried out in 23 mongrel dogs weighing from 13 to 24 kg, anesthetized with either sodium pentobarbital, 25 mg per kg, with or without morphine sulfate premedication, 3 mg per kg, or chloralose, 50 to 70 mg per kg, with morphine sulfate premedication. The details of the experimental design have been presented in the preceding paper (15). Obstruction of the proximal ascending aorta was produced by surgical coarctation (umbilical tape tourniquet) in 8 animals and by inflation of an intra-aortic balloon in the remainder. The resultant gradient was utilized to derive instantaneous aortic flow rate (*vide infra*). Catheters were placed in the left ventricle, aorta, pulmonary artery, and great cardiac vein. Coronary flow was determined by the nitrous oxide desaturation method (16). Systemic arterial, pulmonary arterial, and coronary venous oxygen contents were measured by the method of Van Slyke and Neill (17).

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Left ventricular volume was determined by the thermal dilution technic (18). The error and reproducibility of this method have been presented (15).

Each study consisted of the simultaneous measurement of cardiac output, left ventricular and aortic pressures, heart rate, left ventricular volume and left ventricular coronary blood flow, and oxygen extraction. Alterations of the hemodynamic state were achieved by changing the degree of aortic obstruction, volume loading by the rapid infusion of 500 to 1,500 ml of whole blood or inotropism induced by the infusion of isoproterenol in a dose of 1 to 5 μg per minute.

At the conclusion of each experiment, the left ventricle with the interventricular septum was dissected from the remainder of the heart and was weighed.

Definitions and calculations. All terms and measurements refer to the left ventricle. Stroke volume was derived from the cardiac output and heart rate, and with the ratio of end-diastolic volume to end-systolic volume obtained from the thermal dilution curve, the end-diastolic chamber volume was calculated (18). Instantaneous aortic flow rate was derived as described in the preceding paper (15). The instantaneous ventricular volume (V) at each 0.02-second interval during systole was derived by integration of the flow rate curve up to that time and by subtraction of this integral (the volume ejected) from the end-diastolic volume. The ventricle was assumed to be spherical, and the instantaneous radius, r, was obtained from the formula $V = 4\pi r^3/3$.

The circumferential fiber shortening rate (CFSR), defined as the rate of fiber shortening at the equator of a sphere, was calculated at each 0.02-second interval during systole, as flow rate/$2r^2$ (15) and is expressed as centimeters per second. Myocardial tensile force (F) was calculated at similar intervals as $F = \pi r^2 P$[1], where F = total tangential myocardial force in dynes, r = internal radius of the left ventricle in centimeters, and P = intraventricular pressure in dynes per cm^2. The rate of change of $F(dF/dt)$ was derived at each 0.02-second interval by measuring the slope of the force-time plot.

In our analysis of the muscle mechanics of the heart, the three-component model of Hill (13, 14) has been employed (see Figure 2, reference 15). Since it is apparent from this model that the contractile effort of the heart may be expressed as either shortening of the muscle fiber or lengthening of the series elastic component (SEC), at any one instant the shortening velocity of the contractile element (CE) must be equal to the sum of the fiber shortening rate (CFSR) plus the lengthening velocity of the SEC (dl/dt). The latter, in turn, is responsible for force generation within the fiber and is related to the rate of force development (dF/dt) by the stiffness of the SEC (dF/dl) as follows: $dF/dt = (dF/dl)(dl/dt)$ (13, 14).

To derive dl/dt, both dF/dt and dF/dl must be known. Although dF/dt may be measured in these experiments as described above, dF/dl must be estimated from *in vitro* experiments of mammalian heart muscle. In the isolated cat papillary muscle, Sonnenblick found that dF/dl increased linearly with increasing force and was independent of stimulation frequency, initial fiber length, and inotropic interventions such as norepinephrine or calcium (20, 21). To estimate the dF/dl of the dog's left ventricle, the relationship between dF/dl and F in the cat papillary muscle was normalized for unit dimensions and extrapolated to the specific dimensions of each dog's left ventricle. This formula, which was derived in the preceding paper (15), is as follows: dF/dl (dynes per centimeter) = [28.8 $\times$ F (dynes)]/[l_o (centimeters)] + [241,000 (dynes per centimeter) $\times$ A_o (cm^2)]/[l_o (centimeters)], where l_o, the muscle length, was obtained as $2\pi r_o$, where r_o is the smallest end-diastolic chamber radius measured in a given dog, and A_o, the cross-sectional area of muscle, was derived as $2\pi r_o t$, where t is the wall thickness at that end-diastolic chamber size. The smallest end-diastolic chamber size was used to approximate the resting dimensions of the muscle. Wall thickness, t, was derived by the subtraction of r_o from the radius of a sphere whose volume was equal to the smallest end-diastolic chamber volume plus the left ventricular muscle volume in milliliters (left ventricular weight in grams).

Using the measured dF/dt and the above approximation of dF/dl, a value of dl/dt was obtained at each 0.02-second interval of systole. This dl/dt was then added to the CFSR to yield the contractile element velocity (Vce) at each interval.

Instantaneous shortening power in dyne-centimeters per second was derived as the product of force (dynes) and shortening velocity (centimeters per second). Thus, shortening power of the muscle fiber was calculated as $F \times$ CFSR, whereas shortening power of the contractile element was calculated as $F \times Vce$. These shortening powers were then plotted against time for one complete systole. This plot for a typical experiment is shown in Figure 1. Since the area under a power-time curve represents work done, the area under the fiber shortening power curve (area B + area C) equals the fiber shortening work (FSW) per beat, and the area under the contractile element power curve (area A + area B) equals the contractile element work (CEW) per beat.

Fiber shortening work per minute was derived by multiplying the heart rate times the directly planimetered area under the fiber shortening power curve (B + C) and is expressed as dyne-centimeters per minute per 100 g left ventricle (LV).

Contractile element work per beat was derived as the sum of area A + area B. Area B was obtained by direct planimetry, but because of the difficulties in accurately determining the Vce during the isometric period (15), area A, which represents the work done by the CE in stretching in the SEC to peak force, was derived by mathematical integration as follows:

[1] From the Laplace equation, surface tension per unit length = $rP/2$. Multiplying this by the total length along which tension exists ($2\pi r$), total tension = ($2\pi r$) ($rP/2$) or $\pi r^2 P$. Hefner, Sheffield, Cobbs, and Klip have found this force to vary directly with the measured force necessary to keep together the two edges of a slit in the ventricular wall (19).

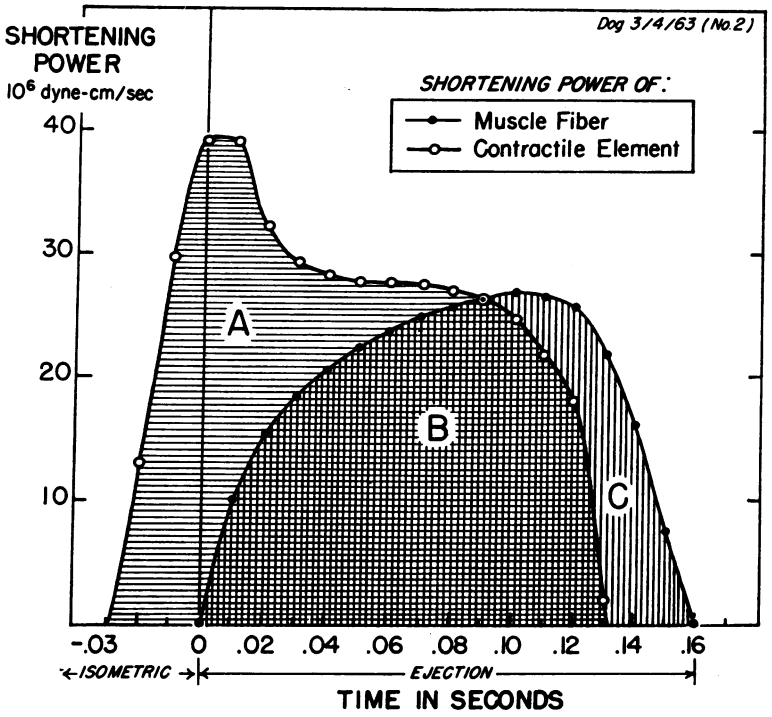

FIG. 1. TIME COURSE OF THE SHORTENING POWER OF THE CONTRACTILE ELEMENT AND THE MUSCLE FIBER. Contractile element shortening power (open circles) and fiber shortening power (solid circles) are plotted throughout the course of one systole. The areas under these curves represent work (work = $\int$ power $\times$ dt). These two curves cross at the point where peak force is achieved, since at that point, dF/dt, and therefore dl/dt, are equal to zero, and thus fiber shortening velocity is equal to the contractile element velocity. It follows that the respective shortening powers would also be equal at that point.

From the onset of the isometric period until the point where the power curves cross, the power of the contractile element exceeds that of the fiber by an amount used for lengthening of the SEC. Thus, area A represents the work done by the contractile element in stretching the SEC to peak force. Beyond the point of crossing of the curves, the CE power is less than that of fiber shortening, since the recoiling SEC is now assisting the CE in shortening of the fiber. Beyond the point where the CE power falls to zero, the CE begins to lengthen, and the remaining fiber shortening is entirely performed by the recoiling SEC. Thus, area C represents the work done by the recoiling SEC in shortening the fiber, whereas area B represents that portion of fiber shortening work performed directly by the contractile element. Area A + area B represent the total work done by the contractile element, and area B + area C equal the total fiber shortening work performed.

In stretching a spring from initial length l_i and force F_i, to peak length l_p and force F_p, work done = $\int_{l_i}^{l_p} Fdl$. For the SEC, $dF/dl = S \times F + (dF/dl)_o$, where $S = 28.8/l_o$ (*vide supra*). Because the stiffness of the SEC at zero load $(dF/dl)_o$ constitutes a small contribution to total dF/dl (except at very low force), it was ignored in this derivation. Thus $dl = dF/(S \times F)$, and the expression for work done becomes

$$\int_{F_i}^{F_p} \frac{FdF}{S \times F}, \quad \text{or} \quad \frac{l}{S}\int_{F_i}^{F_p} dF.$$

By integration, work = $l/S\ (F_p - F_i)$. F_i is equal to the fraction of the end-diastolic force at the onset of isometric contraction borne by the SEC. Since most of the end-diastolic force is thought to be borne by the parallel elastic component rather than by the SEC, and further, since the total end-diastolic force is small compared with the peak force, F_i was ignored. Thus, the work performed in stretching the SEC (area A) was calculated as F_p/S.

Contractile element work (CEW) per minute was obtained by multiplying the heart rate times the CEW per

beat as derived above and is expressed as dyne-centimeters per minute per 100 g LV.

Left ventricular work was derived as the product of LV systolic mean pressure and cardiac output and is expressed as kilogram-meters per minute per 100 g LV. Mechanical efficiency in per cent was obtained as the ratio of left ventricular work to the energy equivalent (2.06 kg-m per milliliter O_2) of left ventricular oxygen consumption minus 3 ml per minute per 100 g (the oxygen consumption of the beating, nonworking heart) (22).

Pressure-time per minute (PTM) was calculated as the product of left ventricular systolic mean pressure and systolic ejection period per minute and is expressed as mm Hg-seconds per minute.

Force-time per minute (FTM) was derived by multiplying heart rate times the directly planimetered area under the force-time curve during the ejection period of a single systole and is expressed as dyne-seconds per minute per 100 g LV.

Left ventricular oxygen consumption ($LVqO_2$) was calculated as the product of the myocardial a-v oxygen difference and the left ventricular coronary flow per 100 g and is expressed as milliliters per minute per 100 g LV.

Results

Relationship of pressure-time per minute to left ventricular oxygen consumption. The relationship between PTM and $LVqO_2$, shown in Figure 2, has an r of 0.74 ($p < 0.001$). The regression line for these points has a negative y intercept (−2.22 ml). When only those studies with a $qO_2 < 15$ ml per minute per 100 g were analyzed (18 studies), an r of 0.81 ($p < 0.001$) was obtained, and the regression line for these points has a slope significantly different ($p < 0.001$) from the slope of the previous line, with a positive y intercept of 4.15 ml. Analysis of the remaining 16 studies with $qO_2 > 15$ ml yielded no statistically significant correlation ($p > 0.10$).

Relationship of force-time per minute to left ventricular oxygen consumption. The relationship of FTM and $LVqO_2$, shown in Figure 3, has an r of 0.74 ($p < 0.001$). The y intercept of this regression line is +5.25 ml. In this case, no significant correlation was found for either the subgroup with $qO_2 < 15$ ml ($p > 0.05$) or the subgroup with $qO_2 > 15$ ml ($p > 0.10$). Four of the 5 isoproterenol studies lie above the regression line.

Relationship of fiber shortening work per minute to left ventricular oxygen consumption. Figure 4 shows the relationship of FSW to $LVqO_2$ ($r = 0.74$; $p < 0.001$). The y intercept of this regression line is +6.75 ml. In this case, analysis of the population with $qO_2 < 15$ ml yielded an r of 0.68 ($0.001 < p < 0.01$), but the slope was not significantly different ($p > 0.10$). The points with high qO_2 yielded no significant correlation ($p > 0.10$). Four of the 5 isoproterenol points lie below the regression line.

Relationship of contractile element work to left ventricular oxygen consumption. Figure 5 shows the relationship of CEW to $LVqO_2$. The r for this relationship is 0.91 ($p < 0.001$) and is significantly better than each of the previous correlations ($0.01 < p < 0.05$). The y intercept of this regression line is +4.33 ml. When the analysis was made of the point with $qO_2 > 15$ ml, a significant correlation was found ($r = 0.74$; $p = 0.001$). This is in contrast to the absence of such a correlation in the case of the three previous determinants. Analysis of those points with $qO_2 < 15$ yielded an r of 0.77 ($p < 0.001$) and a slope not significantly different from that of the entire group. Despite the improved correlation of qO_2 with CEW, 4 of the 5 isoproterenol points lie below the regression line.

Relationship of fiber shortening work to left ventricular work. Figure 6 shows the linear relationship between FSW per minute per 100 g LV and LV work per minute per 100 g LV. This linearity can be predicted from theoretical considerations. Per beat, FSW = $\int F \times \text{CFSR}\, dt$. As $F = \pi r^2 \times P$ and CFSR = $(dV/dt)/2r^2$, this becomes FSW = $\pi/2 \int P \times [(dV/dt)dt]$, or FSW = $\pi/2\, P\, dV$. Since $P dV$ = stroke work, LV work per minute = $(2/\pi)$ FSW per minute.[2] Introducing the units conversion factor (0.0102 kg-m per 10^6 dyne-cm), LV work (kilogram-meters per minute) = 0.00649 FSW (10^6 dyne-cm per minute). This shows excellent agreement with the slope of the regression equation for the LV

[2] The reason for the $2/\pi$ factor lies in the tacit assumption that the spheric muscular shell of radius r is equivalent to a sheet of muscle of width $2\pi r$ and length $2\pi r$, and in the fact that shortening in only one dimension was considered. However, since the surface area of a sphere is $4\pi r^2$, a more reasonable representation of the muscular shell would be a sheet of muscle of dimensions $2\sqrt{\pi}\, r \times 2(\sqrt{\pi}\, r)$. From the law of Laplace, surface tension per unit length is given by $(r \times P)/2$, where P is the intracavitary pressure. Thus the total tension (force) in one direction would be $(2\sqrt{\pi}\, r) \times (rP/2)$ or $\sqrt{\pi}\, r^2 \times P$. If we now let the sphere contract so that the radius changes an increment dr and the volume changes dV, the side of the above considered square would shorten a distance of $2\sqrt{\pi}\, dr$, and the work done in one dimension would be $(\sqrt{\pi}\, r^2 \times P) \times (2\sqrt{\pi}\, dr)$ or $P \times 2\pi r^2\, dr$. Since shortening clearly occurs in two dimensions, the total true fiber shortening work is $P \times 4\pi r^2 dr$. Since, by differentiation, $dV = 4\pi r^2 dr$, the total true fiber shortening work can readily be seen to equal the pressure volume work ($p\, dV$).

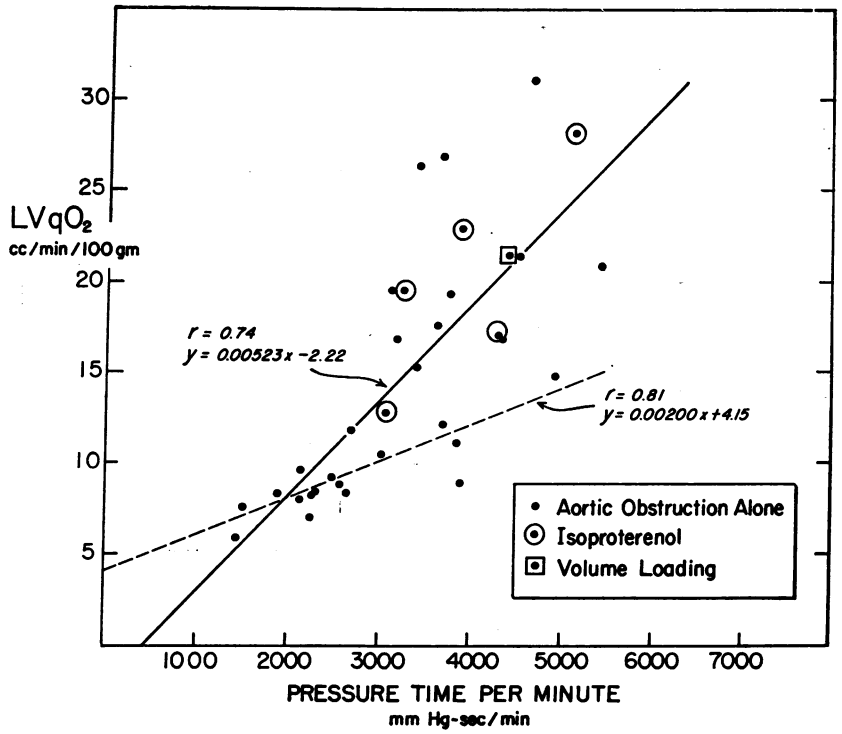

FIG. 2. RELATIONSHIP OF PRESSURE–TIME PER MINUTE TO LEFT VENTRICULAR OXYGEN CONSUMPTION ($LVqO_2$). Two regression lines are shown, one obtained from all points and one from only those points with $qO_2 < 15$ ml per minute per 100 g (see text).

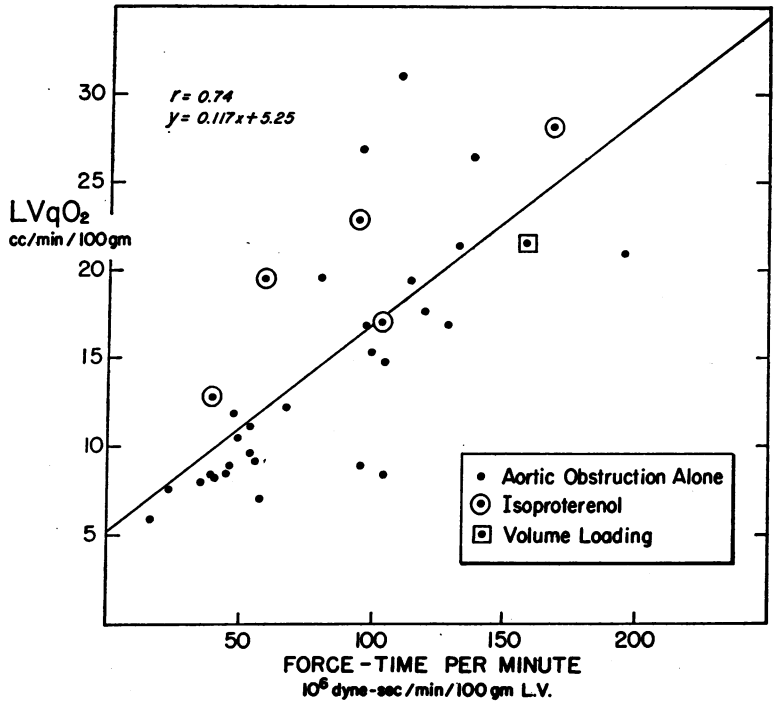

FIG. 3. RELATIONSHIP OF FORCE–TIME PER MINUTE TO LV OXYGEN CONSUMPTION.

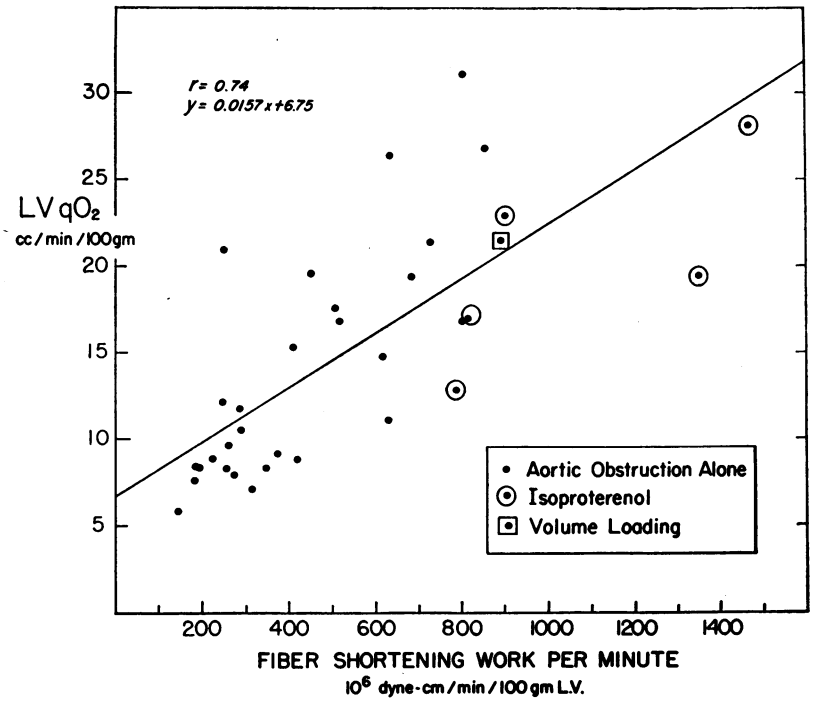

FIG. 4. RELATIONSHIP OF FIBER SHORTENING WORK TO LV OXYGEN CONSUMPTION.

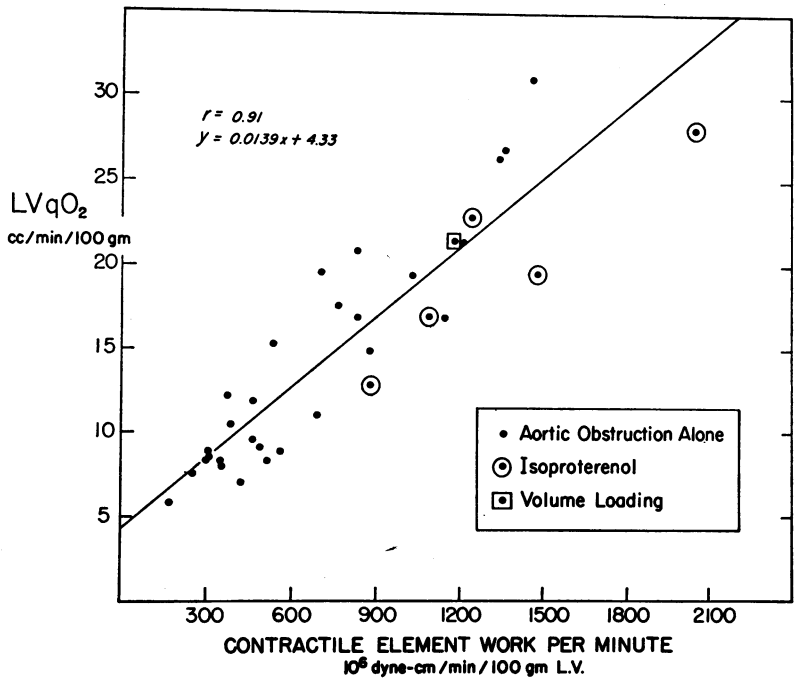

FIG. 5. RELATIONSHIP OF CONTRACTILE ELEMENT WORK (CEW) TO LV OXYGEN CONSUMPTION.

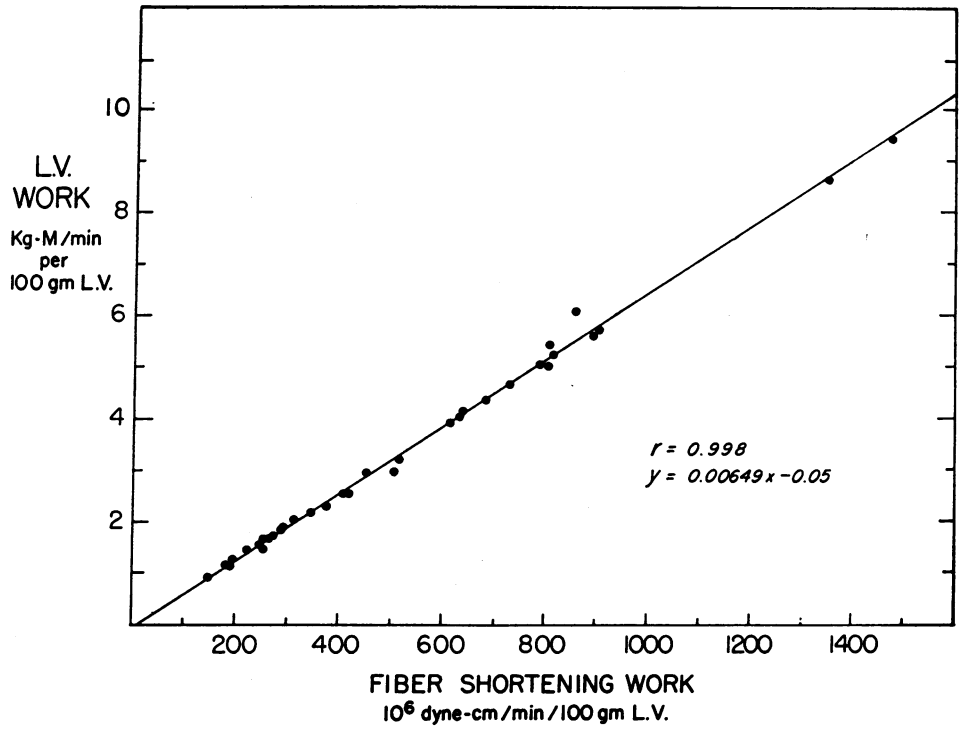

FIG. 6. RELATIONSHIP OF LEFT VENTRICULAR WORK TO FIBER SHORTENING WORK (FSW).

work-FSW plot. Thus, the FSW-qO_2 plot (Figure 4) reflects the relation of LV work to oxygen consumption, and the deviations of the points from the regression line represent variations in mechanical efficiency.

Contractile element work index. Because the derivation of CEW involves laborious calculations and further requires the measurement of instantaneous flow, an attempt was made to derive an index of CEW, which could be calculated from the readily obtainable parameters of heart rate (HR), stroke volume (SV), left ventricular systolic mean pressure ($\bar{P}$), and left ventricular mean volume ($\bar{V}$). The last term is defined as the volume when half of the stroke volume is ejected. The equation for this contractile element work index is as follows: CEW index = $[HR][\bar{P}][SV + [\bar{V}/9.6]$.

This index yielded an excellent linear correlation with the calculated CEW ($r - 0.995$), although the correlation between this index and the true CEW has been tested only under the specific conditions of these experiments. This index was derived in the following manner: CEW per beat = (F_p/S) (area A, Figure 1) + FSW (area B + area C) minus the work returned by the recoiling SEC (area C). Since area C is relatively small and a relatively constant fraction of area A, an approximation of A-C was made by using mean force instead of peak force. Since $S = 28.8/l_o$, $l_o = 2\pi r_o$, FSW = $\pi/2(\bar{P} \times SV)$, and $\bar{F}$ is approximately equal to $\pi\bar{r}^2 \times \bar{P}$, then CEW index = $[2\pi^2\bar{r}^2 r_o \bar{P}/28.8] + [\pi \bar{P} (SV)/2]$. Making the further approximation that $r_o = \bar{r}$ and since $V = 4\pi\bar{r}^3/3$, this expression reduces to CEW index = $[3\pi\bar{V}\bar{P}]/2(28.8)] + \bar{P}\, SV/2$ or $[\pi\bar{P}/2]$ $[SV + (3\,\bar{V}/28.8)]$ per beat. Since this is an index, the constant $\pi/2$ can be ignored, and the final form is $\bar{P}$ [SV + $(\bar{V}/9.6)$] per beat or [HR][$\bar{P}$] [SV + $(\bar{V}/9.6)$] per minute.

Examination of this index shows that it is composed of two basic terms: *1)* $\bar{P} \times$ SV, representing external stroke work, and *2)* $\bar{P} \times \bar{V}$, representing internal pressure generation work. This index resembles in its general form a recently described expression for the total energy involved in cardiac contraction (23). This expression was given as the sum of E_1 and E_2, where E_1 is the product of mean isometric pressure and left ventricular end-diastolic volume, and E_2 is

the conventional stroke work $\bar{P} \times SV$. This sum of E_1 and E_2 was reported to correlate well with left ventricular oxygen consumption.

Discussion

Determinants of myocardial qO_2. That LV work correlates poorly with myocardial oxygen consumption has long been appreciated. (1–3, 5–8). Our study again confirmed this observation by the fact that fiber shortening work, which is proportional to LV work, showed only a fair correlation with $LVqO_2$. Although other workers have demonstrated a remarkably constant relationship between pressure-time per minute and $LVqO_2$ in the dog heart (7, 9, 24), in our experiments this relationship was observed to be no better than that found for LV work. The explanation for this is not entirely clear, although certain differences in experimental design may be relevant. We attempted to produce wide variations in end-diastolic volume and thus achieve changes in myocardial wall force that would not be reflected in the PTM measurement. Similarly the isoproterenol experiments were designed to produce a high ratio of FSW/CEW in order that the energy cost of fiber shortening might be examined more clearly.

Thus, although a good correlation between PTM and qO_2 was observed at low $LVqO_2$ values, no significant correlation was observed in the higher range ($LVqO_2 > 15$ ml). When force-time per minute was examined, again the correlation was not improved. In this case, however, the spread was generalized, and no significant correlation could be obtained in either the lower oxygen consumption group or the higher one. Because in comparing hearts of different sizes it is not the force alone that might reasonably be expected to vary with energy utilization, but rather the product of force times the distance through which it is generated, we decided to examine also the effect of multiplying the FTM by the mean chamber radius (radius when half the stroke volume has been ejected). However, this did not significantly improve the correlation ($r = 0.78$).

Contractile element work showed a significantly higher correlation with oxygen consumption than any of the other three determinants studied. In addition it was the only determinant yielding a significant correlation when only those points with qO_2 sbove 15 ml were examined.

From a theoretical standpoint as well, contractile element work is a more satisfactory determinant of oxygen consumption, since it takes into account the total contractile effort of the heart muscle, namely, both force generation and fiber shortening. With the three-component model as a dynamic representation of muscle contraction, the former may be considered as "internal work," whereas the latter represents the "external work" of the heart. Just as consideration of only the external work (LV work or FSW) has not proved to be a satisfactory determinant of myocardial qO_2, so too consideration of only the internal work (PTM and FTM) has its shortcomings. The relative success of PTM and FTM as determinants of oxygen consumption may in part be due to the fact that ventricular pressure (or force) enters into the calculation of both the internal and external work of the heart. Secondly, inherent in the derivation of PTM and FTM is a consideration of the duration of systole, which in turn often varies directly with stroke volume and thereby external work.

Gorlin and his associates (25) have recently found that with increased fiber shortening (external work) induced by catecholamines in human subjects, the observed oxygen consumption was greater than that which could be predicted from either pressure-time or force-time alone. Figure 3 shows a similar observation, in that 4 of the 5 isoproterenol studies lie above the regression line, indicative of a higher oxygen consumption than that predicted by force-time per minute. In the case of the FSW, the fact that the majority of isoproterenol points lie below the regression line is in agreement with the well-known observation that "flow work" is performed with relatively little oxygen cost (5). Since CEW takes into account both fiber shortening and force generation, the relationship between qO_2 and CEW would be expected not to be altered by isoproterenol. This was not the case, however, and the observation that 4 of the 5 isoproterenol points still lie below the regression line must have another explanation (*vide infra*).

Efficiency considerations. If indeed it is the contractile element work that determines myocardial oxygen consumption, then the observed external mechanical efficiency would be dependent on two factors: *1*) the efficiency of the contractile element and *2*) that portion of the total contractile effort expressed externally as fiber shortening. In fact, mechanical efficiency obviously = CE efficiency $\times$ FSW/CEW.

The average CE efficiency was obtained from the slope of the qO_2-CEW regression line (Figure

5). Since the calculation of contractile element work is in error by virtue of the same considerations involved in the calculation of FSW (see footnote 2), the true CEW in kilogram-meters per minute is equal to 0.00649 × CEW in 10^6 dyne-centimeters per minute. Therefore, the CE efficiency is equal to the reciprocal of the qO_2-CEW slope multiplied by 0.00649 and divided by the mechanical equivalent of oxygen (2.06 kg-m per ml). This yielded an average CE efficiency of 22.7%.

We then decided to examine the relationship of external mechanical efficiency and the ratio FSW/CEW (Figure 7). This showed a significant correlation ($r = 0.77$; $p < 0.001$). Since LV work and therefore external mechanical efficiency fall to zero when FSW is zero, the plot was regressed in such a manner as to force the regression line to pass through the origin of the graph. When this was done, we found that a quadratic equation ($y = bx + cx^2$) fit the points significantly better ($0.001 < p < 0.01$) than a linear one ($y = bx$). Let us now examine the significance of this curvilinear relation between external mechanical efficiency and FSW/CEW. Figure 7 illustrates that as FSW/CEW increases, the ratio of external mechanical efficiency to FSW/CEW increases. This is to say that the CE efficiency rises with increasing FSW/CEW. Indeed, a direct plot of (CEW/qO_2)—4.33[3] and FSW/CEW showed a significant correlation ($r = 0.50$; $0.001 < p < 0.01$).

This increase in CE efficiency with increasing FSW/CEW explains the location of most of the isoproterenol points below the regression lines in Figure 5, as the ratio FSW/CEW is markedly increased by isoproterenol.

If the CE itself is unable to distinguish between force generation and fiber shortening, the implication of this rise in CE efficiency with FSW/CEW is either that the fiber shortening work of the contractile element has been overestimated in these studies or that the force generating work of the CE has been underestimated. Since FSW is equivalent to LV work and the error in its measurement is small, that FSW has been consistently overestimated is unlikely. Therefore, it would seem appropriate to examine the possible causes of an underestimation of the force generation work. A likely source of error is the gross approximation of the active stiffness, S (the slope of the $dF/dl - F$ relationship), which was derived by extrapolation from the isolated cat papillary muscle to the intact dog heart. Since the force generation work was calculated as F_p/S, an overestimation of S would lead directly to an underestimation of the calculated force generation work. A second possible explanation is the effect of the asynchronicity of cardiac muscle contraction. In this instance, the noncontracting fibers act functionally as passive elastic structures in series with the contracting fibers. Since the stiffness of resting muscle fiber is much less than that of the SEC, more work might be involved in developing a given wall force than that calculated on the basis of the stiffness of the SEC. A third consideration involves the role played by the fibrous mitral valve, which is in series with the muscle fibers. The stiffness of fibrous tissue is constant (26) and does not increase with increasing load as in the case of the SEC. The energy involved in stretching such a spring is proportional to F_p^{2},[4] and ignoring this factor would again lead to an underestimation of force generation work. Lastly, the exact shape of the left ventricle may play a role. The work involved in generating a given intraluminal pressure might be greater in a nonspherical one of the same volume.

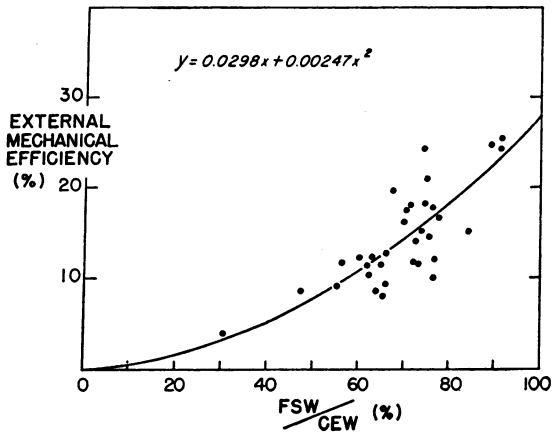

FIG. 7. RELATIONSHIP OF EXTERNAL MECHANICAL EFFICIENCY TO FSW/CEW.

The qO_2 of the beating, empty heart. The y intercepts of the regression lines of Figures 2 to 5 represent the oxygen consumption of the heart when each parameter (PTM, FTM, FSW, or CEW) is zero, i.e., the beating, empty heart. Kohn (22) recently found the oxygen consumption in such hearts to be 3.0 ml per minute per

[3] 4.33 = the y intercept of the CEW-qO_2 line.

[4] $dF/dl = k$, $dW = Fdl$, or $W = \int FdF/k$. Integrating, this becomes $(1/2k)(F_p^2 - F_i^2)$. Ignoring F_i for the reasons discussed earlier, work = $F_p^2/2k$.

100 g. The CEW-qO_2 regression line yielded the y intercept closest to this value (4.33 ml per minute per 100 g). In the case of the PTM regression line, the y intercept was negative (−2.22 ml), which is not meaningful in physiologic terms. This was also true of the results published by Neill, Levine, Wagman, and Gorlin (8).

Kohn further found that the oxygen consumption of the nonbeating heart (KCl asystole) was only 1.5 ml per minute per 100 g. The significance of this difference (1.5 ml) can be appreciated from a consideration of classical skeletal muscle energetics. Heat studies of a twitch have shown that a small amount of heat is liberated due to activation alone (27). Thus, the difference between the oxygen consumption of the beating empty heart and that of the nonbeating heart can be considered to reflect the energy of activation per minute (heart rate times activation energy per beat).[5] From the stimulation frequency used by Kohn, the activation energy per beat can be calculated to be 0.0125 ml per beat per 100 g.

Since in our studies a wide range of heart rates was observed (70 to 207), we decided to reexamine the CEW-$LVqO_2$ data in terms of a possible additional effect of heart rate on the total oxygen consumption. To do this, we performed multiple regression for qO_2 as a linear function of both CEW and heart rate (HR), as follows: $qO_2 = a + b$ (CEW) $+ c$ (HR), where a = the oxygen consumption of the nonbeating, empty heart; $b = qO_2/CEW$, or the reciprocal of CE efficiency; and c = the activation energy per beat. The result of this regression was as follows: $qO_2 = 1.93 + 0.0129$ CEW $+ 0.0202$ HR. Thus the extrapolated oxygen consumption of the nonbeating, empty heart was 1.93 ml per minute per 100 g, fairly good agreement with Kohn's figure of 1.5 ml, and the activation energy per beat was 0.0202 ml per beat per g, also showing reasonable agreement with that calculated from Kohn's data. The coefficient of CEW was not much different from that obtained in the original regression (0.0138, Figure 5). Statistically, however, the addition of the heart rate term in the multiple regression analysis did not significantly add to the determination of qO_2 by CEW alone ($p > 0.20$).

Fenn effect in the heart. The classic work of Fenn (28) and Hill (13) has shown that on shortening, skeletal muscle liberates an additional amount of heat that is directly proportional to the shortening distance (Fenn effect). Since the Fenn effect is considered to be a fundamental property of the contractile process of muscle (13, 29), it follows that a consideration of the extra energy cost associated with shortening should take into account the total shortening of the contractile element, rather than fiber shortening alone.

In shortening a distance d at a force F, the work done equals $F \times d$, and the extra energy cost of shortening equals $a \times d$, where a = the shortening heat per unit distance. Thus, the efficiency of the shortening process would be given by $(F \times d)/(Fd + ad)$, or $1/[1 + (a/F)]$. It is, therefore, necessary to examine the ratio a/F in order to assess the consequences of the Fenn effect on CE efficiency, i.e., as a/F increases, CE efficiency would decrease.

The shortening heat constant a has not been measured in cardiac muscle. There are, however, good theoretical grounds for the belief that the heat constant a is identical to the constant a of Hill's classic force-velocity relation: $(F + a)$ $V = b(F_o - F)$ (13, 30). Further, in the frog sartorius muscle, the constant a was derived experimentally from both heat and mechanical studies, and fairly good agreement was found (13).

The mechanical constant a has been studied in isolated cat papillary muscle, and the ratio a/F_o (isometric tension) was found to be constant in the face of inotropic interventions, different stimulation frequencies, and different initial fiber lengths (21). If the constancy of this ratio holds for the intact dog heart, and further if the mechanically derived constant a is assumed to be equivalent to the shortening heat constant a, then the ratio of F_o to F would also be an index of shortening efficiency, since a varies as F_o. As F_o/F increases, efficiency would decrease.

In the case of cardiac contraction, contractile element shortening occurs through a range of force from F_i to F_p, so that the average force should be considered in the above evaluation of CE efficiency. However, since F_i is generally close to zero, changes in average force will generally be reflected by similar changes in peak force, F_p. Therefore, we may consider the ratio F_o/F_p as an index of the theoretical CE shortening efficiency.

In the studies described in this paper, force-velocity curves for the contractile element were

[5] When calculated in this way, activation energy includes both the classical heat of activation (27) and the energy consumed in overcoming the resistance of the heart wall to shortening.

constructed from the instantaneous values of force and contractile element velocity. These curves and their interpretation form the subject of the preceding paper (15). In 22 of the 34 studies, the curves were well enough defined to permit a reasonably fair estimate of the projected isometric force F_o. In these cases, the relationship between CE efficiency and the ratio F_o/F_p was examined, but no significant correlation was found. Thus, in these studies, we were unable to demonstrate a Fenn effect in the intact heart. However, this problem warrants further study.

It is reasonable to assume that ultimate comprehension of the energetics of cardiac muscle will be predicated on an understanding of basic muscle mechanics. Although our study suggests that CEW is the major determinant of myocardial oxygen requirements, the ultimate formulation of muscle energetics will include a consideration of the energy cost of resting cardiac muscle, the activation energy per beat, and perhaps other factors such as the Fenn effect or the role played by the parallel elastic component.

Summary

Cardiac contraction in the intact dog heart has been analyzed in terms of Hill's series elastic model for muscle, and the total work performed by the contractile element was calculated. Contractile element work was derived as the sum of the work done in stretching the series elastic component to peak force, plus the work performed by the contractile element in shortening of the muscle fiber. The latter quantity was calculated as the total fiber shortening work minus the amount performed by the recoiling series elastic component.

Over a wide range of altered hemodynamics, an excellent correlation between contractile element work and left ventricular oxygen consumption was observed ($r = 0.91$). This relationship was significantly better ($p < 0.05$) than that found between oxygen consumption and pressure-time per minute ($r = 0.74$), force-time per minute ($r = 0.74$), or fiber shortening work ($r = 0.74$).

An index of contractile element work was derived using only heart rate, left ventricular systolic mean pressure, and mean left ventricular volume and was shown to correlate well with the calculated contractile element work ($r = 0.995$).

External mechanical efficiency depends on the proportion of total contractile element work that is expressed as fiber shortening work. From an analysis of the contractile element work-oxygen consumption relationship, the oxygen consumption of the beating empty dog heart has been estimated to be 4.3 ml per 100 g per minute. Multiple regression of oxygen consumption as a linear function of both contractile element work and heart rate was also performed in an effort to examine activation energy per beat as a possible determinant of myocardial oxygen consumption. In this manner the energy requirement of the nonbeating heart was estimated to be 1.9 ml per 100 g per minute and the energy requirement of activation estimated to be 0.02 ml per beat per 100 g.

A method is described by which the Fenn effect may be studied in the intact dog heart. Using this approach, our attempts to demonstrate the Fenn effect were unsuccessful.

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