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 depolarized by propranolol. The addition of 2% (v/v) of isoproterenol improved the Fenn effect in an excised contracting canine ventricle in an isolated ventricle as compared to the situation in which the canine ventricle was an intact ventricle. The pressure-volume area (PVA) of the canine ventricle was determined as a function of pressure and volume. The PVA was a specific area in the pressure-volume diagram, which represented the total mechanical energy generated by each contraction, and consisted of external mechanical work (EW) and mechanical potential energy. Because potential energy was constant in the isolosynthetic and ejection contractions producing the same end-systolic pressure, PVA of the ejection contraction was greater than that of the isolosynthetic contraction. The slope of the additional V0 of ejection contractions plotted against their EW was at a slope close to the slope of the V0-PVA relation. Thus, the load-independent linear V0-PVA relation can be reconciled with the cardiac Fenn effect.

(Circulation Research 1989;65:1380-1389)

There is more energy used in an overloaded shortening contraction than in an isometric contraction at the same force.1,2 This result was originally discovered in skeletal muscle and is known as the Fenn effect.3,4 Cardiac muscle has a similar effect in that energy utilization of shortening contraction is greater than isometric contraction at the same force.5,6 However, the cardiac version of the Fenn effect appears to be different from the original Fenn effect in that the isotonic (or isometric) contraction consumes greater energy than any shortening (or ejection) contractions from the same initial length (or end-diastolic volume) in myocardium (or heart).7-9

The Fenn effect of skeletal muscle proved inconsistent with the energetic property of the elastic or viscoelastic model.10 However, we have found that a measure of the energetic property of the left ventricle (LV) assessed by our time-averaging elastance model of the ventricle can reasonably simulate its oxygen consumption (Vo2) fraction that is dependent on mechanical contraction in excess of the V02 fraction for both excitation-contraction coupling and basal metabolism.11,12 This mechanical-energetic measure is called pressure-volume area (PVA) and is defined as the area circumscribed by the end-systolic and end-diastolic pressure-volume curves and the systolic pressure-volume trajectory in the pressure-volume diagram.14

The purpose of the present study was to test experimentally the hypothesis that the cardiac version of the Fenn effect is reconcilable with the PVA concept as has been suggested by Gibbs and Chapman.15 To this end, we produced a specific set of isovolumetric and ejection 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 V0 of the ejection contraction would be proportional to its external work.

Materials and Methods

Preparation

We used the excised cross-circulated dog heart preparation as described before.9,11 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 experimental dog. The aorta was cannulated (1,000 units/kg). Arterial and venous cross-circulation tubes were cannulated into the common carotid arteries and jugular vein in the larger dog (supporter). The smaller dog (heart donor) was then ventilated under artificial ventilation. The arterial and venous cross-circulation tubes from the support dog were cannulated into the left subclavian artery and the right ventricle (RV) via the right atrium, respectively. Then, the heart was isolated from the systemic and pulmonary circulation by ligating the azygos vein, descending aorta, inferior and superior vena cava, brachiocephalic arteries and bilateral pulmonary hilum. Cross circulation was then started. A 16- or 18-gauge donor dog vent was excited from the chest.

Pressure-Venous Area

PVA is the area circumscribed by the end-systolic pressure-volume curve, the end-diastolic pressure-volume curve, and the systolic 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.16 We determined PVA, EW, and PE as ventricular pressure and volume data sampled on line at a rate of 500 Hz with a signal processing computer (model 7718, NEC San-ei). PVA was determined as the sum of small triangular areas with their apices at the ventricular volume at 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, including 10% dextrose 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, P02, and Pco2 with a blood gas analyzer (IL system 1360). 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±5.6%.
Preparation

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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, 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±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 line, the end-diastolic pressure-volume relation; Pes, end-systolic pressure-volume relation; Pes, end-systolic pressure; V0, volume axis intercept of ESPVR line; Ves, end-systolic volume; Ved, end-diastolic volume. Dashed line is the approximated ejection pressure-volume trajectory assumed in the theoretical consideration.
FIGURE 2. Graphs showing pressure-volume trajectories and isotonic curves. Panel A: Experimentally obtained pressure-volume trajectories of seven isovolumic and five quasi-isobaric ejecting (rectangular) contractions that are superimposed in the same pressure-volume diagram. The end-diastolic volumes of ejecting contractions were made equal to the volume of the greatest isovolumic contraction (Viv). The volumes of the other isovolumic contractions except one at the volume axis intercept (Vo) were made equal to the corresponding end-systolic volumes of the five ejecting contractions. Pes, end-systolic pressure. Panel B: A family of isotonic curves (thin) and pressure-volume trajectories (thick) in a pressure-volume plane in the quasi-isotonic run. Each isotonic curve relates ventricular pressure (P) and volume (V) for a constant ventricular wall force (F): F = 1.65 P - V<sup>W</sup>. Pressure-volume loops, in which ventricular pressure increased during ejection phase, show quasi-isotonic ejecting contractions. Isovolumic and quasi-isobaric ejecting (rectangular) contractions are also superimposed.

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. Coronary arteriovenous oxygen content difference was continuously measured with an AVOX system that was calibrated against a Lex-O<sub>2</sub>-Con oxygen-content analyzer in each experiment. The bypassed venous blood was returned to the venous tube upstream of the flowmeter.

VO<sub>2</sub> of the heart was determined as the product of coronary flow and arteriovenous oxygen content difference with the signal processor. VO<sub>2</sub> per beat was obtained by dividing VO<sub>2</sub> per minute by heart rate in a steady state. We minimized the contribution and fluctuation of RV VO<sub>2</sub> in the measured VO<sub>2</sub> regardless of LV PVA and VO<sub>2</sub> by keeping the RV collapsed by continuous hydrostatic drainage of the coronary venous blood from the right heart. We considered that VO<sub>2</sub> of the collapsed RV was equal to RV weight/(LV weight - RV weight) times the total VO<sub>2</sub> measured when the RV was also unloaded with zero PVA. This unloaded VO<sub>2</sub> was subtracted from the measured total VO<sub>2</sub> in each contractile state. VO<sub>2</sub> was expressed in ml O<sub>2</sub>/beat or in J/beat, where 1 ml O<sub>2</sub> is biochemically equivalent to approximately 20 J. E<sup>m</sup>, PVA, EW, PE, and VO<sub>2</sub> 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 Vo (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 μg/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 μg/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(cm²)⋅P (mm Hg), and thus, 1 mm Hg=1.36 g/cm².19 Since S=πr² (internal radius)² and ventricular internal volume (V)=(4/3πr³) (internal radius)³, S=1.21 V²/3. Therefore, F=1.65 P⋅V²/3. 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 P⋅V²/3, 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.10,20 The appendix describes the details of the mathematical formulation.

To obtain the appropriate coefficient values for the Equations relating PVA, PE, EW, and Vo2 to end-systolic pressure, we used a nonlinear regression technique.21 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.22

Statistics
Analysis of covariance21 was applied to compare the regression lines of Vo2 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 Vo2 and PVA in each of the control and dobutamine runs, we assumed little uncertainty in the estimated values for the slope and Vo2-axis intercept of the regression line in the same way as before.13 Then, the slope and Vo2-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.21 Only when the F test was significant, the differences of the mean values of the slope and Vo2-axis intercept were tested by the least significant difference method.21 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. Heart rate was constant in each run, and the mean heart rate in all experiments was 165±9 beats/min. The correlation coefficient between $V_{O_2}$ and PVA was always close to unity in any run in all hearts.

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

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|c|c|}
\hline
 & $E_{\text{max}}$ (mm Hg/ml/100 g LV) & $HR$ (beat/min) & $r$ & Slope & $Ec$ (%) & Intercept (J/beat/100 g LV) \\
\hline
Control & 7.6±2.3 & 165±9 & 0.977 & 2.21±0.29 & 45.2±5.8 & 0.56±0.10 \\
& (n=12) & & & & & \\
Dobutamine & 10.8±3.0* & 165±9 & 0.985 & 2.45±0.09† & 40.8±5.8 & 0.72±0.12* \\
& (n=8) & & & & & \\
Propranolol & 3.6±0.5* & 165±10 & 0.982 & 2.12±0.09† & 47.2±2.0 & 0.42±0.04* \\
& (n=4) & & & & & \\
Mean & ... & 165±9 & 0.981 & 2.27±0.32 & 44.0±6.1 & ... \\
& (n=24) & & & & & \\
\hline
\end{tabular}
\caption{Effects of Dobutamine and Propranolol on Ventricular Mechanics and Energetics}
\end{table}

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.
FIGURE 4. Oxygen consumption (\(V_O^2\))-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. \(\Delta V_O^2\) curves are obtained by subtracting mathematically the \(V_O^2\) curve in isovolumic contractions from the \(V_O^2\) curve in the corresponding quasi-isobaric ejecting contractions. The dotted lines between the ejecting and isovolumic \(V_O^2\)-Pes curves connect the data points obtained at the same end-systolic volumes.

panel A was lower than the control line in panel B because \(E_{\text{max}}\) of the control state in panel A happened to be lower than that in panel B in the two different hearts. In all the other hearts, dobutamine always significantly elevated the regression line but did not significantly change the slope except in one heart. In this heart, the slope significantly increased from 2.12 to 2.85 by dobutamine (\(p<0.05\)). Propranolol significantly lowered the regression line but did not change the slope in all four hearts. Therefore, the upward or downward shift of the \(V_O^2\)-PVA regression line with dobutamine or propranolol, respectively, was generally in parallel with the control line in individual hearts.

\(V_O^2\)-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). \(V_O^2\) 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 \(V_O^2\) and propranolol decreased \(V_O^2\) 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 \(V_O^2\)-fitting curves were obtained in all hearts. Dobutamine elevated these curves, and propranolol lowered them. \(\Delta V_O^2\) curves at the bottom of the graphs in Figure 4 show the difference between the \(V_O^2\)-fitting curve of isovolumic contractions and the curve of ejecting contractions. The \(\Delta V_O^2\) curve was always parabolic downward in any of the control, dobutamine, and propranolol runs.

Figure 4C shows that \(V_O^2\) 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, \(V_O^2\) 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.

PVA\(- PE\), \(PE\), 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 those 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 ($Ec \times \text{EXCESS VO}_2$) 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 $Ec \times \text{EXCESS VO}_2$ 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. $\Delta \text{EXCESS VO}_2$ and $\Delta PVA$ are the curves obtained by subtracting the $Ec \times \text{EXCESS VO}_2$ 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 $E_{max}$, 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 curves) 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 VO$_2$ (ΔVO$_2$) values of all ejecting contractions above VO$_2$ values of the corresponding isovolumic contractions plotted against EW of the same ejecting contractions in all of the control, dobutamine, propranolol, and quasi-isotonic runs. There was a close and linear correlation between ΔVO$_2$ and EW with a correlation coefficient of 0.88 (p<0.01). The slope coefficient of this regression line was 2.14 (dimensionless), and ΔVO$_2$ intercept of the regression line was almost zero. This slope coefficient was close to the slope coefficient of the VO$_2$-PVA relation listed in Table 1. This slope coefficient indicates inversely the efficiency of energy conversion from ΔVO$_2$ to EW. This efficiency was 47%. The slope coefficient of the ΔVO$_2$-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 VO$_2$ in an ejecting contraction was always greater by an amount proportional to its EW than VO$_2$ in the corresponding isovolumic contraction having the same end-systolic pressure and volume as this ejecting contraction. This effect of EW on VO$_2$ 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. When VO$_2$ values in ejecting and isovolumic contractions are expressed as functions of end-systolic pressure, the difference (ΔVO$_2$) of these VO$_2$ 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 ΔVO$_2$ curve multiplied by Ec to the EW curve as well as the linear ΔVO$_2$-EW relation supports the relatively constant stoichiometry between ΔVO$_2$ and EW. This is also evidence of the Fenn effect in a more quantitative way.

The present results show that ΔVO$_2$ between ejecting and isovolumic contractions at matched end-systolic pressure and end-systolic volume is compatible with the load-independent linear VO$_2$-PVA relation. PVA correlates linearly with VO$_2$ in a given LV in any stable contractile state in this study in the same way as in our previous studies. The parallel elevation of the VO$_2$-PVA regression line by dobutamine is similar to that caused by epinephrine or elevated calcium. The VO$_2$-PVA regression line is lowered in a parallel manner by propranolol. The parallel shift is evidenced by the relatively constant slope of the VO$_2$-PVA regression line regardless of contractile states and the mode of contraction (Table 1). The sensitive change in VO$_2$ intercept by contractile state (Table 1) is similar to that observed in our previous study.

The relatively constant Ec from the excess VO$_2$ (total VO$_2$−unloaded VO$_2$) to PVA of 44% (Table 1), which is the reciprocal of the slope coefficient, was consistent with the constant efficiency from ΔVO$_2$ to EW of 47% (Figure 6). Moreover, the efficiency from ΔVO$_2$ to EW was comparable among the control, dobutamine, and propranolol runs (Figure 6). These findings indicate that the VO$_2$ cost of unit PVA is equal to that of unit EW regardless of the contractile states, and hence, as greater EW is performed, greater VO$_2$ is required for the work. Thus, the VO$_2$-PVA relation is compatible with the Fenn effect.

We assumed in the present study that 1 ml O$_2$ 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. Therefore, changes, if any, in the metabolic substrates would have a negligible effect in the present study.

Mommaerts 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. In the heart, however, wall force is not constant (isotonic); it decreases during the ordinary quasi-isobaric ejection. The force during the early ejection phase is greater than end-systolic force in quasi-isobaric ejecting contractions, as seen in Fig-
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 superimposible; 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 pressure derived from the concept of PVA. The Vo2 curve for isovolumic contractions was concave upward and that for ejecting contractions was concave downward. Vo2 in ejecting contractions was greater than that in isovolumic contractions by an amount proportional to EW. Thus, we could show that the additional energy utilization that accompanies EW production, that is, the Fenn effect, is reconcilable with the PVA concept.

Appendix

As seen in Figure 1, PE and EW are expressed as a function of end-systolic pressure (Pes) as follows.10

\[
PE = \frac{1}{2} \cdot \text{Pes} \cdot (\text{Ves} - \text{Vo}) = \left[1/(2 \cdot E_{max})\right] \cdot \text{Pes}^2
\]

(1)

\[
EW = \frac{\text{PE} \cdot \text{SV}}{\text{Pes}} = \frac{(\text{Ved} - \text{Vo} - \text{Pes}/E_{max})}{\left[1/(E_{max})\right] \cdot \text{Pes}^2 + (\text{Ved} - \text{Vo}) \cdot \text{Pes}}
\]

(2)

where Ves is end-systolic volume, Ved is end-diastolic volume,Vo is volume at which peak pressure is zero, and SV is stroke volume. In Equations 1 and 2, we assume for simplicity that ventricular pressure during ejection is constant, that is, isotropic, and equal to Pes as shown in Figure 1. From Equations 1 and 2,

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

(3)

Thus, PVA, PE, and EW can be mathematically expressed as quadratic functions of Pes. In the present study, E_{max} and Vo 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:

\[
\text{Vo2} = A \cdot \text{PVA} + B = A \cdot (\text{PE} + \text{EW}) + B
\]

(4)

In isobaric ejecting contractions, from Equations 3 and 4,

\[
\text{Vo2} = \left[\frac{A}{2 \cdot E_{max}}\right] \cdot \text{Pes}^2 + B
\]

(5)

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.

Acknowledgment

The first author (T.N.) greatly appreciates throughout this study the continuous encouragement of Prof. Shigetake Sasayama of the 2nd Department of Internal Medicine, Toyama Medical and Pharmaceutical University, from which T.N. was on leave for two years (1986–1988).

References

1. Fenn WO: A quantitative comparison between the energy liberated and the work performed by the isolated sartorius muscle of the frog. J Physiol (Lond) 1923;58:175–203


**KEY WORDS** • cardiac mechanics • total mechanical energy • cardiac energetics • potential energy • external mechanical work
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_Circ Res._ 1989;65:1380-1389
doi: 10.1161/01.RES.65.5.1380
_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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