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THE RELATION OF WORK AND OXYGEN CONSUMPTION IN ISOLATED STRIPS OF CAT AND RAT MYOCARDIUM

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In previous studies (Whalen, 1959, 1960) it was reported that initial length and, to a much greater extent, frequency of the isometric contractions were the factors which most significantly affected the oxygen consumption of excised strips of parallel-fibred mammalian myocardium. The amount of the developed or resting tension did not appear to be consistently related to the Q_{O_2}. Recently a sensitive isotonic gauge was devised in order that the influence of shortening and load on the Q_{O_2} could be assessed. If the energetics of mammalian heart muscle and amphibian skeletal muscle are similar, additional oxygen should be consumed (see Fenn, 1923; Fischer, 1931; Hill, 1953). The experimental results presented here are also compared with the results from studies on the effect of work and tension on the oxygen consumption of the intact heart.

METHODS

One of the trabeculae carneae or a papillary muscle of the cat (Cattell & Gold, 1938) or rat (Ullrich & Whitehorn, 1956) was excised and fastened to the muscle holder as previously described (Whalen, 1957). During dissection the muscle was constantly aerated with 98% oxygen and 2% (v/v) carbon dioxide.

The respiration chambers previously described (Whalen, 1957) permit the simultaneous measurement of muscle tension and oxygen consumption. Modifications of the chambers have improved the accuracy of the measurement of the oxygen uptake (see Fig. 1). A compensating chamber has been added and oxygen consumption is now measured volumetrically, essentially as described by Scholander & Edwards (1942) and modified by Wennesland (1949). The mercury seal, through which a monofilament nylon thread transmits muscle tension to a Statham strain-gauge (or isotonic lever), was also modified by embedding a ring of nickel around the mercury well. Previously the essentially non-wettable plastic surface permitted the occurrence of a small unpredictable leak around the mercury 'seal'. The nickel ring, which is wetted by the mercury, has eliminated this source of error.

The muscle and weights were attached to the isotonic lever as shown in Fig. 1. To reduce the effect of inertia the weight was hung 1 cm from the potentiometer shaft and the muscle attached 2 cm distant. (In the text reference will be made to the *actual* load on the muscle, one half of the attached weight.) In considering whether the contraction was indeed isotonic, the reaction force on the muscle was calculated on the basis of an estimated maximum acceleration of 150 cm/sec^2 seen at the lightest muscle load of 0·5 g. The moment of inertia (I)

of the lever was obtained from the formula for a thin homogeneous rod, $I = \frac{1}{12} \times 0{\cdot}32\ g \times (4)^2 = 0{\cdot}43\ g.cm^2$; the total moment ($I$) being $1{\cdot}43\ g.cm^2$. With an angular acceleration (α) of 75 radians/sec^2 the force due to acceleration was about 11 % of the force due to gravity. (With heavier loads the reaction force would be somewhat less.) When these calculations were checked empirically by attaching the lower end of the muscle to an isometric gauge, the departure from isotonicity was found to be about 15 %.

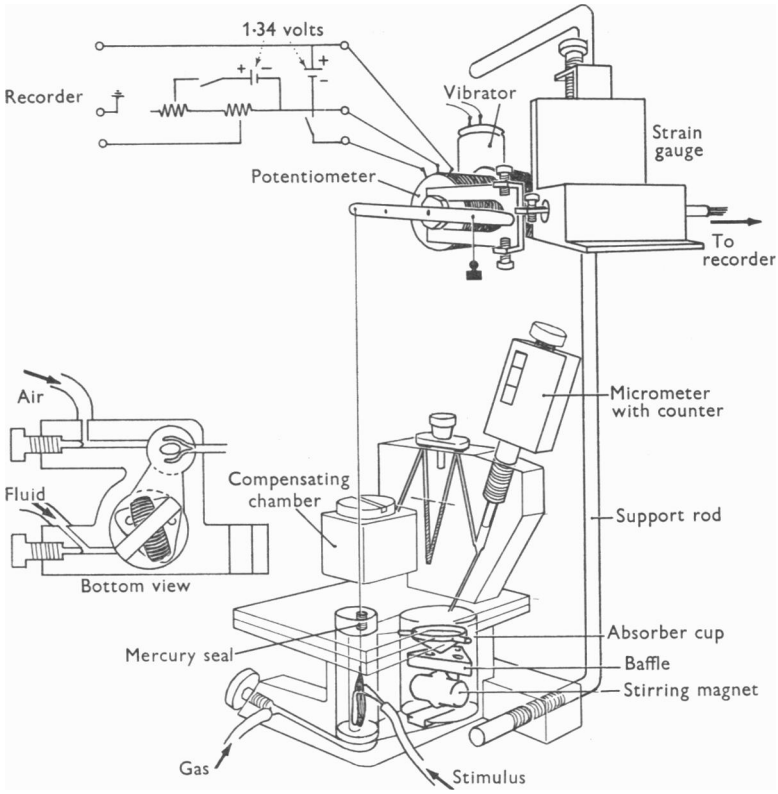

Fig. 1. Drawing of chamber and isotonic gauge. The potentiometer is a Giannini Microtorque, model no. 85113. When vibrated at 400/sec the starting torque is nearly zero. With the Offner Dynograph recorder used, movements of the tip of the lever arm could be measured with an accuracy of 0·025 mm.

The work done was calculated from the final height to which the load was raised, since, except for any frictional force, the kinetic energy imparted to the system would be converted to potential energy during deceleration. Since the acceleration did not exceed that due to gravity, no 'over-shoot' would be expected, and changes in muscle length could also be measured from the total excursion of the recording pen.

Three chambers filled with 8 ml. of Feigen's solution (Feigen, Masuoka, Thienes, Saunders & Sutherland, 1952) were placed in a constant-temperature bath held at $31{\cdot}7 \pm 0{\cdot}01°$ C. Two chambers contained tissue, the other served as a thermobarometer and as an additional control for the oxygen uptake by the diethanolamine CO_2 'absorber' (Pardee, 1949; Krebs, 1951). After gassing the chambers with 98 % O_2 and 2 % CO_2 (v/v) the gas was turned off and the chambers were allowed to equilibrate for 45 min.

In a preliminary series of experiments (series *A*) the muscles were free-loaded during the periods of isotonic contraction. A 1 g load was placed on each muscle (see Fig. 1) and the two muscles allowed to extend passively for 10 min, at which time one muscle was then connected to the strain-gauge for registration of isometric tension. Stimulation of both muscles with biphasic, supramaximal pulses of 1 msec duration at 30/min was then begun through the mass platinum electrodes lying alongside each muscle. In successive periods of 50 min each, during which oxygen consumption and contractile force, or shortening, were recorded the type of contraction was alternated. Ten-minute 'change-over' intervals were interspersed between the experimental periods to allow for any oxygen debt or lag in the system (Whalen, 1957). A day's run usually consisted of two or three isometric periods and two or three isotonic periods.

In the second series of experiments (*B*) the muscles were after-loaded. Thus, the initial length of the muscle was held constant during the paired periods of isotonic and isometric contraction. In addition, a wide range of loads was used over a wide range of initial lengths, and the experimental periods were shortened to 30 min. Also, the strain-gauge was not used in series *B* since it did permit a small amount of shortening. Instead, the isotonic lever was held rigidly by a set-screw, which limited the amount of shortening to less than 3%. At the end of the experiments the muscles were measured, blotted, and weighed immediately. The tissues were dried overnight at 100° C and weighed again. The dry weight was $23{\cdot}0 \pm 4\%$ (S.D.) of the wet weight. Q_{O_2} was calculated in the usual manner, it being expressed as $\mu l.O_2$ (s.t.p.)/mg dry wt./hr.

In series *A* (and *C*) only muscles which measured less than 1·2 mm in diameter were employed. In series *B* the measured diameter of the 32 muscles used ranged from 0·4 to 1·8 mm, with a mean of approximately 1·1 mm.

The critical diameter for adequate oxygen diffusion. Calculation of the critical radius for oxygen diffusion was carried out by Hill's (1928) equation, $r' = \sqrt{(4Ky_0)}/a$ where K is the diffusion coefficient of oxygen through the tissue, y_0 is the external oxygen tension, and a is the oxygen consumption in ml. O_2/ml. wet tissue/min. The Krogh (1918) diffusion coefficient as used by Hill (1928), extrapolated to 31·7° C, gave a value of $1{\cdot}57 \times 10^{-5}$ (cf. Creese, Scholes & Whalen, 1958). To determine the appropriate value for the oxygen consumption, a curve was drawn relating oxygen uptake and the cross-sectional area as calculated from the net weight and length. In this calculation, which gave a somewhat higher value for the diameter, the specific gravity was assumed to be 1·05 as found by Creese (1954) for the rat diaphragm. Up to a cross-sectional area of 1·35 mm^2 the trend of the oxygen consumption was upward, though the rise was not significant. With thicker muscles the Q_{O_2} fell somewhat. It was also observed that most of the thinner muscles showed less decrement in contractile force with time. Thus, the oxygen consumption of 0·023 ml./ml. wet tissue/min obtained from the twelve thinnest muscles in series *B* was chosen as being the most accurate value. The value for y_0 was taken as 0·98. Substituting these values in the Hill equation revealed that the diameter of the muscle should not have exceeded 1·0 mm in order to insure adequate diffusion through the entire muscle. It is obvious that some of the muscles in series *B* must have become anoxic at the core, but the results from thick and thin muscles were qualitatively similar.

RESULTS

Table 1 summarizes the data from the first series of twelve experiments with the cat papillary muscle. The mean amount of shortening during isotonic contraction in this series was 1·4 mm, a change of about 12·2 % from the mean final measured resting length of 11·6 mm. Since the muscles were free-loaded during the isotonic periods, some extension over the original unstretched length occurred during the course of the experiments.

The extension amounted to about 30 % of the unstretched length at the beginning. Most of the extension occurred in the first 10 min after adding the weight. This degree of stretch is below the point at which efficiency is maximum (see below), but about at the point where contraction amplitude is maximum, the 'optimum length' (Whalen, 1960).

Table 1 shows that regardless of the statistical method of treatment the Q_{O_2} during periods of isotonic contraction was significantly lower than during periods of isometric contraction. It would appear that any extra energy liberated as a result of shortening or work does not increase the total oxidative metabolism of heart muscle.

TABLE 1. Comparison of the Q_{O_2} during isotonic and semi-isometric contraction at frequency (F) of 30/min. Paired data from each of twelve strips were averaged in determination of percentage change. The absolute values are unpaired, and here N refers to the number of determinations.

		Q_{O_2} (%)		
N	F	Isotonic (1 g wt)	Isometric	P
12	30	100	116 ±3·0 (S.E.)	> 0·01
		Q_{O_2} (absolute values)		
30	30	3·23 ± 0·15	3·73 ± 0·18	0·05

In order to determine whether this lack of correspondence between work or shortening and oxygen consumption was limited to cat myocardium, rat trabeculae carneae were tested. The experimental conditions were the same as in series *A*, except that the bath temperature was 28° C and the stimulation rate was 60/min. The mean Q_{O_2} of twelve muscles for the isotonic periods was 6·0 ± 0·48 (S.E.) and 5·9 ± 0·40 for the isometric periods—obviously not significantly different.

The question arose as to whether the apparent lack of direct correspondence between oxygen consumption and work or shortening was obscured at the near-optimum length used. By extending the range of length and loads to include both sides of the optimum length an increased 'isotonic' Q_{O_2} might be seen. Fenn (1923) did find that the extra heat passed through a maximum at about the point of maximum work output, after which both work and heat declined to the isometric level (see also Fenn & Latchford, 1933).

The results from series *B* are shown in Fig. 2. Since cat papillary muscles and trabeculae carneae responded similarly, the data were pooled. In none of the sixteen experimental conditions was the isotonic Q_{O_2} significantly different, at the 5 % level of confidence, from the isometric level. This was true even when analysed on the basis of percentage change to eliminate inter-individual variability. The points for the lowest load at each length are replotted in Fig. 3, to reveal more clearly the increase in Q_{O_2} accom-

panying an increase in both the length and the load. That this increase is mainly due to the increased length is illustrated in Fig. 4, in which the results obtained at the 1250 mg point are plotted to reveal the effect of increasing length at a constant load. Here the isotonic and isometric Q_{O_2}

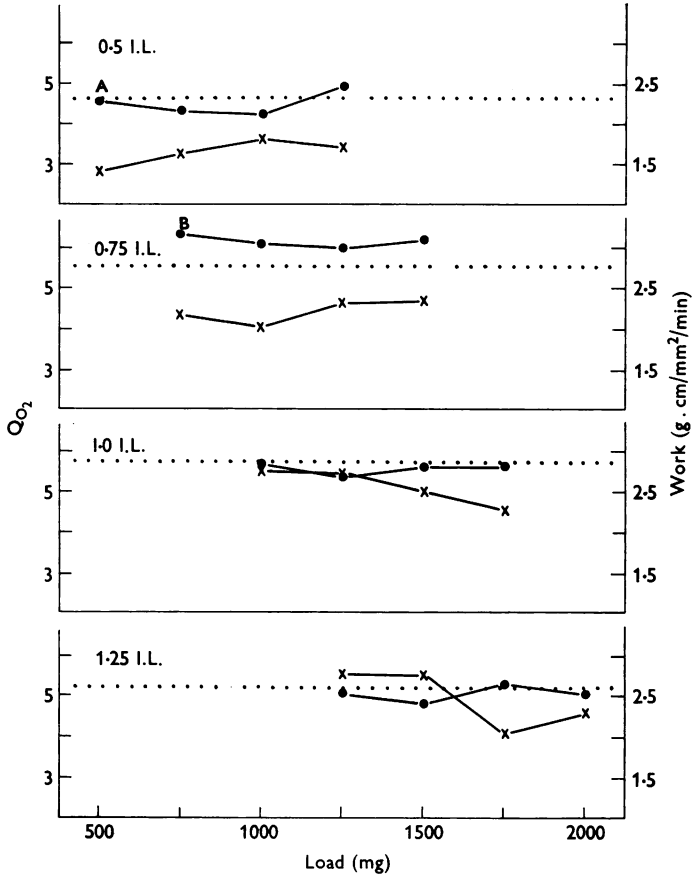

Fig. 2. Data from 22 cat papillary muscles and 10 trabeculae carneae stimulated at 30/min. Each point plotted represents 11–15 determinations. The S.E. of the Q_{O_2} value of each point ranged from 0·37 to 0·67. Work, ×, is expressed as g.cm/mm²/min. ●—●, isotonic Q_{O_2}; ------, isometric Q_{O_2}. I.L. refers to the initial length attained with the various loads (see Methods).

rise together. The increase in Q_{O_2} with length is about that to be expected from previous work (Whalen, 1960). The declining limb with extensive stretch was not, however, seen in the earlier work on heart muscle (Whalen, 1960), although it was found in rat diaphragm muscle (Whalen, Dernberg & Jenden, 1958). Hill (1958) found a decline in the heat production beyond resting length during isometric twitches of the frog's sartorius muscle. The decline in Q_{O_2} with greater extensions in the present experi-

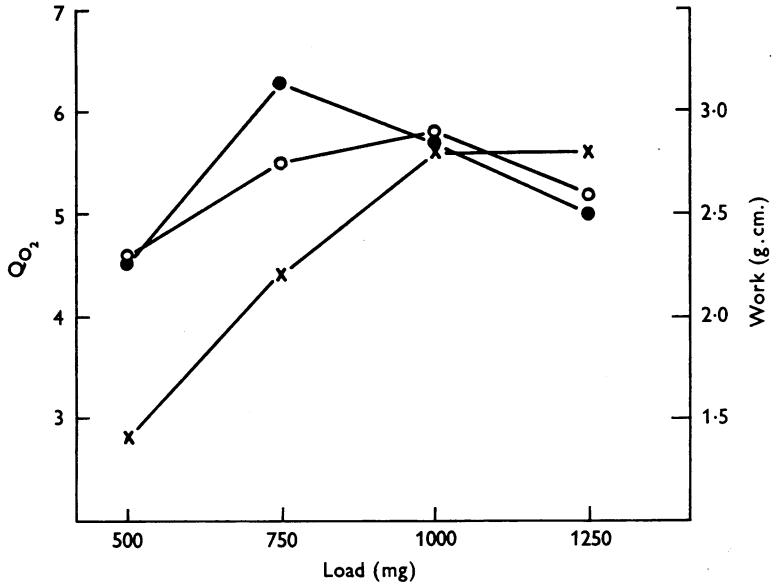

Fig. 3. Plot from data shown in Fig. 2 illustrating the effect on Q_{O_2} and work of increasing length up to about 60 % over the relaxed length and weight from 500 to 1250 mg. × work; ● isotonic Q_{O_2}; ○ isometric Q_{O_2}.

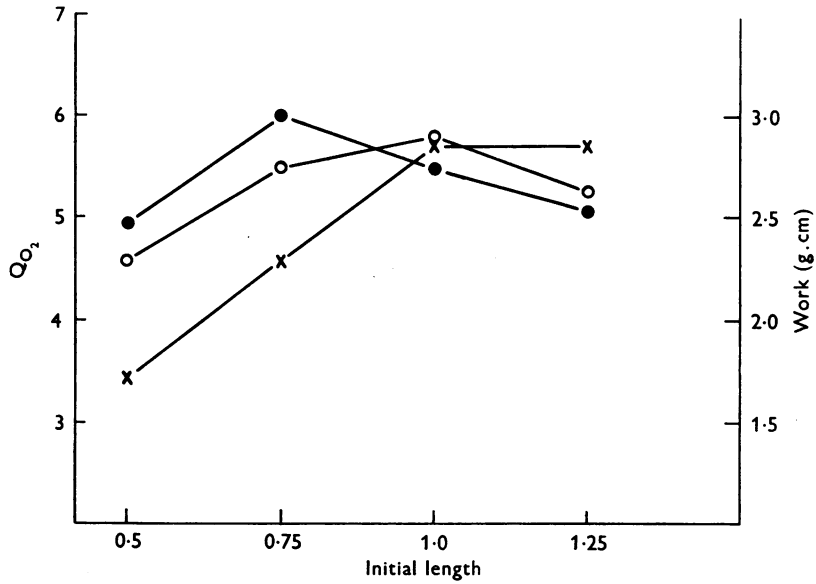

Fig. 4. Plot from data in Fig. 2 showing the effect on Q_{O_2} and work of increasing length at constant load of 1250 mg; symbols as in Fig. 3.

ments is almost certainly due to a fault in the experimental design, in that the largest extensions were almost invariably used in the last periods of the day's run when the Q_{O_2} had fallen about 20 %. For the present it is most important to know that the work performance had exceeded maximum where in Fenn's (1923) paper the greatest excess heat was reported. That such was the case is apparent from Fig. 2, where the work curve is seen to reach a plateau at the 1·0 g length and to decline somewhat with increasing weight, although the Q_{O_2} remained high. Five additional experiments with a load of 3 g gave similar results. Summarizing, it is apparent that with a twofold change in work the Q_{O_2} did not vary significantly; nor did the isotonic Q_{O_2} vary from the isometric Q_{O_2}.

With regard to the heat of shortening it might have been expected to be greatest at the points marked *A* or *B* in Fig. 2, for the mean shortening (1·3 mm) was maximal and identical at these points. The change in length was about 13 % in both cases. The fact that the isotonic Q_{O_2} was close to the lowest value at one of these points and highest in the other argues against an extra energy release attributable solely to shortening.

Because there was some disparity in the results between series *A* and *B*, and in order to test the effects of fatigue, six additional experiments were performed. In these experiments, as in series *A*, the muscles were free-loaded during isotonic periods, but the range of loads was extended and the set-screw was used instead of the strain-gauge. The experiments were designed to allow comparison to be made between a certain initial length at the beginning and at the end of the day's run. Three of the cat papillary muscles were loaded with 500 mg., and after two paired periods of isotonic–isometric contraction the load was increased to 750 mg for two more paired periods. Two muscles were first loaded with 750 mg, then at 1250 mg. One muscle was loaded with 1250 mg for all eight periods, and since the decrement was zero could be included in the graph without unduly biasing the results. Series *C* is graphically presented in Fig. 5.

As in series *A*, the Q_{O_2} of isotonic periods is significantly below that of the isometric periods. It apparently does not matter whether the muscle is 'fresh' or 'used'. Nor is it only at the 1·0 g length that free-loaded muscles contracting isotonically consumed less oxygen than during isometric contraction at the same length.

In series *C* the Q_{O_2} did not decrease with time under conditions in which some extension of the muscle took place. This fact suggests that the decrement in Q_{O_2} with time, which occurs at constant length, is almost exactly balanced in free-loaded muscles by the increment in Q_{O_2} with increasing initial length.

As in the afterloaded series (*B*), the work increased with increasing load, although the plateau of maximum work appears to have been reached at

about the 0·75 g point rather than at the 1·0 g point as before. Work and Q_{O_2} at the lower weight range showed a negative relationship, even though a greater Q_{O_2} might have been expected on the basis of greater initial length alone (Whalen, 1960).

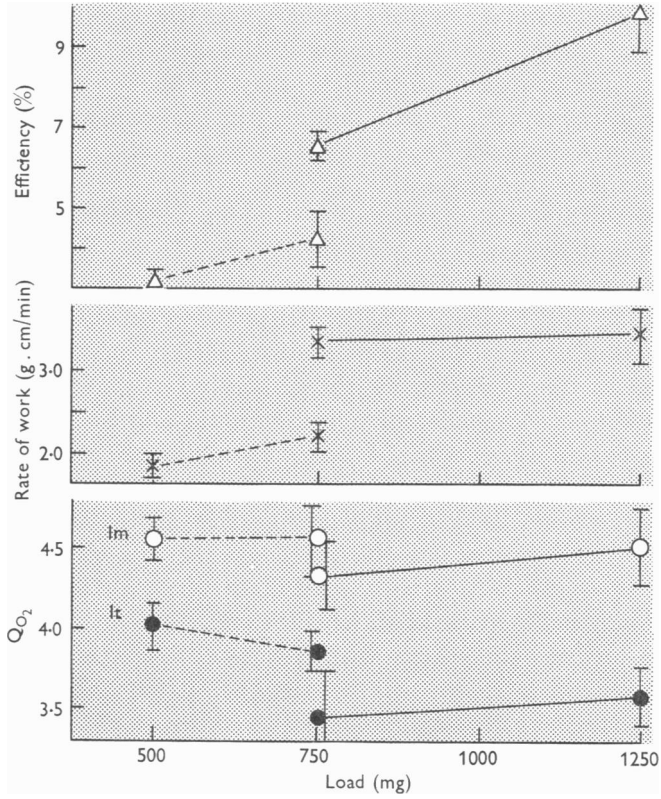

Fig. 5. Mean Q_{O_2}, total work and efficiency of six cat papillary muscles; three with light loads (------), and three different muscles with heavier loads (——). The S.E. of each point is represented by the vertical bars. Symbols as in Fig. 3. (For further explanation, see text.)

Percentage efficiency

The over-all percentage efficiency was calculated according to the equation

$$\% E = 100 \times \frac{\text{g.cm (total } W\text{/min).}}{\text{g.cm (total } O_2\text{/min)}}$$

It was assumed that the caloric equivalent of O_2 was 4·85 kcal/l. (Lorber, 1953). Conversion of the heat units to units of work gives a value of 213 g.cm/μl. O_2. The mean over-all efficiency at which work was done in series *A* was 6·9 %. In series *B* the efficiency ranged from a mean of 3·9 %

at the lightest load and shortest initial length to 6·3 % at the 1·25 g initial length loaded with 1·5 g. With larger loads at the latter initial length efficiency declined to 5·2 %. The lower efficiencies in series *B* were partly due to the influence of the thicker muscles. The mean efficiency of the muscles less than 1·35 mm^2 in cross-section was 9·7 %; about the same as in series *C* (see Fig. 5). These calculations of the over-all efficiency include the fraction of the metabolism necessary for maintenance at rest. After subtracting the resting oxygen consumption, obtained by extrapolating from data of previous experiments (Whalen 1960), the calculated external efficiencies are from two to four times higher. The thin strips in series *B* averaged 17·9 %. In series *A* and *C* the mean external efficiencies were 41 and 33 % respectively.

DISCUSSION

It would appear from the present results that there may be major differences between the energetics of isolated frog skeletal muscle and isolated mammalian cardiac muscle. These differences are most evident when comparison is made with heat measurements during tetanic contractions of frog sartorius muscle (e.g. Fenn, 1923; Abbott, 1951). The most closely related studies, however, are those of Fischer (1931), who measured the oxygen consumption of frog sartorius during a series of single twitches. The differences from my results are not so striking. Fischer reported that while he found a 13 % increase in oxygen consumption with work, it only occurred at small shortenings with relatively heavy loads. As in the current studies, with large shortenings much less O_2 was consumed. Fischer who, of course, had not the later experiments of Hill (1949*a*, *b*; 1953) with which to draw comparison, concluded that, 'with single twitches the amount of shortening occurring during the contraction is of much greater influence than the work done'. He called upon the experiments of Hill (1925; see Hill, 1958) showing that the heat liberated during tetanic contraction increased as muscle length increased, as has recently been shown to hold true for twitches of isolated heart muscle also (Whalen, 1960). Thus, since the mean muscle length was shorter during isotonic contraction the energy liberated would be expected to be less. Quantitatively this explanation appears to fall short of accounting for the significantly lower 'isotonic' Q_{O_2} in series *A* and *B*, although it is still an open question.

The possibility was entertained that the extra oxygen liberated with work was too little to be measured by the present method. The amount of extra oxygen, above the isometric, which might have been expected during the isotonic periods was calculated from the data of Fenn (1923). It was assumed that the temperature difference (approximately 7° compared with 32° C) is negligible. Fenn (1923) found that efficiency did not vary

within a range of 0–15° C. However, efficiency of the dog heart increased about 50 % with a change from 37° to 27° C (Reissman & Van Citters, 1956).

In series *A* the muscles lifted 1 g an average distance of 1·4 mm at a rate of 30 times/min for 50 min or a total of 1500 times. Thus,

$$\frac{\text{total work (g.cm)}}{\text{O}_2 \text{ equiv (213 g.cm/mm}^3\text{)}} = 0{\cdot}98 \text{ mm}^3 \text{ O}_2,$$

and since additional heat above the work equivalent was given off in the experiments of Fenn (1923), to the extent of 80 %, the initial O_2 equivalent would be expected to be about 1·75 mm^3. The total extra O_2 would be at least twice this amount (Hill, 1939*a*) to allow for recovery, or 3·5 mm^3.

Since the standard deviation of a series of 50 min determinations on one strip was no more than 0·60 mm^3 this difference should have been detected.

The heat of shortening is a quantity about which there is less controversy. Hill (1949*b*) found that, provided shortening remained constant, the load on a frog sartorius muscle during a twitch could be varied tenfold without affecting the amount of heat liberated. In a later paper (1953) he did find with an inertia lever that a fivefold increase in work increased the heat liberated by about 20 % above the shortening heat.

A number of papers (e.g. Hill, 1949*a*) have established that in amphibian skeletal muscle the heat of shortening per centimetre is approximately 400 g.cm/cm^2 cross-section. Abbott (1951) and Abbott & Wilkie (1953) extended these observations to show that this constant was applicable through a wide range of shortening. Calculation of the extra oxygen equivalent to the heat of shortening showed that an increment of about 10 mm^3 O_2 might have been expected in series *A*. If external shortening had been as much as 3 %, the excess O_2 due to shortening would have been about 7·5 mm^3 O_2—still an easily measurable difference.

It is obvious that the amount of internal shortening complicates the determination of shortening or work energy. On the basis of the increased extensibility of heart tissue it may be that internal shortening is greater than in frog skeletal muscle, in which internal shortening, according to Hill (1949*a*), can be as much as 5–10 % of the length. The data in the present paper provide no evidence on this point, however.

It is possible that the positive effect on Q_{O_2} of work or shortening is a characteristic peculiar to amphibian skeletal muscle. There is some information which indicates that the Q_{O_2} of the isolated rat diaphragm is not dependent on the work done (R. E. Smith & W. J. Whalen, unpublished). Also a recent paper by Fales, Heisey & Zierler (1960) showed that the number of stimuli rather than work or shortening best correlated with the oxygen consumption of the *in situ* gastrocnemius-plantaris muscle group

in the dog. However, Lee (1960) from his work on the relationship between isometric contraction and Q_{O_2} of the cat papillary muscle reached the conclusion that there were no basic differences from frog skeletal muscle.

The present results also give some indication that heart muscle may perform external work more efficiently than skeletal muscle. Fischer (1931) found a mean efficiency of 9 % for the frog sartorius muscle, after he had subtracted the resting O_2 uptake. On the basis of heat measurements Hill (1939*b*) found the efficiency of the initial process, exclusive of recovery, to be around 40 %; or 20 % for the entire cycle. He noted that the efficiency of human skeletal muscle appeared to be of the same order of magnitude. On the other hand, Bing & Michal (1959), after subtracting estimates of the resting O_2 consumption, calculated the efficiency of human and dog heart *in vivo* to be almost 40 %. The latter figure agrees with the estimates of external efficiency in series *A* and *C* found in the present study. It should, however, be mentioned that Lorber (1953), found relatively low values for the over-all efficiency in the isolated blood-perfused cat heart performing light work. Also, the uncertainty regarding the rate of the resting O_2 consumption makes any comparison hazardous. Furthermore, there is no evidence which shows that the resting O_2 consumption remains the same during activity as during rest.

In a previous paper (Whalen, 1960) some evidence was presented which suggested that, for isolated heart muscle (and isolated rat diaphragm (Whalen, Dernbergh *et al.* 1958)), it was the initial length rather than the developed or resting tension which determined the oxygen uptake per contraction, although total tension could not be eliminated as a contributing factor. Lee (1960), on the other hand, reported that resting tension, in the cat papillary muscle was a more significant factor than length. Our combined results lead to the tentative conclusion that, in isolated myocardium, a 'package' of energy is liberated with each beat which is directly proportional to the initial length, and apparently independent of work or shortening. The *in vitro* results further suggest that, in the intact animal, the heart rate should be the major determinant of the oxygen consumption (Whalen, 1960). These hypotheses in some respects are consistent with the results from recent *in vivo* experiments.

Recent research on the whole heart has tended to reduce emphasis on the role of fibre length or end-diastolic volume in the determination of the total energy exchange (see Starling & Vischer, 1927). Katz, Katz & Williams (1955) found in the relatively intact dog that large variations in left atrial pressure (and presumably end-diastolic volume) were not accompanied by corresponding variations in O_2 consumption. Sarnoff, Braunwald, Welch, Case, Stainsby & Macruz (1958) agree that factors other than

length predominantly influenced the Q_{O_2} in their isolated-supported heart preparation. According to Rushmer & Smith (1959) the maximum increase in heart size in their experiments on unanaesthetized dogs was 15 %. If my findings (Whalen, 1960) can be accepted and applied to the intact organism, the increment in O_2 uptake which might be expected from this amount of distension would be only about 15 %.

On the other hand, an increase in frequency over the normal range from 60 to 120 beats/min would double the O_2 consumption (Whalen, 1960). The graphs of Sarnoff *et al.* (1958) show that increasing the frequency alone called forth a substantial increase in the Q_{O_2}. Hoffmeister, Kreuzer & Schoeppe (1959) obtained in the dog heart when empty almost the same increase in O_2 consumption with frequency as that found by Whalen (1960).

Until quite recently there was general agreement that work was a major determinant of the O_2 consumption in heart muscle (cf. Evans & Matsuoka, 1914). However, Sarnoff *et al.* (1958), using their refined dog heart preparation, reported that myocardial Q_{O_2} bore little relation to the heart's external work *per se*. Salisbury, Bor, Lewin & Rieben (1959), using a heart–lung machine bypass, also found little or no change in oxygen consumption with large variations in cardiac work. Katz & Feinberg (1958), from results on a relatively intact mammalian preparation, reached a similar conclusion.

Although the selective manner in which the results from the intact heart were presented above may give the impression of complete accord with the *in vitro* results, this is not quite the case. Sarnoff *et al.* (1958) noted that, if frequency were held constant, large increases in O_2 consumption still occurred in direct proportion to increases in arterial pressure. Further experimentation led them to suggest that the area under the systolic pressure curve, 'the tension–time index, or T.T.I.', was the primary determinant of the 'Q_{O_2}' per beat. Thus, (heart rate) × (T.T.I.) most accurately predicted the total O_2 consumption. Katz & Feinberg (1958), stimulated by Sarnoff's studies, reanalysed their data from the intact dog and found that (heart rate) × (aortic pressure) yielded a very high correlation with myocardial O_2 consumption.

The major significance of aortic pressure or tension development is, therefore, at variance with the *in vitro* results. A possible explanation for the discrepancy is the following. In the studies of Sarnoff *et al.* (1958) a very high correlation between O_2 consumption and coronary blood flow was observed, as others had previously reported (e.g. Alella, Williams, Bolene-Williams & Katz, 1955), although occasional deviations from this relationship have been found in the dog heart subjected *in situ* to stress (Katz *et al.* 1955). In an analysis of the determinants of coronary flow Braunwald, Sarnoff, Case, Stainsby & Welch (1958) came to the conclusion that aortic

pressure was the dominant factor. Thus, both aortic pressure and myocardial O_2 consumption are significantly correlated with the coronary blood flow. This relationship might be interpreted in at least two ways or a combination of both: (1) greater aortic pressure means greater tension development and thus more oxygen consumed, coronary flow being adjusted to the demand for oxygen, or (2) coronary flow primarily determines the oxygen consumption, tension being relatively unimportant. The latter view would tend to eliminate the disparity between the results from the *in vitro* and intact heart experiments.

There is some evidence which supports the hypothesis that coronary flow is a major determinant of myocardial oxygen consumption. For example, Gregg, Rayford, Khouri, Kattus & McKeever (1957) demonstrated in dogs that by increasing the coronary perfusion pressure by 5–35 mm Hg myocardial oxygen uptake increased 20–70 %, although there was no change in heart rate, cardiac output or aortic pressure. When the coronary perfusion rate was reduced below normal, the oxygen consumption was depressed with apparently little change in other functions. On the other hand, Berne (1958) did not always observe an increase in myocardial oxygen consumption with an increase in coronary blood flow in the fibrillating dog heart. Wegria, Nakano, McGiff, Muraviev, Zekert & Blumenthal (1959) increased coronary flow with ERL-239, which produced no change, or lowering, of arterial pressure, cardiac output, and work; yet they found a significant increase in myocardial O_2 consumption.

This hypothesis is tantamount to saying that the heart is in a continual state of oxygen debt, which it may be, depending on the definition of the term. Verzar (1912) may have been the first to suggest this hypothesis for skeletal muscle. The evidence is fragmentary but suggestive. In this sense the heart cannot incur an oxygen debt simply because heart muscle contains the essential ingredients to turn over oxygen at a much faster rate than it is normally supplied, turning the energy into heat unless an alternative pathway is available (or necessary). Should this assumption prove to be correct, it would mean that heart muscle differs from skeletal muscle, since O_2 consumption in the latter is independent of the O_2 tension down to extremely low pressures (Hill, 1948).

The question arises whether, in the present experiments, the oxygen supply was equal to the demand. This has been discussed under Methods (see also Whalen, 1957, 1960) and, except for the very thick muscles, answered affirmatively. If so, it becomes necessary to explain why the calculated values for Q_{O_2} are below most of the values for the *in vivo* and blood-perfused heart studies mentioned earlier. It is probable that the catechol amines present in the blood would contribute significantly to the metabolic demand (e.g. Whalen, 1957). Further, lactate and pyruvate

available in the blood-perfused heart might be expected to increase the oxygen consumption (Bernheim & Bernheim, 1944).

A complicating factor in the analysis of the over-all results is the possibility that the amount of the 'available' intracardiac catechol amines probably varies with the activity of the heart muscle (Whalen, Fishman & Erickson, 1958; Sarnoff, Mitchell, Gilmore & Remensnyder, 1960). If muscle tension (or stretch), no matter how produced, facilitates the 'spontaneous' intracardiac liberation, or use, of the catechol amines, the qualitative differences between our results and those from the intact heart preparation would tend to disappear. The attractive possibility of the more general applicability of this hypothesis must await further proof.

SUMMARY

1. By means of a newly developed microrespirometer the oxygen consumption and external work output of excised, parallel-fibred cat and rat trabeculae carneae and papillary muscles were simultaneously measured during isotonic contractions at a frequency of 30 to 60 per minute. In alternate periods shortening was limited to less than 3% of the initial length, and thus, essentially no external work was performed. A wide range of initial lengths and loads was used.

2. In experiments in which the muscles were free-loaded the Q_{O_2} during periods of isometric contraction was significantly higher than during periods of isotonic contraction. When the muscles were after-loaded there was no significant difference in the Q_{O_2} for the two types of contractions. No explanation was offered for the disparity of the results between free-loaded and after-loaded experiments.

3. Work and Q_{O_2} were found not to be correlated even at the point of maximum efficiency and beyond it; nor was the amount of shortening a significant factor in determining the Q_{O_2}. It was suggested that the lower Q_{O_2} often seen during isotonic periods may have been partly due to the shorter mean length during contraction.

4. The efficiency for doing external work was estimated, and found to be in the same range as that reported for the whole heart, and possibly higher than for skeletal muscle.

5. The results indicated that there may be major differences in the energetics of isolated mammalian heart muscle and isolated amphibian skeletal muscle. It was suggested that for isolated heart muscle, a 'package' of energy is liberated per beat which is directly proportional only to the initial length—or, possibly, the mean length—during contraction. In the intact organism frequency would be expected to be the major determinant of myocardial O_2 consumption.

6. The tentative hypotheses put forth in the preceding paragraph were

found to be consistent with recent results obtained from whole-heart preparations, with the exception that, in the whole heart, muscle tension has been found to be the major determinant of the 'Q_{O_2}' per beat. The suggestion was made that coronary flow may be one of the parameters which determine the O_2 consumption of the heart, and that variations in the coronary flow might be responsible for the lack of agreement regarding the effect of tension on the Q_{O_2}.

7. A possible relation between muscle activity and intracardiac catechol amine liberation was also discussed.

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