Time-Invariant Oxygen Cost of Mechanical Energy in Dog Left Ventricle: Consistency and Inconsistency of Time-Varying Elastance Model With Myocardial Energetics

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We studied whether the oxygen cost of mechanical energy is time-invariant in the excised, cross-circulated canine heart. The total mechanical energy generated by ventricular contraction can be quantified by the total pressure-volume area (PVA) according to the time-varying elastance model. In this model, mechanical energy generated until a specified time (t) during systole can be quantified by the partial pressure-volume area, PVA(t). PVA(t) was obtained by quickly releasing ventricular volume at a varied time during isovolumic contraction. The quick release aborted further development of mechanical energy. We found that PVA(t) at a constant end-diastolic volume linearly correlated with myocardial oxygen consumption (VO₂). This indicates that the oxygen cost of mechanical energy is time-invariant. However, we also found that the slope of the VO₂-PVA(t) relation decreased with increasing quick-release speed. This indicates a decrease in VO₂ by the quick release despite the same PVA(t). The time-invariant oxygen cost of mechanical energy is consistent with the time-varying elastance model of the ventricle, but the decreased VO₂ with increasing quick-release speed despite the same PVA(t) is not.

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Pressure-volume area (PVA) is a specific area in the ventricular pressure-volume (P-V) diagram that is circumscribed by the end-systolic and end-diastolic P-V curves and the systolic segment of the P-V trajectory. PVA has been shown to correlate linearly with myocardial oxygen consumption (VO₂) regardless of loading conditions in a stable contractile state in the dog left ventricle. PVA is theoretically the sum of the mechanical energies generated with the progress of contraction, and the development of the mechanical energy stops at end systole according to the time-varying elastance model of the ventricular contraction. The total mechanical energy generated until end systole consists of external work and end-systolic potential energy.

If the oxygen cost of the mechanical energy is time-invariant throughout contraction, PVA generated until time (t) in contraction will also correlate linearly with its VO₂. To examine this hypothesis, we aborted the development of PVA of isovolumic contractions by quickly releasing ventricular volume at a varied timing during systole. To express PVA of the contraction quickly released at t before end systole, we defined partial PVA, PVA(t), as the area circumscribed by the P-V trajectory drawn until t, the instantaneous P-V relation line at t, and the end-diastolic P-V curve. When t is end systole, PVA(t) should be equal in magnitude to PVA. Because PVA(t) of the quick-release contraction was considered to be a variable fraction of PVA, we studied the relation between VO₂ and PVA(t) of quick-release contractions with different timings and speeds of release at a fixed end-diastolic volume.

Although Cooper and Teplick et al have made similar studies by quickly releasing isometric and isovolumic contractions and relating VO₂ to the time integrals of pressure and force, there is a major difference between these studies and our present study. They found the oxygen cost of the time integral of force production to be time-variant, whereas we found the oxygen cost of the mechanical energy to be time-invariant. We will show that the time-variant oxygen cost of the time integral of force production is equivalent to the time-invariant oxygen cost of the mechanical energy that we found...
here. The other important finding is that $V_0$ for the same $PVA(t)$ decreases with increasing quick-release speed. This finding is inconsistent with the time-varying elastance model despite the consistency of the time-invariant oxygen cost of mechanical energy with the time-varying elastance model.

**Materials and Methods**

**Preparation**

We made an excised cross-circulated heart preparation from two adult mongrel dogs in each experiment as previously described. Briefly, the dogs were anesthetized with 25 mg/kg i.v. pentobarbital sodium after premedication with 5 mg/kg i.m. ketamine hydrochloride. Then they were heparinized (1,000 units/kg i.v.). Arterial and venous cross-circulation tubes were cannulated into the common carotid arteries and right jugular vein in the larger (support) dog. The smaller (heart donor) dog was thoracotomized midsternally, and the cross-circulation tubes from the support dog were cannulated into the left subclavian artery and the right ventricle via the right atrial appendage. Then, the heart was isolated from the systemic and pulmonary circulation by ligating the azygos vein, descending aorta, inferior and superior venae cavae, brachiocephalic artery, and bilateral pulmonary hilum. Cross circulation was then started. The supported beating heart was excised from the chest.

The left atrium was opened widely, and all chordae tendineae were cut. The apex of a thin latex balloon was opened and tied on a plastic connector (15 mm i.d., 18 mm o.d., 5 cm long). A Konigsberg Model P-7 miniature pressure gauge (Pasadena, California) was inserted into the balloon through its mouth and ligated at its neck. The cable of this pressure gauge was pulled out through an apical stab, and the balloon was fitted in the left ventricle. The mitral portion of the balloon was fixed on the mitral valve by tightening three threads that had been tied on the balloon and needled through the left ventricular wall. The balloon connector was fixed at the same location of the left atrium. The pump could withdraw ventricular volume (i.e., intraballoon water) at a commanded speed and specified timing and push it back, in synchrony with every cardiac contraction. Quick-release contractions were produced by maximizing the speed of ejection. The onset of the quick release was varied in several steps between the onset and the end systole of the isovolumic contraction at a fixed end-diastolic volume. We measured the peak speed of ejection as the quick release speed from the volume signal with a signal processor. The peak speed of ejection in the electrical model. The difference between $P_m$ and $P_s$ varies among the models as described in detail in the "Appendix."

We extrapolated the PVA calculation to the $PVA(t)$ of a quick-release contraction. By using either $P_m$ or $P_s$, according to these three types of models, the total mechanical energy was calculated as the area circumscribed by the $P-V$ trajectory until the time $t=T_{max^*}$, where the asterisk means quick-release contraction) of maximal elastance, the maximal elastance line (E$_1$ or E$_3$), and the diastolic $P-V$ curve. The maximal elastance lines were drawn from $V_0$ tangent to the $P_m$-V and $P_s$-V trajectories as shown in Figures 1C and 1D, respectively. We defined the total mechanical energy determined in this way as $PVA(t)$. $PVA(t)$ under E$_1$ in the three-element model is thus equal in magnitude to that in the most simple, one-element $E(t)$ model. $PVA(t)$ under E$_1$ and E$_2$ is equal to $PVA(t)$ under E$_1$ and E$_2$ was, in fact, relatively small.

After the experiment, the left ventricle, including the septum, and the right ventricular free wall were weighed.

**Volume Servo Pump and Quick Release**

The design and performance of the volume servo pump were described in detail elsewhere. Briefly, the pump could withdraw ventricular volume (i.e., intraballoon water) at a commanded speed and specified timing and push it back, in synchrony with every cardiac contraction. Quick-release contractions were produced by maximizing the speed of ejection. The onset of the quick release was varied in several steps between the onset and the end systole of the isovolumic contraction at a fixed end-diastolic volume. We measured the peak speed of ejection as the quick release speed from the volume signal with a signal processor. The peak speed of ejection in the electrical model.
Tmax* was slightly behind (4±3 msec in the one- and three-element models and 8±2 msec in the two-element model) the actual onset of quick release because of the finite acceleration of the quick-release speed at the onset of the withdrawal of volume in our servo system as shown in Figure 2A. We considered that generation of mechanical energy ceased at Tmax* (≤Tmax) because ventricular elastance calculated as the ratio of Pm or P5 to ventricular volume above V0 decreased after Tmax*, as shown in Figures 1C and 1D. In this sense, we regarded Tmax* as the practical onset of quick release. Although the potential energy that constituted a part of PVA(t) degraded thereafter, the details of the degradation process do not matter to the magnitude of PVA(t). They will be discussed later, using Figures 1E, 1F, and 1G.

When Tmax* is equal to Tmax of the isovolumic contraction, PVA(Tmax) should correspond in magnitude to the originally defined PVA of the entirely isovolumic contraction followed by isovolumic relaxation. However, we differentiated PVA(Tmax) from PVA in this study: PVA(t) always refers to quick-release contractions, whereas PVA always refers to entirely isovolumic contractions.

We computed the PVA(t) of quick-release contractions and the PVA of isovolumic contractions from ventricular pressure and volume signals on-line with the signal processor at a sampling rate of 2 msec (500 Hz). In this computation, we employed the same algorithm of PVA computation as described elsewhere. PVA(t) was expressed in mm Hg·ml/beat and normalized for a 100-g left ventricle. We adopted as a representative value...
FIGURE 2. Quick-release contractions and isovolumic contraction in the variable-timing run. Small letters a–d in each panel correspond to four different steady-state quick-release contractions. Maximum release speeds were a) 17.8, b) 17.3, c) 18.1, and d) 17.4 EDV/sec. IV indicates isovolumic contraction. Panel A: Time course (T) of volume (V). Panel B: Time course of pressure (P). Panel C: P-V trajectories. Panel D: The mechanical energy production, PVA(t), of each quick-release contraction corresponding to a through d and IV. The onset of quick release in contraction a corresponds to end systole. Quick-release time was advanced in a direction from a to d.

We calculated Emax of entirely isovolumic contractions and quick-release contractions in which the onset of quick release was end systole (endsystolic quick-release contraction) with the signal processor from the same pressure and volume signals used for calculation of PVA and PVA(t). The dimensions of Emax are in millimeters of mercury per milliliter.

Although we obtained Emax of quick-release contractions in which the onsets of quick release were before end systole of the isovolumic contraction (pre-end-systolic quick-release contraction), we did not use it as an index of contractility because the otherwise isovolumic contractions were aborted before end systole. Therefore, we compared the rising limbs of the isovolumic pressure time tracings among quick-release contractions to detect the change in the contractile state. When peak dP/dt of a pre-end-systolic quick-release contraction occurred later than that of the end-systolic quick-release contraction, we also used peak dP/dt (mm Hg/sec) as an index of the contractile state.

Oxygen Consumption

Total coronary flow was measured with an electromagnetic flowmeter (model MFV-2100, Nihon...
Koden, Tokyo, Japan) and an in-line probe (FF-050T, Nihon Koden) placed in the venous cross-circulation tube, which continuously drained all coronary venous blood from the right heart. We neglected left ventricular thebesian venous blood flow because of its small fraction (less than 3%) in the total coronary flow. Coronary arteriovenous oxygen content difference was continuously measured with an AVOX system, which was calibrated against a Lex-O2-Con oxygen content analyzer in each experiment. To speed up the response of the AVOX measurement, we minimized the transit time (10–20 seconds) of the part of coronary venous blood flow to the AVOX cuvette by using a short, small-bore polyethylene tube (i.d. = 1.2 mm). The coronary venous blood bypassed through the AVOX cuvette was returned to the upstream of the flowmeter.

The right ventricle was maintained collapsed by continuous hydrostatic drainage so that it consumed oxygen at a minimal constant rate. We then neglected V02 of the right ventricular free wall as in our previous study. VO2 of the left ventricle was determined as the product of coronary flow in milliliters per minute and arteriovenous oxygen content difference in vol% O2 with the signal processor. VO2 per beat of steady-state contractions was obtained by dividing VO2 per minute by heart rate. VO2 was expressed in milliliters of oxygen per beat and normalized for a 100-g left ventricle. VO2 was determined on-line with the signal processor. We made measurements when VO2 as well as Emax and PVA or PVA(t) reached steady state 2–3 minutes after each change in ventricular loading conditions.

Protocols

I. Variable timing run. Ten hearts were used in Protocol I [heart donor, 11±1 (SD) kg; left ventricle, 56±5 g; right ventricle, 23±6 g]. We first produced a steady state entirely isovolumic contraction at a midrange volume (about 20 ml) and determined Emax.

Next, we produced steady-state quick-release contractions at given onsets of quick release. The release volume and speed were adjusted on the servo pump so that the ventricular P-V trajectory fell monotonically during the quick release in the P-V diagram as shown in Figure 2C. PVA(t) and VO2 were determined in steady-state contractions.

After the end-systolic quick-release contraction, several sets of PVA(t) and VO2 were obtained from pre-end-systolic quick-release contractions whose onsets of release were changed in several steps as shown in Figure 2. From these sets of PVA(t) and VO2, we obtained a quick-release VO2-PVA(t) relation in each heart as shown in Figure 5.

At the end, we again produced a steady-state entirely isovolumic contraction at the same end-diastolic volume and obtained Emax to examine the stability of the contractile state.

II. Variable end-diastolic isovolumic run. After the variable-timing run, we produced steady-state entirely isovolumic contractions at several different end-diastolic volumes to obtain an isovolumic VO2-PVA relation. This VO2-PVA relation was to be used as the reference to that of the quick-release contractions obtained in the variable-timing run. Emax was determined in these contractions.

In addition, steady-state end-systolic quick-release contractions and entirely isovolumic contractions at the same end-diastolic volume were obtained in each of four other dogs to compare VO2 and Emax. VO2 and Emax of the end-systolic quick-release contraction were designated as [VO2]w and [Emax]w; those of the entirely isovolumic contraction at the same end-diastolic volume were designated [VO2]m and [Emax]m.

III. Variable-speed run. Six hearts, three of which had been used in the variable-timing run, were used in this run [heart donor, 11±1 (SD) kg; left ventricle, 56±6 g; right ventricle, 21±3 g]. We examined the influence of the quick-release speed on the VO2-PVA(t) relation. We produced only end-systolic quick-release contractions in this run and changed the release speed in several steps as shown in Figure 3. Emax was determined in these contractions.

Statistics

Values are given as mean±SD. Paired and pooled t tests were appropriately used to determine significance of differences of the data between isovolumic and quick-release contractions as specified for individual tests in "Results." To show the constancy of the quick-release speed in the individual hearts in the variable timing run and the stability of Emax in the individual hearts in the variable speed run, we used the coefficient of variation, that is, SD/mean. Additionally, the linear regression analysis was used, and correlation coefficients were determined for the VO2-PVA(t) and VO2-PVA relations.

Analysis of covariance (ANCOVA) was used to compare VO2-PVA(t) and VO2-PVA regression lines. Values of p<0.05 were taken as significant.

Results

Cardiac Dynamics

In the variable timing and variable end-diastolic isovolumic runs, mean coronary perfusion pressure was 69±10 mm Hg, and pacing heart rate was 148±12 beats/min. End-diastolic volume in the variable timing run was fixed at a constant in each experiment, and its mean value was 21.0±1.9 ml. In the variable-speed run, mean coronary perfusion pressure was 65±12 mm Hg, end-diastolic volume was 20.0±2.5 ml, and pacing heart rate was 151±7 beats/min. Table 1 lists heart rate values in individual hearts.

Assurance of Constant Contractility

Table 1 lists Emax values of entirely isovolumic contractions before and after the variable-timing run in 10 hearts. The ratio of Emax after the variable-timing run to Emax before the run in
FIGURE 3. Quick-release contractions in the variable-speed run. Small letters a–d on each panel correspond to four different steady-state contractions. Panel A: Time course (T) of volume (V). Panel B: Time course of pressure (P). Panel C: P-V trajectories. Panel D: These four contractions have the same mechanical energy production [PVA(t)]. PVA(t) was calculated in the one- or three-element model. Quick-release speed was decreased from 19.2 to 9.92 EDV/sec (from a to d).

In the variable-speed run, the coefficient of variation (i.e., SD/mean) of Emax was 0.01 ± 0.01 regardless of the changes in release timing. In the variable-speed run, the contractile state also remained unchanged during the variable-speed run. A slight difference of Emax between the isovolumic contraction and end-systolic quick-release contraction is discussed later.

Quick-Release Speed

Figures 2A and 2B shows a set of representative tracings of volume and pressure in four different steady-state quick-release contractions that had different onsets of quick release in the variable-timing run. With the changes in the onset of quick release, we slightly adjusted the release volume and speed so as not to produce an excessive negative pressure at the end of the quick release. Therefore, the quick-release speed in the variable-timing run was not rigorously constant in each heart. However, the coefficient of variation of the quick-release speed in each heart was small, ranging between 0.03 and 0.19 (0.09 ± 0.05) among hearts. We averaged the peak quick-release speeds of contractions with different quick-release timings in each heart. Then, we used these mean values for the quick-release speed in individual hearts in the analysis. They ranged between 9.4 and 18.5 EDV/sec (13.5 ± 3.1) in the variable-timing run.

Figures 3A and 3B shows a set of representative tracings of volume and pressure in four different quick-release contractions that had different quick-release speeds in the variable-speed run. The quick-release speed was changed so that the maximum peak speed was 2.1 ± 0.2 times greater than the minimum peak speed in each heart. The mean maximum peak speed was 19.1 ± 1.2 EDV/sec, and the mean minimum peak speed was 9.2 ± 0.5 EDV/sec.
TABLE 1. Ventricular Mechanics and Energetics in the Variable Timing Run

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Exp no., experiment number; iv₁, entirely isovolumic contraction before the variable timing run; iv₂, the entirely isovolumic contraction in the variable end-diastolic volume run; qr₁ and qr₂, the variable-timing run. qr₁, PVA(t) calculated by the one- or three-element model. qr₂, PVA(t) calculated by the two-element model. HR, heart rate fixed by pacing. Emax, slope of end-systolic pressure-volume line; n, number of different loading conditions under which steady-state contractions were produced; r, correlation coefficient between VO₂ and PVA or PVA(t); Slope, regression coefficient of VO₂ on PVA or PVA(t); Inttcp, VO₂ axis intercept (I₉₀ or I₉₅) of the regression line, equal to VO₂ for unloaded contraction at zero PVA or PVA(t); Sᵥ/Sᵥ, the ratio of the slope of qr₅ or qr₆ over the slope of iv₁; QRS, quick release speed of ventricular volume.

Analysis of covariance (ANCOVA) was applied to the comparison between VO₂-PVA(t) and VO₂-PVA regression lines. Differences of the slope (sl) and the elevation (el) of the regression lines were tested by F test.

- NS, statistically insignificant at p>0.05.
- *Statistically significant at p<0.05.
P-V Trajectory and PVA(t)

Figures 2C and 3C show the P-V trajectories drawn from the volume and pressure tracings shown in Figures 2A, 2B, 3A, and 3B in the variable-timing and variable-speed runs, respectively. Figure 2D shows PVA(t)s at different onsets of quick release in the one- or three-element model. Figure 3D shows the same PVA(t) regardless of quick-release speed in the variable-speed run in the one- or three-element model. The P-V trajectory during the quick release was convex downward in the P-V diagram as shown in Figures 2C and 3C, consistent with data in literature.19,20 In the variable-speed run, the early portions of the actual P-V trajectories during quick release were virtually identical, and then they separated from each other depending on the quick-release speed as shown in Figure 3C.

Figure 4C compares the actually observed P(Pm)-V trajectory (solid curve) applicable to both one- and three-element models and the estimated P(Pv)-V trajectory (dashed curve) applicable to the two-element model obtained from the pressure (Figure 4B) and volume (Figure 4A) curves. Pm was obtained by adding R(−dU/dt) to Pm. The Pm-V trajectory was also convex downward as was the Pm-V trajectory. The area under the solid maximal elastance line (E1) is PVA(t) in both one- and three-element models. The area under the dashed maximal elastance line (E2) is PVA(t) in the two-element model. PVA(t) under E1 was 22±13% greater than PVA(t) under E2 on the average in all hearts.

VO2-PVA(t) Relation

Figures 5A and 5B show two representative VO2-PVA(t) relations in quick-release contractions (O and •) at a given end-diastolic volume in the variable-timing run together with VO2-PVA relations in entirely isovolumic contractions (x) in the variable end-diastolic isovolumic run in two hearts. The VO2-PVA(t) relation of the quick-release contractions (O) in either the one- or the three-element model was always highly linear (r=0.972–0.997) like the VO2-PVA relation of entirely isovolumic contractions (x) (r=0.983–1.000) (Table 1). The VO2-PVA(t) relation of the quick-release contractions (•) in the two-element model was also highly linear (r=0.956–0.995), although this linearity was slightly inferior to the former linearity (Table 1). Therefore, VO2 could be linearly related with PVA(t) in the quick release contractions as with PVA in the entirely isovolumic contractions in a given heart in any one of the one-, two-, and three-element models. Namely,

\[ VO_2 = S_{qr} \cdot PVA(t) + I_{qr} \]
\[ VO_2 = S_{ir} \cdot PVA + I_{ir} \]
where $S_q$ is the slope and $I_q$ is the $V_O_2$ axis intercept of the $V_O_2$-PVA(t) relation line of the quick-release contractions, and $S_v$ is the slope and $I_v$ the $V_O_2$ axis intercept of the $V_O_2$-PVA relation line of the entirely isovolumic contractions.

In Figure 5A, $S_q$ was significantly smaller than $S_v$ (p<0.01 by ANCOVA) irrespective of the models, whereas in Figure 5B, both $S_q$s were only slightly smaller than $S_v$, (not significant, p>0.05 by ANCOVA). $S_q$ was variably smaller than $S_v$ in all 10 hearts. Significantly smaller $S_q$ than $S_v$ was observed in five of 10 hearts in the variable-timing run regardless of the models, as summarized in Table 1. The $S_q$S in both the one- and the three-element models were close to $I_v$, regardless of quick-release speed. The same holds in the other hearts, as summarized in Table 1. $I_q$ in both the one- and the three-element models was 0.0455±0.0095 ml $O_2$/beat/100 g, $I_v$ in the two-element model was 0.0428±0.0062 ml $O_2$/beat/100 g, and $I_v$ was 0.0452±0.0072 ml $O_2$/beat/100 g. We compared both $I_q$s with $I_v$ using the paired t test because correlations between both $V_O_2$ and PVA(t) and between $V_O_2$ and PVA were quite high, as shown in Table 1, and hence both $I_q$s and $I_v$ were considered to be reliable estimates of the $V_O_2$ axis intercept. We could not find significant differences between both $I_q$s and $I_v$.

Quick-Release Speed and $V_O_2$

The dependence of $V_O_2$ on quick-release speed was confirmed in the variable-speed run. Figure 7 shows that $V_O_2$ consistently increased with decreases in the quick-release speed at an almost constant PVA(t) calculated in either the one- or the three-element model in each of six hearts (a-f). While we gradually halved the quick-release speed from 19.1±1.2 to 9.2±0.5 EDV/sec, $V_O_2$ increased significantly by 15±5% (p<0.05 by paired t test).

Oxygen Cost of PVA(t) and Force-Time Integral

Equations 1 and 2 can be modified to

$$S_q = (V_O_2 - I_q)/PVA(t) \quad (3)$$

$$S_v = (V_O_2 - I_v)/PVA \quad (4)$$
Because Equation 1 holds regardless of the models, Equation 3 also holds in any of the models. Equation 3 indicates that excess VO2 above \( \hat{I}_x \) (or PVA(t)-dependent VO2) per unit PVA(t) was equal to a constant slope value of \( S_a \) regardless of the onset (t) of quick release as shown in Figure 8C (O). This indicated the time-invariant oxygen cost of PVA(t). However, as shown in Figure 8C (×), FTI-dependent VO2 per unit FTI decreased with the delayed onset of quick release. This indicated the time-variant oxygen cost of FTI. The time-invariant oxygen cost (O) of PVA(t) was recognized in all hearts pooled after normalizing Tmax* relative to Tmax* of the end-systolic quick-release contraction in individual hearts as shown in Figure 9. The oxygen cost (O) of PVA(t) relative to that of end-systolic PVA(t) calculated in the one- or three-element model was 1.07±0.30 on the average, not significantly different from 1 (p>0.05 by paired t test). However, the oxygen cost (×) of FTI relative to that of end-systolic FTI markedly increased with the advanced onset of quick release in all hearts as shown in Figure 9.

**Difference of \( V_{O2} \) and \( E_{max} \) Between End-Systolic Quick-Release Contraction and Entirely Isovolumic Contraction**

Slight changes in not only \( V_{O2} \) but also \( E_{max} \) were observed when steady-state, entirely isovolumic contractions were switched to steady-state, end-systolic quick-release contractions at the beginning of the variable timing and speed runs. We analyzed the relations of the ratio of \( [V_{O2}]_v \) to \( [V_{O2}]_w \) (\( [V_{O2}]_v/[V_{O2}]_w \)) and the ratio of \( [E_{max}]_v \) to \( [E_{max}]_w \) (\( [E_{max}]_v/[E_{max}]_w \)) against the quick-release speed in individual hearts. \( [V_{O2}]_w/[V_{O2}]_v \) in all hearts was 0.95±0.07, significantly smaller than 1 (p<0.05 by paired t test). In six hearts where the quick-release speed was smaller than 15 EDV/sec, the ratio was 0.99±0.05, not significantly smaller than 1, whereas in eight other hearts where the quick-release speed was higher than 15 EDV/sec, the ratio was 0.91±0.07, significantly smaller than 1 (p<0.05 by paired t test). [\( V_{O2}]_v/[V_{O2}]_w \) in all hearts negatively correlated with the quick-release speed (r=-0.600, p<0.05). On the contrary, \( [E_{max}]_v/[E_{max}]_w \) was 1.09±0.08, significantly greater than 1 (p<0.01 by paired t test). This indicates that \( E_{max} \) of end-systolic quick-release contractions tended to be slightly greater than that of isovolumic contractions at the same end-diastolic volume. There was no significant correlation between this ratio and the quick-release speed.

We examined whether the \( E_{max} \) (\( E_1 \) in Figure 1C) of the pre-end-systolic quick-release contraction was greater than the instantaneous elastance, \( E(t) \), of the isovolumic contraction at Tmax* in the variable-timing run. The ratio of \( E_1 \) to \( E(Tmax^*) \) decreased from 1.2 to 0.7 with the advances of the onset of quick release (r=0.744, p<0.05). This correlation indicates that the time course of instantaneous elastance was slightly but systematically affected by the timing of quick release in the steady-state contractions.

**Discussion**

In any of the one-, two-, and three-element time-varying elastance models of the ventricle, the energy given to the elastic body during the time course of systole is partly converted to the external work and partly stored in a form of potential energy having the potential of being converted to external work.\(^1\)\(^4\) Therefore, the total mechanical energy given to the elastic body until a given time, t, during contraction is the sum of the external work that the elastic body has performed until t and the potential energy stored at t. When this t is end systole, the total mechanical energy should be given by PVA.\(^1\)\(^4\) A series of experimental studies in our laboratory have shown a highly linear correlation between \( V_{O2} \) and PVA in the ordinary ejecting and isovolumic contractions.\(^2\)\(^3\) As explained at the beginning of this report, we defined the PVA(t) by extrapolating the concept of PVA as shown in Figure 1 and studied the correlation between PVA(t) and \( V_{O2} \) in pre-end-systolic and end-systolic quick-release contractions. We calculated PVA(t) in a quick-release contraction by the one-, two-, and three-element models of the ventricle. Regardless of the models, we obtained two major findings, which are discussed below in detail. One of them was for and the other against the energetics of the ventricular time-varying elastance model\(^1\) on which the concept of PVA has been based.

The first major finding is that \( V_{O2} \) was a linear function of PVA(t) when time increased from 0 to end systole (Tmax) of an isovolumic contraction as shown in Figure 5. The slope of this relation is \( S_a \).
Figure 8. Oxygen cost of the mechanical energy, $PVA(t)$, and force-time integral, FTI, in the quick-release contraction. $PVA(t)$ was calculated in the one- or three-element model. Panel A: $PVA(t)$s in a variable timing run are shown in the pressure-volume (P-V) diagram. $PVA(t)$ is proportional to the prerelease pressure. Panel B: Pressure curves as a function of time. Panel C: Time course of $PVA(t)$-dependent $V_{O2}$ to generate unit $PVA(t)$ and FTI. $[(V_{O2}-I_{cp})/PVA(t)]$ (○) and $[(V_{O2}-I_{cp})/FTI]$ (×) of pre-end-systolic quick-release contractions were normalized to their values (C) of end-systolic quick-release contractions, where $I_{cp}$ is the $V_{O2}$ intercept of $V_{O2}-PVA(t)$ line.

As for the difference of $PVA$ from FTI, we previously studied $V_{O2}$ in contractions in which ejecting pressures and end-diastolic volumes were variously changed, keeping $PVA$ constant. Despite constant $PVA$ and $V_{O2}$, FTI decreased with increases in stroke volume and decreases in ejecting pressure. From these results, we expect that FTI of an early-onset quick-release contraction whose ejecting pressure is low would be disproportionately smaller than $V_{O2}$, and, hence, the ratio of $V_{O2}$ to FTI would...
Therefore, we do not want to put any specific meaning to these two slightly deviated data points. However, the crosses show obvious and considerable energy increases in \((V_{O2} - I_{qr})/FTI\) as the normalized time decreases below 0.6.

The second important finding is that \(S_u\) in Equations 1 and 3) differed from \(S_w\) in Equations 2 and 4) although \(I_{qr}\) was not different from \(I_{qr}\) (Figure 5 and Table 1). Moreover, \(S_u\) depended on the quick-release speed (Figure 5). This finding is inconsistent with the energetics of the time-varying elastance model.\(^{1}\) In the time-varying elastance model, the total mechanical energy of contraction should be determined solely by \(PVA(t)\), which is the mechanical energy generated until \(t (=T_{max})\), independent of whether the contraction is entirely isovolumic or first isovolumic and then quickly released at \(t\). The present result indicates that pressure and volume events after the completion of \(PVA(t)\) generation can influence \(V_{O2}\) despite the same \(PVA(t)\) (Figure 7). This finding seems inconsistent with our previous finding that \(V_{O2}\) remains virtually unchanged regardless of changes in mechanical events during relaxation, which has supported the time-varying elastance model.\(^{23}\)

We can find two studies supporting this second finding that \(V_{O2}\) of the quick-release contraction is smaller than \(V_{O2}\) of the entirely isovolumic contraction under the same mechanical energy production, which is against the energetics of the time-varying elastance model. Cooper\(^{3}\) demonstrated that only 64\% of the total \(V_{O2}\) was accounted for by the time to peak isometric tension and the remaining 36\% should be attributed to the relaxation phase in cat papillary muscle. He interpreted this finding to indicate that the maintenance of active tension was energy-dependent at all phases of isometric contraction. Hisano and Cooper\(^{24}\) confirmed this finding in ferret papillary muscle. Monroe\(^{1}\) indicated that 91\% of \(V_{O2}\) of the isovolumic contraction was attributed to the contraction phase and that the remaining 9\% was attributed to the relaxation phase in the canine ventricle. Thus, Cooper's\(^{3}\) and Monroe's\(^{1}\) results are different quantitatively.

Cooper\(^{3}\) speculated that Monroe's result\(^{1}\) was due to the progressive deactivation due to the considerable decrease (about 15\%) in the ventricular volume during the quasi-isovolumic phase of contraction against the air-pressure load and the energy requirement of this contraction was completed by end systole. By contrast, Cooper's papillary muscle was rigorously isometric. However, a different mechanism from the one Cooper speculated seems to account for the discrepancy between the results of papillary muscle and the whole ventricle as follows. In the present study, \([V_{O2}]_{qr}/[V_{O2}]_{w}\) was 0.91±0.07 when the quick-release speed was higher than 15 EDV/sec. This mean ratio is close to Monroe's value. The volume change that occurred before release with our servo-controlled system in the variable-speed run was considerably smaller (2.4±1.8\%) than that (15\%) in Monroe's experiment. Therefore, the rigorous isovolumicity may...
not be a determinant of the saving of VO₂ by quick release. However, the energetics and mechanics of the ventricle cannot simply be compared with those of the papillary muscle because of the temporal and spatial inhomogeneity of the property of muscle contraction: ventricular isovolumicity does not mean myocardial isometricity. On the other hand, when the quick-release speed of 10–18 EDV/sec in our preparation is converted to one-dimensional myocardial shortening velocity in the midwall of the ventricle, it is 2–4 muscle lengths/sec, which is comparable to Cooper’s one. However, average myocardial release speed does not guarantee homogeneous distribution of the release speed along the myocardium if there are ventricular shape changes. The temporal and spatial inhomogeneity of the property of muscle contraction may be partly responsible for the different magnitude of VO₂ sparing by the quick release between the myocardium and the whole heart.

To exclude the influence of the relative magnitude of the PVA(t)-independent VO₂, we compared PVA(t)-dependent VO₂, which was obtained by subtracting the PVA(t)-independent VO₂ (Iₘ) and PVA-independent VO₂ (Iₐ) from [VO₂]ₑ and [VO₂]ᵢ, respectively. Then, instead of [VO₂]ₑ/[VO₂]ᵢ, we obtained a different ratio ([VO₂]ₑ-Iₘ)/([VO₂]ᵢ-Iₐ)=Sₑ/Sᵢ, which was about 0.65 in the one- or three-element model at quick-release speeds above 15 EDV/sec as shown in Figure 6. In Cooper’s study, [VO₂]ₑ was about 60% of [VO₂]ᵢ, and Iₚ and Iₐ were 14% and 8% of [VO₂]ᵢ, respectively. Then, Sₑ/Sᵢ, in Cooper’s study can be estimated to be (60–14)/(100–8)=0.50, yet slightly smaller than ours.

The [VO₂]ₑ/[VO₂]ᵢ was higher in our study than in Cooper’s, which may be due partly to the following mechanism. Peak pressure of the end-systolic quick-release contraction or [Emax] was about 10% greater than that of the entirely isovolumic contraction at the same end-diastolic volume. This is consistent with Monroe’s result. Therefore, PVA(t) of the end-systolic quick-release contraction was about 10% greater than that of the isovolumic contraction at the same end-diastolic volume. This is consistent with Monroe’s result. Therefore, PVA(t) of the end-systolic quick-release contraction was about 10% greater than that of the isovolumic contraction at the same end-diastolic volume. However, peak myocardial force was the same between end-systolic quick-release and isometric contractions in Cooper’s experiment. This difference might have come from the difference of Cooper’s excised, artificially superfused cat papillary muscle preparation and Monroe’s and our blood-perfused canine left ventricle preparations and from the difference of the temperature (29°C in Cooper’s vs. 36°C in Monroe’s and our studies) at which the studies were carried out.

The smaller [VO₂]ₑ than [VO₂]ᵢ, despite the same total mechanical energy in terms of PVA(t) and PVA must be explained by a difference of the energy requirement during the relaxation phase between the end-systolic quick-release contraction and the entire isovolumic contraction. The advanced and shortened relaxation in quick-release contractions relative to the isovolumic relaxation seems to lower VO₂ by some mechanisms. One possible mechanism is sparing VO₂ for the decreased maintenance of the active tension after the onset of quick release as Cooper speculated. The superimposable P-V trajectories during an early part of quick release in the variable-speed run regardless of the quick-release speed (Figure 3C) probably reflects shortening of the series elastance, or SE, in the three-element model (Figure 1A). The thereafter separated P-V trajectories depending on the quick-release speed probably reflect the force-velocity relation of the contractile machinery or the velocity-dependent pressure drop by R in the three-element model (Figure 1A). We would speculate that the faster the quick shortening of the contractile machinery is, the more the crossbridges are detached and the more the attachment of crossbridges is suppressed, resulting in sparing ATP and VO₂. This phase may be a complex manifestation of both the force-velocity relation and the shortening deactivation.

Another possibility is that the quick shortening per se of the contractile machinery spares VO₂. On the basis of time-varying elastance model, we have been considering that the amount of PVA(Tmax*) has been produced until Tmax* on the way of an otherwise entirely isovolumic contraction. Therefore, at least the VO₂ to meet PVA(Tmax*) should be paid during this contraction despite the quick release after Tmax*. However, PVA(Tmax*) of this quick-release contraction had, in fact, a smaller oxygen cost than PVA of the entirely isovolumic contraction, which had the same magnitude as the PVA(Tmax*) (Figure 5). Therefore, there may be some mechanisms, though unknown, to spare the VO₂ by quick shortening of the contractile machinery.

The fates of the mechanical energy during quick release are discussed briefly although these are independent of the magnitude of PVA(t). In an ordinary ejecting contraction, we considered that potential energy at Tmax is converted into heat during relaxation. In a quick-release contraction, however, the potential energy at Tmax*, which is the area under Eᵢ or Eₑ, is partly converted to external work (EW) during quick release as shown by the shaded areas in Figures 1E, 1F, and 1G. The magnitude of EW is the same in the three different models. The part other than EW becomes a heat loss (Hᵢ, open area) due to R in the two- or three-element model. The remainder of EW in the potential energy is considered to dissipate as heat (Hₑₑₑ, dotted area), as shown in Figures 1E, 1F, and 1G. This dissipation is considered partly due to the shortening deactivation and partly due to the ordinary relaxation process. The former is dominant in a relatively early onset quick-release contraction and the latter in a relatively late quick-release contraction.

The VO₂ axis intercept of the VO₂-PVA line in the entirely isovolumic contraction (Iₘ) is considered to
reflect mainly the \( V_{O_2} \) of both excitation-contraction coupling and basal metabolism when the total mechanical energy is zero.\(^3\) \( I_w \), or the \( V_{O_2} \) at zero PVA(t), corresponds to the \( V_{O_2} \) of the quick-release contraction ejecting against zero load from a pre-loaded volume greater than unloaded volume. Therefore, the physiological meaning of \( I_w \) is different from \( I_w \) because the \( V_{O_2} \) of excitation-contraction coupling and basal metabolism of the quick-release contraction may be affected by the length-dependent activation\(^29,30\) and metabolism\(^31\). Although papillary muscle\(^5\) had a greater \( I_w \) than \( I_w \), our result of the identical \( I_w \) and \( I_w \) (Table 1 and Figure 5) indicates that the effect of the end-diastolic volume on the \( V_{O_2} \) of excitation-contraction coupling and basal metabolism is negligibly small when PVA(t) is zero.

In summary, PVA(t), which we consider to represent the total mechanical energy generated until time \( t \) during contraction, linearly correlated with \( V_{O_2} \). This indicates that the oxygen cost of the mechanical energy is time-invariant. This finding is consistent with the time-varying elastance model of the ventricle. On the contrary, that the \( V_{O_2} \) of the quick-release contraction is smaller than that of the isovolumic contraction when mechanical energy quantified by PVA(t) or PVA is matched is inconsistent with this model.

Appendix

In an ordinary ejecting contraction (Figure 1B), where ejection velocity is much smaller than that under quick release, \( R \) does not cause a significant pressure drop across it, and, hence, \( P_m \) is only slightly smaller than \( P_e \) as shown in Figure 1B. Therefore, the difference of PVAs under \( P_e \) and \( P_m \) is practically negligible, being less than a few percent of the directly determined PVA under \( P_m \).\(^8\)

In extrapolating PVA of an ordinary ejecting contraction to PVA(t) of a quick-release contraction that we studied here, one must recognize the following points. First, the mechanical energy is generated as long as ventricular elastance increases during contraction.\(^1,4\) In a quick-release contraction, the time \( (t=T_{max}) \) of the maximal elastance \( (E_1 \) and \( E_2 \) in Figures 1C and 1D, respectively) that is attained at the time of quick release is before or at latest equal to the time \( (T_{max}) \) of the end-systolic maximal elastance \( (E_{max}) \) (Figure 1B). Second, as ejection speed increases, one can no longer neglect both \( R \) and SE to assess the mechanical energy production. Namely, \( P_e \) becomes much smaller than \( P_e \) by at most \( R \cdot (-dV/dt) \), where \( V \) is ventricular volume in \( E(t) \). SE serves to buffer the pressure drop across \( R \) because SE can release volume and decrease flow through \( R \) at the beginning of quick release. Because it is difficult to quantitate the separate influences of \( R \) and SE on the pressure drop in the present study, we considered the following three types of models of left ventricle to estimate the total mechanical energy developed by \( E(t) \).

In the one element model that consists of only \( E(t) \), \( P_e \) is equal to \( P_e \) as shown in Figure 1C and expressed by

\[
P_m = P_e = E(t) \cdot [(V(t) - V_0)]
\]

In the two-element model (Figure 1D), consisting of \( E(t) \) and \( R \) with SE neglected, \( P_m \) is expressed by

\[
P_e = P_m + R \cdot (-dV/dt)
\]

This \(-dV/dt\) is the measured flow because the model has no SE and hence no flow from SE. Therefore, we obtained the maximal elastance \( (E_2) \) by adding \( R \cdot (-dV/dt) \) to \( P_m \). We considered that the true maximal elastance would be somewhere between \( E_1 \) in Figure 1C and \( E_2 \) in Figure 1D.

In the three-element model, \( P_e \) is considered to be only slightly greater than \( P_m \) soon after the quick release because the released volume comes primarily from the SE, and \(-dV/dt\) through \( R \), which is expressed in Equation 6, is relatively small. Therefore, we obtained the maximal elastance \( (E_2) \) by using \( P_m \) as an approximation of \( P_e \) in the three-element model as shown in Figure 1C.

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References


**KEY WORDS** • pressure-volume area • quick release • myocardial oxygen consumption
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