Control of Myocardial Oxygen Consumption: Relative Influence of Contractile State and Tension Development

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ABSTRACT Myocardial oxygen consumption was measured in 11 anesthetized, open-chest dogs in order to compare in the same heart the relative influence on oxygen usage of tension development and the contractile or inotropic state, as reflected in V_{max}, the maximum velocity of shortening of the unloaded contractile elements. The isovolumetrically contracting left ventricle was studied with left ventricular volume, heart rate, and systemic perfusion rate controlled. Wall tension, contractile element velocity, and V_{max} were calculated. Peak developed tension was increased at a constant V_{max} by increasing ventricular volume, and the effect on oxygen consumption was determined. Oxygen utilization was then redetermined at an increased V_{max} but at a constant peak developed tension by infusing norepinephrine (0.76 to 7.6 $\mu g/min$) and decreasing ventricular volume to match the tension existing before norepinephrine infusion. Oxygen consumption consistently increased with increases in both developed tension and V_{max} with the following multiple regression equation relating these variables: myocardial oxygen consumption (μl/beat per 100 g in LV) = K + 0.25 peak developed tension (g/cm^2) + 1.43 V_{max} (cm/sec). These data indicate that the oxygen cost of augmentation of contractility is sub-

stantial, can be independent of any change in fiber shortening, and is similar in order of magnitude to the effect of alterations in tension development

INTRODUCTION

The delineation of the factors that regulate myocardial oxygen consumption (MVo_2) has been the objective of extensive research. It was demonstrated by Rohde in 1912 that MVo_2 varied directly as a function of the product of developed pressure and heart rate in the cat isovolumetric left ventricular preparation (1). Shortly thereafter, Evans and Matsuoka (2) concluded from studies on the dog heart-lung preparation that "there is a relation between the tension set up on contraction and the metabolism of the contractile tissue." These demonstrations, that tension [2] development is an important determinant of MVo_2, have been verified repeatedly (3–8). It has also been proposed that the heart's oxygen utilization is determined primarily by a closely related variable, the work performed by the contractile elements (CEW) (9). Several subsequent studies, however, have demonstrated that CEW does not invariably correlate with MVo_2 (10–12).

Recently, it has also become apparent that wall tension is not the sole determinant of the heart's oxygen utilization, and there is substantial evidence that changes in myocardial contractility, or inotropic state, as reflected in V_{max}, the maximum velocity of shortening of the unloaded contractile elements, can exert considerable influence on

[1] Defined herein as either total tensile force or as force/unit cross-sectional area (stress).

MVo_2 (11, 13–18). This effect has been demonstrated both for positive inotropic interventions, which increase MVo_2 when myocardial tension is held constant or falls (13–18), and also for negative inotropic interventions which reduce MVo_2 at constant levels of tension (11). It has been suggested that this effect of the contractile or inotropic state on MVo_2 might be related to changes in (a) the velocity of shortening of the contractile elements (CE) and myocardial fibers, (b) the extent of shortening of the CE and of the myocardial fibers, and (c) the contractile state as reflected in the extrapolated velocity of shortening of the unloaded CE (V_{max}). This last-named variable has the property of being largely independent of changes in myocardial fiber length (19), and for this reason it is the best index currently available for evaluating the contractile state of the heart (20–21).

Thus, while both the contractile state of the myocardium and the developed tension have been shown to affect MVo_2, no direct comparisons of the *relative* quantitative influences of these two variables have been made. Furthermore, the effect on MVo_2 of increasing contractility without altering either the extent of fiber shortening or the CEW has not been defined. The present investigation, therefore, was undertaken to assess, in the same heart, the *relative* effects on MVo_2 of changes in tension development and in the contractile state of the myocardium. This assessment was accomplished by utilizing an isovolumetric, left ventricular preparation in which wall tension could be altered at a constant contractility, and, conversely, the contractile state could be increased at a relatively constant level of peak developed tension and CEW.

METHODS

Experimental preparation. 11 mongrel dogs weighing from 17.3 to 24.6 kg were anesthetized with pentobarbital sodium (35 mg/kg), and a bilateral thoracotomy was performed. Ventilation was provided by a positive pressure respirator. The basic experimental design was first to investigate the effect on MVo_2 of changing peak developed tension (PDT) by altering intraventricular volume at a constant contractility. Thereafter, the effect on MVo_2 of changing contractility at a relatively constant PDT was investigated by infusing norepinephrine and decreasing the intraventricular volume in order to achieve levels of PDT similar to those observed before norepinephrine.

The experimental preparation is depicted schematically in Fig. 1. The right heart was bypassed, and the systemic and coronary venous blood were drained separately into a large reservoir. The blood, which was oxygenated with either 100% O_2 or with 97% O_2 and 3% CO_2, was passed through a heat exchanger and was then pumped back into a femoral artery to provide retrograde systemic perfusion at flow rates which were held essentialy constant in each experiment and averaged 110 ml/min per kg (range 73–146). Heart rate was maintained constant at an average of 141 beats/min (range 100–160) by right atrial stimulation after crushing the sinoatrial node.

In order to control ventricular volume and to achieve isovolumic contractions, we inserted a latex balloon into the left ventricle through the mitral valve and secured it at the apex to a large bore (0.5 mm) metal cannula used to measure left ventricular pressure within the balloon (Fig. 1). The opposite end of the balloon was tied to a small plastic disc which fitted snugly into the left ventricular outflow tract just below the aortic valve and prevented herniation of the balloon through the aortic valve. Stabilization of the disc in the outflow tract was achieved by attaching it to a polyethylene-covered guide wire which was anchored at its opposite end to the metal cannula in the balloon. A separate plastic grooved disc was sutured into the mitral annulus to prevent balloon protrusion at this point. Left ventricular Thebesian flow was drained through perforations in the mitral disc.

The intraventricular balloon was filled with saline, and volumes were varied using a calibrated syringe. The volume of the nondistended balloon was large relative to that of the left ventricular cavity, and the pressure-volume relationship of the balloon alone was determined at the conclusion of each experiment. In 7 of the 11 experiments, there was a detectable pressure (average = 2.8 mm Hg, range 1–5) attributable to the balloon alone at the largest volumes used during the experiments. Whenever it occurred, the pressure contributed by the balloon was substracted from the recorded left ventricular pressure.

Measurements. Aortic pressure (0–200 mm Hg) and left ventricular pressure (LVP, 0–40 mm Hg and 0–200 mm Hg) were measured with cannulae attached directly to Statham P23Db transducers (Statham Instruments Inc., Los Angeles, Calif.). The first derivative of LVP with respect to time (LV dp/dt) was measured with an electronic differentiator.[2] The dynamic characteristics of this instrument have been described previously (21).

Coronary blood flow minus left Thebesian flow (CBF) was measured by timed collection of the right heart drainage. The latter was sampled to provide the coronary venous O_2 content. The coronary arteriovenous oxygen difference (A-V O_2) was monitored continuously with a Guyton analyzer (22) to indicate steady-state conditions, and arterial and coronary venous blood samples

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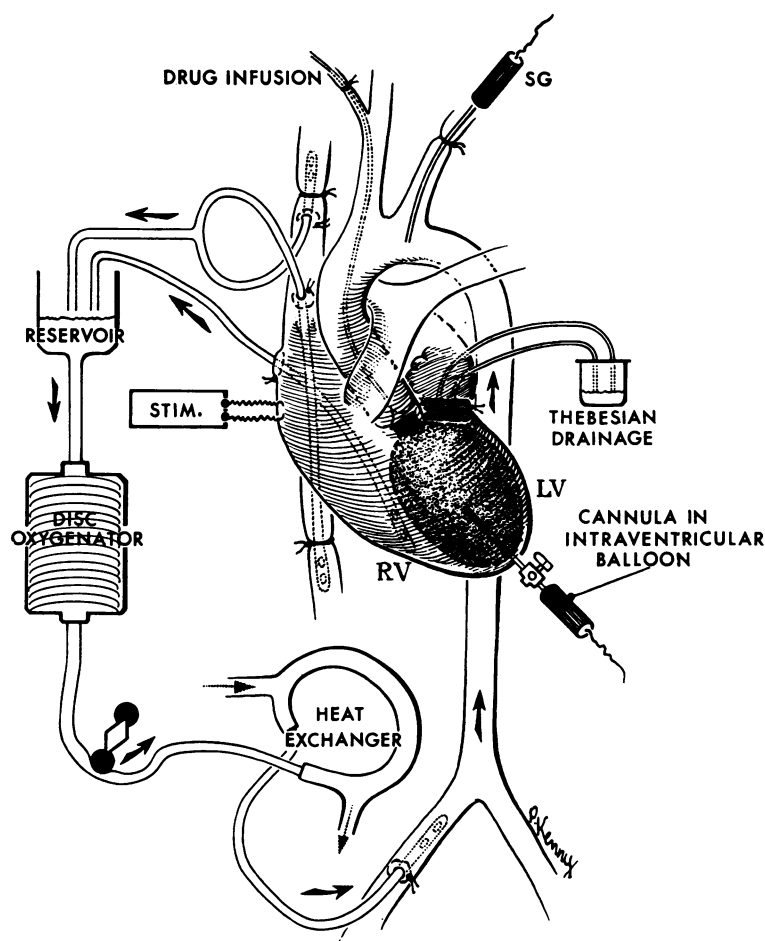[2] Electronic Gear, Inc., Valley Stream, N. Y., Model No. 5602.

were analyzed manometrically for O_2 content (23). MVo_2 was calculated as the product of CBF and the manometrically determined A-V O_2. Experiments were excluded from analysis if arterial unsaturation occurred. The right ventricle was drained by gravity and maintained in a collapsed state. Because right ventricular mechanical activity was minimal, MVo_2 was expressed as ml/min per 100 g of LV or as μl/beat per 100 g of LV. In two experiments the right coronary artery was ligated approximately 2 cm from its origin in order to investigate the possibility that the collapsed right ventricle made a variable contribution to the MVo_2 and importantly influenced the results. However, the changes in MVo_2 in these experiments were similar to those without right coronary ligation.

Myocardial wall tension $(P\pi r^2)$ [3] was monitored with an analogue computer [4] by a method described previously (11) to facilitate the matching of this variable before

[3] P = LV pressure in g/cm^2, r = internal radius in centimeters.

[4] Electronic Associates, Inc., Long Branch, N. J., Model TR 20.

and after norepinephrine. The tension, electrocardiogram, A-V O_2, LV dp/dt, LVP, and aortic pressure were recorded on a multichannel oscillograph [5] at paper speeds of 100 mm/sec. A more definitive estimate of wall force normalized for wall thickness (stress) was calculated at the conclusion of the experiment, as described below.

Experimental protocol. MVo_2 was first measured at varying levels of PDT achieved by varying ventricular volume at the same contractile state. Thereafter norepinephrine (0.76–7.6 μg/min) was infused at a constant rate into the ascending aorta just above the aortic valve (Fig. 1). When a steady state of increased contractility was attained, as evidenced by a stable peak LVP and LV dp/dt, the volume of the LV balloon was decreased in order to match the monitored PDT of each of the prenorepinephrine controls, and MVo_2 was redetermined. Whenever PDT was not returned to the exact control level, the effect on MVo_2 of changing contractility was determined by extrapolation to the appropriate value of PDT, as shown in Fig. 4. In one experiment three separate states of contractility were produced by varying

[5] Sanborn Co., Waltham, Mass., Model No. 350.

Control of Myocardial Oxygen Consumption 377

norepinephrine concentrations while maintaining PDT relatively constant. This procedure was then repeated at a different level of PDT.

In 6 of the 11 dogs, MVo$_2$ was determined at the conclusion of the experiment after the intraventricular balloon had been emptied and the heart had been arrested with 15% potassium chloride. After the conclusion of all experiments, the weight of the LV including the intraventricular septum was determined after the right ventricle and atria had been removed. This value was used to express MVo$_2$/100 g of LV and to derive LV muscle volume for use in the calculations.

Calculations

The following calculations were performed utilizing a digital computer with manual conversion of LVP, LV dp/dt, end-diastolic volume, and LV muscle volume from analog to digital form. Stress, velocity, and power were derived at 10-msec intervals throughout three representative contractions for each experimental state. The three contractions were analyzed in order to obtain a large number of data points on the stress-velocity curves and thus achieve a more accurate estimation of V$_{max}$.

Mean wall stress. Wall stress in g/cm^2 was calculated as Pr/2h where P = intraventricular pressure in g/cm^2, r = internal radius in centimeters, assuming a spherical ventricle, and h = wall thickness in centimeters derived from internal volume and muscle volume. The details of this calculation have been discussed previously (11). Stress was chosen as the force parameter for analysis in an attempt to normalize for the cross-sectional area of the muscle producing the force. PDT was defined as peak tension minus one-half of the resting tension (RT) (11). Total developed tension (TDT) was defined as the area under the developed tension-time curve and was calculated as $^b\int_a$ (T) dt − (RT)/2 (n), where a = onset of systole, b = the point at which tension falls to the level of resting tension, and n = the number of 10-msec intervals over which the integration was performed. The definition of peak developed tension was designed to provide some consideration of the progressive unloading of the parallel elastic components (PEC) during fiber shortening that is predicted by the three-component muscle model. Since in this model resting tension is borne partially or entirely by the PEC, during shortening, resting tension must be transferred progressively to the contractile elements (CE) and series elastic components (SEC). In cardiac muscle, when resting tensions are high, the magnitude of this transfer of load during systole can be quite large. Since in the intact heart the PEC stiffness and the distribution of resting tension between PEC and SEC are unknown, the assumption was made that at peak tension one-half of the resting tension had been transferred to the contractile system.

Contractile element velocity (V$_{CE}$). In an isovolumic contraction, V$_{CE}$ is equal to the rate of lengthening of the series elastic components (SEC) of the myocardium. This rate of series elastic lengthening (V$_{SE}$) is directly proportional to the rate of stress development (dT/dt) and inversely related to the stiffness of the SEC, (dT/dl). This relationship then can be written as: V$_{CE}$ = V$_{SE}$ = dl/dt = (dT/dt)/(dT/dl), where dT/dt = the derivative of Pr/2h with respect to time and dT/dl = 28T. In this form V$_{CE}$ is given in muscle lengths or circumferences per second and can be converted to centimeters per second by multiplying by the instantaneous circumference (24). V$_{max}$ was determined by extrapolation of V$_{CE}$ to zero load when V$_{CE}$ (cm/sec) was plotted as a function of stress, Pr/2h. Also, V$_{max}$ was determined by the Hill equation (25); the values of tension and velocity at three separate points on the force-velocity curve, excluding P$_0$, were used to solve the Hill equation (P + a) (V + b) = K, where P = force and V = velocity, and the simultaneous equations were solved for V$_{max}$, i.e., the point on the curve at which P equals zero. Although similar results were obtained by extrapolation and algebraic solution, it is recognized that neither approach provides an absolute measurement of V$_{max}$.

The extent of contractile element (CE) shortening per beat was calculated as $^c\int_a$ (V$_{CE}$) dt where c = peak tension, the point at which CE shortening ceases in an isovolumic contraction.

Contractile element work (CEW). During isovolumic contraction, CEW was calculated as $^b\int_a$ (T) (V$_{CE}$) dt. CEW was calculated both with T determined as Pr/2h and as (Pπr$_2$) (14). The results were directionally similar with either calculation, and only the CEW using Pr/2h is presented in the results section.

RESULTS

MVo$_2$ always increased, both when PDT was increased at a constant V$_{max}$ and when V$_{max}$ was increased at a constant PDT. In 15 observations on 11 dogs MVo$_2$ increased from an average of 41.5 ± 2.2 (SE) to 49.0 ± 2.4 µl/beat per 100 g of LV (+18%) when PDT was increased from an average of 49.7 ± 5.0 to 80.2 ± 5.7 g/cm^2 (+60%) by increasing ventricular volume (Table I). With this increase in PDT, total developed tension increased to an even greater extent, from 9.0 ± 1.1 to 15.9 ± 2.9 g/sec per cm^2 (+76%). The increase in MVo$_2$ was characterized by a significant increase in both coronary blood flow and coronary A-V O$_2$ difference.

In 22 observations on 11 dogs MVo$_2$ increased from an average of 40.7 ± 2.7 to 57.0 ± 3.5 µl/beat per 100 g of LV (+40%) when V$_{max}$ was increased from an average of 41.8 ± 2.4 to 54.6 ± 2.9 cm/sec (+31%) (Table II). This increase in MVo$_2$ occurred despite a constant level of PDT and a 21% *decrease* in total developed tension. Again, this change in MVo$_2$ was achieved with both an increase in coronary flow and a widening of the A-V O$_2$ difference.

TABLE I

Effect of MV̇O2 of Increasing Tension at a Constant V_{max}

	Control	Increased volume
LVEDP, mm Hg	3.3 ±0.6	5.8 ±066*
LV vol, ml	19 ±1	24 ±1*
MAP, mm Hg	81 ±4	81 ±4‡
Flow, ml/min per kg	114 ±5	114 ±5‡
Peak LVP, mm Hg	69 ±6	97 ±6*
Max dp/dt, mm Hg per sec	894 ±84	1189 ±78*
PDT, g/cm² per beat	49.7 ±5.0	80.2 ±5.7*
TDT, g-sec/cm² per beat	9.0 ±1.1	15.9 ±2.9*
TPT, sec	0.130 ±0.003	0.135 ±0.003‡
CEW, g-m/beat	27.0 ±2.9	44.3 ±3.0*
ΔLCE, cm/beat	1.50 ±0.03	1.48 ±0.02‡
CBF, ml/min	134 ±10	142 ±10*
A-V O₂, vol %	5.1 ±0.02	5.7 ±0.2*
MV̇O₂, µl/beat per 100 g of LV	41.5 ±2.2	49.0 ±2.4*

LVEDP, left ventricular end-diastolic pressure; LV vol, left ventricular volume; MAP, mean aortic pressure; flow, systemic flow; peak LVP, peak left ventricular pressure; max dp/dt, maximum rate of rise of LVP; PDT, peak developed tension; TDT, total developed tension; TPT, time from onset of contraction to peak tension; CEW, contractile element work; ΔLCE, extent of contractile element shortening; CBF coronary blood flow; A-V O₂, coronary arteriovenous oxygen difference; MV̇O₂, myocardial oxygen consumption. Data represent mean values ± SE for 15 observations in 11 dogs.

* P < 0.001 Student's t test for paried differences.

‡ Not significant.

TABLE II

Effect on MV̇O2 of Increasing V_{max} at a Constant Peak Developed Tension

	Control	Norepinephrine
LVEDP, mm Hg	4.9 ±0.6	1.1 ±0.4*
LV vol, ml	22 ±1	15 ±1*
MAP, mm Hg	78 ±5	78 ±5‡
Flow, ml/min per kg	105 ±10	100 ±10‡
Peak LVP, mm Hg	80 ±6	95 ±8*
Max dp/dt, mm Hg/sec	1006 ±76	1622 ±143*
TDT, g-sec/cm²	12.9 ±2.2	10.2 ±2.2*
TPT, sec	0.123 ±0.006	0.106 ±0.006*
Vmax, cm/sec	41.8 ±2.4	54.6 ±2.9*
CEW, g-cm/beat	38.0 ±2.5	37.5 ±2.2‡
ΔLCE, cm/beat	1.43 ±0.06	1.68 ±0.06*
CBF, ml/min	133 ±9	156 ±10*
A-V O₂, vol %	4.8 ±0.3	5.8 ±0.3*
MV̇O₂, µl/beat per 100 g of LV	40.7 ±2.7	57.0 ±3.5*

LVEDP, left ventricular end-diastolic pressure; LV vol, left ventricular volume; MAP, mean aortic pressure; flow, systemic flow; peak LVP, peak left ventricular pressure; max dp/dt, maximum rate of rise of LVP; TDT, total developed tension; TPT, time from onset of contraction to peak tension; Vmax, extrapolated velocity at zero tension; CEW-contractile element work; ΔLCE, extent of contractile element shortening; CBF, coronary blood flow; A-V O₂, coronary arteriovenous oxygen difference; MV̇O₂, myocardial oxygen consumption. Data represent mean value ± SE for 22 observations in 11 dogs.

* P < 0.001 Student's t test for paired differences.

‡ Not significant.

When PDT was increased at a constant V_{max}, the calculated extent of contractile element shortening (ΔLCE) did not change significantly. However, when V_{max} was increased at a constant PDT, the calculated ΔLCE showed an average increase from 1.43 ± 0.06 to 1.68 ± 0.06 cm/beat. (Table II). CEW increased when PDT was raised at a constant V_{max} (Table I) but was not significantly
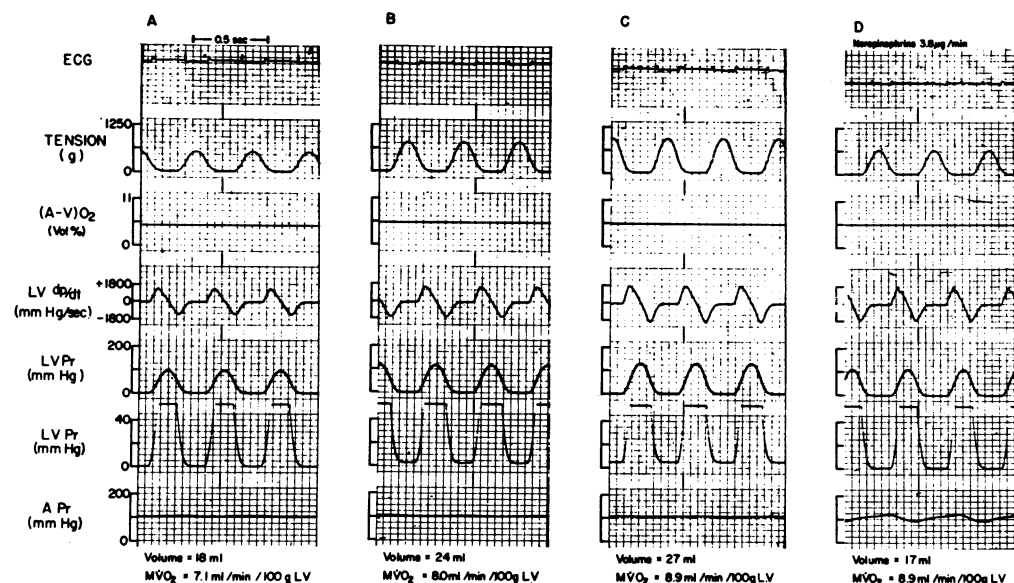

FIGURE 2 The effects of increasing ventricular volume and developed tension (A, B, and C) and the infusion of norepinephrine (D) on hemodynamics and MVo₂ in experiment No. 4. ECG, electrocardiogram; tension = Pπr²; A-V O₂, coronary arteriovenous oxygen difference; LV dp/dt, the rate of left ventricular pressure development; LV Pr, left ventricular pressure; A Pr, aortic pressure.

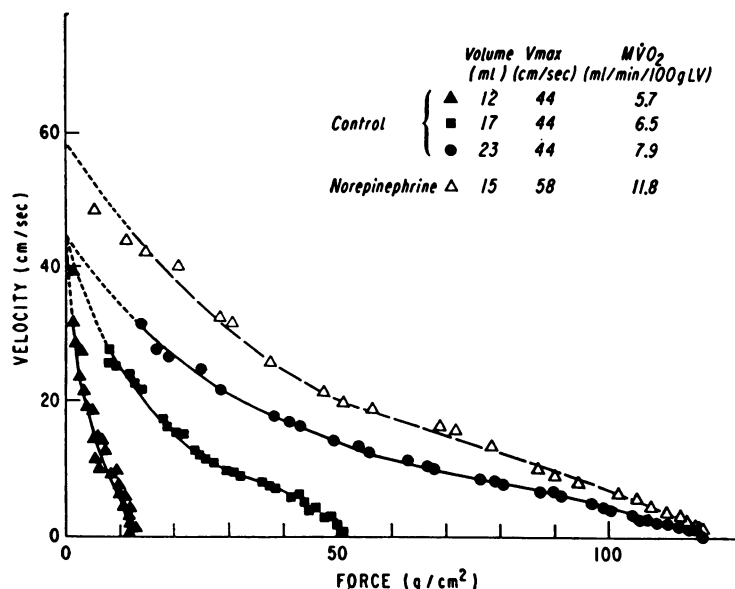|	Volume (ml)	Vmax (cm/sec)	$M\dot{V}O_2$ (ml/min/100g LV)
Control ▲	12	44	5.7
■	17	44	6.5
●	23	44	7.9
Norepinephrine △	15	58	11.8

FIGURE 3 Left ventricular contractile element force-velocity relationships in experiment 8. Velocity = contractile element velocity; force = force/unit area $(Pr/2h)$. V_{max} = intercept on the ordinate. Closed symbols = effects of varying ventricular volume at a constant V_{max}; open symbols = effect of increasing V_{max} with norepinephrine. Values of V_{max} are estimates and not absolute values. (See Results).

altered when V_{max} was increased at a constant PDT due to the decrease in total developed tension (Table II).

In Fig. 2, tracings from one experiment are illustrated. In panels A, B, and C, ventricular volume was increased at a constant V_{max}, and as a consequence LV end-diastolic pressure, peak LVP, peak LV dp/dt, and wall tension $(P\pi r^2)$ all increased progressively, along with $M\dot{V}O_2$. During norepinephrine infusion, contractility increased, and in order to achieve a level of PDT in the range of that observed during the control period, ventricular volume was decreased by re-

moving saline from the intraventricular balloon. At this point (panel D), $M\dot{V}O_2$ was 8.9 ml/min per 100 g of LV, and, when compared to the control state at a similar PDT (a tension midway between that shown in panels A and B), $M\dot{V}O_2$ had increased by 1.6 ml/min per 100 g of LV (+21%).

The results from another experiment are shown in Fig. 3 in the form of the left ventricular contractile element force-velocity relationships of representative contractions. The three curves with solid symbols represent three control states in which PDT was increased by increasing ventricu-
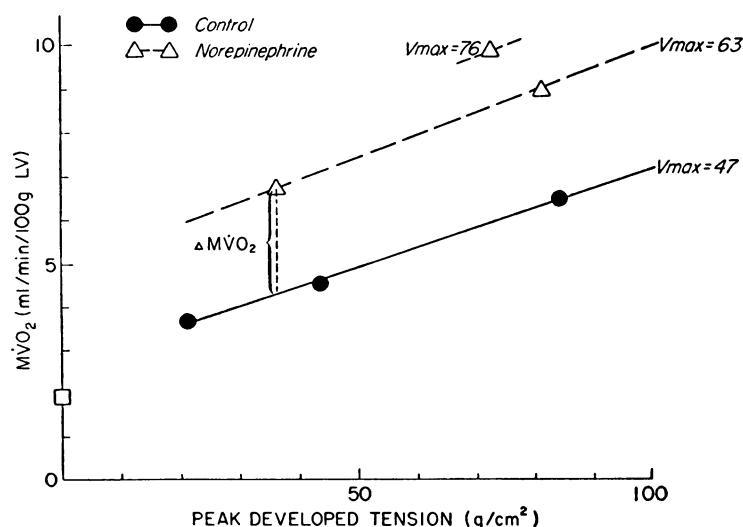

FIGURE 4 $M\dot{V}O_2$ as a function of peak developed tension in experiment 7. Closed circles = increasing tension at a constant V_{max}; open triangles = observations during norepinephrine infusion; open square = $M\dot{V}O_2$ with potassium chloride arrest. The change in $M\dot{V}O_2$ ($\Delta M\dot{V}O_2$) with norepinephrine at a constant tension was obtained by interpolation when tension was not precisely matched, as illustrated here by the dotted vertical line.
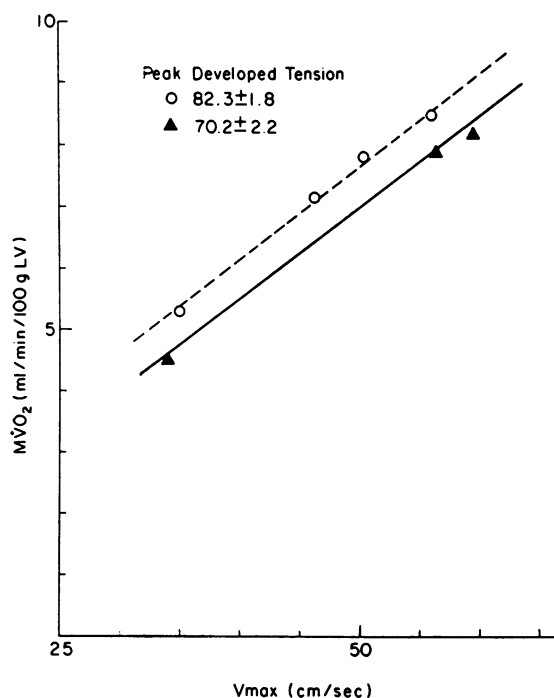
Peak Developed Tension
O 82.3±1.8
▲ 70.2±2.2

FIGURE 5   MVo$_2$ as a function of V$_{max}$ in experiment 11.

0.24 ml/min per 100 g of LV and was always lower than the MVo$_2$ extrapolated to a PDT of zero, as illustrated here.

In Fig. 5, MVo$_2$ is plotted as a function of V$_{max}$ at two distinct levels of PDT in the experiment in which V$_{max}$ was changed by varying the rate of norepinephrine infusion while maintaining PDT constant. A linear increase in MVo$_2$ with increasing contractility at constant levels of wall tension is apparent.

The data are summarized in Fig. 6 both graphically and by the equation: MVo$_2$ = K + 0.25 PDT + 1.43 V$_{max}$. This equation was obtained by multiple regression analyses of the data obtained in 7 of the 11 experiments. These seven experiments were chosen for these analyses because they had at least two values of MVo$_2$ for changes in PDT at a constant V$_{max}$ and at least two values of MVo$_2$ for changes in V$_{max}$ at a constant PDT.

lar volume. The extrapolated velocity intercept of these curves at zero tension (V$_{max}$) was unchanged with this intervention, indicating that the contractile state was unchanged. The intercept on the abscissa, i.e. peak tension, however, was increased, and MVo$_2$ changed directionally with this variable. In contrast, V$_{max}$ was clearly increased during norepinephrine infusion (open triangles), signifying an augmentation of contractility, and LV volume was reduced to match the highest tension existing before norepinephrine infusion. With this increase in V$_{max}$, MVo$_2$ rose substantially.

MVo$_2$, plotted as a function of PDT, for another experiment, is shown in Fig. 4. The solid line illustrates the linear increase in MVo$_2$ as PDT was increased at a constant V$_{max}$. The broken line demonstrates the upward shift of the PDT-MVo$_2$ relationship when V$_{max}$ was increased. The open triangle lying above the broken line was obtained with further increases in V$_{max}$ and MVo$_2$ produced by increasing the norepinephrine infusion rate. The open square on the ordinate represents MVo$_2$ after cardiac arrest with potassium chloride. MVo$_2$ determined after potassium chloride arrest in six dogs averaged 1.43 ±
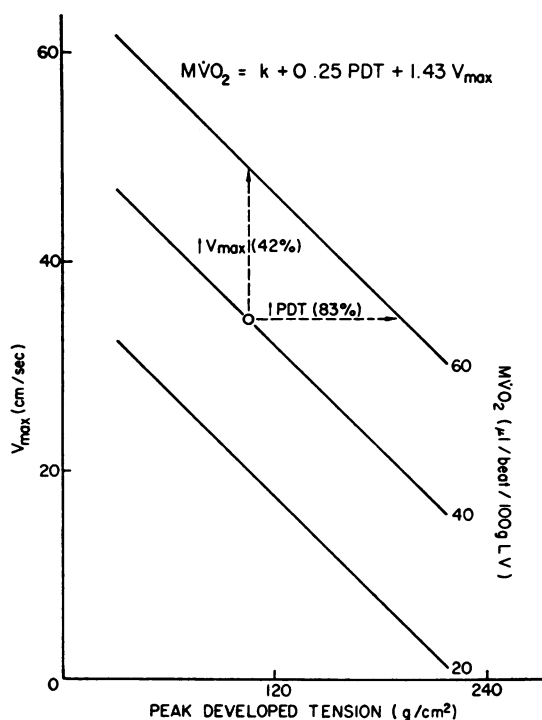

FIGURE 6   MVo$_2$ isopleths as a function of V$_{max}$ and peak developed tension. Isopleths were calculated from the equation at the top of the figure which was derived by multiple regression analysis. Coefficient of PDT = 0.25 ± 0.04 (SE), coefficient of V$_{max}$ = 1.43 ± 0.15, r = 0.99. Broken lines = effect on MVo$_2$ of hypothetical increases in PDT at a constant V$_{max}$ (horizontal line) and in V$_{max}$ at a constant PDT (vertical line).

The coefficients of PDT and V_{max} in this equation are average values for the multiple regression analysis performed in each of the seven animals. The three diagonal parallel lines are MVo_2 isopleths calculated from the multiple regression equation. The broken lines in the center of the figure illustrate the increases in PDT and V_{max} required to increase MVo_2 by 50%, from 40 to 60 μl/beat per 100 g. These particular changes in PDT, V_{max}, and MVo_2 were chosen for illustrative purposes because they are in the physiological range.

DISCUSSION

The major objective of the present investigation was to determine, in the same heart, the relative influences of changes in the contractile state and in tension development on MVo_2. It was observed that elevations of both of these variables are associated with comparable increases in energy utilization. Moreover, the increase in MVo_2 with increased contractility occurred under conditions in which peak developed tension and contractile element work remained constant, and total developed tension actually decreased. These results serve to quantify and to place into perspective previous investigations showing increases in MVo_2 with increases in contractility produced by sympathetic nerve stimulation or excitement (13), isoproterenol (14), norepinephrine (15, 17), cardiac glycosides (16–18), Ca^{++} (15), and paired electrical stimulation (15). It has also been reported that increases in contractility produced by cardiac glycosides (26), norepinephrine (27), and Ca^{++} (28) do not always augment MVo_2. However, in those investigations ventricular volume always declined as cardiac contractility was augmented, and tension development undoubtedly fell as well. From the present investigation in which ventricular volume and tension could be controlled, it seems clear that simultaneous, opposite changes in tension and contractility would tend to cancel out any alteration of MVo_2, and these findings can explain the reported absence of elevations of MVo_2 with augmentation of contractility (26–28).

Although the assumptions involved in the calculations of stress and velocity utilized in this study have been discussed previously (11), certain aspects deserve consideration here. The assumption of a spherical left ventricle with varying ventricular volume undoubtedly involves some error, since the larger the chamber the more spherical its shape. A spherical model, in contrast to an ellipsoidal one, underestimates total wall force (29), and tension may actually have been greater with norepinephrine in the smaller, more ellipsoidal heart than was calculated. We have investigated this problem by means of cineangiocardiography in dogs in which ventricular volumes were varied by blood infusion. With the largest change in the left ventricular major/minor semi-axis ratio which occurred (2.1 : 1–1.4 : 1), the error in tension estimation using a spherical model was found to approximate 5% (11). Thus, even if this large change in the shape of the left ventricle did occur in the course of the present experiments, the resultant error in the calculation of tension could not conceivably account for the reported relations among developed tension, contractility, and MVo_2.

Peak developed tension was defined as the difference between peak tension and one-half of the resting tension in order to take into account the progressive unloading of the parallel elastic elements during contraction (30). The precise distribution of resting tension between the parallel and series elastic components is unknown, and thus the exact contribution of the parallel elastic component to the development of tension cannot be calculated. However, the possible error introduced by this consideration is small, since resting tension constituted such a small fraction of peak tension.

The value used for series elastic stiffness in these experiments (28T) was originally derived from experiments in isolated cat papillary muscles (31), and a similar value has been found recently in the intact dog heart by the quick-release method (32). Furthermore, norepinephrine does not appear to alter series elasticity either in papillary muscle (33) or in the intact heart (32), a consideration of importance in the interpretation of the present results.

This investigation was carried out in an isovolumetric preparation in order to obviate any large alterations in the extent of shortening of the myocardial fibers and contractile elements. It is widely recognized, however, that isovolumetric contractions are not isometric, since shape changes do occur in the course of contraction. However, since the changes in ventricular volume in the course of any

experiment were relatively small, it is unlikely that changes in the extent of fiber shortening could have affected the results materially. The calculated extent of contractile element shortening did increase slightly during norepinephrine infusion. However, since large changes in fiber shortening and therefore contractile element shortening exert only a small effect on MVo_2 (10), the small increase in contractile element shortening which occurred in these experiments could not have affected the results substantially.

The possibility must also be considered that the increase in MVo_2 observed when V_{max} was elevated by norepinephrine resulted largely from a direct metabolic effect of the catecholamine, independent of any effect on the mechanics of contraction. However, this possibility is unlikely since it has been shown that much larger doses of norepinephrine administered to potassium-arrested hearts resulted in far smaller increments of MVo_2 than those observed in the present study (34). Furthermore, it has been shown that when velocity of left ventricular ejection and of pressure development were elevated to comparable levels by norepinephrine and sustained postextrasystolic potentiation, the elevations of MVo_2 were similar (15). This finding suggests that the alterations in myocardial contractility produced by norepinephrine were principally responsible for the stimulation of MVo_2.

In a comprehensive evaluation of the determinants of the MVo_2, factors other than wall tension and contractility must be considered. A formulation which considers the available experimental findings would indicate that at least five factors influence MVo_2. These factors include basal O_2, activation O_2, tension development O_2, external work, i.e. (tension $\times$ shortening) O_2, and contractile state O_2. The first term, the basal O_2, is known and makes up a small proportion of the total MVo_2 of the in situ heart. In the present experiments basal MVo_2 was estimated in hearts arrested with potassium chloride, and it averaged 1.43 ml/min per 100 g, a value similar to those which have been found previously, both with hearts arrested with potassium excess (34–37) and with calcium deficiency (37, 38). The resting, or basal O_2, may be increased slightly with increasing levels of catecholamines (34, 39–42).

The activation energy is a complex term and was defined by Hill in skeletal muscle as resulting from "a 'triggered' reaction setting the muscle in a state in which it can shorten and do work" (43). The activation O_2 of cardiac muscle might be considered to be made up of three components: electrical activation, contractile site activation and deactivation, and the maintenance of the active state. The O_2 cost of electrical activation has been measured in the nonbeating, dog heart and was found to be quite small (38), probably less than 1% of the total MVo_2 of the resting unanesthetized dog (44). Since no mechanical activity took place in the nonbeating heart (38), this electrical activation presumably did not result in the activation of contractile sites on the myofilaments. In present theories of muscle contraction (45, 46), repetitive reactions at these sites occur when Ca^{++} becomes available to them, and it is likely that after each contraction energy is required for the rebinding of Ca^{++}, which is necessary for relaxation (46). It has recently been found that activation heat in frog sartorius muscle is independent of length and temperature but is increased by agents that prolong the duration of the active state (47). However, the energy associated with increasing the duration of the active state in cardiac muscle is not known. Although activation energy has not been quantified in the intact heart, it has been estimated, in isometrically contracting, isolated papillary muscle, from heat measurements (48) as well as from high energy phosphate determinations (49) and is probably only a small fraction of the total energy requirements. Whether or not this fraction is altered by inotropic influences in cardiac muscle remains unknown.

It seems established that the major determinants of MVo_2 relate to the mechanical aspects of contraction. The O_2 utilization associated with stress or tension development in these experiments agreed closely with that found previously. By recalculating the data of Monroe and French (6) and of McDonald, Taylor, and Cingolani (8), coefficients of PDT ($MVo_2 = k$ PDT) of 0.26 and 0.21, respectively, were found, values similar to those found in this study (average 0.25, Fig. 6). The work of Monroe (50), demonstrating that over 90% of the MVo_2 was accounted for by the time peak tension was reached, serves to emphasize the major energetic importance of tension development in contrast to the total developed tension (TDT), i.e., the area under the tension-time curve. Accordingly, in the present study, peak

developed tension rather than total developed tension was held constant when V_{max} was altered.

With the Hill muscle model (25), tension development results from the work performed by the contractile elements in stretching the series elastic component, and in isometric contractions, CEW and PDT are directly proportional to one another and to $M\dot{V}o_2$. The work performed by the contractile elements in shortening the myocardial fibers has recently been found to be associated with considerably lower energy costs than the work performed in developing tension, i.e., in stretching the series elastic component (11, 12). Further evidence that CEW, as presently calculated (9), is not the major factor determining $M\dot{V}o_2$ is provided by the present experiments in which V_{max} was altered at a constant PDT, CEW remained unchanged, and $M\dot{V}o_2$ was altered markedly.

In conclusion, the data presented herein indicate that both developed tension and contractile state are significant factors in the regulation of $M\dot{V}o_2$. Furthermore, a comparative analysis of the effect of altering these two factors demonstrates that the effect on oxygen utilization of changes in contractility is substantial and similar in magnitude to the effect of altering tension development. From the current state of knowledge of myocardial energetics, the major determinants of the $M\dot{V}o_2$ may best be expressed in terms of tension development and contractile state. The basal O_2 requirements, the activation energy, and the cost of contractile element shortening against a load would appear to make relatively smaller contributions than do tension development and contractile state.

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