Comparison of Hemodynamic Determinants for Myocardial Oxygen Consumption Under Different Contractile States in Human Ventricle

Hideyuki Takaoka, MD; Motoshi Takeuchi, MD; Michio Odake, MD; Yoshihiko Hayashi, MD; Katsuya Hata, MD; Masuki Mori, MD; and Mitsuhiro Yokoyama, MD

**Background.** Recently, several indexes such as tension–time index (TTI), tension–time or force–time integral (FTI), rate–pressure product (RPP), pressure–work index (PWI), and systolic pressure–volume area (PVA) have been developed as predictors of myocardial oxygen consumption in experimental and clinical studies. However, it is still unclear whether these indexes are reliable predictors of myocardial oxygen consumption under various contractile states in human hearts.

**Methods and Results.** We assessed the relation between TTI, FTI, RPP, PWI, and PVA and myocardial oxygen consumption per beat (Vo2) in 13 patients with heart disease during volume loading. Left ventricular (LV) volume and pressure were measured simultaneously by the conductance catheter with the tipped micromanometer technique. Vo2 was calculated from arterial coronary sinus oxygen content difference, and coronary sinus blood flow was measured by the thermodilution method. After z transformation of the correlation coefficients, mean z value for the Vo2–PVA relation (1.83±0.60) was greater than those for the Vo2–TTI relation (1.22±0.66; p<0.005), Vo2–FTI relation (1.18±0.61; p<0.05), Vo2–RPP relation (0.95±0.65; p<0.05), and Vo2–PWI relation (1.24±0.58; p<0.05). During dobutamine infusion (5 μg·kg⁻¹·min⁻¹) in five of the 13 patients, Vo2 also correlated best with PVA (z=1.70±0.89) compared with TTI (z=1.43±0.60), FTI (z=1.48±0.95), RPP (z=1.00±0.53), and PWI (z=0.88±0.80). The contractile efficiency (38±14% to 38±20%) of the reciprocal of the slope of the Vo2–PVA relation, remained unchanged, whereas the Vo2PVA (Vo2 at PVA=0.8 J per beat/100 g LV) increased from 1.48±1.16 to 2.06±1.13 J per beat/100 g LV (p<0.05). These results show the parallel upward shift of the Vo2–PVA relation during dobutamine infusion. Because increases in the Vo2–intercept represent the Vo2 for the increased excitation–contraction (E-C) coupling associated with the augmented contractile state, the parallelism of the Vo2–PVA relation could discriminate between Vo2 for mechanical work (PVA-dependent Vo2) and Vo2 for E-C coupling (PVA-independent Vo2).

**Conclusions.** The results of the present study indicate that PVA is a reliable and valuable predictor of myocardial oxygen consumption under different contractile states in human hearts. The Vo2–PVA relation could provide useful information about mechanoenergetics in diseased human hearts. (Circulation 1993;87:59–69)

**KEY WORDS** • myocardial energetics • myocardial oxygen consumption • pressure–volume relation • ventricular function

Several indexes have been used to predict myocardial oxygen consumption from hemodynamic data such as tension–time index (TTI), tension–time or force–time integral (FTI), rate–pressure product (RPP), pressure–work index (PWI), and systolic stress–time integral (STI) in experimental and clinical studies. TTI is the area under the systolic portion of the aortic pressure curve, a relatively easily obtainable index that has been shown to correlate with myocardial oxygen consumption in excised, supported dog left ventricle (LV). FTI also correlated well with myocardial oxygen consumption in excised or in situ animal LV. STI has been shown to be related to myocardial oxygen consumption by using left ventriculography or echocardiography in human diseased hearts. However, whether these indexes can consistently serve as reliable predictors of oxygen consumption under various contractile conditions in humans is unclear.

Recently, systolic pressure–volume area (PVA) has also been proposed as a predictor of myocardial oxygen consumption in the excised, supported dog heart and intact animal heart. PVA is the area circumscribed by the end-systolic pressure–volume relation (ESPVR), end-diastolic pressure–volume relation (EDPVR), and systolic pressure–volume trajectory and has been considered to represent the total mechanical energy generated by the
TABLE 1. Patient Profile

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Dx</th>
<th>HR (min⁻¹)</th>
<th>ESP (mm Hg)</th>
<th>EDP (mm Hg)</th>
<th>EDVI (ml/m²)</th>
<th>ESVI (ml/m²)</th>
<th>EF (%)</th>
<th>Eₘₚₑ (mm Hg/ml/m²)</th>
<th>V₀ (ml/m²)</th>
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Mean 56
SD 8

Dx, diagnosis; HR, heart rate; ESP, end-systolic pressure; EDP, end-diastolic pressure; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; EF, ejection fraction; Eₘₚₑ, slope of the end-systolic pressure-volume relation; V₀, volume-axis intercept of the end-systolic pressure-volume relation; OMI, old myocardial infarction; AP, angina pectoris.

LV has been shown to linearly correlate with LV oxygen consumption per beat (VO₂) independent of loading conditions, mode of contraction, and contractile state. However, Hasenfuss et al have shown by using left ventriculography that STI rather than PVA correlates well with VO₂ in patients with dilated cardiomyopathy. Starling et al have shown that PVA obtained by radionuclide angiography correlates with VO₂ but does not necessarily improve the correlation on other indexes of VO₂ such as RPP and PWI in the intact animal preparation. On the other hand, Suga et al reported that FTI significantly decreased with increases in stroke volume despite constant PVA and VO₂, which indicates that PVA is superior to FTI as a predictor of VO₂ under a variety of loading conditions.

Can we use PVA as a reliable predictor of VO₂ in a clinical setting? It is unknown whether PVA linearly correlates with VO₂ under different contractile states in humans. The purpose of this study was to examine which hemodynamic index correlates best with VO₂ among TTI, FTI, RPP, PWI, and PVA under different contractile states in human diseased hearts.

Methods

Patient Population

Thirteen patients (mean age, 56±8 years; 12 men and one woman; five patients with angina pectoris and eight patients with previous myocardial infarction) undergoing cardiac catheterization for the evaluation of ischemic heart disease were enrolled. Table 1 lists the patient profile. Patients with acute myocardial infarction, valvular heart disease, or high-risk hemodynamic instability were excluded. Patients with idiopathic or ischemic cardiomyopathy were also excluded because the conductance catheter used in the present study did not work well in markedly dilated hearts with low ejection fractions. All patients had no dyskinesia in LV wall motion. Mean ejection fraction (EF) was 54±19%.

Written informed consent was obtained from each patient before the study, and no unfavorable complications occurred as a result of this study.

Catheterization Procedure

All diuretic and vasodilator medications were withheld for 24 hours before the study. The patients received routine catheterization including coronary angiography and left ventriculography as previously described in detail. After completion of routine catheterization, an 8F micromanometer-tipped conductance catheter was advanced to the LV through the 9F femoral sheath. A 7F thermoliation Swan-Ganz catheter (Goodtech Inc.) was advanced to the pulmonary artery through the 8F femoral sheath, and an 8F Webster catheter (Wilton Webster Manufacturing Co.) was inserted into the coronary sinus (CS) through the left subclavian 8F sheath, as confirmed by contrast injection. Right atrial pacing was made by the tipped electrodes of the Webster catheter at 80–90 beats per minute (about 10 beats per minute more than baseline heart rate).

Volume Measurement

The conductance catheter had eight platinum electrodes and generated an electrical field (2 kHz, 30 μA) in the LV from electrodes at the apex and at the aortic valve. Sensing electrodes evenly distributed along the catheter measured conductance between electrode pairs located within the LV. The conductances are summed and converted to the volume using a signal coordinator, Sigma 5 (Leycom Inc.). The volume (V) of the LV at any time is calculated as

\[ V(t) = 1/\alpha \cdot [L^2 \cdot \rho \cdot G(t) - \alpha V_c] \]

where G(t) is the instantaneous sum of the conductances, α is a dimensionless constant, L equals distance between sensing electrodes, ρ equals resistivity of blood,
which is inversely related to conductivity, and \( \alpha V_c \) is the correcting volume for the conductance of the surrounding tissues.

To determine \( \alpha V_c \), 10 ml of hypertonic saline (5% NaCl) was injected as a bolus into the main pulmonary artery through the distal port of the thermodilution catheter, causing a transient increase in measured volume, \( G(t) \), without significantly altering cavity volume. The calculation of parallel conductance by the saline method assumes that \( V(t) \) remains constant and that ejection fraction does not change.\(^{32,33}\) In addition, stroke volume (SV) determined by the conductance catheter does not always agree with SV determined by the thermodilution method or cineventriculography. Thus, the relation between the actual volume of blood in the LV and the signal generated from the catheter can be estimated as \( 1/\alpha \). To estimate the gain constant \( 1/\alpha \), we obtained the ratio of “true” SV determined by the thermodilution method to SV determined by the conductance catheter.\(^{34}\)

**Assessment of LV Contractility**

With completion of calibration, a large balloon occlusion catheter (Baxter, Inc.) was advanced to the right atrium–inferior vena cava junction through the 9F femoral sheath. The balloon was rapidly inflated in the right atrium and pulled back to occlude venous return. Pressure–volume loops for the sequence of the beats after the reduction in LV preload resulting in a 30–40-mm Hg drop in LV systolic pressure were recorded (8–10 beats). The balloon then was deflated, and both pressure and volume rapidly returned to baseline. This procedure was repeated at least twice to obtain ESPVRs. The slope of an ESPVR, \( E_{\text{max}} \), as a load-independent index of contractility and the volume intercept of an ESPVR, \( V_0 \), were obtained by linear regression analysis, as shown in Figure 1A.\(^{25–29}\)

**Calculation of Tension–Time Index**

TTI per beat in mm Hg per second was originally obtained from the area under the systolic portion of the aortic pressure curve and is equal to the mean systolic pressure times the duration of systole.\(^1\) We calculated TTI as the area under the systolic portion (from end diastole to end systole) of the LV pressure curve because we did not measure aortic pressure in the present study. However, there was little difference between our TTI and the original TTI.

**Calculation of Force–Time Integral**

FTI is the time integral of total ventricular wall force through one cardiac cycle. Total ventricular force (\( F \)) in grams was calculated as 1.36 (grams per cm\(^2\)/mm Hg) multiplied by the product of ventricular pressure (\( P \)) (mm Hg) and lumen cross-sectional area (\( A \)) (cm\(^2\)) based on the force–equilibrium equation for a sphere.\(^7\) Thus, \( F = 1.36 \cdot P \cdot A \).\(^{1,4,18}\) To obtain FTI, this total force was integrated through one cardiac cycle.\(^5,\text{8,1}8\)

**Calculation of Rate–Pressure Product**

RPP in mm Hg per second was calculated as LV systolic pressure multiplied by heart rate.\(^9\)

**Calculation of Pressure–Work Index**

PWI in milliliters of O\(_2\) per minute per 100 g was calculated according to the modified formula proposed by Rooke and Feigl\(^{10}\) as

\[
\text{PWI} = K_1 \cdot (\text{LVSP} \cdot \text{HR}) + K_2 \cdot (\text{EW} \cdot \text{HR}) / \text{body wt} + 1.43
\]

where LVSP is LV systolic pressure (mm Hg), HR is heart rate (beats per minute), EW is external work (mm Hg·ml/beat/100 g), body wt is body weight (kilograms), \( K_1 \) is 4.08\( \times 10^{-4} \), and \( K_2 \) is 3.25\( \times 10^{-4} \).

**Calculation of Pressure–Volume Area**

PVA was calculated as an area that is bounded by the ESPVR, the EDPVR, and the systolic pressure–volume trajectory of each beat.\(^{14,15}\) As shown in Figure 1B. The unit of PVA, mm Hg·ml per beat/100 g LV, was converted into the unit of energy, joules per beat/100 g LV, where 1 mm Hg·ml is equivalent to 1.33\( \times 10^{-4} \) J.

**Measurement of Myocardial Oxygen Consumption**

Using the Webster catheter advanced into the CS, coronary sinus blood flow (CSF) was measured at least twice during a 30-second continuous injection of room-temperature indicator (5% CSF) through the catheter lumen at a rate of 40 ml/min with use of a Mark IV angiographic injector (Medrad Inc.). CSF measurements were performed with previously established methods.\(^{41,42}\) In all patients, coronary venous blood was sampled from the distal lumen of the Webster catheter for the oximetry and determination of myocardial oxygen consumption. Myocardial oxygen consumption per minute was calcu-
lated as the product of CSF (milliliters per minute) and coronary arteriovenous oxygen content difference (vol%), divided by heart rate to yield myocardial oxygen consumption per beat (Vo2). The unit of Vo2, ml O2 per beat, was converted into the unit of energy, joules per beat, where 1 ml O2 is equivalent to 20 J.

Assessment of LV Mass Weight

We calculated LV wall volume according to the modified method of Rackley et al using a computer system (LVM700, Philips). The total volume of LV chamber and wall, V(C+w), is approximated by that of the corresponding ellipsoid

\[ V_{(C+w)} = \pi h \cdot (1+2h)(4A/\pi+2h)^2 \]

where h is wall thickness measured at end diastole at the LV free wall in the right anterior oblique projection, I is the long axis, and A is the area of the ventricular traced silhouettes in the right anterior oblique projection. LV mass weight (LVM) is calculated as

\[ LVM = 1.050 \cdot V(w) = 1.050(V_{(C+w)} - V(C)) \]

where V(w) is wall volume, V(C) is the chamber volume, and 1.050 is the specific gravity of heart muscle. We normalized Vo2 and its hemodynamic determinants using the LV mass weight.

Study Protocol

Control study. After adequate placement of both the conductance catheter and the Webster catheter, blood resistivity (\( \rho \)) was measured and entered into the signal coordinator, and volume correction by \( \alpha \)Vc and 1/\( \alpha \) was performed. Atrial (CS) pacing then was started at a fixed heart rate. After steady-state hemodynamics, pressure–volume loops, and Vo2 were measured, transient vena caval occlusions were performed several times; 100–200 ml of 10% dextran solution then was carefully infused in 5 minutes. After stabilization of hemodynamics was confirmed, steady-state hemodynamics, pressure–volume loops, and Vo2 were measured. Volume loading was repeated two or three times, and steady-state hemodynamics after volume loading, pressure–volume loops, and Vo2 were measured at each volume loading stage. PVA and Vo2 were measured twice at each stage; therefore, we obtained six or eight points of Vo2 and hemodynamic indexes in an individual heart. At the end of this protocol, transient vena caval occlusion was repeated. We measured \( \rho \) and entered into the signal coordinator every time when more than 400 ml of dextran solution was infused. Our previous study has shown that dextran infusion does not alter myocardial contractility or induce myocardial ischemia.

Dobutamine study. After measurements during control conditions, dobutamine was administered intravenously at a rate of 5 \( \mu \)g·kg\(^{-1}\)·min\(^{-1}\) in five of the 13 patients to increase contractility. We selected only patients without critical coronary artery stenosis to avoid myocardial ischemia during dobutamine infusion. Similar measurements to the control study then were repeated.

Data Analysis

We obtained the slope and the Vo2- intercept of the relation between Vo2 and hemodynamic determinants TTI, FTI, RPP, PWI, and PVA by applying linear regression analysis. The correlation coefficients of the regression lines were compared by paired t test after z transformation.

To minimize the estimation error of the Vo2-intercept of each relation caused by extrapolation of the Vo2- intercept, we calculated Vo2 at the median of the hemodynamic determinants within the working range in the 13 patients, that is, Vo2 at TTI of 20 mm Hg · seconds per beat/100 g LV (Vo2,TTI 20), Vo2 at FTI of 1,000 g · seconds per beat/100 g LV (Vo2,FTI 1,000), Vo2 at RPP of 10,000 mm Hg · seconds per beat/100 g LV (Vo2,RPP 10,000), Vo2 at PWI of 1.0 J per 100 g LV (Vo2,PWI 1.0), and Vo2 at PVA of 0.8 J per 100 g LV (Vo2,PVA 0.8). To determine the shift of these relations during the inotropic intervention, we compared the Vo2,TTI 20, the Vo2,FTI 1,000, the Vo2,RPP 10,000, the Vo2,PWI 1.0, and the Vo2,PVA 0.8 before and during dobutamine infusion. This method could eliminate not only the error in the Vo2- intercept caused by extrapolation but also the influence of the mechanical work on Vo2.

Contractile Efficiency

The reciprocal of the slope of the linear Vo2-PVA relation has been considered to reflect the chemomechanical energy transduction efficiency from excess Vo2 above the Vo2-intercept (PVA-dependent Vo2) to PVA. We call this efficiency “contractile efficiency,” according to Suga. We calculated the contractile efficiency before and during dobutamine infusion.

Statistics

ANOVA was applied to compare the z values for the relations between Vo2 and hemodynamic determinants during control and enhanced contractile states. When ANOVA showed statistical significance by an F test, the mean values were compared by the least significant difference method. The slopes, the intercepts, and other variables of those relations before and during dobutamine infusion were compared by paired t test. The regression lines of those relations before and during dobutamine infusion in an individual heart were also compared by ANCOVA. A value of p<0.05 was considered statistically significant. Data are presented as mean±SD.

Results

Patient Profile

Table 1 lists the patient profile and hemodynamic data during control conditions. There were five patients with angina pectoris (AP) and eight patients with previous myocardial infarction (OMI). EF (74±7% versus 42±10%, p<0.05) and Emax (3.9±1.6 versus 2.9±1.2 mm Hg/ml/m², p<0.05) in patients with AP were significantly larger than those in patients with OMI.

Comparison of the Relation Between Vo2 and Hemodynamic Determinants

Table 2 summarizes the relation between myocardial oxygen consumption and hemodynamic determinants in the 13 patients during control conditions. The mean value of the correlation coefficient was high in each relation. After z transformation of the correlation coefficients of linear regressions, ANOVA showed that the mean z value for the Vo2-PVA relation was significantly greater than those for the Vo2-TTI relation (p<0.05), the Vo2-FTI
### Table 2. Relation Between Myocardial Oxygen Consumption and Hemodynamic Indexes During Control Contractile State

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<tr>
<th>Patient</th>
<th>Slope (joules per mm Hg/sec)</th>
<th>Intercept (joules per beat/100 g LV)</th>
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**Mean** | 0.105                       | 0.01                                | 0.752 | 1.22 | 2.35 | 0.65  | 0.739 | 1.18 |

**SD**  | 0.083                       | 1.98                                | 0.253 | 0.60 | 2.36 | 1.76  | 0.277 | 0.61 |

<table>
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<tr>
<th>Slope (10^{-3} J per mm Hg/sec)</th>
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**Mean** | 1.70                                | 0.46 | 0.625 | 0.95 | 1.161 | 0.36  | 0.767 | 1.24 |

**SD**  | 2.93                                | 3.76 | 0.295 | 0.65 | 1.992 | 2.48  | 0.249 | 0.58 |

<table>
<thead>
<tr>
<th>Slope (ml O2 per mm Hg/ml)</th>
<th>Dimensionless</th>
<th>Contractile efficiency (%)</th>
<th>Intercept (ml O2 per beat/100 g LV)</th>
<th>(joules per beat/100 g LV)</th>
<th>r</th>
<th>z</th>
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<td>0.979*</td>
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<tr>
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<tr>
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<td>-0.108</td>
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<tr>
<td>9</td>
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<tr>
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<td>0.034</td>
<td>0.676</td>
<td>0.943*</td>
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</table>

**Mean** | 1.67          | 2.42                       | 44                                 | 0.001                     | 0.017 | 0.916 | 1.833 |

**SD**  | 0.56          | 0.72                       | 12                                 | 0.049                     | 0.989 | 0.083 | 0.60 |

**O2**, myocardial oxygen consumption per beat; TTI, tension–time index; FTI, force–time integral; RPP, rate–pressure product; PWI, pressure–work index; PVA, systolic pressure–volume area; LV, left ventricle.

*Significant correlation; †values for patients (designated *) who had significant correlation between myocardial oxygen consumption and hemodynamic indexes; §p<0.05 vs. O2–TTI relation, O2–FTI relation, and O2–PWI relation; §§p<0.01 vs. O2–RPP relation.
TABLE 3.  Influence of Dobutamine on Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Control study</th>
<th>Dobutamine study</th>
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<tbody>
<tr>
<td>ESP (mm Hg)</td>
<td>123±18</td>
<td>137±18</td>
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<tr>
<td>EDP (mm Hg)</td>
<td>18±9</td>
<td>17±11</td>
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<td>EDVI (ml/m²)</td>
<td>95±28</td>
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<tr>
<td>ESVI (ml/m²)</td>
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<td>55±38*</td>
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<tr>
<td>EF (%)</td>
<td>39±18</td>
<td>44±19*</td>
</tr>
<tr>
<td>CSF (ml/min)</td>
<td>79±29</td>
<td>105±26*</td>
</tr>
<tr>
<td>VO₂ (ml O₂/beat)</td>
<td>0.135±0.044</td>
<td>0.152±0.038</td>
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<tr>
<td>Eₚₐₓ (mm Hg per ml/m²)</td>
<td>2.4±0.4</td>
<td>3.9±1.4*</td>
</tr>
<tr>
<td>VO₀ (ml/m³)</td>
<td>12±36</td>
<td>14±48</td>
</tr>
</tbody>
</table>

ESP, end-systolic pressure; EDP, end-diastolic pressure; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; EF, ejection fraction; CSF, coronary sinus flow; VO₂, myocardial oxygen consumption; Eₚₐₓ, slope of the end-systolic pressure-volume relation; VO₀, volume-axis intercept of the end-systolic pressure-volume relation. *p<0.05 vs. control study.

relation (p<0.05), the VO₂-RPP relation (p<0.01), and the VO₂-PWI relation (p<0.05). Furthermore, all patients showed statistical significance for the VO₂-PVA relation, whereas nine, eight, five, and five of the 13 patients showed statistical significance for the VO₂-TTI, VO₂-FTI, VO₂-RPP, and VO₂-PWI relation, respectively. Thus, our results indicate that PVA correlated best with VO₂ among TTI, FTI, RPP, PWI, and PVA.

Effect of Dobutamine on the Relation Between VO₂ and Hemodynamic Determinants

Table 3 summarizes the influence of dobutamine on hemodynamics. Eₚₐₓ increased by 62±38% during dobutamine infusion, whereas the volume-axis intercept, VO₀, did not change. EF (11±10%), coronary sinus flow (37±21%), and VO₂ (16±23%) increased, and end-systolic volume index (–15±15%) decreased. End-systolic pressure, end-diastolic pressure, and end-diastolic volume index remained unchanged.

During dobutamine infusion, the mean z values for the correlation coefficients were 1.43±0.86 for the VO₂-TTI relation, 1.48±0.86 for the VO₂-FTI relation, 1.00±0.53 for the VO₂-RPP relation, 0.88±0.80 for the VO₂-PWI relation, and 1.70±0.89 for the VO₂-PVA relation, respectively. The mean z value for the VO₂-PVA relation tended to be larger than others, although it did not reach statistical significance.

Figure 2 compares mean values for the slope of the relation between VO₂ and hemodynamic determinants before and during dobutamine infusion. The mean value for the slope of the VO₂-TTI relation (from 0.066±0.062 to 0.244±0.277 J/mm Hg per second; NS), the VO₂-RPP relation (from 3.21±1.48 to 1.71±1.02 J/100 g LV; NS) and the VO₂-PWI relation (from 1.789±0.366 to 0.509±1.764; NS) remained unchanged. On the other hand, the slope of the VO₂-FTI relation tended to increase from 2.35±2.36 to 4.29±3.15) 10⁻² J per gram/sec (p=0.056).

Figure 3 shows the comparison of the VO₂ at the median of the hemodynamic determinants before and during dobutamine infusion. The VO₂-TTI 28 (from 1.82±0.79 to 1.12±2.51 J per beat/100 g LV; NS) and the VO₂-PWI 1.0 (from 1.24±0.81 to 1.40±2.39 J per beat/100 g LV; NS) remained unchanged, and the VO₂-RPP 1.0 (from 1.71±1.02 to 1.31±0.98 J per beat/100 g LV; p=0.01) decreased. On the other hand, the VO₂-FTI 1.0 (from 2.23±0.56 to 3.35±1.08 J per beat/100

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Bar graphs showing the effect of dobutamine on the mean slope of the VO₂-TTI, VO₂-FTI, VO₂-RPP, VO₂-PWI, and VO₂-PVA relations. The slope of the VO₂-FTI relation tended to increase (p=0.056), whereas others remained unchanged. VO₂, myocardial oxygen consumption per beat; TTI, tension-time index; FTI, force-time integral; RPP, pressure-rate product; PWI, pressure-work index; PVA, systolic pressure-volume area; LV, left ventricle.
Comparison of the $V_{O_2}$-PVA Relation Between AP and OMI

Figure 5 shows the individual data points for PVA and $V_{O_2}$. We have plotted the data from five patients with AP in open circles and those from eight patients with OMI in closed circles. The two bold lines show the mean slope and the $V_{O_2}$-intercept for AP and OMI. The mean values of the slopes of the regression lines for AP and OMI were 2.23±0.70 and 2.55±0.75. The mean values of the $V_{O_2}$-intercepts of the regression lines were −0.19±1.48 and 0.14±0.61. The two regression lines for AP and OMI do not seem to differ from each other.

The contractile efficiency, the reciprocal of the slope of the linear $V_{O_2}$-PVA relation, was 44±12% for pooled data, which is consistent with previous reports. Furthermore, there was no difference in the contractile efficiency between AP and OMI (48±13% versus 42±12%; NS).

Discussion

Our results demonstrate that PVA is the best predictor of $V_{O_2}$ under different contractile states in human diseased hearts. Furthermore, a parallel upward shift of the $V_{O_2}$-PVA relation was observed with dobutamine infusion. Thus, we were able to assess the contractile efficiency and confirmed that it remained unchanged during enhanced contractile state with dobutamine in human diseased hearts.

Compared with TTI, FTI, RPP, and PWI, PVA correlated best with $V_{O_2}$ under different contractile states in the present study. After $z$ transformation of the correlation coefficients of the regression lines, the mean $z$ value for the $V_{O_2}$-PVA relation was significantly greater than those for other relations. Furthermore, all patients showed statistical significance for the $V_{O_2}$-PVA relation, whereas a part of the patients showed statistical significance for other relations. Thus, our results indicate that PVA correlated best with $V_{O_2}$ among TTI, FTI, RPP, PWI, and PVA. These results are consistent with the earlier reports.

Why did FTI correlate less with $V_{O_2}$ than with PVA in this study? Suga et al. have shown that FTI significantly decreased with increases in SV despite constant PVA and $V_{O_2}$. This report indicates that FTI may dissociate from $V_{O_2}$ when SV and EF vary. SV and EF were altered significantly in our protocol as we applied volume loading. Thus, volume loading may be, at least in part, responsible for better correlation of $V_{O_2}$ with PVA than FTI in our study. In addition, we have to take account of calculation of force using a thin-walled...
spherical model. Because it would be quite complicated to measure LV wall thickness and diameter instantaneously in our study, we applied a thin-walled spherical model. Force could have been different using a thick-walled ellipsoid model.

Starling et al.\textsuperscript{22} reported that the relations between PVA and $\dot{V}O_2$ were similar to those for RPP and PWI, and, therefore, PVA does not necessarily improve on other determinants for $\dot{V}O_2$. The results of the present study, however, indicate that PVA is superior as an index of $\dot{V}O_2$ to RPP and PWI in humans. Why PVA was not superior to RPP and PWI in the study of Starling et al. is unclear. One possible explanation of why RPP and PWI dissociated from $\dot{V}O_2$ in the present study is that the volume loading increased $\dot{V}O_2$ significantly, whereas it did not alter the heart rate and the end-systolic pressure. This may also be responsible for the dissociation of TTI from $\dot{V}O_2$ in the present study.

Although STI was not assessed in the present study, it has also been proposed as an important index of $\dot{V}O_2$ in clinical studies.\textsuperscript{11-13} Hasenfuss et al.\textsuperscript{13} reported that $\dot{V}O_2$ correlated well with STI rather than PVA in patients with dilated cardiomyopathy. They described that the better correlation with $\dot{V}O_2$ of STI than PVA may be because LV geometry and wall thickness are inadequately considered in PVA. In the study of Hasenfuss et al, PVA was calculated on the assumption that the volume intercept of the ESPVR, $V_o$, was zero. When we assumed that $V_o$ was zero in the present study, the correlation coefficient of the $\dot{V}O_2$-PVA relation decreased in nine of the 13 patients, but the mean value did not change significantly (from 0.916±0.083 to 0.913±0.071). Thus, the better correlation with $\dot{V}O_2$ of STI in their study may be, at least partially, related to marked LV dilation rather than the assumption that $V_o$ is 0 ml. In the present study, however, a high correlation coefficient was observed ($r=0.970$) even in a patient with marked LV dilation (LV end-diastolic volume =216 ml). Further study will be needed to evaluate myocardial energetics in patients with marked LV dilation.

Because PVA is theoretically an expression of the total mechanical energy, the dimensionless ratio of PVA (in joules per beat) to excess $\dot{V}O_2$ above the $\dot{V}O_2$-intercept (in joules per beat) has been considered...
the ratio of the total mechanical energy output to energy input that is used exclusively for mechanical contraction, which reflects the chemomechanical energy transduction efficiency of the contractile machinery, i.e., contractile efficiency. Sugai reported that the contractile efficiency was approximately 40% in excised, blood-perfused, normal dog hearts. Goto et al. reported 40±4% in excised, blood-perfused, normal rabbit hearts. Chung et al. reported 48±30% with autonomic blockade and 41±12% with norepinephrine infusion in intact dog hearts, using a high-speed computed tomography. Starling et al. reported 25±13% in intact dog hearts using radionuclide ventriculography. The reason for the lower contractile efficiency in the study of Starling et al. is unclear, but it might be due to the difference in methodology they chose. In the present study, we were able to obtain linear $V_{O_2}$-PVA relations in all patients using the conductance catheter method; the contractile efficiency derived from these linear $V_{O_2}$-PVA relations was 44±12% in control contractile state and 38±20% during dobutamine infusion, which is consistent with earlier experimental reports. These results for contractile efficiency confirm the accuracy of our methodology to assess the $V_{O_2}$-PVA relation.

With dobutamine infusion, $E_{max}$ increased significantly, and only the $V_{O_2}$-PVA relations shifted upward without a change in the slopes. To determine the shift of the relation between $V_{O_2}$ and hemodynamic determinants, one should compare the $V_{O_2}$-intercepts before and during dobutamine infusion. However, to minimize the estimation error in the $V_{O_2}$-intercept of these relations caused by extrapolation, we compared $V_{O_2}$ at the median PVA within the working range in five of the 13 patients (0.8 J per beat/100 g LV; $V_{O_2,PVA 0.8}$) before and during dobutamine infusion. Similarly, we also compared $V_{O_2}$ at TTI of 20 mm Hg • sec per beat/100 g LV ($V_{O_2,TTI 20}$), $V_{O_2}$ at TFI of 1,000 g • sec per beat/100 g LV ($V_{O_2,FTI 1,000}$), $V_{O_2}$ at RPP of 10 mm Hg per sec/100 g LV ($V_{O_2,RPP 10}$), and $V_{O_2}$ at PVI of 1.0 J per beat/100 g LV ($V_{O_2,PVI 1.0}$) to determine the shift during dobutamine infusion.

The $V_{O_2}$-intercept of the $V_{O_2}$-PVA relation represents the oxygen consumption for nonmechanical work, that is, oxygen consumption for excitation-contraction (E-C) coupling and basal metabolism. Because the oxygen consumption for basal metabolism is constant regardless of the contractile state,15 the increase in the $V_{O_2}$-intercept represents an increase in the oxygen consumption for E-C coupling. The parallel upward shift of the $V_{O_2}$-PVA relation during dobutamine infusion indicates that the relation can differentiate the increased $V_{O_2}$ exclusively used for the increased E-C coupling (PVA-independent $V_{O_2}$) with augmented contractile state from the increased $V_{O_2}$ exclusively used for increased mechanical work (PVA-dependent $V_{O_2}$). Thus, we interpreted that the PVA is superior to other hemodynamic determinants for evaluating the energetics in humans.

The slope and the $V_{O_2,PTI 1.000}$ of the $V_{O_2}$-FTI relation increased during dobutamine infusion. The $V_{O_2}$-FTI relation did not retain the parallelism of the relation during inotropic intervention to discriminate between $V_{O_2}$ for mechanical work and $V_{O_2}$ for nonmechanical work. The reciprocal of the slope of the $V_{O_2}$-FTI relation is analogous to thermomechanical economy (the ratio of TTI to tension-dependent heat) as measured by myothermal studies.4-6 Thus, our results show that the economy tended to decrease by dobutamine infusion ($p=0.056$), and this was consistent with the earlier report.8

As shown in Figure 5, there was little difference in the $V_{O_2}$-PVA relation between AP and OMI. It has been shown that the reciprocal of the slope of the $V_{O_2}$-PVA relation, contractile efficiency, could be influenced by the altered myosin ATPase activity in the hyperthyroid rabbit heart.18 Thus, the results of the present study suggest that the contractile protein or cross-bridge cycling may not be impaired in our patients with OMI. On the other hand, the small difference in the $V_{O_2}$-intercept of the $V_{O_2}$-PVA relation between AP and OMI may be due to the interheart variation of the nonmechanical $V_{O_2}$. It has been reported that there was no significant correlation between the baseline $E_{max}$ and the $V_{O_2}$-intercept in canine hearts.45 In that study, however, they found that the relations between the $V_{O_2}$-intercept and $E_{max}$ during stepwise positive inotropic intervention were closely superimposable on each other, and they termed this sensitivity oxygen cost of $E_{max}$.45,46 This oxygen cost of $E_{max}$ has been reported to be increased in stunned canine LV.46 Although we did not assess the oxygen cost of $E_{max}$ in the present study, there might be some important differences in this oxygen cost of $E_{max}$ between AP and OMI. Our approach has potential to characterize the altered myocardial energetics in failing human hearts.

We used a new method that combines the measurement of LV pressure and volume by means of a conductance catheter introduced by Baan and coworkers32,33 to assess the relation between $V_{O_2}$ and hemodynamic indexes. The conductance catheter can measure LV volume accurately and continuously by measuring intra-ventricular conductance and provide real-time pressure-volume loops. Volume measurement by conductance catheter method has been validated in experimental32-35 and clinical34,33 studies. In our previous studies, we compared the LV volume–time curves measured by the conductance catheter method with those by biplane cineventriculography in patients with normal and reduced LVEF.39,40 Although regional wall motion abnormalities caused by previous myocardial infarction existed in patients with reduced LVEF, we found no difference in the slopes, intercepts, correlation coefficients, and standard error of estimates of the time–volume curves between patients with normal and reduced LVEF.40 Furthermore, applying the conductance catheter method, biplane cineventriculography is not suitable for repeated pressure–volume loop measurements in a stable contractile state because contrast medium affects hemodynamics, LV size, and contractility. Fast enhanced computed tomography has been applied to assess the pressure–volume loops in the intact animal preparation30,21; however, it may also affect myocardial contractility in a similar manner to cineventriculography in clinical settings.

There are some potential sources of error in calculation of the $V_{O_2}$-PVA relation in the present study. First, our measurement of $V_{O_2}$ might contain right ventricular $V_{O_2}$, whereas our measurement of PVA did not contain
right ventricular PVA. It is well recognized that right ventricular wall stress and dP/dt are quite low compared with those of the LV. In addition, right ventricular–to–LV pressure ratio and mass weight ratio are so small that the right ventricular PVA would also be quite low compared with LV PVA. Although we were not able to measure right ventricular VO₂ in the present study, we could thus speculate that the influence of right ventricular VO₂ on the total myocardial oxygen consumption may be minimal.

The second potential problem is that coronary sinus sampling may yield a mixture of blood from areas with perfused scar; normal areas and those with compensatory hypertrophy may exist. We assessed the LV weight angiographically including the scar area. This method might affect the estimation of the normalized VO₂ intercept of the VO₂–PVA relation. However, it is difficult to assess only the “viable” LV mass weight in clinical settings. On the other hand, the slope of the VO₂–PVA relation would not be affected because we normalized both VO₂ and PVA by the LV weight. Furthermore, it has been reported that nonworking energy demands and contractile efficiency of hypertrophic hearts are equivalent to those of normal hearts. Thus, our normalization may affect neither the slope of the VO₂–PVA relation (contractile efficiency) nor the parallelism of the VO₂–PVA relation during inotropic intervention in the present study.

Third, we must consider the potential error in the assumption of the linear ESPVR. Burkhoff et al.²⁴ and Kass et al.²⁵ suggested that contractility-dependent curvilinearity of the ESPVR may exist. Little et al.²⁶ also suggested that minor curvilinearity of the ESPVR might occur in intact dog hearts. In the present study, although the correlation coefficient of the linear fitting to the ESPVR was close to unity, possible curvilinearity of the ESPVR may still exist because of the relatively narrow range of altered loading conditions. If the ESPVR was curvilinear, the measured PVA would be larger than the true PVA. The overestimated area of PVA would remain constant while loading conditions were altered because there was no significant change in end-systolic pressure during volume loading.²⁷ Thus, in some patients, the VO₂–PVA relation might have shifted to the right in a parallel manner compared with the true VO₂–PVA relation. The contractile efficiency, however, would not be affected whether the ESPVR is linear or nonlinear. Moreover, we had to extrapolate the VO₂ at zero PVA to obtain the VO₂–PVA intercept of the VO₂–PVA relation from a relatively narrow range of sampling points compared with those in the experimental studies. These situations might have been responsible for the negative VO₂–PVA intercept in some of our patients.

Summary

Using the conductance catheter, we compared the relation between VO₂ and hemodynamic determinants (RPP, PWI, TTI, FTI, and PVA) under different contractile states in the human LV. Our results demonstrate that among those hemodynamic variables, PVA is the best predictor of VO₂ under different contractile states in human diseased hearts. Our approach makes it possible to assess the mechanoenergetics in human hearts such as the contractile efficiency and the VO₂ for E-C coupling.

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