The Linear Relation Between Oxygen Consumption and Pressure-Volume Area Can Be Reconciled With the Fenn Effect in Dog Left Ventricle

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We studied the Fenn effect in 12 excised cross-circulated dog left ventricles in control contractility and in a contractility enhanced by dobutamine or depressed by propranolol. The addition of end-systolic (VES) PVA in an ejecting contraction compared with that found in an isovolumic contraction at a comparable end-systolic pressure was considered to constitute the cardiac Fenn effect. We examined whether this load-dependent VES could be reconciled with the linear relation between VES and pressure-volume area (PVA) common for both ejecting and isovolumic contractions that has so far been consistently observed and was presently confirmed.

PVA is a specific area in the pressure-volume diagram, represents the total mechanical energy generated at each contraction, and consists of external mechanical work (EW) and mechanical potential energy. Because potential energy is common in the isovolumic and ejecting contractions producing the same end-systolic pressure, PVA of the ejecting contraction is greater by EW than that of the isovolumic contraction. Despite this difference in PVA by EW, the VES-PVA relation was always linear and load independent regardless of the isovolumic and ejecting contractions in a given heart in any given contractile state. By contrast, the upward convex VES-end-systolic pressure relation was higher for ejecting contractions than the downward curves VES-end-systolic pressure relation for isovolumic contractions in each contractile state. The difference of VES between the ejecting and isovolumic contractions was proportional to EW at comparable end-systolic pressure. The slope of the additional VES of ejecting contractions plotted against their EW had a slope close to the slope of the VES-PVA relation. Thus, the load-independent linear VES-PVA relation can be reconciled with the cardiac Fenn effect.

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Figure 1. Schematic illustration of pressure-volume area (PVA), which consists of potential energy (PE) and external work (EW). ESPVR, end-systolic pressure-volume relation; EDPVVR, end-diastolic pressure-volume relation; PES, end-systolic pressure; VES, volume axis intercept of ESPVR curve line; VED, end-systolic volume; Ved, end-diastolic volume. Dashed line is the approximated ejection pressure-volume trajectory assumed in the theoretical consideration.

There is more energy used in an afterloaded shortening contraction than in an isometric contraction at the same force. Cardiac muscle has a similar effect in that energy utilization of shortening—ejecting contraction is greater than isometric contraction at the same force. However, the cardiac version of the Fenn effect appears to be different from the original Fenn effect in that the isometric or isovolumic contraction consumes greater energy than any shortening (or ejecting) contractions from the same initial length (or end-diastolic volume) in myocardium (or heart).

The Fenn effect of skeletal muscle proved inconsistent with the energetic property of the elastic or viscoelastic model. However, we have found that a measure of the coupling between the left ventricle (LV) assessed by our time-varying elastance model of the ventricle can reasonably simulate its oxygen consumption (VO2) fraction that is dependent on mechanical contraction in excess of the VO2 fraction for both excitation-contraction coupling and basal metabolism. Therefore, we propose a new mecha

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The arterial blood pressure of the support dog served as the coronary perfusion pressure. Systemic hypotension due to allergic reaction under control circulatory conditions with diphenhydramine hydrochloride (30-60 mg i.m.). The mean level of this pressure in all experiments was 79±12 mm Hg (mean±SD). It was relatively constant throughout each experiment and, when necessary, was corrected by transfusing blood collected from the heart donor dog, including 10% dextan solution, or giving phylephrine (5-10 mg i.m.). The support dog was ventilated with room air, and arterial blood was occasionally sampled for measurements of pH, Po2, and Pco2 with a blood gas analyzer (IL system 1303). Supplemental oxygen and intravenous sodium bicarbonate were given when necessary, to maintain these parameters within their physiological ranges.

After the experiment, the LV including the septum and the RV were weighed. LV was 67.4±2.4 g, and RV was 27.2±3.6 g. The weight ratio of RV to LV (RV/LV) was 28.4±9.5%. Pressure-Volume Area PVA is the area circumscribed by the end-systolic pressure-volume curve, the end-diastolic pressure-volume curve, and the systolic segment of the pressure-volume trajectory, as shown in Figure 1. PVA represents the total mechanical energy generated by a ventricular contraction. PVA consists of external mechanical work (EW) and mechanical potential energy (PE). EW is the area under the systolic pressure-volume relation line on the left side of EW. We determined PVA, EW, and PE am ventriculographic pressure and volume data sampled on line at a rate of 500 Hz with a signal processing computer (model 7F-15, NEC San-ei). PVA was determined as the sum of small triangular areas with their apexes at the ventricular volume at
sion of the Fenn effect is reconcilable with the PVA concept as has been suggested by Gibbs and Chapman. To this end, we produced a specific set of isovolumic and ejecting contractions in the excised cross-circulated dog hearts whose LV volume was controlled and measured with a servo pump. We also studied whether the Fenn effect would be affected by enhanced and depressed contractile states and whether the additional \( V_o \) of the ejecting contraction would always be proportional to its external work.

**Materials and Methods**

**Preparation**

We used the excised cross-circulated dog heart preparation as described before. Briefly, two adult mongrel dogs (9–20 kg) were anesthetized with ketamine hydrochloride (5 mg/kg i.m.) followed by sodium pentobarbital (25 mg/kg i.v.) in each experiment. The dogs were heparinized (1,000 units/kg). Arterial and venous cross-circulation tubes were cannulated into the common carotid arteries and jugular vein in the larger dog (support). The smaller dog (heart donor) was thoracotomized under artificial ventilation. The arterial and venous cross-circulation tubes from the support dog were cannulated into the common carotid arteries and right ventricle (RV) via the right auricle, respectively. Then, the heart was isolated from the systemic and pulmonary circulation by ligation of the azygos vein, descending aorta, inferior and superior venae cavae, brachiocephalic artery, and bilateral pulmonary hili. Cross circulation was then started. The donor heart was excised from the chest.

The left atrium was opened, and all chordae tendineae were cut. A thin rubber balloon with an unstressed volume from 55 to 60 ml was placed in the LV, and its mouth was fixed at the mitral anulus. The cable of a miniature pressure gauge (model P-7, Konigsberg Instruments, Pasadena, California), placed inside the apical end of the balloon, was pulled out of the ventricular apex through a stab incision. A balloon was connected to the same servo pump as described before, and the balloon and pump were primed with water. The servo pump controlled LV volume precisely and measured it accurately.

The temperature of the heart was maintained between 35° and 37° C by warming the arterial cross-circulation tube coiled in a thermostat bath. Heart rate was fixed by electrically pacing the left atrium. LV surface electrocardiogram was used to trigger the volume servo pump in synchrony with ventricular contraction and to determine the onset of contraction.

The systemic arterial blood pressure of the support dog served as the coronary perfusion pressure. Systemic hypotension due to allergic reaction under cross circulation was prevented with diphenhydramine hydrochloride (30–60 mg i.m.). The mean level of this pressure in all experiments was 70±12 mm Hg (mean±SD). It was relatively constant throughout each experiment and, when necessary, was corrected by transfusing blood collected from the heart donor dog, infusing 10% dextran solution, or giving phenylephrine (5–10 mg i.m.). The support dog was ventilated with room air, and arterial blood was occasionally sampled for measurements of pH, \( P_{O_2} \), and \( P_{CO_2} \) with a blood gas analyzer (IL system 1303). Supplemental oxygen and intravenous sodium bicarbonate were given, when necessary, to maintain these parameters within their physiological ranges.

After the experiment, the LV including the septum and the RV were weighed. LV was 67.4±9.4 g, and RV was 27.3±5.8 g. The weight ratio of RV to (LV+RV) was 28.4±3.5%.

**Pressure-Volume Area**

PVA is the area circumscribed by the end-systolic pressure-volume line, the end-diastolic pressure-volume curve, and the systolic segment of the pressure-volume trajectory, as shown in Figure 1. PVA represents the total mechanical energy generated by a ventricular contraction. PVA consists of external mechanical work (EW) and mechanical potential energy (PE). EW is the area under the systolic pressure-volume trajectory. PE is the area under the systolic pressure-volume relation line on the left side of EW. We determined PVA, EW, and PE from ventricular pressure and volume data sampled on line at a rate of 300 Hz with a signal processing computer (model 7T-18, NEC San-ei). PVA was determined as the sum of small triangular areas with their apexes at the ventricular volume at...
which peak pressure is zero (V₀) and their bases between adjacent (2 msec apart) pressure-volume data points on the systolic segment of the pressure-volume trajectory.¹¹ EW was obtained by subtracting PE from PVA. End systole of each contraction was identified as the time at which the P(t)/[V(t)−V₀] ratio became maximal.¹⁶ This maximum pressure-volume ratio was identified as Eₘₐₓ of this contraction with P(t) and V(t) given as pressure and volume, respectively, as a function of time. We used Eₘₐₓ as an index of ventricular contractile state.¹¹,¹⁶ For more details of the computer algorithm, see our previous paper.¹¹ PVA, EW, and PE were expressed in mm Hg ml/beat or in J/beat, where 1 mm Hg ml is physically equivalent to 1.33×10⁻⁴ J.¹¹

**Oxygen Consumption**

The total coronary flow was measured with an electromagnetic flowmeter (model MVF-2100, Nihon Kohden, Tokyo, Japan) by placing an in-line probe (model FF-050T, Nihon Kohden) in the venous cross-circulation tube that continuously drained all venous blood from the right heart. We neglected the LV thebesian venous blood flow because of its small fraction in the total coronary flow.¹¹ Coronary arteriovenous oxygen content difference was continuously measured with an AVOX system that was calibrated against a Lex-O₂-Con oxygen-content analyzer in each experiment. The bypassed venous blood was returned to the venous tube upstream of the flowmeter. V₀₂ of the heart was determined as the product of coronary flow and arteriovenous oxygen content difference with the signal processor. V₀₂ per beat was obtained by dividing V₀₂ per minute by heart rate in a steady state. We minimized the contribution and fluctuation of RV V₀₂ in the measured V₀₂ regardless of LV PVA and V₀₂ by keeping the RV collapsed by continuous hydrostatic drainage of the coronary venous blood from the right heart. We considered that V₀₂ of the collapsed RV was equal to RV weight/(LV weight−RV weight) times the total V₀₂ measured when the LV was also unloaded with zero PVA. This unloaded RV V₀₂ was subtracted from the measured total V₀₂ in each contractile state. V₀₂ was expressed in ml O₂/beat or J/beat, where 1 ml O₂ is biochemically equivalent to approximately 20 J.¹⁸ Eₘₐₓ, PVA, EW, PE, and V₀₂ were normalized for 100 g LV.

**Protocol**

**Control run.** A control run was performed without any inotropic interventions in 12 hearts. Steady-state isovolumic contraction was first produced at an LV volume of 20–30 ml. The peak pressure of this contraction (maximum end-systolic pressure in Figure 2A) was between 80 and 170 mm Hg in the control before dobutamine and between 140 and 210 mm Hg in the control before propranolol. Then we alternately produced steady-state quasi-isobaric ejecting (rectangular pressure-volume loop) and isovolumic contractions in the following specific combinations. The end-diastolic volumes of these ejecting contractions were fixed at the same volume as in the initial isovolumic contraction. The end-diastolic volumes of the isovolumic contractions that followed these ejecting contractions were set equal to the end-systolic volumes of the preceding ejecting contractions. We produced steady-state quasi-isobaric ejecting contractions against five to six
different afterload pressures from the same end-diastolic volume, as shown in Figure 2A. Stroke volumes of these ejecting contractions were made to range between 1.5 and 18.0 ml by changing the afterload pressure level. We finally produced unloaded contraction at $V_0$ (Figure 2). Data of all these contractions were collected in steady state and stored on a floppy disk of the signal processor.

**Dobutamine run.** In eight of these 12 dogs, contractile state was enhanced by a continuous intracoronary infusion of dobutamine at a rate of 5–15 $\mu$g/min. Steady-state isovolumic and ejecting contractions were produced in the same specific combination as in the control run, and data were collected and stored on the floppy disk.

**Propranolol run.** In the other four of the 12 dogs, contractile state was depressed by a 0.2 mg intracoronary bolus injection of propranolol, followed by a continuous intracoronary infusion of propranolol at a rate of 15 $\mu$g/min. Steady-state isovolumic and ejecting contractions were produced in the same specific combination as in the control run, and data were collected and stored on the floppy disk.

**Quasi-isotonic (quasi-auxobaric) run.** In two additional hearts, we attempted to produce quasi-isotonic contractions in addition to the specific combination of isovolumic and quasi-isobaric ejecting contractions that were used in the main runs. These quasi-isotonic contractions were made to have the same end-diastolic and end-systolic volumes as the quasi-isobaric ejecting contractions also produced in this run, as shown in Figure 2B. The quasi-isotonic contractions were made to increase LV pressure during ejection phase so that the ejecting pressure-volume trajectory followed closely one of the family of isotonic curves drawn in the pressure-volume plane by the following calculation. We calculated total circumferential wall force (F) of the LV by use of a spherical model. F was assumed to be equal to the product of the internal cross-sectional area (S) and intraventricular pressure (P): $F(g)=S(cm^2)\cdot P(mm\, Hg)$, and thus, 1 mm Hg = 1.36 g/cm². Since $S=\pi \cdot (\text{internal radius})^2$ and ventricular internal volume $(V)=(4/3 \pi \cdot (\text{internal radius})^3)$, $S=1.21 \cdot V^{2/3}$. Therefore, $F=1.65 \cdot P \cdot V^{2/3}$. Then, a family of the isotonic curves were drawn on the pressure-volume diagram by relating P and V so as to satisfy $F=1.65 \cdot P \cdot V^{2/3}$, as shown in Figure 2B.

**Curve Fitting**

To compare the experimental data with theoretical prediction based on PVA, we used mathematical formulas to relate PVA, PE, EW, and $E_{max}$ in the same way as before. The appendix describes the details of the mathematical formulation.

To obtain the appropriate coefficient values for the Equations relating PVA, PE, EW, and $V_0$ to end-systolic pressure, we used a nonlinear regression technique. We used the ready-made program (OPTIM, Tosaka) for a personal computer (model PC9801, NEC) and obtained the least-square-fit parameters in the same way as before.

**Statistics**

Analysis of covariance was applied to compare the regression lines of $V_0$ on PVA obtained in the control, dobutamine, and propranolol runs in each heart. Then, the differences of the slope and the elevation between the regression lines were tested by F test in each heart. Because of the high correlation coefficient between $V_0$ and PVA in each of the control and dobutamine runs, we assumed little uncertainty in the estimated values for the slope and $V_0$-axis intercept of the regression line in the same way as before. Then, the slope and $V_0$-axis intercept were compared between control and dobutamine runs in eight hearts and between control and propranolol runs in four hearts by two-way ANOVA. Only when the F test was significant, the differences of the mean values of the slope and $V_0$-axis intercept were tested by the least significant difference method. Mean values for $E_{max}$ of the variably loaded contractions were compared between the control and dobutamine runs and between the control and propranolol runs in each heart and in all hearts by paired t test. Values of $p<0.05$ were considered statistically significant. Data are presented as mean ± SD.

**Results**

**Pressure-Volume Diagram**

Figure 2A superimposes the pressure-volume trajectories of steady-state isovolumic and ejecting contractions in the specific combination as defined in “Materials and Methods.” The left upper corners (end systoles) of the ejecting contractions were near the end-systolic (peak isovolumic) pressure-volume points of the corresponding isovolumic contractions. However, the end-systolic pressures of ejecting contractions with relatively small stroke volumes (1.5–5.0 ml) were slightly higher than those of the corresponding isovolumic contractions, as shown in Figure 2A. The end-systolic pressure of ejecting contraction with the largest stroke volume (9.0 ml) was slightly lower than that of the corresponding isovolumic contraction. These tendencies were similarly observed in all other hearts. Thus, we could not completely equalize the end-systolic pressures of each pair of ejecting and isovolumic contractions at the same end-systolic volume.

Figure 2B shows pressure-volume trajectories of the quasi-isotonic ejecting contractions that had the same end-diastolic and end-systolic volumes as those of the corresponding quasi-isobaric (rectangular) ejecting contractions. However, we could not completely fit the quasi-isotonic pressure-volume loops during ejection phase for the theoretical isotonic curves derived from a spherical model because of the limitation of the performance of the servo pump. End-systolic pressures of the quasi-isotonic...
contractions were nearly equal to the corresponding quasi-isobaric ejecting and isovolumic contractions at the same end-systolic volumes.

The coefficient of variation (standard deviation/mean value) of \( E_{\text{max}} \) in each run was 0.10±0.03. The mean value of \( E_{\text{max}} \) in all hearts was 7.6±2.3, 10.8±3.0, and 3.6±0.5 mm Hg/(ml/100 g LV) in control, dobutamine, and propranolol runs, respectively. The increase in \( E_{\text{max}} \) with dobutamine from control was 42±9\% (\( p<0.01 \)), and the decrease in \( E_{\text{max}} \) with propranolol from control was 58±20\% (\( p<0.01 \)).

\( V_{O_2} \)-PVA Relation

Figure 3 shows representative examples of the relation between \( V_{O_2} \) and PVA in control and dobutamine runs in one heart (panel A), in control and propranolol runs in another heart (panel B), and in the quasi-isotonic run in a third heart (panel C). \( E_{\text{max}} \) was significantly increased by 48\% with dobutamine in panel A and decreased by 70\% with propranolol in panel B. In each run, the correlation between \( V_{O_2} \) and PVA was good, and the \( V_{O_2} \)-PVA data points were closely fitted by a linear regression line in panels A, B, and C. The data points of isovolumic, quasi-isobarically ejecting, and quasi-isotonically ejecting contractions were on the same \( V_{O_2} \)-PVA regression line in panel C. Thus, the \( V_{O_2} \)-PVA relation in a given heart in any stable contractile state was independent of the loading conditions, that is, whether the contractions were isovolumic or ejecting. The summary of correlation and regression analyses of the \( V_{O_2} \)-PVA relation is shown in Table 1.

In Figure 3, the \( V_{O_2} \)-PVA regression line in the dobutamine run was considerably higher than that in the control run in panel A, and the \( V_{O_2} \)-PVA regression line in the propranolol run was lower than that in the control run in panel B. Analysis of covariance shows that the elevation of the regression lines was significant (\( p<0.01 \)) in panels A and B, and the difference of the slope was not significant in either panel A or B. This indicates that the upward shift by dobutamine and the downward shift by propranolol were virtually parallel in individual hearts. The control \( V_{O_2} \)-PVA regression line in

| Table 1. Effects of Dobutamine and Propranolol on Ventricular Mechanics and Energetics |
|------------------------------------------|-----------------|-----------------|-----------------|------------------|------------------|
| E\(_{\text{max}}\) (mm Hg/ml/100 g LV) | HR (beat/min) | \( r \) | Slope | Ec (%) | Intercept (J/beat/100 g LV) |
| Control \( (n=12) \) | 7.6±2.3 | 165±9 | 0.977 | 2.21±0.29 | 45.2±5.8 | 0.56±0.10 |
| Dobutamine \( (n=8) \) | 10.8±3.0* | 165±9 | 0.985 | 2.45±0.09t | 40.8±5.8 | 0.72±0.12* |
| Propranolol \( (n=4) \) | 3.6±0.5* | 165±10 | 0.982 | 2.12±0.09t | 47.2±2.0 | 0.42±0.04* |
| Mean \( (n=24) \) | . . . | 165±9 | 0.981 | 2.27±0.32 | 44.0±6.1 | . . . |

Values are mean±SD. E\(_{\text{max}}\), maximum pressure-volume ratio; HR, heart rate; \( r \), mean value for correlation coefficient between oxygen consumption (\( V_{O_2} \)) and pressure-volume area (PVA), which was obtained by \( z \) transformation; Slope, the regression coefficient of \( V_{O_2} \) on PVA; Ec, reciprocal of the slope of \( V_{O_2} \)-PVA relation=efficiency of energy conversion from excess \( V_{O_2} \) (total \( V_{O_2} \)-unloaded \( V_{O_2} \)) to PVA; Intercept, \( V_{O_2} \)-axis intercept of the regression line.

*Statistically significant at \( p<0.01 \) compared with the control run.

†Statistically insignificant compared with the control run.
Oxygen consumption ($\dot{V}O_2$)-fitting curves as functions of end-systolic pressure ($P_{es}$) in quasi-isobarically ejecting and isovolumic contractions in the dobutamine (panel A), propranolol (panel B), and quasi-isotonic (panel C) runs in the same hearts as those in Figures 3A, 3B, and 3C, respectively. Solid squares are data points of isovolumic contractions, open squares are those of quasi-isobaric ejecting contractions, and open triangles are those of quasi-isotonic ejecting contractions. $\Delta \dot{V}O_2$ curves are obtained by subtracting mathematically the $\dot{V}O_2$ curve in isovolumic contractions from the $\dot{V}O_2$ curve in the corresponding quasi-isobaric ejecting contractions. The dotted lines between the ejecting and isovolumic $\dot{V}O_2$-$P_{es}$ curves connect the data points obtained at the same end-systolic volumes.

Figure 4C shows that $\dot{V}O_2$ of the quasi-isotonic contraction was slightly lower than that of the corresponding quasi-isobaric contraction at the same end-systolic volume. The difference between them increased as end-systolic pressure decreased with increases in stroke volume. However, $\dot{V}O_2$ of quasi-isotonic contraction was still greater than that of the corresponding isovolumic contraction at any comparable end-systolic pressure. A similar result was obtained in the other heart subjected to the quasi-isotonic run.

$\dot{V}O_2$-End-Systolic Pressure Relation

In Figure 4, panels A and B show representative examples of the data points of quasi-isobarically ejecting and isovolumic contractions in the control and dobutamine runs in one heart (panel A) and those in the control and propranolol runs in another heart (panel B). $\dot{V}O_2$ in ejecting contraction was greater than that in isovolumic contraction at any comparable end-systolic pressure in each of control, dobutamine, and propranolol runs. Dobutamine increased $\dot{V}O_2$ and propranolol decreased $\dot{V}O_2$ of both ejecting and isovolumic contractions. These experimental data of isovolumic and ejecting contractions in each run were separately fitted by the two theoretical curves (Equations 5 and 6 in the Appendix as shown in Figure 4A and 4B). The curve fitted to ejecting contractions was always convex upward, and the curve fitted to isovolumic contractions was always convex downward. The two curves merged together near both ends, namely, near zero and maximum end-systolic pressures. Similar parabolic $\dot{V}O_2$-fitting curves were obtained in all hearts. Dobutamine elevated these curves, and propranolol lowered them. $\Delta \dot{V}O_2$ curves at the bottom of the graphs in Figure 4 show the difference between the $\dot{V}O_2$-fitting curve of isovolumic contractions and the curve of ejecting contractions. The $\Delta \dot{V}O_2$ curve was always parabolic downward in any of the control, dobutamine, and propranolol runs.

$PVA$, $PE$, and $EW$-End-Systolic Pressure Relations

We also fitted parabolic curves (Equations 1, 2, and 3 in the Appendix) relating $PE$, $EW$, and $PVA$ to end-systolic pressure. Figure 5 shows the representative examples of these fitting curves (solid) in control (panel A), dobutamine (panel B), and propranolol (panel C) runs in the same hearts as shown in Figures 4A and 4B. The $PE$ curve (solid) obtained from the ejecting contractions was concave upward, and the $EW$ curve was parabolic downward. $EW$ was maximal near one half of maximum end-systolic pressure in each run. The $PVA$ curve of the ejecting contractions was the sum of these $PE$ and $EW$ curves and was concave downward. The data points of ejecting contractions were close to these $PE$, $EW$, and $PVA$-fitting curves in each run. The $PVA$ data points of the isovolumic contractions, where $PVA=PE$, were almost on the $PE$ curve (solid) of the ejecting contractions. The $PVA$ curves (dotted) of the isovolumic contractions were concave upward and very close to the corresponding...
FIGURE 5. Graphs showing pressure-volume area (PVA), potential energy (PE), external work (EW), and excess oxygen consumption multiplied by energy conversion efficiency (Ec×EXCESS VO2) curves as a function of end-systolic pressure (Pes). Solid curves are the fitting curves for PVA, PE, and EW as functions of Pes in quasi-isobaric ejecting contractions in control (panel A), dobutamine (panel B), and propranolol (panel C) runs. Dotted curves are PVA-fitting curves (PVA = PE) obtained in isovolumic contractions. Solid squares are data points of isovolumic contractions, and open squares are those of quasi-isobaric ejecting contractions. Heart rate was 160 beats/min in panels A, B, and C. The Ec×EXCESS VO2 curves (solid), obtained by the multiplication of EXCESS VO2 curves by Ec (efficiency from EXCESS VO2 to PVA, that is, 44.0%), and PVA curves (dashed) as function of Pes are superimposed in control (panel D), dobutamine (panel E), and propranolol (panel F) runs. ΔEXCESS VO2 and ΔPVA are the curves obtained by subtracting the Ec×EXCESS VO2 curve and the PVA curve in isovolumic contractions from those in quasi-isobaric ejecting contractions, respectively.

PE curves of the ejecting contractions in Figures 5A, 5B, and 5C. In all other hearts, we obtained similar PE-, EW-, and PVA-fitting curves as functions of end-systolic pressure regardless of the control, dobutamine, and propranolol runs. EW values always became maximal near one half of maximum end-systolic pressure in each run. The PVA curves obtained from the isovolumic contractions were very close to the PE curves obtained from the ejecting contractions in all the hearts.

Excess VO2 Versus PVA

In the present study, the slope coefficient of the VO2-PVA regression line (coefficient A in Equation 4) was 2.27±0.32 and nearly constant regardless of loading conditions and Ea, as shown in Table 1. The reciprocal of the slope coefficient A was assumed to indicate the energy conversion efficiency (Ec) from excess VO2, which is total VO2 minus unloaded VO2, to PVA, as explained in an earlier publication.11 Ec was approximately constant at 44.0±6.1%.

Multiplication of the excess VO2 curves by the Ec value produced curves that could be compared with the PVA versus end-systolic pressure curves. In Figure 5, panels D, E, and F show the curves obtained by these two different methods in the same hearts as shown in panels A, B, and C. The solid curves (Ec×excess VO2) were obtained by the multiplication of the excess VO2 curves by Ec, and the dotted curves (PVA curves) are the PVA-fitting curves. The solid and dotted curves closely resembled each other in both isovolumic and ejecting contractions. In all other hearts, these two curves also resembled each other in both isovolumic and ejecting contractions regardless of the control, dobutamine, or propranolol runs. In panels
Ejecting contractions include 10 quasi-isotonic contractions regardless of contractile states. LV, left ventricle.

Figure 6 shows the scatter diagram of the additional VO₂ (ΔVO₂) values of all ejecting contractions against end-systolic pressure in all the control run, dobutamine, propranolol, and quasi-isotonic runs. There was a close and linear correlation between ΔVO₂ and EW with a correlation coefficient of 0.88 (p<0.01). The slope coefficient of this regression line was 2.14 (dimensionless), and ΔVO₂ intercept of the regression line was almost zero. This slope coefficient was close to the slope coefficient of the VO₂-PVA relation listed in Table 1. This slope coefficient indicates inversely the efficiency of energy conversion from ΔVO₂ to EW. This efficiency was 47%. The slope coefficient of the ΔVO₂-EW relation was not significantly different among the experimental runs (1.88 in the control run, 2.23 in the dobutamine run, and 2.00 in the propranolol run), and neither were the efficiency values among them (53%, 45%, and 50%, respectively).

Discussion

The present results show that VO₂ in an ejecting contraction was always greater by an amount proportional to its EW than VO₂ in the corresponding isovolumic contraction having the same end-systolic pressure and volume as this ejecting contraction. This effect of EW on VO₂ indicates the difference of energy utilization between the ejecting and isovolumic contractions. This is evidence of the Fenn effect in the dog LV. The present study shows that the Fenn effect can be reconciled with the PVA concept.11,12,14 When VO₂ values in ejecting and isovolumic contractions are expressed as functions of end-systolic pressure, the difference (ΔVO₂) of these VO₂ curves looks analogous to EW (part of PVA) as a function of end-systolic pressure, as seen in Figures 4 and 5. The similarity of the ΔVO₂ curve multiplied by Ec to the EW curve as well as the linear ΔVO₂-EW relation supports the relatively constant stoichiometry between ΔVO₂ and EW. This is also evidence of the Fenn effect in a more quantitative way.

The present results show that ΔVO₂ between ejecting and isovolumic contractions at matched end-systolic pressure and end-systolic volume is compatible with the load-independent linear VO₂-PVA relation. PVA correlates linearly with VO₂ in a given LV in any stable contractile state in this study in the same way as in our previous studies.10-13 The parallel elevation of the VO₂-PVA regression line by dobutamine is similar to that caused by epinephrine or elevated calcium.11 The VO₂-PVA regression line is lowered in a parallel manner by propranolol. The parallel shift is evidenced by the relatively constant slope of the VO₂-PVA regression line regardless of contractile states and the mode of contraction (Table 1). The sensitive change in VO₂ intercept by contractile state (Table 1) is similar to that observed in our previous study.11

The relatively constant Ec from the excess VO₂ (total VO₂−unloaded VO₂) to PVA of 44% (Table 1), which is the reciprocal of the slope coefficient, was consistent with the constant efficiency from ΔVO₂ to EW of 47% (Figure 6). Moreover, the efficiency from ΔVO₂ to EW was comparable among the control, dobutamine, and propranolol runs (Figure 6). These findings indicate that the VO₂ cost of unit PVA is equal to that of unit EW regardless of the contractile states, and hence, as greater EW is performed, greater VO₂ is required for the work. Thus, the VO₂-PVA relation is compatible with the Fenn effect.

We assumed in the present study that 1 ml O₂ is biochemically equivalent to approximately 20 J. This calorific equivalent ranges between 19.36 and 20.84 J and is only slightly (±5%) affected by substrates.25 Therefore, changes, if any, in the metabolic substrates would have a negligible effect in the present study.

Mommaerts24 recommended the use of an “equivalent force base line” for comparing isotonic and isometric contractions to avoid the confusions about the generality of Fenn’s observations. This approach helps unify the concept of the Fenn effect.2 In the heart, however, wall force is not constant (isotropic); it decreases during the ordinary quasi-isobaric ejection.25 The force during the early ejection phase is greater than end-systolic force in quasi-isobaric ejecting contractions, as seen in Fig-

**FIGURE 6.** Scatter diagram of the additional oxygen consumption (VO₂) against external work (EW) in 337 ejecting contractions against end-systolic pressure in all hearts regardless of contractile states. LV, left ventricle. Ejecting contractions include 10 quasi-isotonic contractions. Solid line is the linear regression line.
ure 2B. By contrast, the pressure-volume trajectories of quasi-isotonic ejecting contractions were made close during ejection phase to the theoretical isotonic curves on the pressure-volume diagram, as shown in Figure 2B. Comparison of the quasi-isobaric and quasi-isotonic contractions in Figure 2B shows that EW of the quasi-isotonic contraction is smaller by the triangular areas between the quasi-isobaric and quasi-isotonic pressure-volume trajectories during ejection than the corresponding quasi-isobaric contraction with the same end-diastolic and end-systolic volumes. In plotting AV02 and EW data in Figure 6, quasi-isobaric and quasi-isotonic ejecting contractions were superimposable; this finding indicates that the Vo2 energy cost of unit EW is always relatively constant regardless of contractile force during ejection. Therefore, the smaller EW of the quasi-isotonic contraction is considered to cause a proportionally smaller Vo2 as seen in Figure 4C. This result also supports the existence of the Fenn effect in the heart.

The Fenn effect of the LV that we observed in this study is consistent with that of myocardium.15,26 Gibbs26 showed in papillary muscle that the relation between total isotonic enthalpy and load is curvilinear (concave downward). Moreover, the ratio of the total isotonic enthalpy minus activation heart to the sum of EW and PE, which was calculated from the tension-length relation, is constant regardless of different loads.26 This similarity between rabbit papillary muscle and dog LV suggests that the concept of PVA may have widespread application to cardiac energetics.

In summary, we have examined the additional cardiac energy utilization associated with EW in the excised cross-circulated dog LV. Vo2 in both isovolumic and ejecting contractions could be fitted by the theoretical curves as functions of end-systolic volume during ejection is constant, that is, isotonic, and equal to Pes as shown in Figure 1. From Equations 1 and 2,

\[ PVA = PE + EW = \frac{-1}{2(E_{max})} \cdot Pes^2 + (Ved - V_o) \cdot Pes \]  

Thus, PVA, PE, and EW can be mathematically expressed as quadratic functions of Pes. In the present study, E_max and V_o were practically constant in each run, and Ved in ejecting contractions was also constant in each run as described in "Results." Since PVA, PE, and EW are quadratic functions of Pes, the experimental data could be fitted with the appropriate equations.

The empirical relation between PVA and Vo2 has been shown to be formulated as follows10,11,20:

\[ Vo2 = \frac{A}{2(E_{max})} \cdot Pes^2 + B \]  

In isobaric ejecting contractions, from Equations 3 and 4,

\[ Vo2 = -\frac{A}{2(E_{max})} \cdot Pes^2 + A \cdot (Ved - V_o) \cdot Pes + B \]

Thus, Vo2 is also expressed as a quadratic function of Pes. The present experimental data were fitted with the quadratic equation relating Vo2 to Pes.

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