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Influence of ventricular contractility on non-work-related myocardial oxygen consumption

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Summary. The relationship between myocardial oxygen consumption (MVO_2) and the total pressure-volume area (PVA), which represents the total mechanical work performed during a cardiac cycle, has been shown to be linear and independent of loading conditions: $MVO_2 = a\text{PVA} + b$. When inotropic state is enhanced, the MVO_2-PVA relation shifts upward (increase in b), and when inotropic state is depressed the relation shifts downward (decrease in b). However, the *quantitative* relationship between contractility and b (the non-work-related myocardial oxygen consumption) determined over a wide range of contractilities is not known. In seven isolated blood perfused canine hearts, left ventricular (LV) contractility was increased by dobutamine and decreased with nifedipine or reduction of coronary blood flow. At each level of contractility, the end-systolic pressure-volume relationship (ESPVR) and the MVO_2-PVA relation were determined. For each heart, the resulting values of b (ml O_2/beat) were plotted as a function of E_{max} (mmHg/ml), an index of contractility defined as the slope of the ESPVR. There was a linear relation between Emax and b over a wide range of contractilities; on average, b (ml O_2/beat) = 0.0036 E_{max} (mmHg/ml) + 0.0101 [r = 0.929–0.978 (95% confidence interval)], when E_{max} was varied over an average range of 2.8–9.6 mmHg/ml. These results suggest a common underlying determinant of contractility and non-work-related oxygen consumption.

Key words: End-systolic pressure-volume relationship – Ventricular efficiency – MVO_2-PVA relationship – Metabolism

Suga and colleagues have shown that at a given contractility myocardial oxygen consumption per beat (MVO_2) is linearly related to the "pressure-volume area" (PVA): $MVO_2 = a\text{PVA} + b$ [1, 2]. PVA is considered to represent the total mechanical energy generated by the ventricle and is defined on the ventricular pressure-volume plane as the area contained within the end-systolic pressure-volume relationship, the end-diastolic pressure-volume relationship, and the systolic portion of the ventricular pressure-volume trajectory. The intercept of the MVO_2-PVA relationship b reflects the myocardial oxygen consumption when the heart is not generating any mechanical energy. Thus, b should represent the sum of the basal energy requirements and the energy required for excitation-contraction (e-c) coupling [3]. The slope a reflects inversely the efficiency with which oxygen is utilized to generate mechanical energy [4–6].

Alterations in contractility, in large part, parallel alterations in the amount of Ca^{2+} released to the myofilaments per beat [7]. Such variations in Ca^{2+} release would consequently alter the energy required for sequestration of Ca^{2+} by the Ca^{2+}-ATPase of sarcoplasmic reticulum [8]. Thus, based upon previous studies at the cellular level and the considerations presented above, one would anticipate a tight covariation between contractility and non-work-related O_2 consumption (b). This prediction has only been examined to a limited extent in previous studies. The contractility index E_{max}[9] and b covaried in the same direction when E_{max} was either enhanced [5] or depressed [10]. The scope of previous studies was limited because enhancement and depression of contractility were never studied in the same hearts.

The purpose of the present study, therefore, was to determine quantitatively the interrelation between contractility and non-work-related oxygen consumption at the ventricular level. This was

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accomplished by determining the dependence of *b* on E_{max} with both enhancement and depression of contractility in the same heart accomplished by different inotropic agents. Studies were performed on isolated canine hearts using dobutamine, nifedipine, and reduction of coronary blood flow to alter the contractile state. The results reveal that within a given heart, the relationship between *b* and E_{max} is linear over a wide range of contractile states.

A preliminary report of some of these results has already appeared [11].

Methods

Surgical preparation

A total of seven isolated canine hearts were studied. The procedures used to isolate and support the canine heart were similar to those described previously [9]. A pair of mongrel dogs were anesthetized with sodium pentobarbital (30 mg/kg i.v.). The femoral arteries and veins of one dog (support dog) were cannulated and connected to a perfusion system that was used to supply oxygenated blood to the isolated heart. The chest of the second dog (donor dog) was opened under artificial respiration and the heart removed while metabolically supported by arterial flow from the support dog. The left and right atria were opened, and all the chordae tendineae were freed from the mitral valve leaflets. A metal adapter that held the isolated heart to a ventricular volume servopump system was sutured to the mitral ring [12]. When the surgical preparation was complete, a water-filled latex balloon connected to the servopump system was placed inside the left ventricular cavity. Ventricular volume could be measured and controlled by the servopump as described previously.

Coronary artery blood flow was regulated by a pulsatile pump, which controlled the flow rate of arterial blood from the support dog. To determine blood flow to the left ventricular muscle, the coronary sinus was cannulated and *outflow* measured by an electromagnetic flow meter; with this measurement, we neglect the small amount of blood draining directly into the cardiac chambers (i.e., the Thebesian flow). From this point on, we will refer to this coronary sinus outflow as "coronary blood flow" (CBF). The difference in oxygen content between arterial and coronary venous blood (A-V O_2) was measured continuously by absorption spectrophotometry [13]. The arterial pH, PO_2, and PCO_2 were measured periodically during each experiment to ensure near 100% O_2 saturation of the arterial blood during the periods of data collection.

The temperature of the perfusate was maintained at approximately 37°C by a heat exchanger. Pacing electrodes were sutured to atrial tissue to control heart rate at a constant level between 100 and 130 beats/min.

Protocol

All studies were performed with the hearts constrained to contract isovolumically. Our goal was to make measurements of ESPVRs and MVO_2-PVA relations at as many different contractile states as possible in each heart. To accomplish this, we took advantage of the fact that both the ESPVR and the MVO_2-PVA relation have been shown to be represented well by linear relations over a fairly wide range of contractile states and over a reasonably broad range of ventricular volumes and pressures [9]. Thus, to save time, because of the known limited duration of viability of our preparation (approximately 4–5 h), we recorded data only at two volume settings at each contractile state—one very low (approximately 10 ml) and one relatively high volume (approximately 30–40 ml). After recording such data under one set of conditions, contractility was altered by infusion of dobutamine, nifedipine, or by reducing CBF, and the measurements were repeated at roughly the same volumes.

Measurements were made during infusion of several different doses of each drug so that a wide range of contractilities was created. The drug doses were titrated to produce desired changes in contractile state, and these doses varied from one heart to the next. CBF was not reduced to less than 30% of control, since below this level it is not possible to attain a steady mechanical state for any period of time. Furthermore, periods of reduced CBF were limited to less than 20 min. Before switching from one inotropic intervention to another, the heart was allowed to return to control conditions, at which time measurements were made so that baseline stability of the preparation could be assessed.

In general, it was not possible to examine all of the different inotropic interventions in each heart studied. Dobutamine was tested in six hearts, nifedipine in five, and reduced coronary blood flow in six.

Data analysis

All data were recorded on an eight-channel pen recorder (Gould) and digitized at a sampling rate of 200 Hz. Data analysis was performed off-line by computer. The data were analyzed for end-systolic pressure (P_{es}), end-diastolic pressure (P_{ed}), left ventricular volume (LVV), mean CBF, and A-V O_2 difference. Several parameters were then determined as follows. The slope (E_{max}) and volume-axis intercept (V_0) of the ESPVR were determined from a straight line passed through the two end-systolic pressure and volume points measured at each contractile state. Oxygen consumption (MVO_2) was calculated as the product of coronary blood flow and A-V O_2 difference and was expressed on a per beat basis. The pressure-volume area (PVA) on each of the isovolumic beats was estimated as:

$$PVA = [LVV\text{-}V_0][P_{es}\text{-}P_{ed}]/2.$$

MVO_2 was plotted as a function of PVA for the high and low volume settings at each contractility, and the slope (*a*) and intercept (*b*) of the relation between these two were determined from a straight line passed through the two points (i.e., $MVO_2 = aPVA + b$).

After performing the analysis outlined above, we assessed the interrelation between contractile state and non-work-related oxygen consumption by plotting *b* (the zero-work MVO_2) as a function of E_{max}, the slope of the ESPVR. Both E_{max} and *b* were normalized to account for left ventricular mass to a standard of 100 g; the normalized indices will be referred to as E^n_{max} and b^n, respectively. These interrelations were then quantified by linear regression analysis applied to the data in each heart separately.

Results

Original experimental recordings of left ventricular pressure (LVP), LVV, CBF, arterial-venous oxygen content difference (A-V O_2), and coronary perfusion pressure (CPP) obtained from a single canine heart at two different contractile states are shown in Fig. 1. These recordings serve to illustrate the experimental protocol. The recordings in the panel on the

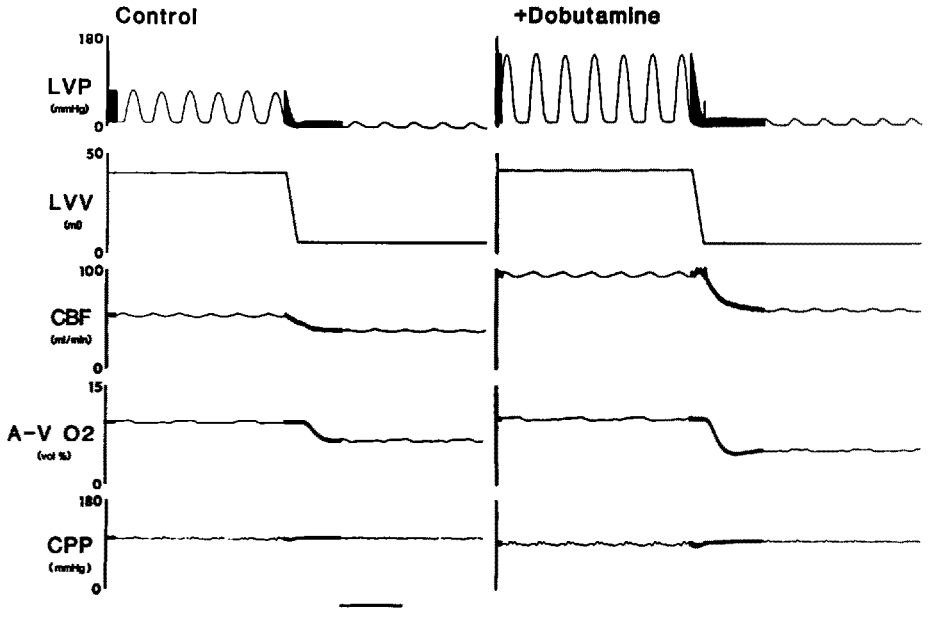

Fig. 1. Original experimental recordings of left ventricular pressure (*LVP*), LV volume (*LVV*), coronary blood flow (*CBF*), arterial-venous oxygen content difference ($A\text{-}V\ O_2$), and coronary perfusion pressure (*CPP*). Data are taken from one experiment under control conditions and after the administration of dobutamine at one level. *Horizontal calibration bar* corresponds to 1 s. Slight delays in the change of A-V O_2 signals with respect to changes in LVV are due to the dead volume of tubing connecting the spectrophotometer to the preparation

left were obtained under control conditions. Initially, ventricular volume was at a high level (40 ml). After recording several beats, the ventricular volume was reduced over about 30 s to a low value (5 ml in this example). Enough time was allowed after the volume reduction for all the signals to attain a steady state, which usually took several minutes. After reaching the new steady state, data were recorded at the low volume. In the next experimental run (right panel in Fig. 1), volume was restored to its high value and dobutamine was administered at a rate adjusted to enhance peak isovolumic pressure by approximately 100%. As can be seen, at a constant perfusion pressure, both A-V O_2 and CBF are increased at this enhanced contractile state, indicating an increased rate of myocardial oxygen consumption. Data collection was repeated in the manner described above at this enhanced contractile state. This sequence was subsequently repeated at several contractile states.

Examples of ESPVRs and MVO_2-PVA relations obtained from a single canine heart are shown in Fig. 2. In Fig. 2a, we present ESPVRs obtained under control conditions with the administration of dobutamine at two different infusion rates, and with the administration of nifedipine at three different infusion rates. Data from other *control* runs have been omitted for clarity in Fig. 2a, b. Compared with the control ESPVRs, those measured following the adminstration of dobutamine show an increase in slope (E_{max}) with relatively little change in volume axis intercept (V_0). The ESPVRs measured following nifedipine administration have slopes which are less than those of the control, but with essentially the same volume-axis intercepts. The corresponding MVO_2-PVA relations for the data in Fig. 2a are presented in Fig. 2b. Consistent with previous studies, MVO_2-PVA relations measured during dobutamine infusion demonstrate a roughly parallel upward shift (increase in b) relative to the control relation, and those measured following nifedipine infusion show a roughly parallel downward shift (decrease in b). The greater the change in contractility created by drug infusion, the greater the change in the intercept. In Fig. 2c, we summarize the data by plotting b^n as a function of E^n_{max} (where the superscript "n" indicates variables normalized for a 100-g ventricle) for each contractile state studied in this heart. In addition to the nifedipine and dobutamine data, we have also included data obtained with the reduction of CBF to two levels and additional control runs. These points fall along the line defined by the other data points. In this heart, E^n_{max} was varied from approximately 2.5 to 12 mmHg/ml. The E_{max}-b relationship was well represented by a linear relation—$b^n = 0.0028\ E^n_{max} + 0.0079$ (both b and E_{max} normalized for 100 g) with a correlation coefficient (r) of 0.986.

The results from the remaining six ventricles studied are summarized in Fig. 3 and Table 1. Figure 3 presents the data for the remaining six ventricles in a similar fashion to Fig. 2c. In Table 1, we present the mass of each left ventricle, the range over which E^n_{max} was varied, the slope and intercept of the relation between E^n_{max} and b^n, and the correlation coefficient of the linear regression to the data. In every case, the linear correlation coefficient was high ($r \geq 0.900$). On average, b^n was $0.036\ E^n_{max} + 0.0101$ ($r = 0.960$, where this mean r value determination is based on a z-transformation method outlined in detail in Snedecor and Cochran [14]). However, the relationship between E^n_{max} and b^n

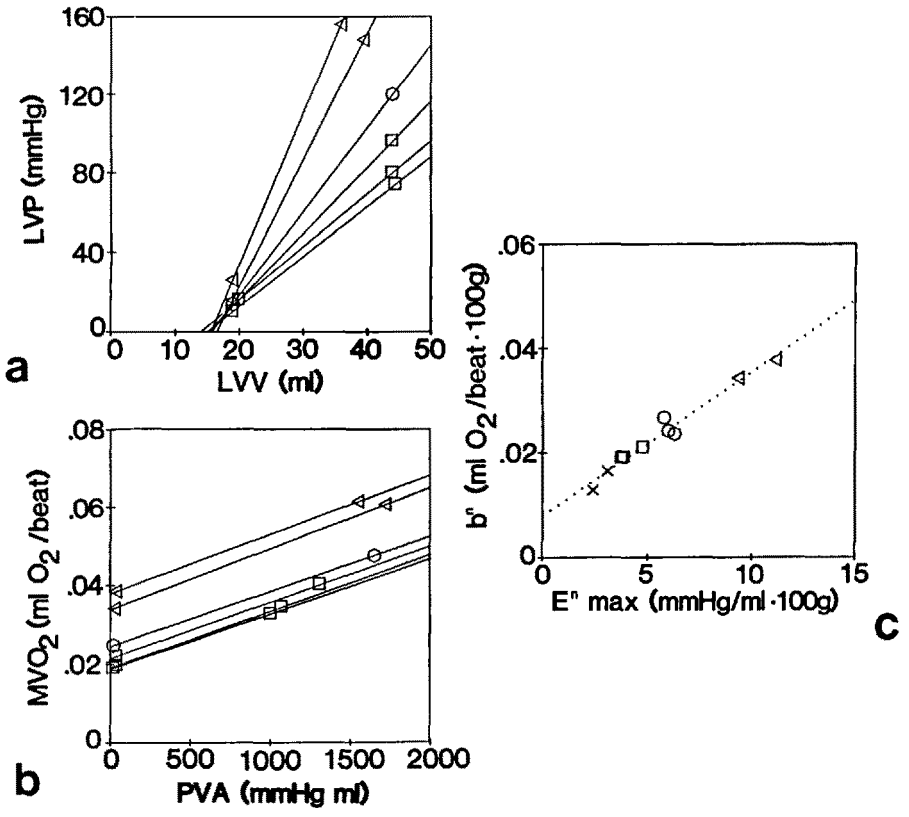

Fig. 2a–c. Results from one experiment. **a** End-systolic pressure-volume relationships (ESPVR) under control conditions (*circles*), with the administration of two different doses of dobutamine (*triangles*), and with the administration of three different dose of nifedipine. With changes in contractile state, the slope of the ESPVR changes but the volume axis intercept is not significantly affected. **b** MVO_2-PVA relations corresponding to the data in **a**. With changes in contractile state, the relations shift up and down in a parallel fashion. **c** The relation between E^n_{max} (the slope of ESPVR) and b^n, MVO_2 at zero PVA, both normalized for an LV weight of 100 g. Included are data from **a** and **b**, two additional control runs, and data obtained during reduction of coronary blood flow to two different levels (*crosses*). The relationship between E^n_{max} and b^n is linear. See Table 1 (experiment 1) for results of quantitative analysis. Data in this figure were obtained from a different heart than in Fig. 1

differed from heart to heart. Thus, there were differences in the relationship of E_{max} to b between hearts that were not accounted for by normalization for myocardial mass.

Discussion

The results of the present study indicate that within a given heart the relationship between non-work-related myocardial oxygen consumption (b) and contractile state as quantified by E_{max} is well represented by by a single linear relation. This high degree of linearity was observed over a reasonably wide range of contractility created by both enhancement and depression from control conditions. Among different hearts, however, there were significant differences between the coefficients of the linear regression with regard to E_{max} and b.

These results extend the work of previous studies, which reported that non-work-related myocardial oxygen consumption approximately covaried with contractility [3]. In a previous study, also performed in isolated canine hearts, Suga and co-workers plotted b as a function of E_{max} for data *pooled from many hearts* during infusion with epinephrine or Ca^{2+} [5]. The average results of linear regression applied to the pooled data were quantitatively similar to our results. However, no attempt was made in that study to investigate the interrelation between E_{max} and b within a given heart, nor were the effects of negative inotropic agents investigated. In another preliminary study, we investigated the E_{max}-b relation within a given heart, but only with contractility decreased from control [10]. Results of that study were also quantitatively similar to those presented here with regard to the relationship between E_{max} and b. Here, we provide evidence that within a given heart there exists a unique and linear relationship between contractility and non-work-related oxygen consumption when contractility is varied over a reasonably wide range by both positive and negative inotropic agents.

It is of interest to note the similarity between the mean intercept value of the relation between E_{max} and b we observed, namely 0.0101 ml O_2/beat/100 g (Table 1) and the value of oxygen consumption obtained by Suga in KCl-arrested hearts of 0.0108 ml O_2/beat/100 g [3]. Conceptually, our intercept value is the oxygen consumption extrapolated to an E_{max} of O, a condition possibly similar to KCl arrest.

The strikingly parallel changes in contractility and non-work-related oxygen consumption are consistent with the hypothesis raised at the beginning of this paper that both may be modulated by a common factor—presumably the amount of calcium released to the myofilaments per beat. The observed *linearity* of the E_{max}-b relation is consistent with the linearity of the relation noted between calcium and contractility [15]; it would also be consistent with a

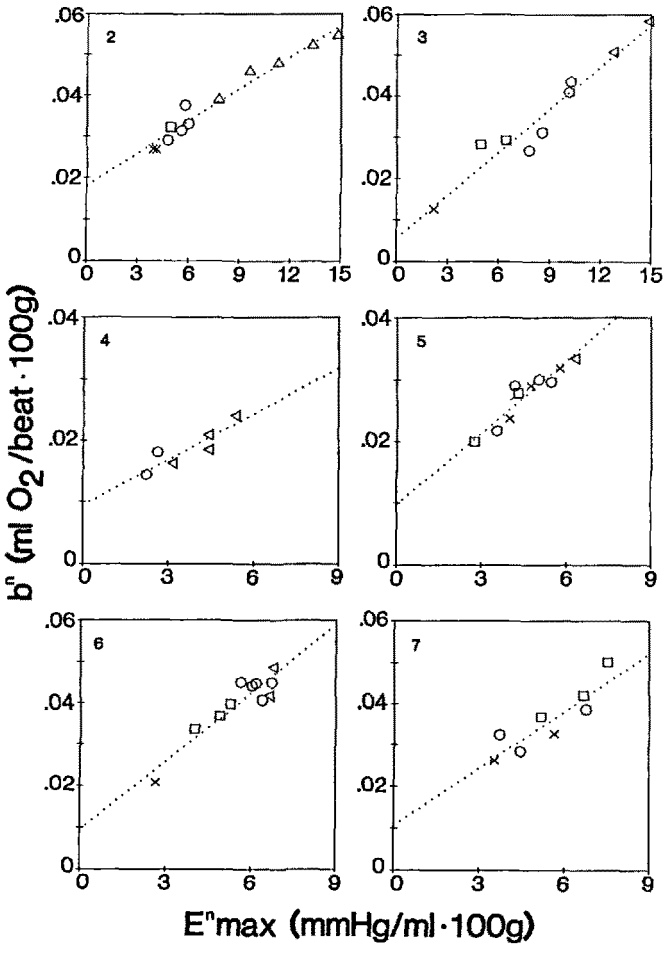

Fig. 3. Summary of the E^n_{max}-b^n relationship from the remaining six ventricles. See legend of Fig. 2 for more details and Table 1 for further analysis of the data. The *number* in *top left corner* of each *panel* corresponds to the experiment number in Table 1. *Circles* control data, *triangles* dobutamine data, *crosses* data from reduced coronary blood flow, *squares* nifedipine data

fixed and linear stoichiometry between calcium uptake and ATP consumption by the sarcoplasmic reticulum, independent of the contractile state (which has not yet been reported).

That the locus of E^n_{max} vs. b^n data points defined a single linear relationship suggested initially that zero-work O_2 consumption is determined uniquely by contractility, independent of the inotropic agent. While this is true for the interventions investigated in the present study, it seems likely on two grounds that certain agents could cause deviations from this simple behavior. First, if an agent were to exert its inotropic actions by predominantly changing the sensitivity of the myofilaments to calcium, rather than by altering the amount of calcium provided to the myofilaments, deviations from the unique E_{max}-b relation described here would be anticipated. One example of such an agent might be caffeine which augments the Ca^{2+} sensitivity of the myofilaments [16]. Secondly, certain inotropic agents may also change the basal O_2 consumption in addition to changing the energy required for e-c coupling. Such a change in basal O_2 consumption might occur as a result of agent-induced changes in the preference of metabolic substrates used by the heart for energy production [17]. The simplest explanation for the unique E_{max}-b relation found for the inotropic maneuvers used in the present study is that alterations in contractility resulted primarily from changes in the amount of calcium provided to the myofilaments and that basal O_2 consumption was not affected.

In relation to the above discussion, one would anticipate differences between the E^n_{max}-b^n relationships obtained in different experiments (Table 1) because there is no reason to expect that all the factors that determine basal O_2 consumption would be the same from one ventricle to the next. These

Table 1. Relationship between E^n_{max} and b^n from all seven hearts studied

Exp	LV weight (g)	Range of E^n_{max} $\left(\frac{mmHg \cdot 100g}{ml}\right)$	E^n_{max} vs. b^n		
			Slope $\left(\frac{ml\ O_2 \cdot ml}{beat \cdot mmHg(100g)^2}\right)$	Intercept $\left(\frac{ml\ O_2}{beat \cdot 100g}\right)$	r
1	145	2.5–11.2	0.0028	0.0079	0.986
2	109	3.9–14.8	0.0026	0.0181	0.980
3	120	2.1–15.1	0.0034	0.0056	0.973
4	124	2.2–5.5	0.0025	0.0094	0.900
5	115	2.8–6.3	0.0039	0.0098	0.938
6	115	2.6–6.9	0.0055	0.0094	0.928
7	139	3.4–7.6	0.0046	0.0106	0.900
Average	124	2.8–9.6	0.0036	0.0101	0.960[a]
±SD	13		0.0011	0.0039	0.929–0.978[b]

[a] Mean r value determination is based on z-transformation method which normalizes the distribution of r values [14]
[b] 95% confidence intervals of r value, calculated from SD of z values

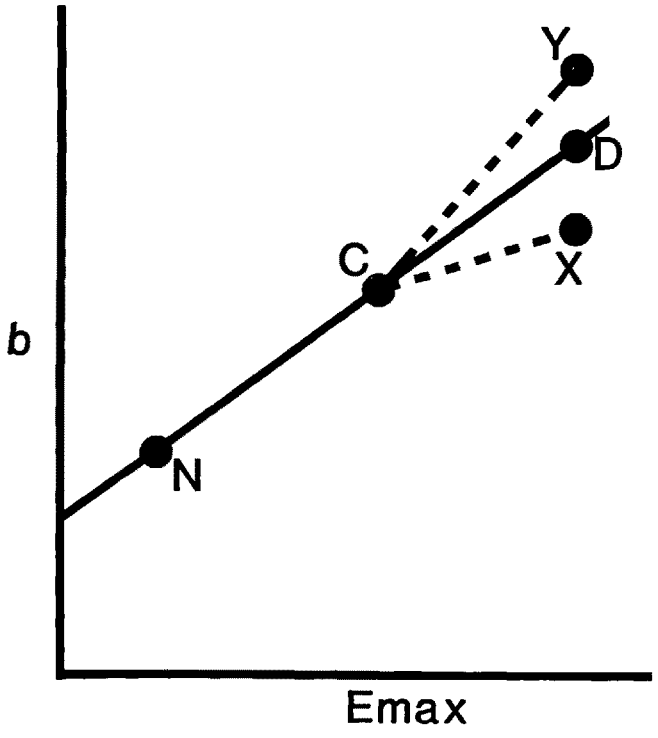

Fig. 4. Hypothetical data demonstrating potential value of the E_{max}-b relationship for comparing energy costs incurred by different inotropic agents. *Solid line* represents the E_{max}-b relationship determined from control conditions (*C*) with the contractility enhanced by dobutamine (*D*) and depressed by nifedipine (*N*). Points *X* and *Y* are of two hypothetical inotropic agents

factors might include differences in glucose, free fatty acid, and electrolyte concentrations in the blood of different support dogs [6, 17]. Furthermore, it is likely that the E_{max}-*b* relationship of a given heart is not necessarily invariant but may change with metabolic substrate availability, which varies depending on the nutritional status of the animal (e.g., fasting vs. feed states).

Independent of their mechanistic interpretation, the results of the present study provide information that is essential to understanding the energetics of the integrated cardiovascular system. Improved understanding of ventricular-aortic coupling has resulted in the development of mathematical models which predict ventricular work output, myocardial oxygen consumption, and ventricular efficiency as a function of ventricular contractility, afterload, and preload [5, 18]. Such models predict that ventricular efficiency depends crucially upon the interrelation between E_{max} and *b*. From such models, it is clear that deviations from the observed linear relationship between E_{max} and *b* would necessarily entail differences in ventricular efficiency.

Finally, the approach used in the present study (i.e., plotting *b* as a function of E_{max}) provides a simple way of comparing the energy costs incurred by different inotropic agents, relative to each other, to achieve a given contractility. This is illustrated in the hypothetical plot of Fig. 4. The effects of two hypothetical inotropic agents X and Y are considered; both agents increase contractility to the same level as dobutamine. However, in the state created by agent X *b* is less, and in the state created by agent Y *b* is greater than with dobutamine. Thus, from an energetic standpoint, X would be a more "efficient" inotropic agent than dobutamine, and Y would be a less "efficient" agent. Of course, the influence of any agent on the slope of the MVO_2-PVA relationship would have to be considered in the assessment of its relative "efficiency." Obviously, from a clinical standpoint, it is desirable to identify drugs which improve contractility but minimize increases in (or even decrease) oxygen requirements.

The influences of only a very few positive inotropic agents on the MVO_2-PVA relationship have been looked at (calcium, epinephrine, dobutamine). These agents exert their influences predominantly by increasing calcium availability and it appears that for a given level of enhancement of contractility the MOV_2-PVA relationship is the same under the influence of each of these agents. However, new inotropic agents are becoming available for clinical use which may exert their influences through different mechanisms. Therefore, E_{max}-*b* plots might prove useful in evaluating and comparing these new agents, at least with regard to their influences on intrinsic cardiac energetics. In view of the fact that many of these agents also alter ventricular loading conditions, it is naturally necessary that these be taken into account when evaluating the influence of the agents on overall cardiac energetics. In this regard, recently developed analytical models may be useful [5, 18].

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