Relation Between Maximum Time-Varying Elastance Pressure–Volume Areas and Myocardial Oxygen Consumption in Dogs

Mark R. Starling, MD; G.B. John Mancini, MD; Daniel G. Montgomery, BS; and Milton D. Gross, MD

To establish whether pressure–volume areas (PVAs) calculated using the maximum time-varying elastance ($E_{\text{max}}$) have a relation with myocardial oxygen consumption ($\text{MVO}_2$) that improves on other indexes of myocardial oxygen demand, we studied nine dogs of either sex weighing 19–39 kg, which were instrumented with a micromanometer left ventricular (LV) catheter and a Wilton-Webster coronary sinus flow catheter and had red blood cells tagged with technetium-99m for radionuclide angiography. Hemodynamics, coronary sinus flow determinations, and radionuclide angiograms were obtained under control conditions and during three to five steady-state loading conditions (mean±SD, 5.6±0.7). Isochronal pressure–volume data points from each pressure–volume loop were subjected to linear regression analysis to calculate $E_{\text{max}}$. The $E_{\text{max}}$ relations, diastolic curves, and systolic portions of each pressure–volume loop were used to obtain calibrated PVAs. The $E_{\text{max}}$ PVA (mm Hg · ml · beat$^{-1} · 100$ g$^{-1}$) and $\text{MVO}_2$ (ml O$2$ · beat$^{-1} · 100$ g$^{-1}$) values correlated in each animal ($r=0.77$ to 0.99). Their slopes averaged $(3.48±1.68) \times 10^{-5}$ ml O$2$ · mm Hg$^{-1} · $ml$^{-1}$, and their y-axis intercepts averaged 0.07±0.04 ml O$2$ · beat$^{-1} · 100$ g$^{-1}$. When the $\text{MVO}_2$ relations were compared with $E_{\text{max}}$ PVA, LV systolic pressure–rate product, LV stroke work, and a modification of the LV pressure–work index, the $E_{\text{max}}$ PVA, LV systolic pressure–rate product, and LV pressure–work index had similar relations with $\text{MVO}_2$, whereas LV stroke work was a weaker index of $\text{MVO}_2$ ($p<0.05$ versus $E_{\text{max}}$ PVA). This occurred because the $E_{\text{max}}$ PVA:$\text{MVO}_2$ slopes and y-axis intercepts differed in each dog, which was due to differences in basal LV contractility. The $E_{\text{max}}$ PVA:$\text{MVO}_2$ slopes correlated with $E_{\text{max}}$ ($r=0.73$, $p<0.05$), and the y-axis intercepts were also weakly related to $E_{\text{max}}$ ($r=0.48$, $p=0.19$). We conclude that the $E_{\text{max}}$ PVAs calculated using data acquisition techniques that are clinically applicable have relations with $\text{MVO}_2$ that in general do not improve on other indexes of myocardial oxygen demand in this animal preparation. (Circulation 1991;83:304–314)

The left ventricular (LV) maximum time-varying elastance ($E_{\text{max}}$) and end-systolic pressure–volume ($E_s$) relations have been applied in the excised, supported left ventricle, various intact animal preparations, and humans to assess LV contractility under basal conditions$^{1-11}$ and during pharmacological alterations in the contractile state.$^{2,6,11}$ It has been reported$^{12-19}$ that the pressure–volume area (PVA) inscribed by the $E_s$ and diastolic curves and the systolic portion of ejecting beats is linearly related to myocardial oxygen consumption ($\text{MVO}_2$).

Steady-state alterations in LV loading conditions are required to generate multiple PVAs in an animal or humans as it necessitates 3–5 minutes for myocardial blood flow and oxygen extraction to equilibrate with the oxygen demands of a new hemodynamic load.$^{20,21}$ Although these relations are consistently linear in an excised, supported left ventricle,$^{12-19}$ whether PVAs generated using $E_{\text{max}}$ and $E_s$ are also linearly related to $\text{MVO}_2$ when more clinically applicable methodologies are used to generate these relations is not known. It is also not evident whether these PVAs generated over a range of LV loading...
conditions are more closely related to M\(\text{VO}_2\) than are other indexes of myocardial oxygen demand.\(^{22,23}\)

Accordingly, as a prelude to the clinical application of this concept, this investigation was undertaken to determine whether PVAs calculated using \(E_{\text{max}}\) are more closely related to M\(\text{VO}_2\) and therefore improve on other indexes of myocardial oxygen demand in an intact animal preparation.

**Methods**

**Animal Instrumentation**

Nine dogs of either sex weighing 19–39 kg (mean±SD weight, 27±6 kg) were anesthetized with intravenous sodium pentobarbital (35 mg/kg), intubated, and ventilated with 15 ml/kg/min oxygen-enriched room air. Arterial and venous sheaths were inserted for vascular access through a left carotid arteriotomy and internal jugular venotomy. Electrocardiographic limb leads were attached to monitor heart rate. Then a left thoracotomy was performed through the fifth intercostal space, and the descending thoracic aorta and inferior vena cava were isolated and encircled with elastic tubing, which provided a means for the variable constriction of the aorta or inferior vena cava to produce stable alterations in LV loading conditions. The pericardium was incised parallel to the phrenic nerve and left unopposed. A precalibrated micromanometer catheter (Millar Instruments, Houston) was inserted into the left ventricle through an apical stab wound and secured. A Wilton-Webster coronary sinus flow catheter (model CCS-7U-90B, Webster Laboratories, Altadena, Calif.) was passed into the coronary sinus through the right atrial appendage and secured. Then each animal received 1 mg/kg i.v. propranolol to minimize the effects of catecholamines on heart rate and contractility.\(^{23,24}\) Finally, each animal was anticoagulated with 3,000 units heparin.

**Protocol**

Each animal was positioned under the gamma scintillation camera in an obliquity that optimally separated the left ventricle from the adjacent structures. An electrocardiogram, micromanometer LV pressure, and the first derivative of LV pressure (dP/dt) were recorded for 10–20 cardiac cycles at the beginning, middle, and end of each radionuclide acquisition; coronary sinus flow measurements were recorded during the midpoint of each radionuclide acquisition on a Gould 2800S eight-channel physiological recorder at a speed of 100 mm/sec (Gould Electronics, Cleveland, Ohio). The Wilton-Webster coronary sinus flow catheter was interfaced to the physiological recorder through a Wilton-Webster CF-300 control unit, which converts resistance changes in the catheter due to alterations in temperature into calibrated voltages. Using a constant infusion of a room temperature indicator (5% dextrose infused at 38 ml/min), coronary sinus blood flow was calculated from the simultaneously recorded deflections of the calibration constant, the indicator, and the coronary sinus thermostor.\(^{25}\) Finally, systemic arterial and coronary sinus blood samples (0.5 ml) were obtained for analysis. All data were acquired under control conditions and during five additional steady-state hemodynamic conditions produced by either aortic or inferior vena caval constriction. At the completion of the protocol, each animal was killed, the hearts were excised, and the left ventricles were separated from the rest of the cardiac structures. The left ventricles were then weighed (mean weight, 121±18 g; range, 85–142 g).

**Hemodynamics**

The micromanometer LV pressure signals recorded during each radionuclide angiogram were averaged over a minimum of 30 cardiac cycles, and the average LV pressure waveforms were hand digitized using a Calcomp 9100 inductance digitizing surface (resolution, 0.02 mm) at 200 Hz to obtain instantaneous LV pressures and dP/dt using a program developed in this laboratory.\(^{9–11}\) M\(\text{VO}_2\) was calculated using the technique of Ganz et al.\(^{25}\) The systemic arterial and coronary sinus blood samples were analyzed using an ABL2 acid–base laboratory (Radiometer, Copenhagen) to obtain pH, P\(\text{CO}_2\), P\(\text{O}_2\), hemoglobin, and oxygen saturations. Using the measured hemoglobin and oxygen saturations and the oxygen-carrying capacity of hemoglobin, the systemic arterial and coronary sinus oxygen contents were calculated.\(^{27}\) By dividing coronary sinus blood flow obtained using the thermodilution technique by the systemic arterial–coronary sinus oxygen content difference, M\(\text{VO}_2\) was obtained.\(^{25,27}\) M\(\text{VO}_2\) values are given as milliliters of O\(\text{2}\) per beat per 100 g of LV weight.

**Radionuclide Angiography**

Red blood cells were tagged with 30 mCi technetium-99m using a modified in vitro labeling technique.\(^{28}\) A standard field of view gamma scintillation camera (Siemens Gammascience, Inc., Solna, Sweden) equipped with an all-purpose parallel-hole collimator was used. The radionuclide images were acquired under control conditions and during each hemodynamic steady state without altering the camera position into a 64×64 byte matrix of consecutive corresponding 20-msec frames until information from 500 R-R intervals was processed. Midway through the radionuclide acquisition, a 2-ml blood sample was obtained, and the time was recorded. Each blood sample was counted on the collimator at the completion of the protocol for 2 minutes to obtain counts per 2 minutes per 2 ml. The distance from the gamma camera to the center of the left ventricle was obtained directly at the completion of the protocol.

Radionuclide frame-by-frame LV volumes were calculated from hand-drawn region-of-interest count data.\(^{10,11,29,30}\) Briefly, the LV images were background subtracted and smoothed. Then, a hand-drawn LV region-of-interest was outlined by the operator for each frame throughout the cardiac cycle. The frame-by-
frame background-subtracted LV counts were standardized to frame duration and cardiac cycles acquired and were converted to counts per minute. The blood sample counts were corrected for radioisotope decay \( e^{\lambda t} \) where \( \lambda = 0.693/t_{1/2} \), \( t_{1/2} \) of \( ^{99m} \text{Tc} \) is 360 minutes, and \( r \) is the time from drawing to counting the blood sample. The standardized LV counts were then divided by decay-corrected blood sample counts and multiplied by \( (e^{ud}) \) where \( u \) is assumed to represent the linear attenuation coefficient of the \( ^{99m} \text{Tc} \) 140-KeV photons of 0.15 cm\(^{-1}\), and \( d \) represents the directly measured distance from the center of the left ventricle to the gamma scintillation camera.

**Calculation of Left Ventricular Chamber Elastance and Pressure–Volume Areas**

The corresponding micromanometer LV pressures and radionuclide LV volumes for each steady-state loading condition were plotted to obtain pressure–volume loops.\(^{10,11}\) Then, isochronal LV pressure–volume data points from each pressure–volume loop were subjected to linear regression analysis, and the maximum slope of these relations was defined as \( E_{\text{max}} \). This definition of LV chamber performance\(^{5,4,9,11}\) differs from \( E_{\text{es}} \) used in other animal preparations to assess LV contractility\(^{5,7,24,31,33}\) and to generate PVAs to compare with determinations of \( \text{MVO}_{2} \).\(^{12,19,34,35}\) Thus, both \( E_{\text{max}} \) and \( E_{\text{es}} \) relations were calculated in these animals, and they are shown for a representative animal in Figure 1.

PVAs for \( E_{\text{max}} \) and \( E_{\text{es}} \) relations were obtained for each LV loading condition using a calibrated planimeter. As shown in Figure 2, all of the pressure–volume loops were displayed. The pressure–volume data points from minimum LV pressure to end diastole from each pressure–volume loop were used to generate the diastolic curve, which was then extrapolated to meet the similarly extrapolated \( E_{\text{max}} \) and \( E_{\text{es}} \) relations at their corresponding unstressed volumes. The area enclosed by the \( E_{\text{max}} \) and \( E_{\text{es}} \)
relations, the diastolic curves, and the systolic portions of each pressure–volume loop were planimetered to yield areas. These areas were planimetered irrespective of whether they crossed the y axis to a negative extrapolated volume–axis intercept, which occurred in only one animal for $E_\text{es}$ but not for $E_\text{max}$. These areas were then standardized to a planimetered area (mm Hg·ml) of known size for each animal. As schematically illustrated in Figure 2, the PVA includes both the external work performed by the ejecting left ventricle and the potential energy stored within the left ventricle at end systole. The PVA and external work are given in millimeters of mercury per milliliter per beat per 100 g of LV weight.

For comparison to the $E_\text{max}$ PVA:M$\text{VO}_2$ relation, other indexes of myocardial oxygen demand were also compared with determinations of M$\text{VO}_2$ in each animal, including LV systolic pressure–rate product, LV stroke work, and a modification of the LV pressure–work index of Rooke and Feigl. The formula for the modified LV pressure–work index is:

$$M\text{VO}_2=K_1(LVP\times HR)+K_2\frac{(EW\times HR)}{Bwt}+1.43$$

where M$\text{VO}_2$ is LV myocardial oxygen consumption (ml O$_2$/min/100 g), LVP is LV systolic pressure (mm Hg), HR is heart rate (beats/min), EW is LV external work (mm Hg·ml·beat$^{-1}$·100 g$^{-1}$), Bwt is body weight (kg), $K_1$ is $4.08\times10^{-4}$, and $K_2$ is $3.25\times10^{-4}$. In this equation, LV systolic pressure is substituted for systolic arterial pressure, and LV external work is substituted for the arterial pressure–stroke volume product originally used by Rooke and Feigl.

**Statistical Analysis**

All values are given as mean±SD. M$\text{VO}_2$ values (ml O$_2$·beat$^{-1}$·100 g$^{-1}$) were compared with their corresponding PVA values (mm Hg·ml·beat$^{-1}$·100 g$^{-1}$). LV systolic pressure–rate products, LV stroke work (mm Hg·
ml ÷ beat⁻¹ ÷ 100 g⁻¹), and LV pressure–work indexes using linear regression analyses in each animal to obtain slopes, SEEs of the slopes, correlation coefficients, and y-axis intercepts. The mean slopes and y-axis intercepts for the Eₘₐₓ and Eₑₐ PVA: MVo₂ relations were compared by t-tests. The correlation coefficients for the slopes of the Eₘₐₓ PVA: MVo₂ and the other indexes of myocardial oxygen demand: MVo₂ relations were subjected to Z transformation to convert these nonnormally distributed data to more symmetrically distributed data for comparison using t tests with a Bonferroni correction.36 To determine whether the Eₘₐₓ PVA: MVo₂ slopes were similar among animals, an analysis of covariance was used. To establish the variables that affected the slope of this relation, a multiple regression analysis was performed. When a probability value was 0.05 or less, a significant difference or relation was considered present.

Results

Hemodynamic Data

The objective in each animal was to acquire micro-manometer LV pressures and radionuclide angiograms under control conditions and during five additional steady-state hemodynamic conditions produced by either aortic or inferior vena caval constriction. This was achieved in six of the nine animals, whereas two animals had four and one animal had only three additional hemodynamic steady-state acquisitions achieved. Thus, there were from four to six steady-state loading conditions (mean, 5.6 ± 0.7) presented to the left ventricle during which determination of MVo₂, LV pressures, and radionuclide angiograms for LV volumes were satisfactorily accomplished. The range over which LV systolic pressures were varied in each animal by aortic or inferior vena caval constriction was 67–86 mm Hg. The average range of LV systolic pressure achieved was 72±8 mm Hg. The average heart rate in these nine animals was 128±12 beats/min. The mean variance in heart rate for the range of loading conditions achieved by aortic or inferior vena caval constriction was only 5±5 beats/min.

Eₘₐₓ and Eₑₐ Pressure–Volume Area: Myocardial Oxygen Consumption Relations

Eₘₐₓ slopes ranged from 2.78 to 8.85 mm Hg/ml and averaged 6.05±1.86 mm Hg/ml. They did not differ from the Eₑₐ slopes, which ranged from 2.52 to 8.59 mm Hg/ml with a mean of 5.20±1.69 mm Hg/ml. Eₘₐₓ extrapolated volume–axis intercepts ranged from 2 to 20 ml with an average unstressed volume, Vₑₐ, of 10±7 ml. They also did not differ from the Eₑₐ Vₑₐ values, which ranged from -9 to 11 ml with a mean of 4±6 ml.

Slopes relating the Eₘₐₓ and Eₑₐ PVAs to their corresponding MVo₂ values were similar. These slopes averaged (3.48±1.68)×10⁻⁵ for Eₘₐₓ and (3.15±1.38)×10⁻⁵ ml O₂ ÷ mm Hg⁻¹ ÷ ml⁻¹ for Eₑₐ. Moreover, the Eₘₐₓ and Eₑₐ y-axis intercepts averaged 0.07±0.04 and 0.06±0.04 ml O₂ ÷ beat⁻¹ ÷ 100 g⁻¹, respectively, and they did not differ. Representative examples of these relations from one animal are shown in Figure 3. Because the Eₘₐₓ and Eₑₐ PVAs demonstrated comparable relations with determinations of MVo₂ per beat per 100 g of LV weight in these animals, only the Eₘₐₓ PVA: MVo₂ relations were used in subsequent analyses.

The Eₘₐₓ PVA: MVo₂ slopes and y-axis intercepts differed among animals (p<0.05 for both). To establish whether the variability in the Eₘₐₓ PVA: MVo₂ slopes and y-axis intercepts observed might be related to variations in basal contractile state, these values were compared with their corresponding Eₘₐₓ slopes. As shown in Figure 4, the Eₘₐₓ PVA: MVo₂ slopes were related to Eₘₐₓ (r=0.73, p<0.05), whereas the y-axis intercepts were only weakly related to Eₘₐₓ (r=0.48, p=0.19).

Comparison of Eₘₐₓ Pressure–Volume Area, Pressure–Rate Product, Stroke Work, and Pressure–Work Index: Myocardial Oxygen Consumption Relations

The ranges of correlation coefficients for the LV systolic pressure–rate product, LV stroke work, and LV pressure–work index: MVo₂ relations were greater than that for the Eₘₐₓ PVA: MVo₂ relation, suggesting that this latter index of myocardial oxygen demand had a more consistent relation with MVo₂ in an individual animal than did the other three indexes of myocardial oxygen demand (Table 1). However, after Z transformation of the correlation coefficients to convert them from nonnormally to symmetrically distributed data, this was only partially confirmed. The mean Z value of 1.56±0.51 for the Eₘₐₓ PVA: MVo₂ relation was similar to those for the LV systolic pressure–rate product and LV pressure–work index: MVo₂ relations of 1.23±0.59 and 1.35±0.67, respectively, but it was greater than that for the LV stroke work: MVo₂ relation (0.94±0.49, p<0.05).

Discussion

Several indexes of myocardial oxygen demand have been shown to have a relation with determinations of MVo₂.12–23,34,35,37–44 One such index, the PVA, has been shown to be predictive of MVo₂ in the excised, supported left ventricle.12–15,35 This index represents a potentially powerful tool for understanding the relation between MVo₂ and total mechanical energy expended by the left ventricle. It can also measure the efficiency of converting total mechanical energy to external work in the normal human heart and hence investigate the effects of pathophysiological conditions and pharmacological agents on these relations. Before the clinical application of this concept, however, it must be determined whether the PVA: MVo₂ relation can be generated using clinically applicable methodologies and whether this index has a relation with MVo₂. It is also important to determine whether this approach improves on other previously evaluated indexes of myocardial oxygen demand.
The data in the present investigation indicate that steady-state alterations in LV loading conditions, micromanometer LV pressures, and radionuclide LV volumes can be used to calculate PVAs, which are linearly related to determinations of M\(\dot{V}O_2\). \(E_{\max}\) and \(E_{es}\) PVAs demonstrated similar relations with their corresponding M\(\dot{V}O_2\) values in each animal. Consequently, only the \(E_{\max}\) PVA: M\(\dot{V}O_2\) relation was used in the subsequent analyses. The \(E_{\max}\) PVA: M\(\dot{V}O_2\) slopes and \(y\)-axis intercepts differed among animals, which was due in part to the effects of basal LV contractility on this relation. The slopes of the \(E_{\max}\) PVA: M\(\dot{V}O_2\) relation were correlated with \(E_{\max}\) \((r=0.73, p<0.05)\), whereas the \(y\)-axis intercepts were only weakly correlated with \(E_{\max}\) \((r=0.48, p=0.19)\). Thus, the relation between \(E_{\max}\) PVAs and their corresponding M\(\dot{V}O_2\) values were similar to those for the LV systolic pressure–rate product and the LV pressure–work index but better than for LV stroke work and their corresponding M\(\dot{V}O_2\) values. Therefore, these data indicate that the \(E_{\max}\) PVAs have a linear relation with M\(\dot{V}O_2\) when clinically applicable methodologies are used to generate these data, but they do not necessarily improve on other indexes of myocardial oxygen demand, except in the case of LV stroke work.

The PVA represents a physiologically sound measure of the total mechanical energy that can be used by the left ventricle to perform work, irrespective of the mode of LV contraction (i.e., isovolumic, isobaric, or auxobaric\(^{13-15}\)), regardless of whether normal or abnormal contractions are evaluated,\(^9\) or during pharmacological alterations of LV contractility.\(^6\) The PVA differs somewhat from other indexes of myocardial oxygen demand.\(^{20,23,37-44}\) These previously investigated indexes represent only a portion of the total mechanical energy that is incorporated into the PVA. They concentrate, in general, on either the external work performed by the left ventricle, which has as their corollary the fraction of the total mechanical energy performed by the left ventricle as external work, or that portion of total contractile element work stored as internal work at end systole, which is incorporated by the \(E_{\max}\) PVA as the potential energy stored within the left ventricle. Suga\(^{12}\) demonstrated that as much as two thirds of the

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**Figure 3.** Scatterplots of relations among myocardial oxygen consumption (M\(\dot{V}O_2\)) per beat per 100 g (ordinates) and the maximum time-varying elastance top \((E_{\max})\) (top panel) and end-systolic pressure–volume \((E_{es})\) (bottom panel) pressure–volume areas (PVAs) (\(\text{mmHg} \cdot \text{ml} \cdot \text{beat}^{-1} \cdot \text{100 g}^{-1}\)) (abscissas) shown for animal 7. Individual data points from each steady-state left ventricular loading condition, regression line, and correlation coefficient are shown.
potential energy stored within the left ventricle at end systole could be converted to external work under appropriate loading conditions, whereas the remaining one third was assumed to be released as heat during relaxation. The stronger relation demonstrated in the present investigation between the $E_{\text{max}}$ and $\text{MVO}_2$ in each animal, in contrast to that observed between external work and $\text{MVO}_2$, further substantiates that the potential energy incorporated into the PVA contributes significantly to $\text{MVO}_2$.

The previously investigated indexes used to predict $\text{MVO}_2$ are also variably affected by loading conditions, heart rate, and contractility, which may limit their association with $\text{MVO}_2$. Alterations in preload and afterload are used to generate $E_{\text{es}}$ slopes and therefore are incorporated into the PVA. Also, Suga demonstrated that changes in heart rate do not produce an alteration in the PVA:$\text{MVO}_2$ relation over a wide range of loading conditions as both factors are expressed relative to heart rate. In the present investigation, $\beta$-adrenergic blockade minimized the potential variability in heart rate (5±5 beats/min) and, therefore, the LV contractility within each animal due to reflex changes in heart rate that might have been caused by the steady-state alterations in LV load. LV contractility did, however, differ among animals, and it did affect the slopes and, to a lesser extent, the $y$-axis intercepts of the PVA:$\text{MVO}_2$ relation, which may be a limiting factor in the ability of this relation to predict $\text{MVO}_2$ across animals or between patients.

The mean slope and $y$-axis intercept of the $E_{\text{max}}$ PVA:$\text{MVO}_2$ relations in our animals exceeded those in the excised, supported left ventricle, which confirms a similar observation made in a different

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**Figure 4.** Scatterplots of relations among slopes (top panel) and $y$-axis intercepts (bottom panel) of the relations of maximum time-varying elastance ($E_{\text{max}}$) pressure–volume areas (PVAs) to myocardial oxygen consumption ($\text{MVO}_2$) (ordinates) and the $E_{\text{max}}$ relations (abscissas). Individual data points from each animal, regression lines, and correlation coefficients are also displayed.
intact animal preparation by Nozawa et al. Two possible explanations for the steeper slopes and lower correlations for the $E_{\text{max}}$, PVA:MVO$_2$ relation observed in this investigation compared with those reported in the excised, supported left ventricle might be the contribution of the mechanically loaded right ventricle to MVO$_2$ and the importance of basal LV contractility. In the excised, supported LV preparation, the right ventricle was collapsed so that the LV PVA was compared with only LV MVO$_2$. If right ventricular load increases comparably with LV load, then the right ventricular PVA may represent a fraction of "total" ventricular PVA, which if ignored, as in this investigation, may lead to a higher slope for the $E_{\text{max}}$, PVA:MVO$_2$ relation. If one assumes a right ventricular-to-left ventricular pressure ratio of 1:4 to 1:3, then "total" ventricular PVA would be 25–33% greater, and the average PVA:MVO$_2$ slope would decrease proportionately from 3.48 x 10$^{-5}$ to 2.62 or 2.78 x 10$^{-5}$, respectively. These values more closely approximate those in the excised, supported left ventricle. By incorporating the right ventricular PVA, the correlations between the PVAs and determinations of MVO$_2$ in each animal may also have improved. Moreover, in contrast to the initial observations in the excised, supported left ventricle, the slopes of the $E_{\text{max}}$, PVA:MVO$_2$ relation were affected by differences in basal LV contractility among animals, whereas the y-axis intercepts were less affected, which may also have contributed to steeper $E_{\text{max}}$, PVA:MVO$_2$ slopes than in the excised, supported left ventricle. This further suggests that basal LV contractility may be important for defining the $E_{\text{max}}$, PVA:MVO$_2$ relation in an intact heart.

There are several other potential sources of error in the calculation of the relation between the $E_{\text{max}}$ PVAs and determinations of MVO$_2$ that must be considered when clinically applicable methodologies are used to acquire the data in an intact animal or human. The slope of the LV chamber elastance relation may vary due to the limited number and/or range of pressure–volume data points used to generate these relations, the variance in the radionuclide volumetric data, or other factors. Although more than an average of five pressure–volume data points, which is what we used to generate these relations in our animals, may have reduced this potential variance, the range of loading conditions presented to the left ventricle in this investigation should have been sufficient as the LV pressure range in each animal averaged 75 mm Hg. The number of pressure–volume data points is similar to the number used in prior animal studies to generate these relations. However, because one dog had a marginally significant correlation coefficient for the $E_{\text{max}}$, PVA:MVO$_2$ relation, more data points may have been beneficial in increasing the correlations and reducing the variance in the slope calculations.

The radionuclide volumetric technique has been shown in humans to provide highly accurate frame-by-frame LV volumes compared with biplane contrast cineangiography. Because this radionu-
clide volumetric technique provides frame-by-frame LV volumes that are similar to those from biplane contrast cineangiography, it allows for greater data acquisition without the volumetric technique affecting hemodynamics, LV size and performance, or contractility. It may therefore overcome one of the potential limitations to the clinical application of the PVA concept in that a sufficient number of data points (i.e., six or more) can be obtained to guarantee a statistically reliable calculation of the E_max PVA: MVo2 relation in humans, which cannot be accomplished with cineangiography.

We also used β-adrenergic blockade to alleviate the effects of variations in autonomic tone on heart rate and, thus, on LV contractility in each animal. Because the variability in heart rate was minimal in our animals, there was probably little effect of heart rate on contractility, the calculation of the elastance slopes, or the E_max PVA: MVo2 slopes and y-axis intercepts. In patients in whom pathophysiological conditions have severely affected LV size and performance, β-adrenergic blockade may not be indicated for this purpose. In the past, we have used right atrial pacing to maintain heart rate constant to avoid the effects of changes in heart rate on the elastance calculation.9–11 This has produced stable, steady-state hemodynamic conditions throughout the radionuclide data acquisitions.10 Consequently, this approach may be adequate for acquiring the kinds of data required to calculate the E_max PVA: MVo2 relation in humans.

Other factors that have been shown to affect the elastance slope calculations but were probably not operative in our animals include coronary blood flow,32 regional myocardial ischemia,33 and contraction sequence.48 In contrast, the method of altering loading conditions on the left ventricle may have influenced the calculation of these slopes.31,49 Aortic constriction would have provided a closer approximation of the isovolumic length–tension relations, whereas inferior vena caval constriction, because of systolic unloading, would reduce the approximation of the isovolumic length–tension relations.31 Nevertheless, we have reported that despite changes in LV loading conditions altering serum catecholamines, they do not affect isovolumic indexes of contractility in humans,50 which is consistent with previous observations in conscious animals.51,52 Therefore, because steady-state alterations in LV load are a prerequisite for generating the E_max PVA: MVo2 relation, this approach may be satisfactory for the acquisition of these kinds of data in humans.

The potential for the E_max slopes to be curvilinear rather than linear may have contributed to the variance and, thus, lower correlations observed for the E_max PVA: MVo2 relation in some of our animals. This curvilinearity may occur at the extremes of LV loading conditions in that a saturation effect may occur at high arterial loads and the relation may curve toward the volume axis when the left ventricle is unloaded below a critical coronary perfusion pressure.32,49 Moreover, Burkhoff et al53 suggested that contractile-dependent curvilinearity of the E_max relation may exist. Only two of our animals had slope values that may have resided in the range of values in which this kind of curvilinearity to the relation may exist. The assumption of linearity for these relations in our animals (Figure 1), which is consistent with those of other investigators,1–11,24,31–33,48,49 is reasonable because LV load manipulations and, therefore, calculations of E_max were performed within the operational range of LV pressure and volume in each animal.54 Nevertheless, because of the inherent requirements for extrapolation to an unstressed volume to calculate PVAs, some estimation errors for each PVA may be systematically included.

The MVo2 calculation is also subject to error. The position of the thermodilution catheter in the coronary sinus must be guaranteed to obtain reproducible MVo2 values. In our animals, the coronary sinus thermodilution catheter was placed through the right atrial appendage and firmly sutured into place so that variation in its position was minimized. It also requires 3–5 minutes for coronary sinus blood flow and oxygen extraction to come to equilibrium with myocardial oxygen demand after a change to a new steady-state hemodynamic condition,21,22 which was performed in this investigation. This will be particularly important in humans, in whom the coronary sinus flow and oxygen saturation determinations should probably be repeated, at least in duplicate, at each level of load to document the stability of coronary sinus blood flow and oxygen extraction. Consequently, rapid transient alterations in LV loading conditions may not be an appropriate approach to generate E_max PVA: MVo2 relations. Finally, the LV thebesian vein flow would have been missed as well as minor tributary drainage of the posterior and anterior walls using the thermodilution approach to the measurement of coronary sinus blood flow, which would have led to a variable underestimation of the total venous drainage from and therefore the total MVo2 in each of our animals. Nevertheless, the potential variance in the MVo2 calculations performed using this methodology should have been minimized.

The data in the present investigation demonstrate that E_max PVAs generated using clinically applicable data acquisition techniques have linear relations with determinations of MVo2 in this animal preparation. The E_max PVA had a relation with MVo2 that was similar to the LV systolic pressure–rate product and the LV pressure–work index: MVo2 relations but superior to the LV stroke work: MVo2 relations. Therefore, the E_max PVA: MVo2 relations did not substantially improve on two of the more easily obtained indexes of myocardial oxygen demand, which may be related to the lack of consideration by researchers of the mechanically loaded ejecting right ventricle and the effects of basal LV contractility on the E_max PVA: MVo2 relation in the intact animal heart. The E_max PVA does, however, improve on
external work as a predictor of M\(\text{V}O_2\) due to the incorporation of the internal work performed by the left ventricle represented by the potential energy portion of the PVA. Although the PVA does not appear to improve substantially on these indexes of myocardial oxygen demand in this intact animal preparation, it does represent an alternative approach for assessing the coupling of LV mechanical performance to energy use that may provide some insight into the effects of pathological processes or pharmacological agents on myocardial mechanics and energetics in humans.

Acknowledgments

We appreciate the assistance of Sheila Squicciarini, BS, Diane Bauer, and Penny Weaver in the preparation of this manuscript.

References


Relation between maximum time-varying elastance pressure-volume areas and myocardial oxygen consumption in dogs.
M R Starling, G B Mancini, D G Montgomery and M D Gross

_Circulation_. 1991;83:304-314
doi: 10.1161/01.CIR.83.1.304

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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