Force-Time Integral Decreases With Ejection Despite Constant Oxygen Consumption and Pressure-Volume Area in Dog Left Ventricle

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We have shown that systolic pressure-volume area (PVA), which is equivalent to the total mechanical energy generated by ventricular contraction, correlates linearly with myocardial oxygen consumption, VO$_2$, in canine left ventricle. Systolic force-time integral, FTI, also correlates with VO$_2$. In this study, stroke volume was increased from 0 (isovolumic) in isolated cross-circulated canine left ventricle in a stable contractile state while keeping constant pressure volume area with a servo pump. Ventricular total force was calculated from ventricular pressure and volume by the force-equilibrium equation and was integrated from the end of diastole to the end of systole as identified with the time of Emax to yield FTI. Under the conditions of constant PVA, FTI significantly ($p < 0.001$) decreased by $10 \pm 7\%$ and $25 \pm 8\%$ with increases in stroke volume from 0 to $8 \pm 4$ ml and $17 \pm 3$ ml and in ejection fraction from 0 to $0.24 \pm 0.10$ and $0.61 \pm 0.05$, respectively, while VO$_2$ and Emax remained constant. Therefore, we conclude that in a stable contractile state, it is possible to keep PVA constant even when stroke volume and ejection fraction are varied and that under such conditions, FTI no longer predicts VO$_2$. PVA remains a reliable predictor of VO$_2$ regardless of ventricular loading conditions. (Circulation Research 1987;60:797–803)

Myocardial peak force has been used as a primary determinant of myocardial oxygen consumption, VO$_2$. However, VO$_2$ for a given peak force considerably increases with shortening and ejection. Therefore, peak force alone cannot serve as a reliable predictor of VO$_2$ when isovolumic and ejecting contractions are examined. Indeed, Weber and Janicki showed that the time integral of total systolic force correlated better with VO$_2$ than peak force in contractions with variable stroke volumes in canine left ventricle.

We have shown that systolic pressure-volume area (PVA), equal to the total mechanical energy generated by ventricular contraction, closely correlates with VO$_2$, regardless of ventricular loading conditions. Gibbs and Chapman have correlated and shown general consistency between our PVA and the contemporary ideas of myocardial energetics. Our previous studies have conclusively shown that tension-time index (TTI), peak pressure, and peak wall force can change considerably despite no changes in VO$_2$ and PVA in canine left ventricle. The next important question to be answered is how Weber and Janicki's force-time integral (FTI) behaves when VO$_2$ and PVA remain constant.

In the present study, how FTI would change with increases in stroke volume while keeping PVA constant was investigated. FTI significantly decreased with increases in stroke volume despite constant PVA and VO$_2$ which indicates that PVA is superior to FTI as a reliable predictor of VO$_2$ under a variety of loading conditions.

Materials and Methods

Preparation

We used the excised cross-circulated canine heart preparation as described before. Briefly, 20 adult mongrel dogs (8–15 kg) were anesthetized intravenously with a mixture of $\alpha$-chloralose (50 mg/kg) and urethane (500 mg/kg) after premedication with ketamine hydrochloride (7 mg/kg i.m.). 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 donor dog's left subclavian artery and right ventricle via the right auricle, respectively. The smaller dog's heart was isolated from both systemic and pulmonary circulation and was excised from the chest. Systemic hypotension due to allergic reaction under cross circulation was prevented with diphenhydramine hydrochloride (30–60 mg im).

The left atrium was opened, and all chordae tendinae were cut. A #9 thin latex balloon with an unstrained volume of 50 ml was fitted in the left ventricle and connected to the volume servo pump described previously. The balloon and the pump were primed with water. The servo pump system enabled the ventricular volume to be precisely controlled and accurate.
Ventricular pressure was measured with a Konigsberg P-7 pressure gauge placed inside the apical end of the balloon. The temperature of the heart was maintained between 35 and 37°C by warming the arterial cross-circulation tube which was coiled in a thermostat bath. The heart was electrically paced with screw-in electrodes placed on the left atrium. The pacing electrodes were not screwed into the right atrial wall because air tended to leak into the right heart through the holes when the right heart was collapsed by the hydrostatic drainage of coronary venous blood. The sucked air would adversely increase oxygen content of coronary venous blood. Left ventricular surface ECG, which was detected by another pair of screw-in electrodes, was used to trigger the volume servo pump in synchrony with ventricular contraction, to count heart rate, and to determine the onset of contraction. After the experiment, the left ventricle, including the septum, weighed 67 ± 8 g and the right ventricular free wall weighed 25 ± 3 g.

Oxygen Consumption
Coronary perfusion flow was measured continuously with a Nihon Kohden (Japan) MFV-2100 electromagnetic flowmeter by placing a 5-mm probe (Nihon Kohden FF-050T) in the venous cross-circulation tube from the right heart. This tube hydrostatically drained total coronary venous blood. Coronary arteriovenous oxygen content difference was continuously measured with an AVOX system by bypassing part (8-10 ml/min) of both coronary arterial and venous blood from the cross-circulation tubes. To speed up the response time of the AVOX system, the transit time (10-20 seconds) of blood to the AVOX cuvettes was minimized by using short small-bore tubes. The bypassed venous blood was returned to the venous tube upstream of the flowmeter. The AVOX system was calibrated against a Leo-O2-Con oxygen content meter (Lexington Instruments) at the beginning of each experiment. Oxygen consumption (Vo2) was determined on-line as the product of coronary flow and arteriovenous oxygen content difference, using an NEC San-ei (Japan) 7T17 signal processor. Vo2 was expressed in milliliters O2/ml/min.

We minimized the contribution of right ventricular Vo2 to the total Vo2 by keeping the right ventricle collapsed through continuous hydrostatic drainage of the coronary venous blood returning into the right heart. We considered that Vo2 of the collapsed right ventricle was equal to [(right ventricular free wall weight)/(total ventricular weight)] × (total ventricular Vo2 as measured when the left ventricle was also unloaded). The fraction of the right ventricular free wall weight in the total ventricular weight was 0.29 ± 0.07 (SD). Vo2 of the collapsed right ventricle was assumed to be constant in each heart because we did not change ventricular contractility, which could change Vo2 of the unloaded ventricle. This constant right ventricular Vo2 was subtracted from the total Vo2 measured directly under different loading conditions in each heart.

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. PVA is equal to the total mechanical energy generated by ventricular contraction. This concept is supported by Piene and Sund and Gibbs and Chapman. PVA consists of external mechanical work and mechanical potential energy.

Ventricular pressure and volume signals were used to determine PVA on-line with the 7T17 signal processor as the sum of small triangular areas with their apices at Vo (ventricular volume at which peak isovolumic pressure was zero) and their bases between adjacent pressure-volume data points (2 milliseconds apart) on the systolic segment of the pressure-volume trajectory. End systole of each contraction was identified as the time at which P(t)/[V(t) - Vo] became maximal. This maximum pressure-volume ratio was identified as Emax of this contraction. (For more details of this ratio's computer algorithm, see our previous paper.)

To keep PVA at a desired constant level despite changes in stroke volume, PVA was continuously computed with a TEAC (Japan) PS-9000 Model 216 computer. The potentiometers of the servo pump system were adjusted to set ventricular afterload pressure and end-diastolic volume to keep PVA constant. When ventricular pressure, coronary flow, and arteriovenous oxygen content difference reached steady state with the desired PVA, the data was collected with the 7T17 processor and stored on a floppy disk.

Force-Time Integral
FTI is the time integral of total ventricular wall force over a period of systole, as originally defined by Weber and Janicki. Although they called it total force integral and abbreviated it to TFI, we called it force-time integral (FTI) after Sarnoff et al's TTI and Gibbs and Gibson's tension-time integral. Like Weber and Janicki's TFI but unlike TTI and tension-time integral, our FTI did not include time integral of force during relaxation, i.e., after the end of systole.

Using the force-equilibrium equation or the Laplace law, we calculated total wall force (F in g) as 1.36 (g/mm Hg) times the product of ventricular pressure (P in mm Hg) and lumen area (π r2 in cm2). The calculated intraventricular radius r, is derived from measured ventricular volume (V) in milliliters by using the volume equation for a sphere: V = (4πr/3)3/2. Therefore, F = 1.36 π r2π P. This formula is the same that Weber and Janicki used. F is considered the total force acting perpendicular to a hypothetical cross section of the wall at the equator of the sphere model of the ventricle.

Systole was defined as the time from the end of diastole (i.e., onset of this contraction) to the time of Emax. The end of diastole was identified with the onset of left ventricular QRS wave. Since a sharp inflection was made at the left upper corner of the pressure-volume loop trajectory in ejecting contractions,
Figure 1A shows the pressure-volume trajectory of a steady-state isovolumic contraction, and Figure 1B shows the pressure-volume trajectory of a steady-state ejecting contraction with a stroke volume of 15.4 ml in 1 heart. Figure 1C superimposes these 2 pressure-volume trajectories. Despite the difference in stroke volume, PVA of these isovolumic and ejecting contractions were equal (1,370 and 1,340 mm Hg ml, respectively, reflecting a 2% difference) by reciprocal changes in afterload pressure and end-diastolic volume. Although the PVA of these 2 contractions were the same in magnitude, they differed in shape. The isovolumic contraction PVA in Figure 1A, consists of only the area for the mechanical potential energy, PE, while the ejecting contraction PVA, in Figure 1B, consists of the sum of the area for external mechanical work, EW, and of PE.

Figure 1D shows a set of contractions with varied stroke volumes and comparable PVA, including the contractions shown in Figures 1A and B. These contractions had different afterload pressures (from 192 mm Hg in isovolumic contraction to 71 mm Hg in the ejecting contraction, with the maximum stroke volume of 15.4 ml), end-diastolic volumes (from 20.4-25.6 ml), stroke volumes (from 0-15.4 ml), and ejection fractions (from 0-0.60). PVA of these contractions remained virtually unchanged at 1,340 ± 41 mm Hg ml with a variation coefficient of 3%. Emax values of these contractions were 15.0 ± 1.5 mm Hg/ml with a variation coefficient of 10%.

Despite the changes in cardiodynamics, Vo2 of these contractions remained unchanged at 0.0533 ± 0.0024 ml O2 with a variation coefficient of 4%. Therefore, both Vo2 and PVA remained unchanged despite the marked changes in stroke volume, afterload pressure, end-diastolic volume, and ejection fraction in a given contractile state in the same heart.

Figure 2 shows left ventricular pressure (top channel), volume (second channel from the top), calculated total wall force (third channel from the top), and force-time integral (bottom channel) as functions of time from the onset of contraction. These contractions are the same as those shown in Figure 1D. Despite the constant PVA and Vo2, as described above, FTI gradually decreased form 164 to 111 g sec (32% decrease) with gradual increases in stroke volume from 0 to a maximum of 15.4 ml. Peak forces, F, of these contractions simultaneously decreased from 2,360 to 1,280 g (46% decrease) with increases in stroke volume.

Figure 3 shows PVA, FTI, and Vo2 as a function of stroke volume in the same contractions as shown in Figures 1 and 2. PVA of these contractions were practically constant within the narrow 95% confidence limits of both regression line and sampled data points. Despite the constant PVA, FTI significantly decreased with increases in stroke volume. Vo2 of these contractions remained unchanged within the narrow 95% confidence limits of both regression line and sampled data points.

In Figure 3, when stroke volume increased from 0 to a relatively small volume of 6.9 ml, the FTI decreased only slightly from the FTI of the isovolumic contraction. At this time, the duration of systole (i.e., time to...
Emax) during which total wall force was integrated increased from 138 milliseconds in the isovolumic contraction to 164 milliseconds (19% longer) in the ejecting contraction. This duration then decreased slightly to 158 milliseconds (but was still 15% longer than isovolumic) with further increases in stroke volume to 15.4 ml. On the average, in 7 hearts, the time to Emax of the ejecting contraction with the minimal stroke volume of 5.1 ± 1.5 ml was 17 ± 3% longer than that of the corresponding isovolumic contraction with the same PVA. In 10 hearts, time to Emax of the ejecting contraction with the maximal stroke volumes of 16.5 ± 3.2 ml was 13 ± 2% longer than that of the corresponding isovolumic contraction with the same PVA. Therefore, the period over which force was integrated to yield FTI was shorter in the isovolumic contraction.

All the hearts studied showed significant decreases in FTI with increases in stroke volume despite constant PVA and VO₂, as shown above by 1 representative heart. Figure 4 shows the summary of the ratios of PVA, FTI, and VO₂ of the ejecting contractions with intermediate (E₁) and maximal (E₂) stroke volumes of 7.8 ± 4.3 ml and 16.5 ± 3.2 ml relative to those of the isovolumic contractions, I, with the same PVA in all hearts. These stroke volumes corresponded to ejection fractions of 0.24 ± 0.10 and 0.55 ± 0.05, respectively. PVA of the ejecting contractions with intermediate and maximal stroke volumes was successfully kept equal to PVA (1,320 ± 350 mm Hg ml)
of the corresponding isovolumic contraction in individual hearts (paired \( t \) test, \( p > 0.2 \)). \( V_0 \) of the ejecting contractions with intermediate and maximal stroke volumes was also equal to \( V_0 \) (0.058 ± 0.013 ml \( O_2/\text{beat} \)) of the isovolumic contraction in individual hearts (paired \( t \) test, \( p > 0.5 \)). Despite the constant PVA and \( V_0 \), FTI of the ejecting contractions with intermediate and maximal stroke volumes were 10 ± 7% and 24 ± 8% smaller than FTI (140 ± 34 g sec) of the isovolumic contraction (statistically significant by analysis of variance, \( p < 0.05 \), and by paired \( t \) test, \( p < 0.001 \)). Furthermore, FTI of the ejecting contractions with maximal stroke volumes was significantly smaller than FTI of the ejecting contractions with intermediate stroke volumes (paired \( t \) test, \( p < 0.05 \)). Emax of the ejecting contractions was not significantly different from Emax (9.6 ± 3.2 mm Hg/ml) of the corresponding isovolumic contraction (paired \( t \) test, \( p > 0.1 \)).

**Discussion**

The present results have shown that FTI of the ejecting contraction considerably decreases with increases in stroke volume and in ejection fraction from FTI of the isovolumic contraction at a constant PVA and \( V_0 \) in the canine left ventricle with a stable contractile state. Therefore, FTI can dissociate from \( V_0 \) when stroke volume and ejection fraction vary. This result indicates that the changes in \( V_0 \) predicted from changes in FTI will not always be correct.

We have shown that TTI, peak pressure, and peak force are considerably smaller in variously ejecting contractions than in isovolumic contractions with comparable \( V_0 \) and PVA.6 PVA has been shown to correlate with \( V_0 \) regardless of ventricular loading conditions.6-8 We do not know any other cardiodynamic parameter or index that will closely correlate with \( V_0 \) in a stable contractile state.

How can we explain the high correlation coefficient (\( r > 0.84 \)) that Weber and Janicki5 obtained between \( V_0 \) and FTI? Figures 5A, 5B, and 5C show the \( V_0 \)-PVA, \( V_0 \)-FTI, and PVA-FTI correlograms, respectively, obtained in an auxiliary protocol in 1 heart in individual hearts (paired \( t \) test, \( p < 0.05 \)). Emax of the ejecting contractions was not significantly different from Emax (9.6 ± 3.2 mm Hg/ml) of the corresponding isovolumic contraction (paired \( t \) test, \( p > 0.1 \)).

**FIGURE 5.** Correlograms between \( V_0 \)-PVA (Panel A), between \( V_0 \) and FTI (Panel B), and between PVA and FTI (Panel C). O, ejecting contraction; ●, isovolumic contraction; diagonal lines, regression lines; inner pairs of dashed curves, 95% confidence limits of regression lines; outer pairs of dashed curves, 95% confidence limits of sampled data.

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We have shown that TTI, peak pressure, and peak force are considerably smaller in variously ejecting contractions than in isovolumic contractions with comparable \( V_0 \) and PVA.6 PVA has been shown to correlate with \( V_0 \) regardless of ventricular loading conditions.6-8 We do not know any other cardiodynamic parameter or index that will closely correlate with \( V_0 \) over such wide experimental conditions as PVA does in a stable contractile state.

How can we explain the high correlation coefficient (\( r > 0.84 \)) that Weber and Janicki5 obtained between \( V_0 \) and FTI? Figures 5A, 5B, and 5C show the \( V_0 \)-PVA, \( V_0 \)-FTI, and PVA-FTI correlograms, respectively, obtained in an auxiliary protocol in 1 heart in the present study. Data include both isovolumic (●) and ejecting (○) contractions. The same set of contractions was used for the 3 correlograms. Correlation coefficient between \( V_0 \) and PVA is 0.980 (\( p < 0.001 \)), and the 95% confidence limits of both the regression line (inner pair of dashed curves) and the sampled data (outer pair of dashed curves) are narrow in Figure 5A. The standard deviation of the sampled data from the regression line is only 0.0015 ml \( O_2/\text{beat} \). This \( V_0 \)-PVA correlogram and the statistical results are similar to those we have obtained in our previous studies.6-8

The \( V_0 \)-FTI correlation in Figure 5B also shows an intriguingly good fit with the correlation coefficient of 0.966 (\( p < 0.001 \)), which is slightly smaller than the 0.980 of the \( V_0 \)-PVA correlation. Transformation of these \( r \) values to \( z \) values17 yielded 2.029 for the \( V_0 \)-FTI relation and 2.298 for the \( V_0 \)-PVA relation. However, the difference between these \( z \) values was statistically insignificant (\( p > 0.5 \)).17 The 95% confidence limits of both the regression line and the sampled data in Figure 5B are slightly wider than those of the \( V_0 \)-PVA correlogram in Figure 5A. Because the PVA-FTI correlation is reasonably good (\( r = 0.963 \)), as shown in Figure 5C, the high correlation between \( V_0 \)-FTI is reasonable despite the result in Figure 4. The result of the present study as shown in Figure 4, however, seems reflected in the slightly lower position of isovolumic data points (●) in Figures 5B and 5C. This is because FTI of isovolumic contractions are slightly greater than FTI of ejecting contractions for comparable PVA and \( V_0 \). A similar analysis was applied to 5 other hearts in our previous studies after calculating FTI using pressure and volume data stored on floppy disks. The correlation between \( V_0 \) and FTI was always good (\( r = 0.948 \pm 0.035 \)). This supports the previously mentioned observation by Weber and Janicki.5 The correlation between \( V_0 \) and FTI was slightly lower than that between \( V_0 \) and PVA (\( r = 0.974 \pm 0.026 \)). However, the differences of \( z \) values17 (\( z = 1.95 \pm 0.41 \)) for the \( V_0 \)-FTI relation vs. 2.34 ± 0.54 for the \( V_0 \)-PVA relation) in individual hearts were not statistically significant (\( p > 0.05 \)).

From Figure 5B, it might easily be concluded that FTI can serve as a good predictor of \( V_0 \). Moreover, mere comparison between Figures 5A and 5B or between their correlation coefficients may let it be concluded that FTI is as reliable a predictor of \( V_0 \) as PVA. However, the present study has clearly indicated the superiority of PVA to FTI as a reliable predictor of \( V_0 \) by holding PVA constant in ejecting contractions. However, if one does not mind the inherently higher scatter of the \( V_0 \)-FTI correlations,3 FTI may be used to predict \( V_0 \).

How can FTI correlate with \( V_0 \) as a whole but not correlate with \( V_0 \) at a constant PVA? The correlation between \( x \) and \( y \) can remain good when they are sampled from two different functions: for example, \( Y = X \) and \( Y = 1.33X \). For a given \( Y, (X \) in \( Y = 1.33X \)) is 25% smaller than \( (X \) in \( Y = X \)). This percent mimics.
the ratio of FTI measured in the ejecting contraction with a maximal stroke volume to FTI measured in the isovolumic contraction with the same PVA and Vo2, shown in Figure 4. Figure 6A shows the correlation when the data points are sampled only from Y = X, where the correlation coefficient is unity. However, when the data points are alternately sampled from both Y = X and Y = 1.33X and pooled as shown in Figure 6B, the regression line is Y = 1.11X, and the correlation coefficient becomes slightly smaller than unity (0.964) but remains amazingly close to unity and statistically significant (p < 0.001). This correlation coefficient is close to that found between Vo2 and FTI.

What can be concluded from Figure 6B? From this correlation alone, we tend to conclude that V correlates reasonably with X and that the most probable relation would be Y = 1.11X with slight scatter ascribed to unknown factors. However, once it is known that these data are obtained from two different relations, the cause of the scatter can be recognized. This situation resembles the correlation between Vo2 and FTI.

FTI did not decrease linearly with stroke volume, as seen in Figure 3. When stroke volume was relatively small, FTI was close to FTI of the isovolumic contraction with the same PVA. With further increases in stroke volume, FTI decreased sharply. In relation to this finding, the duration of systole over which force was integrated was longer by 17% in the contraction with the minimal stroke volume than in the isovolumic contraction. This finding is consistent with previous findings in both left ventricle18 and myocardium preparation.19 We believe that the slightly longer duration of systole in the ejecting contraction with the minimal stroke volume prevented FTI from decreasing although the instantaneous force curve was markedly lower than the isovolumic force curve as seen in Figure 2.

To ascertain the contribution of the longer duration of systole to FTI in ejecting contractions, the following simulation study was made with a digital computer. The left ventricular pressure-volume dynamics were simulated by P(t) = E(t)[V(t) - Vo] in the same way as before.20 E(t) is given a sinusoidal time course: 0.5 Emax[sin(2πt ft - 0.5π) + 1], where f = 1/(2Tmax). Ventricular loading conditions were set so that an isovolumic contraction and three ejecting contractions were produced, as shown in the pressure-volume diagram in Figure 7A. These contractions had a constant Emax of 10 mm Hg/ml and a constant PVA of 2,000 mm Hg ml. Figure 7B shows FTI of these contractions against their stroke volumes. The open circles are the data when Tmax was constant at 150 milliseconds. The crosses are when Tmax of the ejecting contraction with the smallest stroke volume was 17% longer and Tmax of the ejecting contractions with the intermediate and largest stroke volumes was 13% longer than the isovolumic Tmax. These percents of Tmax elongation are equal to the mean values obtained in the present experiment. The simulation result with the longer Tmax in ejecting contractions resembles the reasonable constant FTI for a small stroke volume, as shown in Figure 3B.

In summary, FTI was scrutinized as a determinant of Vo2 in a well-controlled experiment in which PVA was kept constant. FTI decreased considerably with increases in stroke volume and ejection fraction while Vo2 remained constant at the same PVA. Thus, FTI dissociates from Vo2 at a constant PVA. Therefore, FTI cannot always serve as a reliable predictor of Vo2. We conclude that PVA is still a reliable predictor of Vo2 regardless of ventricular loading conditions.

References


**Key Words** • cardiac mechanics • cardiac energetics • pressure-volume diagram • total mechanical energy
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