Experimental Studies

Crossbridge Model Compatible with the Linear Relation between Left Ventricular Oxygen Consumption and Pressure-Volume Area

Yoshio Yasumura, M.D. and Hiroyuki Suga, M.D.

SUMMARY

Ventricular pressure-volume area (PVA) is a specific area in the pressure-volume diagram, which represents the total mechanical energy generated by each contraction, consisting of stroke work and mechanical potential energy at end-systole. Animal experiments have shown that PVA is correlated linearly with the ventricular oxygen consumption (Vo2) per beat under a variety of loading conditions in a stable contractile state. The slope of the Vo2-PVA line has been shown to remain constant in different contractile states, implying a constant stoichiometry between Vo2 and PVA. As a first step to understand the nature of this Vo2-PVA relation, we devised a new crossbridge (CB) model to theoretically relate PVA with the total enthalpy change associated with the ATP hydrolysis for all CB cycles. One of the most important assumptions on which this model analysis depended was that the time-varying elasticity model could simulate the instantaneous pressure-volume relation. The result of this analysis implied that the empirical linear Vo2-PVA relation could be attributed to the energy balance between energy input and output of the chemomechanical transduction associated with CB cycles during a ventricular contraction.

Additional Indexing Words:
Cardiac mechanics Cardiac energetics Pressure-volume diagram Crossbridge

VENTRICULAR pressure-volume area (PVA) has been proposed as a measure of the total mechanical energy generated by ventricular contraction based on a time-varying elasticity model.1) The PVA is defined as the area in the ventricular pressure-volume (P-V) diagram circumscribed by the end-systolic and end-diastolic P-V curves and the systolic segment of the P-V trajectory (Fig. 1A).1) The PVA is correlated linearly with ventricular oxygen consumption (Vo2) under a variety of loading conditions.2),3) The
The constant stoichiometry between the total energy input and PVA can be explained by the time-varying elasticity model. However, PVA only expresses the total mechanical energy at end-systole. It does not reflect the total energy output during one contraction because it does not explicitly express the energy output that is to be converted to heat during systole. Therefore, as the first step to understand the underlying mechanism of the empirical linear $\text{Vo}_2$-PVA relation, we attempted to theoretically relate PVA with $\text{Vo}_2$ in terms of a new, basic CB model.

**METHODS AND RESULTS**

1. Energetics of time-varying elasticity model

The instantaneous P-V relation of the ventricle can be approximated by

$$P(t) = E(t)[V(t) - V_0]$$

where $P(t)$, $V(t)$, and $E(t)$ are the instantaneous pressure, volume, and ventricular elasticity, and $V_0$ is the common volume axis intercept of these instantaneously linear P-V relation lines. This elasticity is assumed to be ideal, i.e., non-viscous. In the time-varying elasticity model of the ventricle, the total mechanical energy generated during systole consists of the potential energy ($U$) and the work ($W$) according to the first law of thermodynamics as shown in Fig. 1A.

Fig. 1. Concept of pressure-volume area, PVA. [A]: $W$ is the external work and $U$ is the potential energy at end-systole. PVA consists of $W$ and $U$. $P_{es}$ and $P_{ed}$ are the end-systolic and end-diastolic pressures, respectively. $V_{es}$ and $V_{ed}$ are the end-systolic and end-diastolic volumes, respectively. $V_0$ is the volume axis intercept of the end-systolic P-V line (ES-PV). ED-PV is the end-diastolic P-V line. [B]: According to the time-varying elasticity model, the concept of PVA holds at any time during systole. $PVA(t)$, $W(t)$, and $U(t)$ are PVA, $W$, and $U$ at time $t$ during contraction.
We have proposed that the total mechanical energy at end-systole corresponds to the area circumscribed by the end-systolic and end-diastolic P-V curves and the systolic segment of the P-V trajectory as shown in Fig. 1A. This area has been called P-V area (PVA). In the time-varying elasticity model, this concept holds at any time during systole, and can be expressed by

\[ PVA(t) = U(t) + W(t) \]  

where \( PVA(t), U(t), \) and \( W(t) \) are functions of time \( t \). \( PVA(t) \) corresponds to the area circumscribed by the P-V relation line at time \( t \), the end-diastolic P-V curve, and the P-V trajectory between end-diastole and \( t \), as shown in Fig. 1B. Eq. 2 can be expressed in a different form by

\[ \frac{d}{dt}PVA(t) = \frac{d}{dt}U(t) + \frac{d}{dt}W(t). \]  

[II] Mechanics and energetics by CB model

The fundamental quantum of chemomechanical energy transduction in muscle contraction is the enthalpy change in hydrolysis of one (or two) molecule(s) of ATP for every CB cycle.

The first law of thermodynamics yields

\[ h + w = \sum_{i=1}^{N} n_i (-\Delta H_i), \]  

which means that heat production \( h \) and work \( w \) are equal to the sum of changes in enthalpy \( (-\Delta H_i) \) in the individual chemical reactions \( (i=1 \sim N) \) during the contraction. \( N \) is the number of the chain reactions and \( n_i \) is the number of the \( i \)-th reaction. Since we are interested in the overall relation between the energy input and output, we substitute the following overall reaction for all reactions accompanied by one CB cycle.

\[ A + M + kATP \rightarrow AM + k(ADP + P_i) \]  

where \( A, M, \) and \( AM \) represent actin, myosin, and actomyosin, respectively, and \( k \) means the constant number of ATP molecules hydrolyzed per CB cycle. We adopt \( k=1 \). Then Eq. 4 is reduced to

\[ h + w = N_c(-\Delta H) \]  

where \( N_c \) is the number of ATP molecules hydrolyzed in one contraction, which is equivalent to the cumulative number of CBs attached in one contraction; \( -\Delta H \) is the enthalpy change accompanied by one ATP hydrolysis \( (-\Delta H > 0) \). Eq. 6 shows that the total enthalpy change is obtained by summing up all the number of CB cycles in one contraction.

To count \( N_c \) and relate the energy input to the energy output in Eq. 6,
Fig. 2. Schematic representation of CB dynamics to count the cumulative number of CB cycles. Each panel shows the time tracing to represent the CB dynamics. 

A: The instantaneous number of attached CBs \( N_{on}(t) \) is shown. The sum of \( N_{on}(t) \) and the number of free CBs \( N_{off}(t) \) is constant, which is equivalent to the total number of available CBs. \( N_{on}(t) \) as a function of \( t \) is drawn sinusoidally for example. 

B: \( (d/dt)N_{on}(t) \) = change rate of the number of attached CBs. \( R_D(t) \) = rate of detachment of CBs, which is assumed to be proportional to the instantaneous \( N_{on}(t) \). \( R_A(t) \) = rate of attachment of CBs. 

C: The cumulative number \( N_c(t) \) of CB cycles is obtained by integrating the rate of attachment until the CB attachment \( t_p \). \( R_A(t) \) is positive until \( t_p \). 

we must prepare a quantitative description of CB dynamics and energetics. Because the real behavior of CB is not yet fully understood\(^{10}\), we devised a model focusing on the energetic aspect of CB behavior to elucidate the physiological meaning of PVA. The following qualitative sequence of the CB cycle that we assumed seems generally accepted\(^{10}\).

For CB attachment, a CB chemically potentiated by ATP attaches to the thin filament, which is followed by development of force as well as generation of mechanical potential energy by stretching the series elasticity (on-state of CB). CB detachment occurs with or without muscle shortening, i.e., performing external work. The shortening accelerates the detachment of CB. The muscle shortening transduces the mechanical potential energy to external work. Each of these detachments is accompanied by the hydrolysis of one molecule of ATP, which in turn potentiates the CB (off-state of CB).

On the basis of this fundamental CB cycle, we assumed the following properties of chemomechanical transduction. First, the instantaneous mechanical potential energy \( U(t) \) stored in the ventricle at \( t \) originates from the chemical energy of ATP, which is associated with the CBs generating force at
t. Namely, U(t) is proportional to the number of attached CBs at t. Second, detachment of CB occurs in the following two ways: spontaneously without either muscle shortening or performance of external work and with muscle shortening and performance of external work.

Fig. 2 shows how to count the cumulative number \( N_C \) of CBs activated during one contraction. Fig. 2A shows schematically an example of instantaneous number \( N_{on}(t) \) of on-state CBs as a function of time. At any time in systole, both attachment and detachment of CBs occur. The increasing rate \( (d/dt)N_{on}(t) \) of on-state CBs is determined by both the CB attachment rate \( R_A(t) \) and the CB detachment rate \( R_D(t) \). Namely,

\[
(d/dt)N_{on}(t) = R_A(t) - R_D(t) \text{ or } R_A(t) = (d/dt)N_{on}(t) + R_D(t) \tag{7}
\]

where \( R_D(t) \) is positive when the detachment occurs. The time integral of \( R_A(t) \) expresses the cumulative number of CBs attached during one contraction (Fig. 2C). Namely,

\[
N_C = \int_{t_0}^{t_f} R_A(t) \, dt \tag{8}
\]

where \( t_p \) is the latency until \( R_A(t) \) is positive.

By multiplying each term of Eq. 7 by \(-\Delta H\), we obtain the equilibrium of energy transduction.

\[
(-\Delta H)R_A(t) = (-\Delta H)(d/dt)N_{on}(t) + (-\Delta H)R_D(t) . \tag{9}
\]

We can regard the left hand term of Eq. 9 as the energy input rate and the right hand terms as the energy output rate in the chemomechanical transduction. We use Gibbs free-energy change \( \Delta G \) instead of the enthalpy change in the right hand of Eq. 9. The relation between \( \Delta H \) and \( \Delta G \) is written by

\[
\Delta H = \Delta G + T\Delta S \tag{10}
\]

where \( T \) is the absolute temperature and \( \Delta S \) is the molar entropy change in thermodynamics. Eq. 9 is modified to

\[
(-\Delta H)R_A(t) = (\Delta H/\Delta G)\{(\Delta G)(d/dt)N_{on}(t) + (\Delta G)R_D(t)\} \tag{11}
\]

The first term \( (\Delta G)(d/dt)N_{on}(t) \) in the brackets of Eq. 11 is considered to be the change in the potential energy stored inside and/or outside the \( (d/dt)N_{on}(t) \) of CBs, which can be transduced to external work, and this is why we used \( \Delta G \) instead of \( \Delta H \).

It is reasonable that some energy loss results from the following two steps in the conversion from the free-energy change of ATP hydrolysis to the ventricular potential energy. One source of energy loss may be the energy transduction from \( -\Delta G \) to the CB's potential energy. The other source of
energy loss may result from conversion of the CB's potential energy to the ventricular mechanical potential energy \(U(t)\). To incorporate these losses, we introduced an efficiency coefficient \(\alpha (\leq 1)\) of the total free-energy change of \((-\Delta G)(d/dt)N_{on}(t)\). Then,

\[
(d/dt)U(t) = \alpha(-\Delta G)(d/dt)N_{on}(t). \tag{12}
\]

The second term \((-\Delta G)R_D(t)\) in the brackets of Eq. 11 corresponds to the free-energy change accompanied by the \(R_D(t)\) of CB cycles. In our CB model, CB detachment occurs either spontaneously at a rate of \(R_{DF}(t)\) only after force generation, or by performing external work \((W(t))\) at a rate of \(R_{DW}(t)\). Namely,

\[
R_D(t) = R_{DF}(t) + R_{DW}(t). \tag{13}
\]

Firstly, we assume that \(R_{DF}(t)\) depends on the number of on-state CBs at \(t\) and the myosin ATPase activity, which determines the CB cycle rate \(r\) (Hz). Then, \(R_{DF}(t)\) is given by

\[
R_{DF}(t) = rN_{on}(t). \tag{14}
\]

Eq. 14 is modified as follows by substituting an integrated form of Eq. 12 for \(N_{on}(t)\).

\[
(-\Delta G)R_{DF}(t) = (1/\alpha)rU(t). \tag{15}
\]

Next, we can relate \(R_{DW}(t)\) with the external work as follows. From Eq. 12, the \(R_{DW}(t)\) of CBs is considered to increase the potential energy at a rate of \(\alpha(-\Delta G)R_{DW}(t)\), unless muscle shortening occurs. In the time-varying elasticity model, work is interchangeable with potential energy because this model has no resistance. Then, \(W(t)\) can be related with \(R_{DW}(t)\) as

\[
(d/dt)W(t) = \alpha(-\Delta G)R_{DW}(t). \tag{16}
\]

Substitution of Eqs. 12, 15, and 16 for \((d/dt)N_{on}(t)\) and \(R_D(t)\) in Eq. 11 yields

\[
(-\Delta H)R_s(t) = (\Delta H/\Delta G)(1/\alpha)[(d/dt)U(t) + (d/dt)W(t) + rU(t)]. \tag{17}
\]

This equation is considered to relate CB energetics (left hand term) with ventricular energetics (right hand terms).

[III] CB energetics in terms of ventricular energetics

We now relate PVA with the CB energetics expressed by Eq. 17. In the time-varying elasticity model, the instantaneous \(U(t)\) is defined as the triangular area on the P-V diagram circumscribed by the instantaneous P-V relation, \(V = V_{ed}\), and the end-diastolic P-V curve, as shown in Fig. 1B. We neglect the resting potential energy which corresponds to the area circum-
scribed by the end-diastolic P-V curve, P=0, and V=V\text{ed} because it is relatively small compared with PVA in the physiological contraction. Therefore, U(t) can be approximated by

$$U(t) = (1/2)P(t)[V(t)-V_0].$$

(18)

Because $(d/dt)U(t)+(d/dt)W(t)$ in Eq. 17 is equivalent to $(d/dt)PVA(t)$ from Eq. 3, Eq. 17 can be expressed in an integrated form using Eq. 8 by

$$(-\delta H)_N = (\delta H/\delta G)(1/\alpha)\{PVA+(1/2)\int_{T_{\text{max}}}^T P(t)[V(t)-V_0]dt\}$$

(19)

where $T_{\text{max}}$ is the time to the peak $E(t)$ ($E_{\text{max}}$) from the onset of systole. Eq. 19 describes the mechanism of the transduction from the total enthalpy change of ATP hydrolysis accompanied by CB cycles to the ventricular total mechanical energy. Eq. 19 indicates that a given quantity of PVA is accompanied by an energy loss (EL) which is due to the spontaneous CB cycle in producing PVA:

$$EL = (1/2)\int_{T_{\text{max}}}^T P(t)[V(t)-V_0]dt.$$  

(20)

The overall energy loss generated in this energy transduction from $(-\delta H)_N$ to PVA increases under the following conditions: (1) an increase in $\delta H/\delta G$ of one mole of ATP hydrolysis, (2) a decrease in efficiency $\alpha$ from the total free-energy change associated with CB cycles to the ventricular potential energy, (3) an increase in the CB cycle rate $r$ and, hence, an increase in energy loss (EL).

[IV] Mechanism of the linear $V_O_2$-PVA relation

About 65% of the energy released by substrate oxidation with $V_O_2$ is transduced into the form of high-energy bonds of ATP.\textsuperscript{11} The total enthalpy change associated with ATP hydrolysis is used for the CB cycle ($(-\delta H)_N$) and the non-mechanical activity of muscle contraction such as basal metabolism and excitation-contraction coupling.\textsuperscript{4} This energy balance is written by

$$0.65V_O_2 = (-\delta H)_N + (-\delta H)_{N_{\text{NM}}}$$

(21)

where $N_{\text{NM}}$ means the number of molecules of ATP consumption for the non-mechanical activity of muscle contraction. If $(-\delta H)_{N_{\text{NM}}}$ in Eq. 21 is assumed to be independent of PVA or proportional to PVA, the empirical linear relation between $V_O_2$ and PVA implies that $(-\delta H)_N$ is a linear function of PVA in Eq. 19. For PVA to be proportional to $(-\delta H)_N$ in Eq. 19, EL defined by Eq. 20 is either 1) proportional to PVA or 2) constant or zero, regardless of the ventricular loading conditions in a given contractile state.
If \( r \) in Eq. 14, which is considered to reflect the myosin ATPase activity, is assumed to be constant during a contraction, we can analyze EL more quantitatively using the time-varying elasticity model. The ratio of EL to PVA is expressed by

\[
\frac{EL}{PVA} = \frac{(1/2) \int_{T_{\text{max}}}^{T} P(t)[V(t) - V_0] \, dt}{PVA}.
\tag{22}
\]

Eq. 22 can be modified (as shown in Appendix) to

\[
\frac{EL}{PVA} = rT_{\text{max}} \int E^*(t) \, dt
\tag{23}
\]

where \( E^*(t) \) is the instantaneous ventricular elasticity normalized with respect to \( T_{\text{max}} \) and \( \text{Emax} \).\(^6\),\(^12\) Because changes in heart rate, end-diastolic volume, and contractility do not affect \( E^*(t) \),\(^12\) the integration of \( E^*(t) \) over systole is constant. Therefore, the constant \( EL/PVA \) ratio which is required by the empirical linear relation between \( VO_2 \) and PVA implies that the product of CB cycle rate \( r \) and \( T_{\text{max}} \) is constant or negligibly small regardless of ventricular loading conditions.

Eq. 19 showing the relation between total enthalpy change and PVA can be modified as follows by substituting Eq. 23 into Eq. 19.

\[
(-\Delta H)_{N_C} = (\Delta H/\Delta G)(1/\alpha)(1 + rT_{\text{max}} K)PVA
\tag{24}
\]

where \( K \) is a constant value for \( \int E^*(t) \, dt \) and close to 0.5 (dimensionless).\(^6\) Eq. 24 enables us to obtain the efficiency (\( e \)) from \( (-\Delta H)_{N_C} \) to PVA as

\[
e = (\Delta G/\Delta H)\alpha(1 + rT_{\text{max}} K)^{-1}.
\tag{25}
\]

If \( \Delta G/\Delta H \), \( \alpha \), and \( rT_{\text{max}} \) are constant, \( e \) is constant and PVA is correlated linearly with \( (-\Delta H)_{N_C} \) by Eq. 24 and further with \( VO_2 \) by Eq. 21.

**DISCUSSION**

We have related the PVA with the total enthalpy change associated with ATP hydrolysis for all CB cycles during one contraction by employing several assumptions about chemomechanical transduction in a basic CB model. This study is the first of its kind that aims to relate PVA with the energetic model of CB behavior.

We consider this energetic model to be acceptable because it can reasonably explain the empirical finding of the linear relation between \( VO_2 \) and PVA.\(^2\) It is the total enthalpy change, not PVA, that is explicitly proportional to \( VO_2 \), as shown in Eq. 21. Therefore, once this model is established,
it yields an insight into the constant stoichiometry between energy input in terms of $V_{o2}$ and mechanical output in terms of PVA.$^{41,51}$

The CB detachment rate, $R_D(t)$ in Eq. 13, is considered to be largely affected by both shortening velocities.$^{13,14}$ We assumed that $R_D(t)$ consists of the spontaneous CB detachment during force generation and the CB detachment accompanied by external work. We also assumed that the increased $R_D(t)$ during the muscle shortening is mainly brought about by the CB detachment accompanied by external work. The spontaneous CB detachment, which is considered to be affected by the myosin ATPase activity, is assumed to be constant during a contraction. Given these assumptions, this model permits analysis of the constant stoichiometry between the energy input ((-$\Delta H$)Nc) and PVA quantitatively.

Let us now discuss the constant nature of the efficiency $e$ in Eq. 25. This efficiency consists of the product of three components, which correspond to each step of chemomechanical transduction:

(a) Chemomechanical transduction between ATP hydrolysis and force production of CB

The enthalpy change ($-\Delta H$) associated with hydrolysis of one mole of ATP is considered to be constant$^{15}$ and independent of types of contraction. On the other hand, the free energy change ($-\Delta G$) varies according to

$$-\Delta G = -RT\ln(K_2/K_1)$$

where $R$ is the ideal gas constant, $T$ is the absolute temperature, $K_1$ is the equilibrium constant in the reaction of CB attachment, and $K_2$ is the equilibrium constant in the reaction of CB detachment.$^{16}$

We may be able to assume that $-\Delta G/\Delta H$ is constant in isovolumic contractions and ejecting contractions in which ejection speeds are relatively low. However, if the detachment of CB is accelerated by a quick shortening of muscle,$^{13,14}$ which corresponds to an increased $K_2$ or $-\Delta G$ would increase as would $-\Delta G/\Delta H$. In such a case, the efficiency from the enthalpy change associated with ATP hydrolysis to PVA will increase by Eq. 19.

(b) Relationship between CB's and ventricular potential energy

Eq. 12 means that the ventricular potential energy ($U(t)$) is proportional to the number ($N_{on}(t)$) of on-state CBs under a constant $\alpha (-\Delta G)$. Although we assumed that one on-state CB generates a unit force, the contribution of this force to both the CB's potential energy and the ventricular potential energy may change along the systolic time course,$^{51,17}$ which indicates the time-dependent energy cost of the ventricular potential energy. Therefore, to assure the validity of Eq. 12, it remains to be clarified whether the energy cost of the ventricular potential energy is time-dependent.
Energy loss due to the CB cycle

The mean CB cycle rate was 2.9 Hz in isometric tetanic contractions of skeletal muscle.\textsuperscript{18} It has been shown to be 2.1±0.2 Hz for V\textsubscript{1}-type myosin and 1.1±0.2 Hz for V\textsubscript{3}-type myosin by pertubation analysis of papillary muscle in barium contracture.\textsuperscript{19} Judging from these data, CB cycle rate r for force generation (Eq. 14) seems slow relative to the duration, 0.6 sec/beat when heart rate is for example, 100 beats/min, during ordinary ventricular contraction. This implies that the energy loss due to the CB cycle for force generation is small. If this loss is negligible, then (a) CB attachment only occurs during the isovolemic contraction phase, increasing the potential energy, and (b) CB detachment occurs only in association with external work and during relaxation. Although these features of the CB cycle may appear to be unrealistic, these features are not necessarily inconsistent with the experimental results that most of the CBs seem to attach to generate force in isometric contraction\textsuperscript{20}-\textsuperscript{22} and that muscle shortening augments the rate of phosphocreatine hydrolysis.\textsuperscript{23} Therefore, this seemingly oversimplified CB model may be useful in respect to the approximation of energetics of ventricular contraction. However, the slow CB cycle rate r for force generation is not necessarily inevitable for the constant EL/PVA ratio in Eq. 22 (described below).

We have assumed that r is constant during systole. The linear \(-JH\)-\(N_c\)-PVA relation requires a constant value of rT\textsubscript{max} in Eq. 24. When contractility is enhanced by catecholamines, T\textsubscript{max} is shortened. Under such a condition, the cycle rate r has to increase to keep rT\textsubscript{max} constant. This increase in r is consistent with the earlier finding that r is increased in the rat papillary muscle with V\textsubscript{1}-type myosin by epinephrine infusion during barium contracture.\textsuperscript{19} On the other hand, when T\textsubscript{max} is prolonged by cooling, r is known to be smaller.\textsuperscript{24},\textsuperscript{25} Thus, r and T\textsubscript{max} seem to change reciprocally to keep rT\textsubscript{max} constant and, in turn, to keep EL/PVA constant.

If E\((t)\) is independent of these interventions and rT\textsubscript{max} remains constant, Eqs. 21 and 24 indicate that the efficiency from \(V_o\) to PVA would be constant. However, it is known that hyper- and hypo-thyroidism and chronic pressure overload alter the efficiency of chemomechanical transduction.\textsuperscript{26},\textsuperscript{27} In these cases, the constancy of \(\int E\((t)\)dt and rT\textsubscript{max} might not be maintained.

Equivalence between potential energy and external work

The efficiency from the total enthalpy change to PVA in Eq. 25 is possibly constant. However, the generalized relation between the total enthalpy change and PVA, i.e., Eq. 19 which derived Eq. 25, is based upon the assumption of the energetic equivalence between U and W in the time-varying elasticity model. Therefore, it seems that the degree of linearity of the empirical
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\( \text{Vo}_2\)-PVA relation also depends on the degree of the approximation of the instantaneous P-V relation by Eq. 1. Strictly speaking, Eq. 1 does not hold even during ventricular contraction.\(^{28),29}\) The instantaneous ventricular pressure reduces from the isovolumic pressure by 10–20% in ordinary ejecting contractions in the canine left ventricle.\(^{28}\) If we are allowed to regard this value to be small in practice, the present model can also explain the important finding that the correlation between \( \text{Vo}_2 \) and PVA in ejecting contractions in a canine heart was maximized when \( W \) and \( U \) of PVA were assumed to have virtually the same energy cost.\(^{30}\)

**Appendix**

In an isovolumic contraction, PVA is equivalent to the triangular area circumscribed by the P-V relation line, the end-diastolic P-V curve, and the systolic segment of the P-V trajectory. When the area under the end-diastolic P-V curve is negligibly small compared to PVA, PVA is approximated by

\[
PVA = (1/2) \text{Pes}(\text{Ved}-V_0)
\]

where \( \text{Pes} \) is the end-systolic pressure and \( \text{Ved} \) is the end-diastolic volume. By substituting Eq. 1 for \( \text{Pes} \) in Eq. 27, we obtain

\[
PVA = (1/2) \text{E}_{\text{max}} (\text{Ved}-V_0)^2.
\]

By substituting Eq. 28 for PVA in Eq. 22, we obtain

\[
\frac{EL}{PVA} = r \int_{t}^{T_{\text{max}}} \frac{E(t)}{\text{E}_{\text{max}}} dt.
\]

Eq. 29 is reduced as follows by the change of variable from \( t \) to \( \tau = t/T_{\text{max}} \)

\[
\frac{EL}{PVA} = r T_{\text{max}} \int_{0}^{1} E^*(\tau) d\tau.
\]

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