Relation Between Left Ventricular Oxygen Consumption and Pressure-Volume Area in Conscious Dogs

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Background The relation between left ventricular (LV) oxygen consumption ($M\dot{V}O_2$) and pressure-volume area (PVA) developed in isolated hearts provides a powerful method to understand cardiac energetics. We investigated application of this relation to the intact circulation, determining its response to steady-state and transient load alterations and enhanced contractility in conscious animals.

Methods and Results Eight dogs were instrumented to measure LV pressure (micromanometer), LV volume (three sonomicrometers), and left circumflex and anterior descending coronary artery flows (ultrasonic flowmeter). Data were acquired after recovery from the surgery with the animals awake and unsedated. After administration of hexamethonium and atropine, steady-state loading conditions were changed with phenylephrine or nitroprusside in four to five steps before and during the infusion of dobutamine (6 to 10 $\mu g \cdot {}^{-1}kg \cdot {}^{-1}min$). $M\dot{V}O_2$ and PVA obtained under steady-state conditions were linearly correlated both before and during dobutamine. The $M\dot{V}O_2$-PVA relation obtained on a beat-to-beat basis during transient caval occlusion was less linear and not coincident with the steady-state relation. Dobutamine shifted the steady-state $M\dot{V}O_2$-PVA relation upward in all hearts, increasing the $M\dot{V}O_2$ axis intercept of the $M\dot{V}O_2$-PVA relation ($P<.01$). This intercept correlated with ventricular contractility assessed by the slope (E_{es}) of the LV end-systolic pressure-volume relation determined by caval occlusion ($r=.76$, $P<.05$). The slope of the $M\dot{V}O_2$-PVA relation increased with dobutamine in seven of eight animals, with the inverse of the slope (representing contractile efficiency) being 31±6% during control and 24±6% after dobutamine ($P=.06$).

Conclusions $M\dot{V}O_2$ and PVA are linearly related during steady-state alterations in loading conditions in conscious dogs but not on a beat-by-beat basis during transient caval occlusion. Increase in contractility by dobutamine produces an upward shift of the $M\dot{V}O_2$-PVA relation. (***Circulation*. 1994; 89:810-817.**)

Key Words • myocardium • pressure • dobutamine

In the isolated heart, the oxygen consumption ($M\dot{V}O_2$) of the left ventricle (LV) is linearly related to the LV pressure-volume area (PVA).[1,2] PVA, which represents the total mechanical energy produced by LV, consists of the area contained in the LV pressure-volume loop and the remaining area between the end-systolic and end-diastolic pressure-volume relations. In isolated hearts, the $M\dot{V}O_2$-PVA relation is independent of LV loading conditions; however, increases in contractile state shift the $M\dot{V}O_2$-PVA relation upward without a change in the slope.[3,4] The inverse of the slope of the $M\dot{V}O_2$-PVA relation indicates the contractile efficiency, and the $M\dot{V}O_2$ axis intercept reflects the energy used for basal metabolism and excitation-contraction coupling.[2] If the PVA concept developed in the isolated heart applies to the intact LV ejecting into the circulation of conscious animals or humans, it would provide a powerful method of understanding the effects of disease states and therapy on cardiac energetics.

There are several differences between the isolated hearts (both isovolumically beating and ejecting into models of the circulation) and the heart of the intact animal. First, in intact animal circulation, the ejection pattern of the LV is determined by the complex interactions between the ventricle and the arterial system. Second, in intact circulation, the coronary perfusion pressure is determined by the arterial pressure that is generated by the LV. Finally, the depressant effects of anesthesia and an acute surgical procedure in the support animal in studies of isolated hearts, or in the experimental subject in acute studies, may alter cardiac performance and metabolism. Therefore, it is important that the relation between $M\dot{V}O_2$ and PVA is evaluated in the intact circulation of conscious animals to determine whether the concepts developed in the isolated heart apply. Some investigators[5,6] have begun to study the $M\dot{V}O_2$-PVA concept in humans. Despite some noise in the data, they found that PVA linearly correlated with $M\dot{V}O_2$, and that catecholamines shifted this relation upward in a generally parallel manner. However, in human studies, there are methodological limitations. For example, it is difficult to accurately measure continuous LV volume and coronary flow while producing a wide range of LV loading conditions under a constant state of contractility. Further, changes in arterial pressure used to generate the LV end-systolic pressure-volume relation may alter the relation.[7]

Before the $M\dot{V}O_2$-PVA relation can be applied to clinical situations, several issues must be resolved. Are $M\dot{V}O_2$ and PVA linearly related over a wide range of loading conditions in the intact circulation of conscious

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animals? Does the $M\dot{V}O_2$-PVA relation apply only to steady-state situations or does it occur on a beat-to-beat basis? This has practical importance. If the $M\dot{V}O_2$-PVA relation operates on a beat-to-beat basis, then data could be conveniently generated during transient load alterations.[8,9] Second, how is the $M\dot{V}O_2$-PVA relation altered by changes in contractility? Can a parallel shift of the relation with increases in contractility be assumed?[10,11] If this is the case, only a single data point would be needed to determine the position of the $M\dot{V}O_2$-PVA relation after an alteration in contractility. Third, the LV end-systolic pressure-volume relation in the intact circulation is curvilinear when evaluated over a wide range.[12] Because PVA is determined by the end-systolic pressure-volume relation (ESPVR), differences between assuming a linear or nonlinear relation may also influence the derived $M\dot{V}O_2$-PVA relation. Accordingly, this study was undertaken to investigate these issues in chronically instrumented animals that were in the conscious, unsedated state.

Methods

Instrumentation

Eight healthy mongrel dogs weighing 23 to 34 kg were instrumented under anesthesia induced with xylazine (2 mg/kg) and sodium thiopental (6 mg/kg, IV) and maintained with halothane (0.5% to 2%). They were intubated and ventilated with oxygen-enriched room air to maintain arterial oxygen tension at more than 100 mm Hg. A sterile, left lateral thoracotomy was performed, and the pericardium was widely opened. A micromanometer pressure transducer (Konigsberg Instruments) and polyvinyl catheter for transducer calibration and blood sampling were inserted into the LV through an apical stab incision. Three pairs of ultrasonic crystals (5 MHz) were implanted in the endocardium of the LV to measure the anterior-posterior, septal-lateral, and base-apex (long axis) dimensions, using the method from our laboratory as previously described.[12-14] Ultrasonic time-transit flow probes (model 2R or 3R, Transonic System Inc) were placed on both the proximal left circumflex coronary artery and the left anterior descending coronary artery just distal to the first diagonal branch for measurement of LV coronary flow. A catheter was inserted into the coronary sinus via the right atrium for coronary venous blood sampling. Two hydraulic occluder cuffs were placed around the superior and inferior venae cavae. In three of these eight dogs, pacing lead wires were fixed on the left atrium. The wires and tubing were tunneled subcutaneously and brought out through the skin of the neck.

Data Collection

Studies were performed after the animals had fully recovered from the instrumentation (1 to 2 weeks after the original surgery). The LV catheter was connected to the pressure transducer (Statham P23Db) calibrated with a mercury manometer. The signal from the micromanometer was adjusted to match that of the catheter. The transit time of 5-MHz sound between the crystal pairs was determined and converted to a distance assuming a constant velocity of sound in blood of 1.55 m/s. The coronary flow probes were connected to an ultrasonic flowmeter (model T201, Transonic System Inc). Coronary arterial and venous oxygen contents were measured with a hemoximeter (Co-oxymeter 482, Instrumentation Laboratory).

Protocol

Before a pharmacological denervation, steady-state data were recorded for 12 to 15 seconds, and then two or three sets of variably loaded pressure-volume loops were generated by transient occlusions of the venae cavae.

$M\dot{V}O_2$-PVA Relation With Blocked Reflexes

Autonomic blockade was induced with hexamethonium chloride (5 mg/kg) and atropine sulfate (0.1 mg/kg) and maintained by continuous infusion at rates of 0.1 and 0.005 $mg \cdot kg^{-1} \cdot min^{-1}$, respectively. After stabilization, blocked control steady-state and vena caval occlusion data were collected. In three of the eight dogs, heart rate was kept constant through the experiment by the left atrial pacing to eliminate the influence of changes in heart rate by dobutamine.

In each heart, left ventricular loading conditions were widely changed with phenylephrine or nitroprusside in 4 to 5 steps. After stabilization for at least 3 minutes, steady-state data were recorded over a period of 12 to 15 seconds to obtain stroke work, PVA, and coronary flow at each loading condition. At the same time, arterial and coronary sinus blood was sampled from LV and coronary sinus catheters to measure the oxygen content. Then, transient caval occlusions were performed to obtain the ESPVR at each loading condition.

Effect of Dobutamine on $M\dot{V}O_2$-PVA Relation

After the control study, the ventricular contractile state was enhanced by a continuous infusion of dobutamine at a rate of 6 to 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Thus, LV loading conditions were changed in the same way as in the control study, and the same data were collected.

Effect of Caval Occlusion on Coronary Sinus Oxygen Saturation

In one additional animal, a fiberoptic catheter (Oximetry TD Catheter, Baxter Corp, Irvine, Calif) was placed in the coronary sinus at the time of instrumentation. After the animal's recovery from surgery, this catheter was used to measure the coronary sinus oxygen saturation beat-by-beat during caval occlusions.

Data Processing and Analysis

Data were digitized, with an on-line analog-to-digital converter (Data Translations Devices), at 200 Hz during each 12-

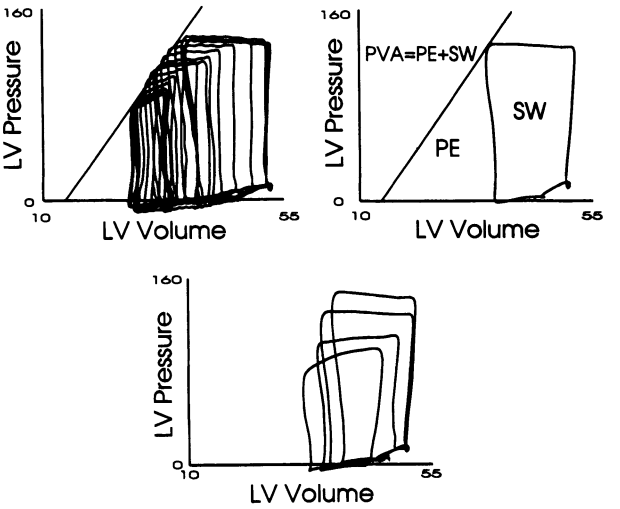

FIG 1. Graphs show pressure-volume loops and end-systolic pressure-volume relation (ESPVR) during caval occlusion before dobutamine (upper left). Upper right, ESPVR obtained by the transient caval occlusion was superimposed on a steady-state averaged pressure-volume loop. Bottom, Steady-state averaged pressure-volume loops at four different loading conditions. LV indicates left ventricular; PVA, pressure-volume area; SW, stroke work; and PE, potential energy.

TABLE 1. Hemodynamic and Oxygen Consumption Data Before and After Denervation

	HR, bpm	EDV, mL	ESV, mL	ESP, mm Hg	dP/dt, mm Hg/s	−dP/dt, mm Hg/s	E_{es}, mm Hg · mL^{-1} · 100 g LV^{-1}	V_O, mL
Before	120±13	39.7±8.2	27.2±5.0	104±12	2713±340	−2249±262	8.6±3.3	13.3±2.4
After	122±19*	35.6±6.4†	26.0±4.4†	70±8†	1893±206†	−1584±174†	8.3±2.4*	16.1±2.8†

HR indicates heart rate; bpm, beats per minute; EDV, end-diastolic volume; ESV, end-systolic volume; ESP, end-systolic pressure; E_{es}, slope of end-systolic pressure-volume relation (ESPVR); V_O, volume axis intercept of ESPVR; Flow, coronary flow; AV, coronary arteriovenous oxygen content difference; $M\dot{V}O_2$/min, oxygen consumption per minute; $M\dot{V}O_2$/beat, $M\dot{V}O_2$ per beat; and LV, left ventricle.
*Not significant.
†$P<.01$.

to 15-second collection period. The LV volume was calculated as a modified general ellipsoid by the following equation: $V_{LV}=(\pi/6)\cdot D_{AP}\cdot D_{SL}\cdot D_{LA}$, where V_{LV} is LV volume, D_{AP} is the anterior-to-posterior LV diameter, D_{SL} is the septal-to-lateral diameter, and D_{LA} is the long-axis LV diameter. We have demonstrated previously that this method gives us a consistent measure of LV volume despite changes in LV loading conditions, configurations, and heart rate.[7,15-17] The LV end-systolic pressure (P_{es}) and volume (V_{es}) data during the caval occlusion were fitted by the least-squares technique to $P_{es}=E_{es}(V_{es}-V_O)$, where E_{es} is the slope of the linear ESPVR, representing the LV end-systolic elastance, and V_O is the intercept with the volume axis.

PVA was determined as the area under the ESPVR and the systolic pressure-volume trajectory and above the end-diastolic pressure-volume relation curve. The ESPVR obtained by transient caval occlusion under each loading condition were superimposed on the corresponding steady-state pressure-volume loop (Fig 1). We did not use steady-state pressure-volume loops to calculate ESPVR because increase in afterload by a vasoconstrictor shifts the ESPVR to the left.[7] We assumed that the end-diastolic pressure-volume relation curve was reasonably approximated by a third-order polynomial. The small area of PVA between the straight line connecting volume-axis intercept (V_O) of ESPVR and end-diastolic point (V_{ed}, P_{ed}) and the downward convex end-diastolic pressure-volume curve was given by $P_{ed}\cdot(V_{ed}-V_O)/4$.[18] To evaluate the effect of nonlinearities of the ESPVR, the end-systolic points were also fitted by a quadratic function curve ($P_{es}=a\cdot V_{es}^2+b\cdot V_{es}+c$, where P_{es} is end-systolic pressure, V_{es} is end-systolic volume, and a,b,c are constants, respectively), and PVA was calculated from this curvilinear ESPVR.

To compare the $M\dot{V}O_2$-PVA relation obtained during transient changes in loading conditions with the steady-state $M\dot{V}O_2$-PVA relation described above, $M\dot{V}O_2$ and PVA were calculated from the data recorded during caval occlusion. In this calculation, oxygen contents of coronary artery and vein were assumed to be constant during transient caval occlusion. Fiberoptic measurement of the coronary sinus saturation in one animal demonstrated that oxygen content actually decreased by <4% during the course of a caval occlusion.

The product of the coronary flow (mL/min) and coronary arteriovenous oxygen content difference (vol%) divided by 100 gives oxygen consumption rate in milliliters of O_2 per minute. This was divided by heart rate to yield oxygen consumption in milliliters of O_2 per beat.

At the conclusion of the studies, the dogs were anesthetized with sodium thiopental (6 mg/kg) and halothane (0.5% to 2%), and thoracotomy was performed to determine the perfusion territories of left circumflex and left anterior descending coronary artery using saturated Evans blue solution. The dogs were killed with T-61 euthanasia solution (0.3 mL/kg IV) after the injection of the Evans blue solution. The hearts were examined to confirm the proper positioning of the instrumentation. Stained and nonstained LVs were weighed. The ratio of the perfused LV weight to the total LV weight was 0.59±0.07.

Statistics

Data recorded before and after the pharmacological denervation were compared by the paired t test. ANCOVA was applied to compare the oxygen consumption per beat ($M\dot{V}O_2$)-PVA regression lines between the control and dobutamine runs obtained under steady-state condition in each heart. The difference in the elevation and slope of the regression lines was tested by F test in each heart. Because of the high correlation coefficient between $M\dot{V}O_2$ and PVA in each run, the slope and $M\dot{V}O_2$ axis intercept of the regression line between the control and dobutamine runs in all hearts (n=8) were compared by ANOVA. The Newman-Keuls test was applied when the F test was significant. In addition, we used multiple linear regression analysis in each individual animal, as well as in pooled data from all eight animals.[19] To test whether dobutamine affected the slope and elevation of the $M\dot{V}O_2$-PVA relation, $M\dot{V}O_2$ was plotted as a function of the transformed PVA data, ie, raw PVA value minus an average PVA value in each heart. In the regression model for the individual hearts, one dummy variable was coded for the presence or absence of dobutamine. In the regression model for pooled data, one additional dummy variable was coded for the experiment number. Linear regression analysis was also applied to the $M\dot{V}O_2$-PVA relation obtained during the transient caval occlusion at a highest afterload in each heart because changes in loading conditions from the highest afterload were close to those under steady-state conditions obtained by phenylephrine or nitroprusside. E_{es} between control and dobutamine was compared by the paired t test. Significance was accepted at $P<.05$. Data are presented as mean value±SD.

Results

Table 1 shows the average data before and after the pharmacological denervation. Autonomic blockade decreased both LV preload and afterload but did not significantly change heart rate. Although maximum LV dP/dt decreased significantly in conjunction with a fall in end-diastolic volume, E_{es} did not decrease significantly. Both coronary flow and arteriovenous oxygen content difference decreased after the denervation. Thus, $M\dot{V}O_2$ decreased.

Fig 1 shows examples of pressure-volume loops during the caval occlusion and averaged pressure-volume loops in each step before dobutamine infusion. Dobutamine increased E_{es} by 128±38% on the average. The coefficient of variation (SD/mean value) of E_{es} during changes in loading conditions caused by phenylephrine or nitroprusside was 0.05 (P=NS) in the control and 0.06 (P=NS) in the dobutamine, indicating that LV contractility was unaffected by the alterations in loading conditions. The heart rate increased significantly with dobutamine except in three dogs that were paced artificially; nevertheless, heart rate was stable in each run. In one dog paced artificially, a spontaneous heart rate during dobutamine infusion slightly exceeded the original stimulating rate set in the

TABLE 1. Continued

Flow, mL · min^{-1} · 100 g LV^{-1}	AV, %	$M\dot{V}O_2$/min (mL O_2 · min^{-1} · 100 g LV^{-1})	$M\dot{V}O_2$/beat (mL O_2 · beat^{-1} · 100 g LV^{-1})
93.3 ±17.9	11.0±1.6	10.15±1.69	0.0857±0.0181
75.7 ±17.8†	9.1±1.5†	6.75±1.37†	0.0562±0.0115†

control, and then the stimulating rate was slightly increased during dobutamine.

Fig 2 shows an example of $M\dot{V}O_2$-PVA relation obtained under steady-state condition before and during dobutamine infusion during sinus rhythm. In both control and dobutamine runs, $M\dot{V}O_2$ was linearly correlated with PVA, and its correlation coefficient was close to unity in all hearts (Table 2).

Fig 3 shows an example of the ESPVR fitted by a quadratic function curve and the relation between $M\dot{V}O_2$ and PVA calculated from the nonlinear ESPVR. PVAs calculated from nonlinear ESPVR were slightly smaller than those from a linear approximation of the ESPVR. The $M\dot{V}O_2$ axis intercept of the $M\dot{V}O_2$-PVA relation was not significantly different from that obtained from the linear ESPVR in both the control and dobutamine runs (Table 3). Similarly, the slope of the $M\dot{V}O_2$-PVA relation was only slightly (<10%), and not significantly, increased in both the control and dobutamine runs compared with that obtained from the linear ESPVR. Thus, the assumption of a linear versus a nonlinear ESPVR does not have an important influence on the resulting $M\dot{V}O_2$-PVA relation in conscious animals.

Fig 4 shows a comparison between the transient and steady-state $M\dot{V}O_2$-PVA relation before (left) and after (right) dobutamine infusion. The transient $M\dot{V}O_2$-PVA relations were determined at highest, middle, and lowest afterload, respectively. The initial few beats were close to their corresponding steady-state data points, but thereafter the transient $M\dot{V}O_2$-PVA data points tended to be higher than the steady-state $M\dot{V}O_2$-PVA regression line and then shifted downward in both control and dobutamine runs. In the pooled data of the transient $M\dot{V}O_2$-PVA relation, the $M\dot{V}O_2$ axis-intercept value obtained from highest afterload in each run was slightly lower with dobutamine ($P<.05$) than in the control and was higher ($P<.05$) than that obtained from steady-state data in both runs (Table 3). The slope of the $M\dot{V}O_2$-PVA regression line was lower ($P<.05$) than that under steady-state condition during control but not significantly different after dobutamine (Table 3). We reanalyzed the transient $M\dot{V}O_2$-PVA relation associating PVA with the $M\dot{V}O_2$ occurring two beats later. This did not alter our results.

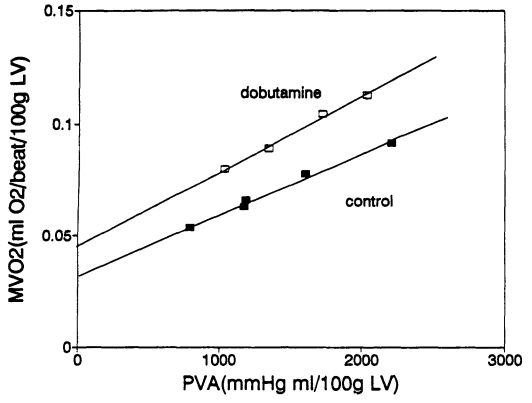

FIG 2. Plot shows the relation between cardiac oxygen consumption (MVO2) per beat and pressure-volume area (PVA) obtained under steady-state conditions before and during dobutamine.

In the steady-state situation, dobutamine significantly shifted the steady-state $M\dot{V}O_2$-PVA regression line upward in all hearts (Table 2). The $M\dot{V}O_2$ axis intercept of the $M\dot{V}O_2$-PVA regression line increased with dobutamine in all hearts. The mean $M\dot{V}O_2$ axis intercept increased in response to dobutamine from 0.257±0.0036 to 0.0364±0.0061 mL O_2 · beat^{-1} · 100 g LV^{-1} ($P<.01$). In seven of eight hearts, the slope of the $M\dot{V}O_2$-PVA relation increased with dobutamine, but in only two animals did the slope change in the individual animal reach statistical significance. There was no difference in the response to dobutamine of the $M\dot{V}O_2$-PVA relation in the five animals in which heart rate increased with dobutamine or in the three animals in which the heart rate was kept constant with pacing. The mean slope of the $M\dot{V}O_2$-PVA relation was 2.23±0.40 during control and 2.85±0.60×10^{-5} mL O_2 · mm Hg^{-1} · mL^{-1} with dobutamine. This change reached statistical significance by ANOVA ($P<.05$) but was just above the level of significance ($P=.061$) by multiple regression analysis. The efficiency of energy conversion, that is, the reciprocal of the slope of the $M\dot{V}O_2$-PVA relation, was 30.9±6.1% during control and 24.5±5.8% with dobutamine ($P<.05$ by ANOVA, $P=.06$ by multiple linear regression analysis). These results were not altered when the ESPVR was assumed to be nonlinear (Table 3). The slope (E_{es}) of the ESPVR relation determined by use of the four to five steady-state pressure-volume loops produced by the steady-state load alterations was steeper than the ESPVR produced by transient caval occlusion (Table 3). Using this steady-state ESPVR results in smaller PVAs than those calculated from the caval occlusion ESPVR. This resulted in a greater slope of the $M\dot{V}O_2$-PVA relation (Table 3). When PVA was calculated in this manner, dobutamine produced an upward shift of the $M\dot{V}O_2$-PVA relation without a significant change in slope.

Fig 5 shows the scatterplots of $M\dot{V}O_2$ axis intercept (left) and slope (right) of the steady-state $M\dot{V}O_2$-PVA regression line measured from linear ESPVR against E_{es} in all hearts before and during dobutamine. The $M\dot{V}O_2$ axis intercept was significantly correlated with E_{es}, and the correlation coefficient (r) was .76. The slope of $M\dot{V}O_2$-PVA regression line tended to increase with E_{es} but did not reach significance ($r=.41$).

Discussion

We found in conscious animals that PVA linearly correlated with $M\dot{V}O_2$ over a wide range of steady-state LV loading conditions under constant ventricular contractility. The inverse of the slope of this relation, which can be interpreted as the efficiency of the contractile machinery,[2] was 30.9%. Furthermore, the $M\dot{V}O_2$-PVA relation was shifted upward by an increase in contractility. These results are consistent with the observations of Suga and colleagues[1-3] in isolated hearts and confirm that the $M\dot{V}O_2$-PVA relation applies to the intact cardiovascular system of conscious animals under steady-state conditions.

TABLE 2. Effect of Dobutamine on the Relation of Oxygen Consumption to Pressure-Volume Area

Dog	n	HR, bpm	E_{es}, mm Hg · mL^{-1} · 100 g LV^{-1}	Slope (×10^{-5}), mL O_2 · mm Hg^{-1} · mL^{-1}	Intercept, mL O_2 · beat^{-1} · 100 g LV^{-1}	r	ANCOVA Elevation	ANCOVA Slope
1								
CON	4	106	8.5	1.99	0.0216	.960		
DOB	4	183	23.9	1.82	0.0419	.995	*	NS
2								
CON	4	104	9.1	2.10	0.0229	.977		
DOB	5	188	24.2	3.00	0.0417	.970	*	NS
3								
CON	4	133	6.3	1.50	0.0247	.992		
DOB	5	199	16.1	2.20	0.0272	.987	*	NS
4								
CON	5	114	7.9	2.73	0.0325	.995		
DOB	4	143	15.6	3.33	0.0458	.997	*	NS
5								
CON	5	120	7.7	2.74	0.0217	.984		
DOB	5	165	16.1	2.89	0.0323	.980	*	NS
6								
CON	4	165	8.0	2.55	0.0269	.999		
DOB	4	165	19.7	3.74	0.0323	.997	*	*
7								
CON	5	165	12.9	2.09	0.0294	.986		
DOB	5	177	26.5	3.30	0.0385	.983	*	*
8								
CON	4	168	6.4	2.11	0.0259	.987		
DOB	4	168	10.3	2.52	0.0315	.997	*	NS
Mean (linear ESPVR)								
CON		134±26	8.4±1.9	2.23±0.40	0.0257±0.0036	.985±0.011		
DOB		174±16	19.1±5.1*	2.85±0.60†	0.0364±0.0061*	.988±0.009		

Pressure-volume area (PVA) was determined from a linear approximation of the end-systolic pressure-volume relation (ESPVR) generated by transient caval occlusion. Oxygen consumption ($M\dot{V}O_2$) and PVA were determined at each steady-state loading condition.

HR indicates heart rate; bpm, beats per minute; E_{es}, slope of end-systolic pressure-volume relation; n, number of steady-state data sampling points; Slope, slope of $M\dot{V}O_2$-PVA regression line; Intercept, $M\dot{V}O_2$ axis intercept of $M\dot{V}O_2$-PVA regression line; Elevation and Slope, ANCOVA to determine if there was a significant change in slope or elevation of $M\dot{V}O_2$-PVA relation in each animal; CON, control run; DOB, dobutamine run; and NS, not significant.

*$P<.05$; †$P<.05$ by ANOVA, $P=.061$ by multiple linear regression analysis (see text).

Recently, Prabhu et al[8] and Lilly et al[9] obtained the $M\dot{V}O_2$-PVA relation by beat-to-beat analysis during transient caval occlusions. This technique provides a convenient way to measure $M\dot{V}O_2$ and PVA over a wide range of loading conditions in a short period of time. LV coronary blood flow and $M\dot{V}O_2$ are closely coupled.[20] Schwartz et al[21] showed that, if the oxygen demand of one cardiac cycle was augmented, coronary flow increased in the following cycle. However, it was not known whether coronary flow on a beat-to-beat basis represents the myocardial energy requirements of each corresponding contraction as LV loading conditions are transiently altered. We found that the $M\dot{V}O_2$-PVA relation obtained on a beat-to-beat basis during a transient caval occlusion was coincident with the $M\dot{V}O_2$-PVA relation determined under steady-state conditions for only the initial 2 to 4 beats, and then it deviated from the steady-state relation. The transient $M\dot{V}O_2$-PVA relations were less linear, and the slopes were significantly different from the steady-state relation during control but not after dobutamine. Even if $M\dot{V}O_2$ from the coronary flow of the following beat was calculated, these two $M\dot{V}O_2$-PVA regression lines were still different.

We did not measure the coronary arteriovenous oxygen content difference on a beat-by-beat basis; instead, we assumed that oxygen content difference remained constant during the caval occlusion. Actually, the arteriovenous oxygen content difference tends to increase slightly during caval occlusions.[8] This would tend to accentuate the difference between the steady-state and transient $M\dot{V}O_2$-PVA relations. Consistent with our observation that the transient $M\dot{V}O_2$-PVA relation is different from the steady-state relation, Dankelman et al[22] recently found that the half-time of the response of coronary flow or

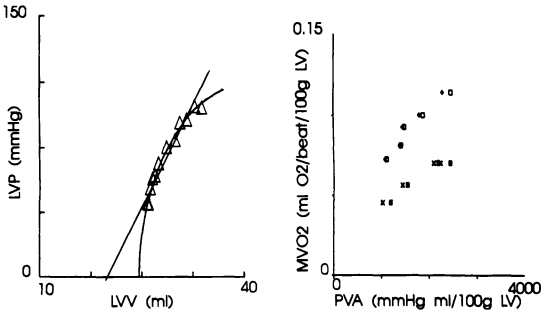

FIG 3. Left, Plot shows an example of curvilinear end-systolic pressure-volume relation (ESPVR). Pressure-volume area (PVA) was calculated from both linearly and curvilinearly fitted ESPVRs. Right, Relation between oxygen consumption (MVO2) and PVA before and during dobutamine. LVP indicates left ventricular pressure; LVV, left ventricular volume; ■ and □, data points obtained by linear ESPVRs; and +, △, and ×, data points obtained by curvilinear ESPVRs.

perfusion pressure to a sudden change of the other was more than 5 seconds. Similarly, the response time for an increase in coronary flow after a sudden increase in heart rate was more than 13 seconds.[23]

In our control study, both the $M\dot{V}O_2$ axis intercept, which is thought to represent the energy cost of basal metabolism and calcium cycling, and the slope of the $M\dot{V}O_2$-PVA relation, whose inverse reflects the efficiency of contractile machinery, were very similar to the values measured in the isolated heart.[3,4] Dobutamine shifted the $M\dot{V}O_2$-PVA relation line upward, and the $M\dot{V}O_2$ axis intercept increased in all hearts. That is, catecholamines increased oxygen usage for a comparable level of mechanical energy.[3,24] We quantified the shift in the middle of the range in which we had data points. Using this method, $M\dot{V}O_2$ at a constant PVA increased by 1.5×10^{-3} mL O_2 for each 1 mm Hg/mL increase in E_{es}. This value is very similar to the findings in isolated hearts of 2.4×10^{-3} mL O_2/(mm Hg/mL).[25] Because the slope of the $M\dot{V}O_2$-PVA relation increased by dobutamine in seven of the eight animals in our study, the magnitude of the shift of the $M\dot{V}O_2$-PVA relation was reduced when it was evaluated by extrapolating to the $M\dot{V}O_2$ axis (ie, PVA=0). Thus, the $M\dot{V}O_2$ axis intercept increased by only 0.8×10^{-3} mL O_2 per 1 mm Hg/mL increase in E_{es}.

In the isolated heart, changes in contractility produce parallel shifts of the $M\dot{V}O_2$-PVA relation without any alteration of the slope.[2,3] Similarly, in two recent clinical studies,[5,6] the slope of the $M\dot{V}O_2$-PVA relation was not significantly altered by catecholamines. However, there are some methodological limitations of the clinical studies, including the accuracy of LV volume measurement and the influence of autonomic reflexes during changes in loading conditions. More recently, only one $M\dot{V}O_2$-PVA point has been determined after altering contractility, and it has been assumed that there was a parallel shift of the $M\dot{V}O_2$-PVA relation.[5] In other studies,[10,11] $M\dot{V}O_2$ was predicted from the $M\dot{V}O_2$-PVA relation assuming a constant slope despite changes in

TABLE 3. Comparison of Relation of Oxygen Consumption to Pressure-Volume Area as Determined by Different Methods of Load Alteration

	E_{es}, mm Hg · mL^{-1} · 100 g LV^{-1}	Slope (×10^{-5}), mL O_2 · mm Hg^{-1} · mL^{-1}	Intercept, mL O_2 · beat^{-1} · 100 g LV^{-1}	*r*
Linear ESPVR determined by caval occlusion				
Steady-state $M\dot{V}O_2$-PVA relation				
CON	8.4±1.9	2.23±0.040	0.0257±0.0036	.985±.011
DOB	19.1±5.1*	2.85±0.60†	0.0364±0.0061*	.988±.009
Transient $M\dot{V}O_2$-PVA				
CON		1.15±0.49‡	0.0540±0.0145‡	.886±.083‡
DOB		2.69±0.62	0.0461±0.0086‡	.970±.016‡
Nonlinear ESPVR determined by caval occlusion				
Steady-state (nonlinear ESPVR)				
CON		2.40±0.41	0.0258±0.0049	.984±.013
DOB		3.03±0.67*	0.0357±0.0067*	.986±.012
Steady-state ESPVR				
Steady-state $M\dot{V}O_2$-PVA				
(Steady-state ESPVR)				
CON	11.4±2.3‡	2.89±0.71‡	0.0217±0.0027‡	.980±.014
DOB	23.1±6.3*‡	3.11±0.91	0.0351±0.0049	.985±.017

Nonlinear end-systolic pressure-volume relation (ESPVR) was calculated from the nonlinear ESPVR under steady-state conditions. Transient oxygen consumption ($M\dot{V}O_2$)–pressure-volume area (PVA) relation represents $M\dot{V}O_2$ and PVA data obtained during the transient caval occlusion. Steady-state ESPVR is ESPVR obtained by steady-state pressure-volume loops at 4 to 5 different loading conditions (see text).

E_{es} indicates slope of end-systolic pressure-volume relation; Slope, slope of $M\dot{V}O_2$-PVA regression line; Intercept, $M\dot{V}O_2$ axis intercept of $M\dot{V}O_2$-PVA regression line; CON, control run; and DOB, dobutamine run.

Comparison to control: *$P<.05$ by ANCOVA, †$P<.05$ by ANOVA, $P=.061$ by multiple linear regression analysis (see text). Comparison to linear caval occlusion ESPVR, steady-state $M\dot{V}O_2$-PVA relation, ‡$P<.05$.

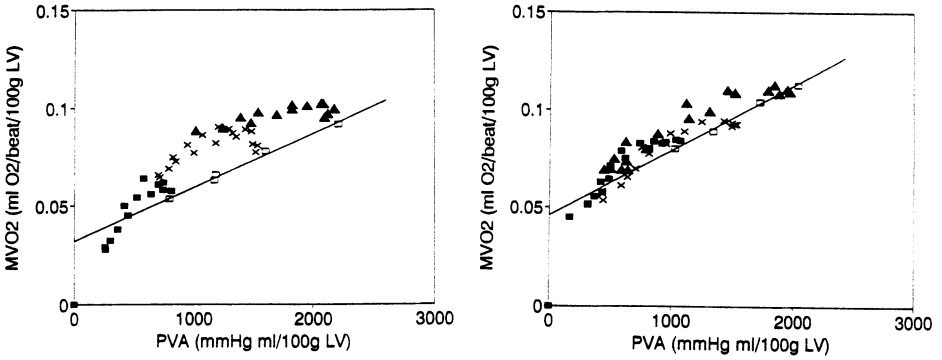

FIG 4. Plots show comparison of the oxygen consumption (MVO2) and pressure-volume area (PVA) relation obtained on a beat-to-beat basis during the transient caval occlusion with that obtained under steady-state conditions before (left) and during (right) dobutamine. The transient data were obtained at highest (▲), middle (×), and lowest (■) afterload. □ and lines are steady-state data. LV indicates left ventricle.

contractile state. However, our results suggest that the slope of $M\dot{V}O_2$-PVA relation in conscious animals may increase in response to enhanced contractility.[26] Therefore, a parallel shift of $M\dot{V}O_2$-PVA relation with increases in contractility may not always occur in the intact circulation of conscious animals and humans.

There are several possible explanations that should be considered for an increase in the slope of the $M\dot{V}O_2$-PVA relation caused by dobutamine. We assumed a linear ESPVR to obtain PVA. However, in some hearts, the ESPVRs were slightly curvilinear, especially after dobutamine.[12,27-29] To assess the importance of this factor, we also calculated PVA by use of a nonlinear quadratic function to approximate the ESPVR. The slope values of the $M\dot{V}O_2$-PVA relation obtained from the nonlinear ESPVRs were slightly higher than those obtained with the linear ESPVR. However, the increase in the slope of the $M\dot{V}O_2$-PVA relation with dobutamine continued to occur in seven of eight animals when the analysis was performed using a nonlinear ESPVR.

Dobutamine infusion significantly increased the heart rate in the present study, although it was nearly constant in each experimental run. Increase in heart rate itself would augment the ventricular contractility,[30-32] and therefore might influence the energy utilization of the myocardium. However, the magnitude of this influence would be constant regardless of changes in PVA, because the increase in heart rate with dobutamine was equal among different PVAs. Therefore, increase in heart rate should shift the $M\dot{V}O_2$-PVA relation upward as it increases the calcium cycling per beat but should not be expected to increase the slope, although it also affects the basal metabolism per beat.[33] Even when the heart rate was kept constant by atrial pacing, the slope of the $M\dot{V}O_2$-PVA relation increased with dobutamine. Therefore, it is unlikely that the increased slope was due to the augmented heart rate. An increase in heart rate by dobutamine may also lower $M\dot{V}O_2$ for basal metabolism[33] and therefore might affect the relation between E_{es} and $M\dot{V}O_2$ axis intercept of $M\dot{V}O_2$-PVA relation in the present study.

Even after the pharmacological denervation, E_{es} determined from transient caval occlusion varied slightly during changes in loading conditions, but this variation did not reach statistical significance and was very small compared with the increase caused by dobutamine. However, E_{es} calculated from the steady-state pressure-volume loops at varying arterial resistances was greater than that obtained by transient caval occlusion. This occurred because the increase in arterial resistance by the phenylephrine shifted the ESPVR generated by caval occlusion to the left, and nitroprusside shifted the relation to the right, consistent with previous observations.[7,34] When the steady-state ESPVR was used to calculate PVA, the resulting $M\dot{V}O_2$-PVA relation continued to shift upward in response to dobutamine. However, the slope did not increase significantly. This suggests that the loading protocol used to generate the ESPVR may influence the response of the $M\dot{V}O_2$-PVA relation to changes in contractility. Because the position of the ESPVR (but not the slope) varies with changes in the arterial resistance, we believe that the ESPVR generated by transient caval occlusion better approximates the ESPVR and PVA at any arterial resistance. However, it must be recognized that the arterial resistance may be altered during the caval occlusion.

We used three dimensions determined by sonomicrometry to calculate LV volume, and ultrasonic flow probes on left circumflex and left anterior descending coronary artery to measure LV coronary flow. The sonomicrometry technique has been extensively validated in past studies and accurately reflects LV volume under a wide variety of normal and pathological conditions.[7,15,17] The slope of the relation between stroke volume calculated from ultrason-

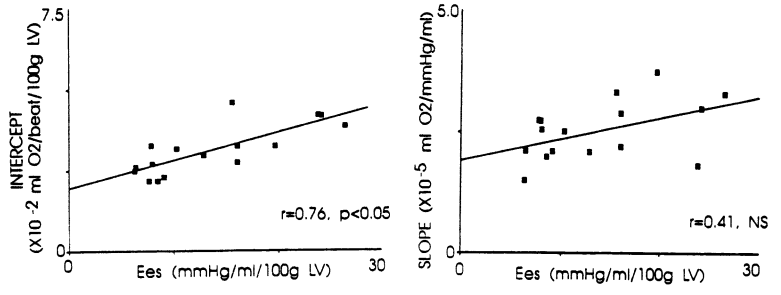

FIG 5. Scatterplots of oxygen consumption (MVO2) intercept values of $M\dot{V}O_2$-pressure-volume area (PVA) relation (left) and the slope of $M\dot{V}O_2$-PVA relation (right) against the slope (E_{es}) of end-systolic pressure-volume relation. LV indicates left ventricle.

ically measured LV dimensions and measured by a flow probe is close to unity (1.1±0.3).[7,17] However, any deviation from 1.0 would alter both E_{es} and PVA. This might account for some of the scatter in the relation between E_{es} and the slope of the $M\dot{V}O_2$-PVA relation in Fig 5.

We could not place the flow probe on the left anterior descending coronary artery proximal to the large first septal branch. We calculated total LV blood flow assuming that coronary flow per unit mass was uniform in LV.[35,36] Consistent with this simplifying assumption, left circumflex coronary artery and left anterior descending coronary artery flows changed in a parallel manner during all interventions. We measured the oxygen saturation in the coronary sinus, which includes blood returning from the right ventricle. However, the large majority of the coronary sinus flow comes from the LV.

In summary, $M\dot{V}O_2$ and PVA are linearly correlated in conscious dogs during steady-state changes in loading conditions. However, the $M\dot{V}O_2$-PVA relation, obtained on a beat-by-beat basis during transient changes in loading conditions, is not coincident with the steady-state $M\dot{V}O_2$-PVA relation. Dobutamine shifted the $M\dot{V}O_2$-PVA relation upward, increasing the $M\dot{V}O_2$ axis intercept. In addition, the slope of the relation increased in seven of eight animals during dobutamine infusion. The $M\dot{V}O_2$-PVA relation is similar whether the ESPVR is assumed to be linear or nonlinear. These results demonstrate that the $M\dot{V}O_2$-PVA relation developed in isolated hearts applies to the intact circulation of conscious animals during steady-state alterations in loading conditions.

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