Myocardial oxygen consumption during isotonic and isovolumic contractions in the intact heart

JOHN W. BURNS AND JAMES W. COVELL

University of California, San Diego, School of Medicine, Department of Medicine, La Jolla, California 92037

In 1915, Evans and Matsuoka (11) first demonstrated that there was a larger increment in myocardial oxygen consumption (MV\textsubscript{O2}) observed when external cardiac work was increased by increasing arterial pressure than when it was increased by increasing cardiac output, and this observation has been substantiated by other investigators utilizing different techniques (10, 16, 21, 29, 30). In 1923, Fenn (12) demonstrated that there is an increment in energy utilization (M\textsubscript{VO2}) observed when external cardiac work is less than that associated with the development of active tension. However, because of the complex geometry of the contracting heart, it has not been possible to measure the oxygen cost of shortening against a load and to directly compare it with that of tension development. In the present study, an isolated supported heart preparation was utilized and left ventricular (LV) wall stress (\sigma) was calculated with an analog computer using a thick-walled spherical model for the LV. Isotonic contractions were produced by rapidly altering LV volume to maintain a constant level of wall \sigma during each beat. In seven experiments myocardial oxygen consumption (MV\textsubscript{O2}) during isovolumic contractions was compared to MV\textsubscript{O2} during isotonic contractions at matched levels of peak LV wall \sigma ranging from 14.8 to 105.3 g/cm\textsuperscript{2}. MV\textsubscript{O2} during isotonic contractions averaged 48.3 \pm 3.4 \textup{ml} \textup{O}_2/\text{beat} per 100 g LV and was increased to an average of 52.1 \pm 3.9 \textup{ml} \textup{O}_2/\text{beat} per 100 g LV during isotonic contractions at comparable levels of wall \sigma. The increment in MV\textsubscript{O2} above that associated with tension development was 5.9 \pm 1.1\% of the total MV\textsubscript{O2}, and there was a significant positive correlation between this increment in MV\textsubscript{O2} and the external work performed. When this relationship is extrapolated to the intact heart performing higher levels of external work and shortening to a greater extent, external work might comprise an average of as much as 17\% and explain the relatively low oxygen cost of augmenting stroke work by increasing stroke volume.

METHODS

The experimental preparation, which has been described in detail previously (7), employed a computer regulated servo system to control wall \sigma during systole. However, in the current study, instead of utilizing total cardiopulmonary bypass, an isolated supported heart preparation was employed (Fig. 1). Hearts were obtained from seven mongrel dogs weighing from 15.9 to 22.7 kg. Both the support dog and the heart donor dog were anesthetized with 25–30 mg/kg of sodium pentobarbital. The heart was exposed through a midsternal incision and ligatures were placed around the superior and inferior venae cavae and the azygos vein. Heparin was then administered (3 mg/kg), the heart rapidly excised, and immediately placed in an iced-saline bath (0 C). With the heart in the iced bath, the left and right coronary arteries were isolated and a 1.5-cm diameter nylon plug was tied in place at the level of the aortic valve just below the coronary ostia (Fig. 1). The mitral valve and chordae tendineae were excised and a purse-string suture was placed around the mitral annulus at the base of the left atrium. The main pulmonary artery was ligated and the heart was removed from the ice bath and suspended over a large collection funnel. A reservoir connected by
The position of the piston and thereby the volume in the left ventricle and LV volume were connected to an analog computer for the on-line calculation of wall $\sigma$ from the equation:

$$\sigma = \frac{PR_1^2}{R_o^2 - R_i^2}$$

where $P$ = intraventricular pressure in grams per square centimeter, $R_i$ = internal left ventricular radius, $R_o$ = external left ventricular radius. This equation assumes a geometric model for the LV (a thick-walled sphere). Recent studies from this laboratory (3) have shown that this relationship tends to underestimate peak wall $\sigma$ (avg 19%) over the range of end-diastolic pressure (EDP) employed in the present experiment (6.0–10.0 mm Hg). However, this error was relatively constant, averaging 18.4% at an LVEDP of 3.0 ± 0.6 (SEM) and 19.5% at an average LVEDP of 6.4 ± 0.8 (3). The analog computer continuously compared calculated $\sigma$ with a preset $\sigma$ control level. When calculated $\sigma$ exceeded the preset control level the servomotor was activated by a $\sigma$ error signal to withdraw volume from the LV at a sufficient rate to achieve wall $\sigma$ control at the desired level.

**Experimental protocol.** The experimental protocol was similar in all experiments. Following calibration of the computing system, the LV end-diastolic volume was varied by adjusting the volume within the balloon to change LVEDP from approximately 2 mm Hg to that necessary to produce an LVEDP of 15 mm Hg while the ventricle was beating isovolumetrically. This sequence was repeated, and the preparation was considered to be stable as soon as two successive curves relating end-diastolic volume (EDV) to peak developed pressure revealed peak pressures within 5 mm Hg for a given EDV. $MV_O2$ was then compared during steady-state conditions with the heart contracting both isovolumically and isotonically. By increasing end-diastolic volume slightly during the isotonic contractions, peak wall stress could be maintained at the same level as that in the isovolumic contraction. In these experiments LVEDP was not increased above 10 mm Hg. The matched pairs of beats analyzed at the same level of active wall $\sigma$ of necessity occurred at different end-diastolic volumes (the isovolumic beats originating at a lower diastolic volume), and the isotonic beats exhibited varying amounts of shortening and therefore external work. With these data a relationship between the increment in $MV_O2$ above that necessary for tension development and external work could be determined at various levels of external work.

**Calculations and data analysis.** During an individual experiment, LV muscle volume was estimated from the average relationship between body weight and muscle volume for the purpose of on-line calculation of wall $\sigma$ (7). LV pressure, LV volume, and the rate of change of volume were recorded on magnetic tape (Honeywell model 7600). Following the experiment these data were replayed, A/D converted, and analyzed utilizing an Electronic Associates, Inc., model 590 hybrid computing system. Wall $\sigma$ and extent of shortening, assuming the ventricle to be a thick-walled sphere, were then calculated using LV pressure, and the LV volume determined from the amount in the balloon. LV muscle volume for these calculations was obtained by weighing the LV. The external work performed by the ventricle was calculated as the product of midwall circumferential shortening and average wall $\sigma$ during systole.

To compare the relative energy cost of “internal” and “external” work performed by the ventricular muscle a model for myocardial contraction was assumed. In this case a simple two-component model for contraction was...
utilized (17). Ignoring shape changes occurring during isovolumic contraction, the rate of contractile element shortening was estimated from the stiffness of the series elastic element (9, 26), and the calculated rate of change in tension and contractile element external work was calculated as the integral of the product of contractile element (CE) velocity and instantaneous pressure (contractile element power). External work and internal work were utilized to compare the relative efficiencies of oxygen utilization in isovolumic and isotonic contractions.

In order to ascertain that changes in the contractile state of the isolated supported heart due to neurohumoral alterations in the support dog did not occur during the experimental period, myocardial force-velocity relationships in isovolumic contractions (14) were determined at the same level of end-diastolic volume prior to and following each determination of MVo₂. Data were then selected for the comparison of isovolumic and isotonic oxygen consumption by two criteria: first, peak wall σ in the isovolumic beat and wall σ in the matching isotonic beat were within 15%; and second, Vmax estimated from the isovolumic contractions at comparable end-diastolic volumes determined just following the MVo₂ determination was within 10% for the two runs. All comparisons of matched data were statistically analyzed by the paired t test (25).

**RESULTS**

Table 1 contains data from seven studies in which myocardial oxygen consumption was measured during isovolumic and isotonic contractions at similar levels of wall σ. Figure 2 illustrates typical oscillographic recordings taken from one of these studies. Panel A shows an isovolumic contraction at a volume of 31.2 ml in which the MVo₂ was 65.0 μl/beat per 100 g LV. Panel B is a succeeding isovolumic beat at an increased ventricular volume of 39.0 ml with a concurrent increase in LV pressure and wall σ. In panel C, at the same end-diastolic volume as in panel B, σ was controlled at the same level as in panel A by withdrawing volume (7.25 ml) from the LV during contraction. In this contraction MVo₂ averaged 71.5 μl/beat per 100 g LV. As shown in Table 1, in all studies the mean increase in end-diastolic volume from the isovolumic contraction (25.4 ± 3.2 ml) to the isotonic contraction (30.5 ± 4.0 ml) was 5.1 ml. Pressure development in the isotonic contraction was slightly lower, averaging 73.5 ± 3.9 mm Hg in the

| TABLE 1. Myocardial oxygen consumption measured during isovolumic and isotonic contraction at similar levels of wall σ |
|---|---|---|---|---|---|---|---|---|---|
| Exp No. | LV wt, g | HR, beats/min | EDV, ml | SV, ml | Pk Press, mm Hg | Δ L, cm | Active σ, g/cm² | Ext Wk, g/cm² X cm | Int Wk, g/cm² X cm | MVo₂, μl/beat per 100 g LV |
| 20-1 ISV | 84.6 | 135 | 6.13 | | 55.0 | 0.31 | 14.82 | 4.59 | 18.06 | 6.55 | 37.85 |
| 20-1 IST | 7.46 | 4.44 | 55.0 | 0.60 | 30.10 | 28.60 | 13.79 | 43.19 | |
| 21-1 IST | 16.43 | 4.26 | 60.0 | 0.30 | 46.72 | 32.49 | 11.25 | 49.92 | |
| 21-1 ISV | 12.33 | 4.27 | 85.0 | 0.30 | 46.72 | 32.49 | 11.25 | 49.92 | |
| 22-1 IST | 20.14 | 4.27 | 81.0 | 0.30 | 46.72 | 32.49 | 11.25 | 49.92 | |
| 22-1 ISV | 17.41 | 4.27 | 81.0 | 0.30 | 46.72 | 32.49 | 11.25 | 49.92 | |
| 23-1 ISV | 84.0 | 120 | 28.50 | | 77.0 | 0.12 | 57.19 | 6.06 | 31.47 | 43.83 |
| 23-1 IST | 20.00 | 1.13 | 73.0 | 0.12 | 57.19 | 6.06 | 31.47 | 43.83 | |
| 24-1 IST | 98.1 | 144 | 26.49 | 5.82 | 47.0 | 0.62 | 25.06 | 15.54 | 13.92 | 44.58 |
| 24-1 ISV | 19.51 | 5.82 | 70.0 | 0.62 | 25.06 | 15.54 | 13.92 | 44.58 | |
| 25-1 ISV | 89.0 | 126 | 31.05 | | 64.0 | 0.61 | 38.07 | 33.34 | 50.00 | |
| 25-1 IST | 44.44 | 7.62 | 57.0 | 0.61 | 38.07 | 33.34 | 50.00 | |
| 26-1 IST | 91.1 | 126 | 39.46 | | 67.0 | 0.62 | 57.15 | 35.43 | 35.43 | 62.14 |
| 26-1 ISV | 35.53 | 7.25 | 69.0 | 0.62 | 57.15 | 35.43 | 35.43 | 62.14 | |
| 27-1 IST | 46.80 | 5.70 | 49.5 | 0.44 | 54.10 | 23.80 | 33.04 | 51.98 | |
| 27-1 ISV | 39.02 | 5.70 | 63.0 | 0.44 | 54.10 | 23.80 | 33.04 | 51.98 | |
| 28-1 IST | 44.43 | 8.89 | 83.0 | 0.73 | 91.80 | 67.01 | 35.06 | 76.27 | |
| 28-1 ISV | 46.43 | 8.89 | 83.0 | 0.73 | 91.80 | 67.01 | 35.06 | 76.27 | |
| Isovolumic | | | | | | | | | |
| Mean | 86.0 | 129.0 | 25.40 | | 73.5 | 32.87 | 29.09 | 48.81 | |
| ± se | ±2.0 | ±3.0 | ±3.24 | | ±3.9 | ±7.21 | ±8.68 | ±3.35 | |
| Isotonic | | | | | | | | | |
| Mean | 30.53 | 4.98 | 64.5 | 0.48 | 49.89 | 25.66 | 28.28 | 52.09 | |
| ± se | ±3.96 | ±0.80 | ±3.8 | ±0.96 | ±6.90 | ±5.82 | ±4.40 | ±3.85 | |

Exp No. = matched isovolumic (ISV) and isotonic (IST) pairs of contractions; LV wt = left ventricular weight; HR = heart rate; EDV = end-diastolic volume; SV = stroke volume; Pk Press = peak left ventricular pressure; ΔL = extent of circumferential shortening; Active σ = peak left ventricular stress minus end-diastolic stress; Ext Wk = external work; Int Wk = internal work (see text).
isovolumic contraction and 64.5 ± 3.8 mm Hg in the isotonic contraction. Moreover, as shown in Fig. 2, there was a consistent fall in LVEDP at the same end-diastolic volume in the isotonically contracting ventricle. Thus, in all matched pairs LVEDP averaged 3.2 ± 0.8 mm Hg lower (range 2.0-7.0 mm Hg) in the isotonically contracting left ventricle when compared to the isovolumic contractions at the same end-diastolic volume. In all experiments the stroke volume was varied from 1.1 to 8.9 ml and the stroke volume-to-end-diastolic volume ratio averaged 16.6 ± 1.8%.

Calculated peak active isovolumic σ ranged from 14.9 to 105.3 g/cm² and the comparable isotonic σ control levels ranged from 14.8 to 91.8 g/cm². During the isotonically contracting the extent of circumferential midwall fiber shortening varied from 0.12 to 0.73 cm (0.8-4.5 % of end-diastolic midwall circumference), for an average of 0.48 ± 0.06 cm of shortening.

Examples of the difference in MV0₂ determined from matched pairs of contractions in two different experimental animals are shown in Fig. 3. In these two experiments, at every level of wall σ MV0₂ in the isotonic beat was greater than that in the corresponding isovolumic beat at the same peak wall σ values. For all but 1 of the 11 matched pairs, MV0₂ from isometric beats was significantly greater than MV0₂ from isovolumic beats at comparable σ levels (P < .005, Table 1). The relation between the difference of MV0₂ in isometric and isovolumic beats (Δ MV0₂) and external work is shown in Fig. 4. The points above the zero line represent data from matched pairs in which the MV0₂ from the isotonic beat was greater than MV0₂ from the corresponding isovolumic beat. The data has a correlation coefficient of .76 and the least-squares linear regression equation was: MV0₂ = .09 ext. work + .94. Moreover, the slope of the relationship between external work and Δ MV0₂ was positive and this slope was significantly different from zero (P < .005), indicating that Δ MV0₂ increased with the amount of external work performed. The intercept in this relationship (.94 ml/beat per 100 g LV) was not significantly different from zero, thus suggesting that basal oxygen consumption in these two types of contractions was similar, since contractile state and heart rate were similar in the isotonic and isovolumic contractions.

If one assumes a fixed stiffness for the series elastic element and a two-component model, it is possible to calculate the extent of contractile element shortening (equal to the series elastic elongation), during an isovolumic contraction (2, 14). The extent of contractile element shortening can then be used to calculate the internal work performed in generating tension. Thus, for each determination of MV0₂, either isotonic or isovolumic, an amount of external and/or internal
work could be calculated. In the isovolumic contraction, the amount of external work performed is assumed to be zero (ignoring possible shape changes). Utilizing data from seven experiments (all pairs of data, Table 1), an average relationship between M\(\text{VO}_2\), internal work, and external work was determined using a multivariate regression analysis technique. The average relationship for all experiments was M\(\text{VO}_2 = 31.2 + .19\) external work + .57 internal work, where 31.2 in the linear regression equation would represent the remaining determinants of oxygen consumption such as contractile state and basal oxygen consumption (14).

**DISCUSSION**

The results of the current study clearly indicate that when the level of peak stress generation is maintained constant, there is an increment in oxygen consumption associated with performing external work. Moreover, there was a significant positive relationship between the level of external work performed and the amount of oxygen consumption required above that necessary for generation of tension. In the present study this additional increment in oxygen consumption averaged 5.9 \(\pm\) 1.1 % of the total oxygen consumption in isometric contractions. These hearts were developing an average peak isovolumic LV pressure of 74 mm Hg at an LVEDP of 6–10 mm Hg and the amount of external work done in this isolated supported heart preparation was considerably lower than that usually encountered in the intact circulation. Thus the extrapolation of these data to a more intact preparation capable of developing more pressure and shortening to a greater extent is hazardous. However, in order to evaluate the distribution of myocardial oxygen consumption in a more intact preparation, an average relationship which expressed the portion of M\(\text{VO}_2\) that could be attributed to external and internal work as a percentage of total oxygen consumption was calculated using a multivariate linear regression technique. These average values were then applied to distribution of M\(\text{VO}_2\) in a single contraction from an intact ejecting left ventricle utilizing a right heart bypass preparation (15). In this preparation the circulation is essentially intact. The left ventricle ejects normally into the aorta and the average SV/EDV (ejection fraction) is similar to that observed clinically (4). Of the total M\(\text{VO}_2\) in this example 48.1 % (90.2 \(\mu\)l/beat per 100 g LV) could be related to internal or pressure generation work, 17.5 to external work, and 34.4 % was associated with other factors such as contractile state and basal M\(\text{VO}_2\). The proportion of M\(\text{VO}_2\) related to basal factors, contractile state, and tension development is similar to that observed previously (14). In many previous studies, even in isolated muscle preparations it has been difficult to specifically determine whether the increment in energy expenditure associated with performing external work can be related to shortening against a load or to shortening alone (13). Moreover, Mommaerts has recently made a critical summary of the shortening heat controversy and has argued that shortening should be accompanied by a waste heat because this process cannot be carried out with unit enthalpy efficiency. In the final analysis the energy requirements must be related to the turnover of cross links between actin and myosin and in this sense the distinction between tension generation and shortening may be artificial. However, in the intact heart it is clear that the efficiency of augmenting cardiac work by increasing tension generation and by augmenting shortening is different, and this study has provided the first direct evidence that the oxygen cost associated with performing external work is related to the amount of work performed and is substantially less than the oxygen cost associated with the generation of tension.

Several factors, all the result of the preparation and experimental design, could have influenced the augmentation of M\(\text{VO}_2\) in the isometric contraction. First, in order to produce an isometric contraction having a level of peak wall \(\sigma\) equivalent to that in an isovolumic beat, it was necessary to increase end-diastolic volume. Although augmentation of resting tension has been shown to significantly increase high-energy phosphate utilization (23), no augmentation of resting oxygen consumption with increases in muscle length has been observed in the intact heart or papillary muscle (13, 21). Moreover, in the present study the differences in end-diastolic volume were small, and in the isometric contraction ventricular volume decreased during contraction, continuously reducing the length difference during contraction. As might be anticipated from the shape of the resting and active length-tension curves in the intact heart, the relationship between the increment in end-diastolic volume necessary to match peak left ventricular tensions and increment in oxygen consumption associated with shortening at this slightly higher end-diastolic volume, was not statistically different (correlation coefficient = .26; probability of a nonzero correlation = .54), while the correlation of \(\Delta\) M\(\text{VO}_2\) with external work was significant. Thus, it is not likely that in the present study the augmentation of end-diastolic volume significantly influenced the results. Secondly, since Monroe (20) has shown that 90 % of the oxygen consumption is determined by the time peak \(\sigma\) is reached, it is quite likely that matching peak wall \(\sigma\) in the isovolumic contraction to the \(\sigma\) developed by the isometric contraction is the most appropriate way to compare the relative energy utilization. However, since the alterations in oxygen consumption observed were small and since previous studies have clearly shown that under certain circumstances oxygen consumption is directly related to tension or pressure area (24), several contractions were examined in which isovolumic wall \(\sigma\) was greater than peak isovolumic \(\sigma\) and the area under the tension curve in the two contractions was similar. For example, in Fig 5, the \(\sigma\) area (expressed in g/cm\(^2\) \(\times\) sec) was slightly larger in the isovolumic contraction. However, M\(\text{VO}_2\) was 9.7 \(\mu\)l/beat greater in the isometric contraction despite the fact that peak wall \(\sigma\) was significantly less. Thus, in this particular example, it is apparent that the amount of external work performed (in this case 25.1 g/cm per cm\(^2\)) was sufficient to exceed the influence of both tension area and the difference in peak wall \(\sigma\) in the two contractions. It also is possible that the geometric model used to calculate wall \(\sigma\) influenced the comparison between isovolumic and isometric contractions. However, recent studies (3, 18) have shown that there is relatively good agreement between different methods of calculating wall \(\sigma\) and the correlation between directly measured wall \(\sigma\) and that calculated using a spheli-
ing volume withdrawal. The factors responsible for this apparent decrease in the diastolic pressure-volume relation-
for average work. These assumptions and of the validity of the calculation of these data would clearly depend on the validity of
left ventricular work where the alterations in ventricular changes in fiber orientation could also be expected to in-
fluence the extrapolation of these data to higher levels of
fibers have been shown to produce isovolumic tension development (1) beyond that proportional to the increase in length alone (and in proportion to the time and rate of stretch), and it is possible that these essentially viscous changes may also be responsi-
ble for alterations in the diastolic pressure-volume relation-
ship during the control cycle. However, since intracavity volume was directly measured in the present studies and
changes in pressure were small (3.2 ± 0.8 mm Hg) it is
unlikely that these changes significantly influenced the results.

In summary, the present study has demonstrated a sig-
nificant relationship between the amount of external work performed in isotonic contractions and the increment in myocardial oxygen consumption above that required for tension generation. Accordingly, it is now possible to quantitatively add a fifth important determinant of myo-
cardial oxygen consumption to those elucidated by earlier studies (14): 1) basal oxygen consumption, which is neces-
sary for maintenance of membranes, electrical activity, etc.; 2) oxygen consumption associated with tension develop-
ment; 3) oxygen consumption associated with con-
tractile state; 4) oxygen consumption related to variations in
heart rate; and 3) oxygen consumption associated with external work.

The authors wish to acknowledge the excellent technical assistance of Mr. Richard S. Pavellec, Mr. Frank R. Truesdale, and Mr. Donald F. Rippon, and the editorial efforts of Mr. Charles E. Smith.

This paper was presented at the Federation of American Societies for Experimental Biology. Federation Proc. 29: 1150, 1970.

This study was supported by National Heart and Lung Institute Program Grant No. HE12373.

During the course of this work, J. W. Burns was a Postdoctoral Fellow of the National Heart and Lung Institute, Grant No. HE20547. His present address is Biodynamics Branch (VNB), United States Air Force School of Aerospace Medicine, Brooks Air Force Base, Texas 78235.

J. W. Covell is the recipient of National Heart and Lung Institute Career Development Award No. HE21132.

Received for publication 10 February 1972.

REFERENCES

1. BRADY, A. J. Time and displacement dependence of cardiac con-


7. COVELL, J. W., E. BRAUNWALD, J. ROSS, JR., AND E. H. SONNEN-

8. COVELL, J. W., J. S. FUHRER, R. C. REYTH, AND J. ROSS, JR.
Production of isotonic contractions in the intact canine left ven-


10. DECHERI, G., AND M. B. VINCER. The relative importance of the performance of work and the initial fiber length in determining the magnitude of energy liberation in the heart. Am. J. Physiol. 103: 400-406, 1933.


15. GRAHAM, T. P., JR., J. ROSS, JR., J. W. COVELL, E. H. SONNEN-
BLICK, AND R. I. CLANCY. Myocardial oxygen consumption in
MVO₂ in Isotonic Contractions


