Increased Myocardial Oxygen Consumption and Contractile State Associated with Increased Heart Rate in Dogs

By Robert C. Boerth, M.D., Ph.D., James W. Covell, M.D., Peter E. Pool, M.D., and John Ross, Jr., M.D.

ABSTRACT

The effects of increasing the frequency of contraction on myocardial oxygen consumption per minute (MVO_2) were examined in eight dogs using an isovolumic left ventricular preparation. MVO_2 was determined at two to four levels of heart rate in each animal. Peak wall stress was maintained constant in each animal so that changes in it would not influence the effects of heart rate on oxygen consumption per beat. As heart rate was increased, there was a highly significant linear increase in MVO_2. Oxygen consumption per beat was shown to be a negative linear function of the reciprocal of heart rate. Thus, as heart rate increased there was a significant increase in oxygen consumption per beat; when basal oxygen consumption was subtracted from total oxygen consumption, there was a much larger increase in oxygen consumption per beat. Myocardial contractile state, defined as the maximum observed contractile element velocity at the lowest common level of wall stress, was significantly increased by increasing heart rate. The data suggest that the increased MVO_2 associated with augmented heart rate is secondary to augmentation of contractile state, as well as to the increase in stress development per minute.

ADDITIONAL KEY WORDS myocardial metabolism inotropic state stress-velocity relation peak myocardial wall stress isovolumic left ventricular contractions

There is general agreement that increasing the frequency of contraction augments the inotropic or contractile state of the myocardium, as reflected by a shift of the force-velocity relationship, both in isolated cardiac muscle (1-3) and the intact heart (4, 5). Recently, it has been shown that the contractile state of the heart is an important determinant of myocardial oxygen consumption (6-9), and therefore, it might be expected that increasing the frequency of cardiac contraction would be associated with increased myocardial oxygen utilization. Since 1885, when Yeo showed that a beating heart consumes more oxygen than a nonbeating heart (10), a number of investigators have demonstrated that tachycardia produces an augmentation of myocardial oxygen consumption per minute (11-15). However, the question whether oxygen consumption per beat is augmented has remained unanswered because systolic pressure and the level of myocardial wall stress are altered by increasing the heart rate, and both of these factors are now recognized to be important determinants of myocardial energy utilization (9, 14, 16-18). Thus, in previous experiments a decrease (11, 15), no change (13), or an increase (14) in oxygen consumption per beat has been found to accompany increased heart rate. To circumvent this problem in the present investigation the effect of increased contractile state, produced by increasing heart
rate, on the myocardial oxygen consumption per beat was examined in the isovolumically contracting canine left ventricle. The peak wall stress was maintained constant as heart rate was increased, so that the inotropic effect of tachycardia alone on energy utilization per beat could be determined.

**Methods**

Mongrel dogs of either sex were anesthetized with intravenous pentobarbital sodium (average 34 mg/kg). Respiration was maintained with a positive-pressure respirator, and the heart and great vessels were exposed through a midline sternotomy. The preparation (Fig. 1) has been presented in detail previously (9). In brief, the animal was placed on total cardio-pulmonary bypass, blood from the venae cavae being oxygenated and pumped retrogradely into a femoral artery. Aortic pressure remained constant throughout each experiment (mean = 89 mm Hg). A thin latex balloon attached to a wide-bore metal cannula was placed within the left ventricle; plastic discs were placed in the mitral annulus and in the left ventricular outflow tract to keep the balloon within the left ventricular cavity. The ventricle contracted isovolumically, and ventricular volume and pressure were regulated by introducing known amounts of saline into the balloon through the metal cannula using a calibrated syringe. The sinoatrial node was crushed, and the heart was electrically paced from the right atrium. A drainage tube in the right ventricle collected coronary venous blood, and this effluence was used to measure coronary blood flow and to collect coronary venous blood samples; it has recently been shown that this effluence represents 95% of the total coronary blood flow (19). Oxygen content of the blood was determined manometrically by the method of Van Slyke and Neill (20). The weight of the left ventricle including the septum was obtained by removing the atria and free wall of the right ventricle. Myocardial oxygen consumption in ml/min/100 g left ventricle (MVo2) was calculated as the product of coronary blood flow and the coronary arteriovenous oxygen difference.

Systemic arterial and left ventricular pressures were measured using Statham P23Db transducers. The first derivative of left ventricular pressure with respect to time (LV dP/dt) was measured using an electronic differentiator, the dynamic characteristics of which have been previously described (21). Myocardial wall stress, expressed as the tangential force per unit cross-sectional area of the left ventricular wall, was continuously calculated by an analog computer, and maintained constant by altering internal ventricular volume. Stress in g/cm² was calculated as \( \frac{P}{2h} \) assuming a thick-walled spherical model, where \( P \) = intraventricular pressure in g/cm², \( r \) = internal radius in centimeters, and \( h \) = wall thickness in centimeters derived from internal volume and muscle volume (obtained from a previously determined curve of left ventricular muscle volume vs. body weight). Myocardial wall stress, the electrocardiogram, and pressures were recorded on a direct-writing oscillograph at paper speeds of 100 mm/sec.

After completion of each experiment, the heart was weighed and this actual value used for

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1Electronic Gear, Inc., Elmont, New York, Model No. 5602.

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LV wt. = left ventricular weight; HR = heart rate; CBF = coronary blood flow; A-Vo2 = coronary arteriovenous oxygen difference; MVo2 = myocardial oxygen consumption; LV vol. = left ventricular volume; LVP = peak left ventricular pressure; TTP = time from onset of LV contraction to peak wall stress; Dur. = duration of contraction; LV dP/dt = maximum rate of rise of left ventricular pressure; Po = peak wall stress; Max V = maximum contractile element velocity observed at lowest common levels of stress.
muscle volume (assuming a sp. gr. of 1.0), and values for left ventricular pressure and left ventricular dP/dt were determined at 10-msec intervals from two successive beats for every level of heart rate and utilized for calculation of the reported values for wall stress and contractile element velocity (V_CE). The duration of contraction was measured as the interval from end diastole to the time when left ventricular pressure returned to end-diastolic pressure. The derivations of the equations for stress and for contractile element velocity have been presented in detail previously (9). In an isovolumic contraction, V_CE is equal to the rate of lengthening of the series elastic component (SEC) of the myocardium. The rate of series elastic lengthening (VSEC) is directly proportional to the rate of stress development (dS/dt) and inversely related to the stiffness of the series elastic component (dS/dl). This relationship then can be written as: V_CE = VSEC = (dS/dt)/(dS/dl), where dS/dl = 28S (5). V_CE is expressed in muscle lengths (or circumferences) per second and was converted to cm/sec by multiplying by the instantaneous circumference. Since the extrapolation of contractile element velocity to zero stress (Vmax) may be difficult and subject to error, the inotropic state of the heart was characterized by determining the maximum observed contractile element velocity (max V) at the lowest common level of wall stress in any experiment (21).

In each of eight dogs, from two to four different levels of heart rate were studied, ranging between 98 and 202 beats/min. The sequence of heart rate variations in each experiment was selected at random. Systemic arterial and coronary venous blood samples were drawn simultaneously during steady state conditions. As the heart rate was increased or reduced, the volume of saline within the left ventricular balloon was usually diminished or increased, respectively, to maintain peak myocardial wall stress constant.

Linear regression lines were calculated for the data using the method of least squares (22). Significance of the slopes of the regression lines was calculated using paired t-tests (23), and the criterion of significance chosen was P < 0.05.

**Results**

The effects of heart rate on the characteristics of left ventricular isovolumic contractions and MVO2 are given in Table 1. In all

**FIGURE 2**

Oscillographic tracings obtained at two different heart rates. ECG = electrocardiogram; LV dP/dt = first derivative of left ventricular pressure; LVP = left ventricular pressure; LVEDP = left ventricular end-diastolic pressure; AP = aortic pressure.
experiments there was a marked increase in left ventricular dP/dt as heart rate was increased, and the time to peak wall stress and the duration of contraction were significantly decreased. In 6 of the 8 experiments, as heart rate was increased it was necessary to reduce left ventricular volume (range 0 to 3.5 ml) in order to maintain peak wall stress constant. Figure 2 shows the oscillographic tracings from dog no. 8: the tracings in panel A were taken at a heart rate of 137 beats/min and those in panel B at a rate of 202 beats/min. Peak wall stress was maintained constant without a change in ventricular volume in this experiment. At the higher heart rate, left ventricular dP/dt was increased from 1327 mm Hg/sec to 1637 mm Hg/sec; oxygen consumption was increased when expressed both as ml/min and as μliters/beat. As heart rate increased, coronary blood flow usually increased as did the coronary arteriovenous oxygen difference (Table 1).

In each experiment, the relationship between heart rate in beats/min and MVo₂ was examined by linear regression analysis (Fig. 3). The values for the slopes and the Y intercepts in the eight experiments were then averaged, and a mean regression line of MVo₂ vs. heart rate was computed. The positive slope for this regression was $0.05 \pm 0.003$ ml/beat/100 g left ventricular weight (mean ± SEM), and this slope was highly significant ($P < 0.001$).

Using analysis of variance, the function was shown statistically not to deviate from linearity ($F < 0.03$). However, as heart rate was increased, the total peak wall stress generated during 1 minute also increased; for example, in experiment no. 8, the product of peak wall stress ($P_o$) and heart rate increased from 6644 g/cm²/min to 9898 g/cm²/min. Since peak stress is a major determinant of energy utilization (9, 14, 16-18), it might be predicted that the MVo₂ also would be increased. Therefore, to determine whether the oxygen consumption at higher heart rates was aug-

![Figure 3](image-url)

*FIGURE 3*

The effect of increasing heart rate on myocardial oxygen consumption per minute per 100 g left ventricular weight. Each symbol represents the value obtained in a single experiment, wall stress being maintained constant within the experiment.
Calculated mean regression lines of oxygen consumption per beat on the reciprocal of heart rate times 10^3. See text for derivation of mean regression lines; MVO_2 = myocardial oxygen consumption per beat per 100 grams left ventricular weight; N = number of dogs; numbers in parentheses on the abscissa are locations of heart rates of 100 and 200 beats/min.

mVO_2 = myocardial oxygen consumption per minute; N = number of dogs; numbers in parentheses on the abscissa are locations of heart rates of 100 and 200 beats/min.

Changes in inotropic or contractile state were characterized by changes in V_CE at the lowest common stress (max V) within each experiment. The values for max V were obtained from the force-velocity relations as determined from isovolumic contractions (21, 24). These relations at heart rates of 100 and 200 beats/min in a representative experiment are shown in Figure 5. The augmentation of V_CE at the higher rate is evident, indicating that inotropic state was enhanced. With only two exceptions (dogs 5 and 7; Table 1), max V increased whenever heart rate was increased, and this augmentation of max V was statistically significant (P < 0.001). To determine whether the increased oxygen consumption per beat at higher heart rates was related
Stress-velocity relations in dog no. 3 at heart rates of 100 and 200 beats/min. Velocity = contractile element velocity; stress = force/unit area (see Methods); myocardial oxygen consumption per 100 g left ventricular weight expressed both as ml/min and as μl/beat.

Discussion

In 1871, Bowditch reported that increasing the frequency of contraction augmented the force of contraction of the heart (25). More recently, it has been shown that there also is an augmentation of the velocity of contraction with increasing heart rate (1-5), an effect confirmed in the present investigation. In the present study, augmentation of the force of contraction was usually but not invariably observed when heart rate was increased, a finding in agreement with studies in isolated cardiac muscle (3). The maximum observed contractile element velocity at the lowest common wall stress (max V) was used to define the contractile or inotropic state of the left ventricle, and using this index the inotropic state was enhanced by increased heart rate in 21 of 23 observations. Although it is possible that the values for max V were influenced by changes in muscle length, ventricular volume was usually decreased as heart rate was increased, and this would tend to lower the values for max V at the high heart rates (9). Thus it is probable that the increase in contractile element velocity at zero stress (Vmax) was even greater than the observed augmentation of max V.

A number of investigators have examined the influence of heart rate upon the heart's oxygen requirements (11-15), and some of these studies have indicated that a linear relationship exists between heart rate and myocardial oxygen consumption per minute (11, 14, 15). The findings in the present study...
investigation (Fig. 3) were in agreement with this conclusion, and using analysis of variance the regression of \( \text{MVox} \) on heart rate was shown statistically not to deviate from linearity. However, as mentioned earlier, to determine whether the amount of oxygen consumed at the higher heart rates was in excess of that necessary for stress production per minute, it was necessary to determine the effects of increasing heart rate upon the myocardial oxygen consumption per beat. In this connection, Laurent et al. (11) and Van der Veen and Willebrands (15) have reported that myocardial oxygen consumption per beat decreased with increasing heart rate, and Maxwell et al. (13), studying intact dogs, have reported that increasing heart rate from an average of 92 to 193 beats/min resulted in no change in oxygen consumption per beat. On the other hand, Monroe and French (14) found an increase in oxygen consumption per beat with increasing heart rate, although this occurred when there was a marked increase in the force of contraction. In the present study, oxygen consumption per beat was shown to be a linear function of the reciprocal of heart rate. The negative slope of the regression of oxygen consumption per beat on the reciprocal of heart rate (top line of Fig. 4) indicated that as heart rate increased there was a significant increase in oxygen consumption per beat.

In examining the effects of heart rate upon myocardial oxygen consumption, it is important to consider the various factors which determine the total oxygen consumption of the heart. It has been suggested that there are at least five such factors (9): stress development, external work, contractile or inotropic state, activation, and basal requirements. Since both wall stress and the contractile state of the myocardium have been postulated to be important determinants of myocardial oxygen consumption (6, 9), comparisons of oxygen consumption at different heart rates were made at matched levels of peak wall stress to minimize the effects of wall stress on oxygen consumption. Since Monroe (26) and others (27, 28) have found that peak tension rather than the integrated tension is most closely related to \( \text{MVox} \), peak wall stress levels were matched in this study. This resulted in a marked reduction in integrated wall stress per beat at the higher heart rates, and it is possible that this reduction may have minimized the augmentation of oxygen consumption per beat observed at higher heart rates. The amount of shortening of myocardial fibers against load (external work) is a determinant of total energy utilization in isolated muscle (29). In an isovolumically contracting ventricle there is little shortening of the myocardial fibers. Although a small amount of shortening could be associated with changes in the shape of the ventricle (30), this contribution should be similar at all heart rates and therefore probably did not influence the present results.

It has been shown recently that the oxygen cost of electrical activation of the intact heart is less than 1% of the total oxygen consumption (31). The remainder of the activation energy (i.e., that required for activation of the contractile sites of the myocardium) probably represents only a small percentage of the total \( \text{MVox} \) (32, 33). It is not known, however, whether changing heart rate affects the per beat expenditure of oxygen for activation.

In the isovolumic preparation used in this study, the basal oxygen consumption determined during arrest with 15% KCl was found to be 1.43 ml/min/100 g left ventricle. This value represented a considerable portion of the total myocardial oxygen consumption (Table 1). If it is assumed that the basal oxygen consumption is not affected by changing heart rate, then the amount of basal oxygen consumption per beat must decrease with increasing heart rate, since the basal oxygen consumption per minute is divided among more contractions per minute. The lower line in Figure 4 shows that when basal oxygen consumption per beat is subtracted from the total oxygen consumption per beat, there is a much larger increase in oxygen consumption per beat with increasing heart rate than when total oxygen consumption alone is utilized.

Since the increased oxygen consumption per
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bead seen at the higher heart rates does not appear to be explained by changes in stress development, external work, activation energy, or basal energy requirements, it seems reasonable to associate the increased oxygen consumption with the increased contractile state produced by the increasing heart rate. However, this observed increase in oxygen consumption is of a smaller magnitude than that reported in a study by Graham et al. from this laboratory (9) in which inotropic state was increased by the administration of norepinephrine. It is possible that a fundamental difference exists in the relation between contractile state and energy utilization during these two procedures; on the other hand, if basal oxygen consumption was subtracted from the total oxygen consumption (lower line of Fig. 4), the increased oxygen consumption associated with the increased contractile state in the present study would more closely approach that reported by Graham et al. (9).

It is concluded that a positive, linear relation exists between myocardial oxygen consumption per minute and heart rate. In addition, when peak wall stress is constant, contractile state (as reflected by max V) is increased by increasing heart rate and this enhanced contractility is associated with an increase in myocardial oxygen consumption per beat.

Acknowledgments

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