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

Takashi Nozawa, MD; Che-Ping Cheng, MD, PhD; Toshiyuki Noda, MD; William C. Little, MD

Background The relation between left ventricular (LV) oxygen consumption (MV\textsubscript{O2}) 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 µg·kg\textsuperscript{-1}·min\textsuperscript{-1}). MV\textsubscript{O2} and PVA obtained under steady-state conditions were linearly correlated both before and during dobutamine. The MV\textsubscript{O2}-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 MV\textsubscript{O2}-PVA relation upward in all hearts, increasing the MV\textsubscript{O2} axis intercept of the MV\textsubscript{O2}-PVA relation (P<.01). This intercept correlated with ventricular contractility assessed by the slope (E\textsubscript{es}) of the LV end-systolic pressure-volume relation determined by caval occlusion (r=.76, P<.05). The slope of the MV\textsubscript{O2}-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 MV\textsubscript{O2} 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 MV\textsubscript{O2}-PVA relation. (Circulation. 1994; 89:810-817.)

Key Words • myocardium • pressure • dobutamine
animals? Does the \( MV_{O_2}-\text{PVA} \) relation apply only to steady-state situations or does it occur on a beat-to-beat basis? This has practical importance. If the \( MV_{O_2}-\text{PVA} \) relation operates on a beat-to-beat basis, then data could be conveniently generated during transient load alterations.\(^8\) Second, how is the \( MV_{O_2}-\text{PVA} \) relation altered by changes in contractility? Can a parallel shift of the relation with increases in contractility be assumed?\(^9\)\(^10\) If this is the case, only a single data point would be needed to determine the position of the \( MV_{O_2}-\text{PVA} \) 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 \( MV_{O_2}-\text{PVA} \) 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.\(^12\)\(^13\) 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.

**\( MV_{O_2}-\text{PVA} \) 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·kg\(^{-1}\)·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 \( MV_{O_2}-\text{PVA} \) 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·kg\(^{-1}\)·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-
TABLE 1. Hemodynamic and Oxygen Consumption Data Before and After Denervation

<table>
<thead>
<tr>
<th>HR, bpm</th>
<th>EDV, mL</th>
<th>ESV, mL</th>
<th>ESP, mm Hg</th>
<th>dP/dt, mm Hg/s</th>
<th>-dP/dt, mm Hg/s</th>
<th>End-systolic pressure-volume relation (ESPVR)</th>
<th>VO2, mL</th>
<th>MVo2/min</th>
<th>End-diastolic pressure-volume relation (Ees, mm Hg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>120±13</td>
<td>39.7±8.2</td>
<td>27.2±5.0</td>
<td>104±12</td>
<td>2713±340</td>
<td>-2249±262</td>
<td>8.6±3.3</td>
<td>13.3±2.4</td>
<td></td>
</tr>
<tr>
<td>After</td>
<td>122±19*</td>
<td>35.6±6.4</td>
<td>26.0±4.4</td>
<td>70±8*</td>
<td>1893±206*</td>
<td>-1584±1741</td>
<td>8.3±2.4*</td>
<td>16.1±2.8t</td>
<td></td>
</tr>
</tbody>
</table>

HR indicates heart rate; bpm, beats per minute; EDV, end-diastolic volume; ESV, end-systolic volume; ESP, end-systolic pressure; Ees, slope of end-systolic pressure-volume relation (ESPVR); VO2, volume axis intercept of ESPVR; Flow, coronary flow; AV, coronary arteriovenous oxygen content difference; MVo2/min, oxygen consumption per minute; MVo2/beat, MVo2 per beat; and LV, left ventricle.

*Not significant.

†P<.01.

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 (MVo2/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 MVo2 and PVA in each run, the slope and MVo2 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. To test whether dobutamine affected the slope and elevation of the MVo2/PVA relation, MVo2 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 MVo2/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. Ees 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, Ees did not decrease significantly. Both coronary flow and arteriovenous oxygen content difference decreased after the denervation. Thus, MVo2 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 Ees by 128±38% on the average. The coefficient of variation (SD/mean value) of Ees 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...
control, and then the stimulating rate was slightly increased during dobutamine.

Fig 2 shows an example of $\text{MV}_2\text{O}_2$-PVA relation obtained under steady-state condition before and during dobutamine infusion during sinus rhythm. In both control and dobutamine runs, $\text{MV}_2\text{O}_2$ 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 $\text{MV}_2\text{O}_2$ 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 $\text{MV}_2\text{O}_2$ axis intercept of the $\text{MV}_2\text{O}_2$-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 $\text{MV}_2\text{O}_2$-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 $\text{MV}_2\text{O}_2$-PVA relation in conscious animals.

Fig 4 shows a comparison between the transient and steady-state $\text{MV}_2\text{O}_2$-PVA relation before (left) and after (right) dobutamine infusion. The transient $\text{MV}_2\text{O}_2$-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 $\text{MV}_2\text{O}_2$-PVA data points tended to be higher than the steady-state $\text{MV}_2\text{O}_2$-PVA regression line and then shifted downward in both control and dobutamine runs. In the pooled data of the transient $\text{MV}_2\text{O}_2$-PVA relation, the $\text{MV}_2\text{O}_2$ 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 $\text{MV}_2\text{O}_2$-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 $\text{MV}_2\text{O}_2$-PVA relation associating PVA with the $\text{MV}_2\text{O}_2$ occurring two beats later. This did not alter our results.

In the steady-state situation, dobutamine significantly shifted the steady-state $\text{MV}_2\text{O}_2$-PVA regression line upward in all hearts (Table 2). The $\text{MV}_2\text{O}_2$ axis intercept of the $\text{MV}_2\text{O}_2$-PVA regression line increased with dobutamine in all hearts. The mean $\text{MV}_2\text{O}_2$ axis intercept increased in response to dobutamine from 0.257±0.0036 to 0.364±0.0061 mL O$_2$·beat$^{-1}$·100 g LV$^{-1}$ ($P<.01$). In seven of eight hearts, the slope of the $\text{MV}_2\text{O}_2$-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 $\text{MV}_2\text{O}_2$-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 $\text{MV}_2\text{O}_2$-PVA relation was 2.23±0.40 during control and 2.85±0.60×10$^{-2}$ 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 $\text{MV}_2\text{O}_2$-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 ($E_a$) 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 $\text{MV}_2\text{O}_2$-PVA relation (Table 3). When PVA was calculated in this manner, dobutamine produced an upward shift of the $\text{MV}_2\text{O}_2$-PVA relation without a significant change in slope.

Fig 5 shows the scatterplots of $\text{MV}_2\text{O}_2$ axis intercept (left) and slope (right) of the steady-state $\text{MV}_2\text{O}_2$-PVA regression line measured from linear ESPVR against $E_a$ in all hearts before and during dobutamine. The $\text{MV}_2\text{O}_2$ axis intercept was significantly correlated with $E_a$, and the correlation coefficient ($r$) was .76. The slope of $\text{MV}_2\text{O}_2$-PVA regression line tended to increase with $E_a$, but did not reach significance ($r=.41$).

**Discussion**

We found in conscious animals that PVA linearly correlated with $\text{MV}_2\text{O}_2$ 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, was 30.9%. Furthermore, the $\text{MV}_2\text{O}_2$-PVA relation was shifted upward by an increase in contractility. These results are consistent with the observations of Suga and colleagues in isolated hearts and confirm that the $\text{MV}_2\text{O}_2$-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

<table>
<thead>
<tr>
<th>Dog</th>
<th>n</th>
<th>HR, bpm</th>
<th>E(_{se}), mm Hg \cdot mL(^{-1}) \cdot 100 g LV(^{-1})</th>
<th>Slope (x10(^{-3})), mL</th>
<th>Intercept, mL O(_{2}) \cdot mm Hg(^{-1}) \cdot mL(^{-1})</th>
<th>ANCOVA</th>
<th>Elevation</th>
<th>Slope</th>
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<tbody>
<tr>
<td>1</td>
<td>CON</td>
<td>4</td>
<td>106</td>
<td>8.5</td>
<td>1.99</td>
<td>0.0216</td>
<td>.960</td>
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<tr>
<td></td>
<td>DOB</td>
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<td>183</td>
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<td>1.82</td>
<td>0.0419</td>
<td>.955</td>
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<tr>
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<td>CON</td>
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<td>104</td>
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<td>2.10</td>
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<tr>
<td></td>
<td>DOB</td>
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<td>188</td>
<td>24.2</td>
<td>3.00</td>
<td>0.0417</td>
<td>.970</td>
<td>*</td>
</tr>
<tr>
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<td>CON</td>
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<td>133</td>
<td>6.3</td>
<td>1.50</td>
<td>0.0247</td>
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</tr>
<tr>
<td></td>
<td>DOB</td>
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<td>199</td>
<td>16.1</td>
<td>2.20</td>
<td>0.0272</td>
<td>.987</td>
<td>*</td>
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<tr>
<td>4</td>
<td>CON</td>
<td>5</td>
<td>114</td>
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<tr>
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<td>CON</td>
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<td>0.0217</td>
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<td>.980</td>
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<tr>
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<tr>
<td></td>
<td>DOB</td>
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<td>165</td>
<td>19.7</td>
<td>3.74</td>
<td>0.0323</td>
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<td>DOB</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>DOB</td>
<td>4</td>
<td>168</td>
<td>10.3</td>
<td>2.52</td>
<td>0.0315</td>
<td>.997</td>
<td>*</td>
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</table>

Mean (linear ESPVR)

<table>
<thead>
<tr>
<th>Dog</th>
<th>n</th>
<th>HR, bpm</th>
<th>E(_{se}), mm Hg \cdot mL(^{-1}) \cdot 100 g LV(^{-1})</th>
<th>Slope (x10(^{-3})), mL</th>
<th>Intercept, mL O(_{2}) \cdot mm Hg(^{-1}) \cdot mL(^{-1})</th>
<th>ANCOVA</th>
<th>Elevation</th>
<th>Slope</th>
</tr>
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<tr>
<td>CON</td>
<td>134±26</td>
<td>8.4±1.9</td>
<td>2.23±0.40</td>
<td>0.0257±0.0036</td>
<td>.985±0.011</td>
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<td></td>
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<tr>
<td>DOB</td>
<td>174±16</td>
<td>19.1±5.1*</td>
<td>2.85±0.60†</td>
<td>0.0364±0.0061*</td>
<td>.988±0.009</td>
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</table>

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\(\text{Vo}_2\)) and PVA were determined at each steady-state loading condition. HR indicates heart rate; bpm, beats per minute; E\(_{se}\), slope of end-systolic pressure-volume relation; n, number of steady-state data sampling points; Slope, slope of M\(\text{Vo}_2\)-PVA regression line; Intercept, M\(\text{Vo}_2\) axis intercept of M\(\text{Vo}_2\)-PVA regression line; Elevation and Slope, ANCOVA to determine if there was a significant change in slope or elevation of M\(\text{Vo}_2\)-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\(\text{Vo}_2\)-PVA relation by beat-to-beat analysis during transient caval occlusions. This technique provides a convenient way to measure M\(\text{Vo}_2\) and PVA over a wide range of loading conditions in a short period of time. LV coronary blood flow and M\(\text{Vo}_2\) 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\(\text{Vo}_2\)-PVA relation obtained on a beat-to-beat basis during a transient caval occlusion was coincident with the M\(\text{Vo}_2\)-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\(\text{Vo}_2\)-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\(\text{Vo}_2\) from the coronary flow of the following beat was calculated, these two M\(\text{Vo}_2\)-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.\(^{4}\) This would tend to accentuate the difference between the steady-state and transient M\(\text{Vo}_2\)-PVA relations. Consistent with our observation that the transient M\(\text{Vo}_2\)-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 +, Δ, 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.

In our control study, both the MVO2 axis intercept, which is thought to represent the energy cost of basal metabolism and calcium cycling, and the slope of the MVO2-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 MVO2-PVA relation line upward, and the MVO2 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, MVO2 at a constant PVA increased by 1.5×10⁻³ mL O₂ for each 1 mm Hg/mL increase in Eₚₑ. This value is very similar to the findings in isolated hearts of 2.4×10⁻³ mL O₂/(mm Hg/mL).25Because the slope of the MVO2-PVA relation increased by dobutamine in seven of the eight animals in our study, the magnitude of the shift of the MVO2-PVA relation was reduced when it was evaluated by extrapolating to the MVO2 axis (ie, PVA=0). Thus, the MVO2 axis intercept increased by only 0.8×10⁻³ mL O₂ per 1 mm Hg/mL increase in Eₚₑ.

In the isolated heart, changes in contractility produce parallel shifts of the MVO2-PVA relation without any alteration of the slope.23 Similarly, in two recent clinical studies,4,6 the slope of the MVO2-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 MVO2-PVA point has been determined after altering contractility, and it has been assumed that there was a parallel shift of the MVO2-PVA relation.5 In other studies,10,11 MVO2 was predicted from the MVO2-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

<table>
<thead>
<tr>
<th>Method of Load Alteration</th>
<th>Eₚₑ, mm Hg · mL⁻¹ · 100 g LV⁻¹</th>
<th>Slope (×10⁻³), mL O₂ · mm Hg⁻¹ · mL⁻¹</th>
<th>Intercept, mL O₂ · beat⁻¹ · 100 g LV⁻¹</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear ESPVR determined by caval occlusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steady-state MVO2-PVA relation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CON</td>
<td>8.4±1.9</td>
<td>2.23±0.040</td>
<td>0.0257±0.0036</td>
<td>.985±.011</td>
</tr>
<tr>
<td>DOB</td>
<td>19.1±5.1*</td>
<td>2.85±0.60†</td>
<td>0.0364±0.0061*</td>
<td>.986±.009</td>
</tr>
<tr>
<td>Transient MVO2-PVA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CON</td>
<td>1.15±0.49‡</td>
<td>0.0540±0.0145‡</td>
<td>.886±.083‡</td>
<td></td>
</tr>
<tr>
<td>DOB</td>
<td>2.69±0.62</td>
<td>0.0461±0.0086‡</td>
<td>.970±.016‡</td>
<td></td>
</tr>
<tr>
<td>Nonlinear ESPVR determined by caval occlusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steady-state (nonlinear ESPVR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CON</td>
<td>2.40±0.41</td>
<td>0.0256±0.0049</td>
<td>.984±.013</td>
<td></td>
</tr>
<tr>
<td>DOB</td>
<td>3.03±0.67*</td>
<td>0.0357±0.0067*</td>
<td>.986±.012</td>
<td></td>
</tr>
<tr>
<td>Steady-state ESPVR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steady-state MVO2-PVA</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(Steady-state ESPVR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CON</td>
<td>11.4±2.3‡</td>
<td>2.89±0.71‡</td>
<td>0.0217±0.0027‡</td>
<td>.980±.014</td>
</tr>
<tr>
<td>DOB</td>
<td>23.1±6.3*‡</td>
<td>3.11±0.91</td>
<td>0.0351±0.0049</td>
<td>.985±.017</td>
</tr>
</tbody>
</table>

Nonlinear end-systolic pressure-volume relation (ESPVR) was calculated from the nonlinear ESPVR under steady-state conditions. Transient oxygen consumption (MVO2)—pressure-volume area (PVA) relation represents MVO2 and PVA data obtained during the transient caval occlusion. Steady-state ESPVR is ESPVR obtained by steady-state pressure-volume loops at 4 to 6 different loading conditions (see text). Eₚₑ indicates slope of end-systolic pressure-volume relation; slope of MVO2-PVA regression line; Intercept, MVO2 axis intercept of MVO2-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 MVO2-PVA relation, ‡P<.05.
contractile state. However, our results suggest that the slope of \( \text{MV}_2\text{PVA} \) relation in conscious animals may increase in response to enhanced contractility.\(^\text{26}\) Therefore, a parallel shift of \( \text{MV}_2\text{PVA} \) 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 \( \text{MV}_2\text{PVA} \) relation caused by dobutamine. We assumed a linear ESPVR to obtain PVA. However, in some hearts, the ESPVRs were slightly curvilinear, especially after dobutamine.\(^\text{12,27-29}\) 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 \( \text{MV}_2\text{PVA} \) relation obtained from the nonlinear ESPVRs were slightly higher than those obtained with the linear ESPVR. However, the increase in the slope of the \( \text{MV}_2\text{PVA} \) 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,\(^\text{30-32}\) 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 PVA. Therefore, increase in heart rate should shift the \( \text{MV}_2\text{PVA} \) 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.\(^\text{33}\) Even when the heart rate was kept constant by atrial pacing, the slope of the \( \text{MV}_2\text{PVA} \) 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 \( \text{MV}_2\text{PVA} \) for basal metabolism\(^\text{33}\) and therefore might affect the relation between \( \text{E}_{\text{es}} \) and \( \text{MV}_2\text{PVA} \) axis intercept of \( \text{MV}_2\text{PVA} \) relation in the present study.

Even after the pharmacological denervation, \( \text{E}_{\text{es}} \) 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, \( \text{E}_{\text{es}} \) 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.\(^\text{7,34}\) When the steady-state ESPVR was used to calculate PVA, the resulting \( \text{MV}_2\text{PVA} \) relation continued to shift upward in response todobutamine. However, the slope did not increase significantly. This suggests that the loading protocol used to generate the ESPVR may influence the response of the \( \text{MV}_2\text{PVA} \) 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.\(^\text{7,15,17}\) The slope of the relation between stroke volume calculated from ultrason-
ically measured LV dimensions and measured by a flow probe is close to unity (1.1±0.3).\textsuperscript{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 MVo$_2$-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.\textsuperscript{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, MVo$_2$ and PVA are linearly correlated in conscious dogs during steady-state changes in loading conditions. However, the MVo$_2$-PVA relation, obtained on a beat-by-beat basis during transient changes in loading conditions, is not coincident with the steady-state MVo$_2$-PVA relation. Dobutamine shifted the MVo$_2$-PVA relation upward, increasing the MVo$_2$ axis intercept. In addition, the slope of the relation increased in seven of eight animals during dobutamine infusion. The MVo$_2$-PVA relation is similar whether the ESPVR is assume to be linear or nonlinear. These results demonstrate that the MVo$_2$-PVA relation developed in isolated hearts applies to the intact circulation of conscious animals during steady-state alterations in loading conditions.

Acknowledgments

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