Ventriculo-arterial Coupling and the Areas under the End-systolic Pressure-volume Relation

Rachad M. SHOUCRI, PhD

SUMMARY

Ventriculo-arterial coupling is expressed as the ratio $E_{\text{max}}/e_{\text{am}}$ (maximum ventricular elastance/arterial elastance). Different areas under the end-systolic pressure-volume relation (ESPVR) are expressed in terms of $E_{\text{max}}/e_{\text{am}}$. The explicit inclusion of the active force of the myocardium in the mathematical formalism describing the pressure-volume relation (PVR) leads to new insight into the mechanics of left ventricular contraction. Applications to experimental data related to stroke work area $SW$ under ESPVR are discussed and provide further evidence for the consistency of the mathematical formalism used. (Jpn Heart J 1997; 38: 253–262)

Key words: End-systolic pressure-volume relation, Active force of the myocardium, Maximum elastance $E_{\text{max}}$, Mechanics of left ventricular contraction, Ventriculo-arterial coupling

There has been some interest recently in studying ventriculo-arterial coupling, expressed by the ratio $E_{\text{max}}/e_{\text{am}}$ (maximum elastance/corresponding arterial elastance). The purpose of the present study is to review some basic equations used in the study of the end-systolic pressure-volume relation (ESPVR) with the aim of emphasizing the following concepts:

a) The mathematical formalism used to describe the pressure-volume relation (PVR) explicitly includes the active force of the myocardium.

b) Stroke work ($SW$), as well as other areas under ESPVR are used to express ventriculo-arterial coupling as a function of $E_{\text{max}}/e_{\text{am}}$ (note that the corresponding notation $E_a/E_a$ is also used). Clinical applications of different areas under ESPVR as well as their significance for the study of left ventricular adaption to load have been discussed. The following discussion stresses the point of view that the study of the mechanics of left ventricular contraction should be based on an integrated approach to the interrelation between different areas under ESPVR (Figures 3 and 4) rather than an isolated study of the stroke work area $SW$.

From the Department of Mathematics and Computer Science, Royal Military College of Canada, Kingston, Ontario, Canada.

Address for correspondence: Rachad M. Shoucri, PhD, Department of Mathematics and Computer Science, Royal Military College of Canada, Kingston, Ontario, Canada K7K, 5L0.

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c) Following experimental results presented by Burkhoff and Sagawa,\(^5\) Asanori et al,\(^6\) Fourie et al,\(^7\) the present study takes the position that under normal physiological conditions the left ventricle operates near maximum oxygen efficiency with \( E_{\text{max}} / \epsilon_{\text{am}} = 2, \ E_{\text{max}} / \epsilon_{\text{am}} = 1 \) (maximum SW) corresponds to a mildly depressed state of the heart while \( E_{\text{max}} / \epsilon_{\text{am}} \geq 1 \) corresponds to a severely depressed state. Based on experimental observations it has been reported by Burkhoff and Sagawa\(^5\) that “... it does not seem possible to obtain simultaneously a physiological SV (stroke volume), end-diastolic volume, and end-systolic pressure with the condition \( E_a = E_{es} \). \( E_a \) must always be smaller than \( E_{es} \) to obtain physiological conditions ...”.

d) New applications to experimental data related to SW taken from Little and Cheng\(^3\) are given in Table I and applications to simulation data related to SW taken from Takaoka et al\(^1\) are presented in Table II. The factor A introduced in Eq. (10) of Takaoka et al\(^1\) is derived again, and it is shown that \( A = \left( 1 / 2 \right) (SW / TW) \), where \( SW = \) stroke work and \( TW = \) total area under ESPVR (Figure 3). These results provide further evidence for the consistency of the mathematical formalism used in the present study.

e) The concept of “preload recruitable stroke work” is reviewed. It is suggested that the apparent linearity between \( SW \) and the end-diastolic volume \( V_{ed} \) is only an approximation.

Although the ESPVR is slightly curvilinear, the linear model shown in Figure 2 is adopted. This model will simply greatly the mathematical formalism to be developed, without affecting the basic concepts to be discussed.
MATHEMATICAL METHOD

The cross-section of a three-dimensional cavity of the left ventricle is shown in Figure 1. The helical structure of the fibre generates a radial active force/unit volume \( D \), as explained by Shoucri.\(^8,9\) In a quasi-static approximation (inertia and viscous forces neglected), the equilibrium of forces in the radial direction is given by\(^8,9\)

\[
\bar{D}h - P = E \left( V_{ed} - V \right)
\]  

(1a)

where \( \bar{D}h = \int_a^b D \, dr \) = radial active force/unit area developed on the inner surface of the myocardium
- \( h = b - a \) = thickness of myocardium
- \( a \) = inner radius of the myocardium
- \( b \) = outer radius of the myocardium
- \( E \) = left ventricular elastance, slope of the P-V line in Figure 2
- \( P \) = left ventricular pressure
- \( V \) = left ventricular volume
- \( V_{ed} \) = end-diastolic ventricular volume (when \( dV/dt = 0 \))

Near end-systole when \( E \) reaches its maximum value \( E_{\text{max}} \), a suffix \( m \) is added to the variables

\[
(\bar{D}h)_m - P_m = E_{\text{max}} \left( V_{ed} - V_m \right)
\]  

(1b)

Eq. (1a) can be separated into two equations

\[
P = E \left( V - V_a \right) \quad \text{(2a)}
\]

\[
\bar{D}h = E \left( V_{ed} - V_a \right) \quad \text{(2b)}
\]

Figure 1. Simplified cross-section of the left-ventricle, the helical muscular fibre of the myocardium is projected as a circle. \( D \) is the radial active force/unit volume of myocardium. \( h = b - a \) is the thickness of myocardium, \( a \) = inner radius, \( b \) = outer radius, \( P \) = ventricular pressure, \( P_0 \) = outer pressure assumed zero.
Figure 2. Simplified pressure volume relation (PVR), slope E = ventricular elastance, slope $e_{am}$ = arterial elastance when $E = E_{max}$. During an ejecting contraction, PVR is represented by the loop $d_1d_2V_m$, the systolic pressure $P_m$ is assumed constant. Note the changes $\Delta(Dh)$, $\Delta(Dh)_m$ corresponding to $\Delta V_{ed}$ as an expression of the Frank-Starling mechanism. $d_3$ is the middle point of the line $d_3V_{em}$ (ESPVR).

Near end-systole, Eq. (1b) can also be separated as follows

$$P_m = E_{max} (V_m - V_{dm})$$

$$\Delta(Dh)_m = E_{max} (V_{ed} - V_{edm})$$

The intersection $V_d$ or $V_{edm}$ of the PVR with volume axis is shown in Figure 2. If $E$ (or $E_{max}$) is kept constant, and $V_d$ (or $V_{edm}$) kept constant, Eq. (2b) and (3b) give

$$\Delta(Dh) = E \Delta V_{ed}$$

$$\Delta(Dh)_m = E_{max} \Delta V_{ed}$$

The variations $\Delta(Dh)$, $\Delta(Dh)_m$ and $\Delta V_{ed}$ shown in Figure 2 represent another way to express the Frank-Starling mechanism. Eq. (1–4) together with Figure 2 summarize the basic mechanism of cardiac contraction. Experimental verification of Eq. (1–4) has been extensively discussed8-13) and thus will not be repeated here. In this study the focus is rather on the physiological insight that can be gained from an integrated study of the areas under ESPVR, as well as some further experimental evidence of the consistency of the mathematical formalism derived by Shoucri.11,12)

**RESULTS**

**Mechanics of left ventricular contraction:** It is assumed below that during systolic contraction $P \approx P_m$ is nearly constant, and that when $E = E_{max}$ the left ventricular volume $V_m \approx V_{es}$ ($V_{es}$ = end-systolic volume when $dV/dt = 0$). During normal systolic ejection, the point $d$ of coordinates $(Dh, V)$ moves from point $d_2$ to
Figure 3. Areas under ESPVR. \( PE = \) potential energy absorbed by the internal metabolism of myocardial contraction, \( SW = \) stroke work delivered to systemic circulation, \( CW = \) contraction work absorbed by the passive medium of myocardium.

Point \( d_4 \) corresponding to \( (\bar{D}h)_m \) (Figure 2). In a quasi-static approximation (inertia and viscous forces neglected), the maximum active force \( (\bar{D}h)_m \) is equal to the maximum isovolumic pressure \( P_{iso} \) represented by point \( d_3 \) in Figure 2, and in general \( (\bar{D}h) \) is equal to \( P_{iso} \) by the symmetry of the lines \( d_2d_4 \) and \( d_1d_3 \). Different notations have been used for the active force \( (\bar{D}h) \) (ejecting contraction), and the isovolumic pressure \( P_{iso} \) (non-ejecting contraction) to emphasize that \( \bar{D}h \) is a force and has magnitude and direction, whereas \( P_{iso} \) is a scalar quantity.

An immediate and interesting result that can be deduced from Figures 2 and 3 is that when \( d_1 \) moves along the ESPVR \( d_3V_{dm} \), the stroke work \( SW \) represented by the area \( V_{cd}d_{d1}V_m \) is maximum when \( d_1 \) coincides with \( d_5 \) (mid-point of the segment \( d_3V_{dm} \)) [note that \( d_1 \) and \( d_5 \) coincides when \( E_{max}/e_{am}=1 \)]. The condition \( E_{max}/e_{am}=2 \) (maximum oxygen efficiency) corresponds to \( d_1 \) below \( d_5 \) on the line \( d_6V_{dm} \), and the condition \( E_{max}/e_{am} \ll 1 \) corresponds to \( d_1 \) above \( d_5 \). It is seen that when \( E_{max}/e_{am} < 1 \), \( SW \) decreases when \( P_m \) increases, creating cardiac insufficiency. Maximum oxygen efficiency as the normal physiological state of the myocardium has also been suggested by Burkhoff and Sagawa\(^5\), Asanoi et al\(^6\), Fourie et al\(^7\) and Elzinga and Westerhof.\(^{15} \) One can consequently see how the introduction of the active force \( \bar{D}h \) in the formalism describing PVR has led to a simple and consistent description of some aspects of the mechanism of left ventricular contraction as summarized by the different areas under ESPVR in Figures 2 and 3. The application of these areas to the study of physiological adaption of the left ventricle to change of load as well as different clinical applications has been discussed\(^{12,13} \). Some aspects of the relation between \( SW \) and \( E_{max}/e_{am} \) are discussed below, as are possible relations with the areas \( CW \) and \( PE \).

**Experimental verification:** The experimental application to be discussed first in this section is the relation between stroke work \( SW \) and \( V_{ed} \). From Figure 3 and from Shoucri\(^{11,12} \) we obtain
\[
\frac{SW}{TW} = 2 \frac{E_{\text{max}}/e_{\text{am}}}{(1 + E_{\text{max}}/e_{\text{am}})^2} \quad (5)
\]

where \(TW\) is the total area under ESPVR. When \(d_1\) moves along the line \(d_3V_{dm}\) (Figure 2), \(SW\) is maximum and equals \((SW)_{\text{max}} = TW/2\) when \(d_1\) coincides with \(d_5\) (\(d_5\) is the middle point of the segment \(d_3V_{dm}\)). In this case \(E_{\text{max}}/e_{\text{am}} = 1\) and Figure 2 provides direct and simple proof of this result. The fact that \((SW)_{\text{max}}\) corresponds to \(E_{\text{max}}/e_{\text{am}} = 1\) has been experimentally observed by several authors (Asanoi et al.\(^6\) Burkhoff and Sagawa\(^5\) Sunagawa et al\(^1\) and Little and Cheng\(^3\)).

Equation (5) is equivalent to Eq. (7) of Little and Cheng\(^4\) and Eq. (2) of Little and Cheng.\(^3\) There is a difference of a factor of 2 because normalization in Eq. (5) with respect to \(TW\), while Little and Cheng normalized with respect to \((SW)_{\text{max}} = TW/2\). By noting that the total area \(TW\) under ESPVR is given by

\[
TW = \frac{1}{2} (\bar{D}h)_{\text{in}} (V_{ed} - V_{dm}) \quad (6)
\]

Eq. (3b), (5) and (6) give

\[
SW = m(V_{ed} - V_{dm})^2 \quad (7)
\]

with

\[
m = \frac{E_{\text{max}}}{E_{\text{max}}/e_{\text{am}}} \quad (8)
\]

Eq. (7) is quadratic in \(V_{ed} - V_{dm}\), and has been compared in Table I to the linear formula

\[
SW_1 = M(V_{ed} - V_{l}) \quad (9)
\]

given by Little and Cheng\(^3,4\) where \(M\) is preload recruitable stroke work (Glower et al\(^1\)) and \(V_{l}\) the axis intercept of the linear Eq. (9). The intercept \(V_{dm}\) of ESPVR (see Figure 2) has been calculated from the formula \(V_{100} = V_{dm} + 100/E_{\text{max}}\) given by Eq. (2) of Little and Cheng\(^3\). The comparison between \(SW_1\) (linear model) and \(SW\) (Eq. 7) in Table I is good. Note that data taken from Table I of Little and Cheng\(^3\) represent averages for experimental results for 8 animals and not data from a single experiment, so some fluctuation is expected. Since \(SW_1 = (M/(V_{ed} - V_{l}))(V_{ed} - V_{l})^2\) the values of \(M/(V_{ed} - V_{l})\) have also been compared in Table I with the values of 2 m (Eq. 8). This comparison was also good, and factor 2 accounts for the fact that the slopes of a quadratic curve and a linear curve differ by a factor of 2. Statistical t-test of the means shown in Table I indicates that the difference is not statistically significant. The linear model (Eq. 9) appears to be an approximation and does not seem to reflect a basic characteristic of left ventricu-
lar contraction.

We shall now discuss the derivation of the quantity $A$ introduced in Eq. (10) of Takaoka et al.\textsuperscript{1)}

A simple manipulation of Eq. (3b) and (6)-(7) gives

$$SW = E_{\text{max}} (V_{ed} - V_{dm})^2 \frac{(E_{\text{max}}/e_{am})}{(1 + E_{\text{max}}/e_{am})^2}$$

(10)

Eq. (10) has been derived differently by Burkhoff and Sagawa\textsuperscript{5)} and Sunagawa et al.\textsuperscript{18)} One also has

$$SW = P_m (V_{ed} - V_m) = E_{\text{max}} (V_m - V_{dm}) (V_{ed} - V_m)$$

(11)

By making $k = e_{am}/E_{\text{max}}$ and by equating Eq. (10)-(11) we obtain, using Eq. (6)-(7)

$$k/(1 + k)^2 = (1/2) (SW/\text{TW}) = A$$

(12)

The dimensionless quantity $A$ is given in Eq. (10) of Takaoka et al\textsuperscript{1)} and was used by them to calculate $e_{am}$ (or $E_a$), but its relation to the curve for $SW/\text{TW}$ given in Figure 4 is not derived. One should note how the mathematical model used in the present study allows a simple derivation of an expression for $A$. Moreover, by writing $K = 1/k$ we obtain $SW/\text{TW} = 2K/(1 + K)^2$. Derivation with respect to $K$ gives $(d/dK) (SW/\text{TW}) = 2/(1 + K)^2 - 4K/(1 + K)^3$, which is zero when $K = 1$, or $E_{\text{max}}/e_{am} = 1$. This corresponds to the maximum of the curve $SW/\text{TW}$ in Figure 4. For $K = 1$, $(SW)_{\text{max}} = TW/2$, which is the maximum value of the stroke volume ($d_1$ and $d_5$ in Figures 2 and 3).

A further validation of Eq. (7) and (8) is provided by the results of Table II. The values of $V_{dm}$, $E_{\text{max}}/e_{am}$ and $V_{ed}$ are taken from Figure 6A of Takaoka et al\textsuperscript{1)} (with an obvious change in notation, for instance Takaoka et al\textsuperscript{1)} use $E_a/E_{\text{max}}$

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Relations between $SW/\text{TW}$, $CW/\text{TW}$, $PE/\text{TW}$, and $E_{\text{max}}/e_{am}$.}
\end{figure}
while the ratio $E_{\text{max}}/e_{\text{am}}$ is used in the present study). In Table II, $m$ is calculated using Eq. (8) and $SW$ using Eq. (7). The values obtained for $SW$ compare very well with the corresponding values of $SW$ that can be measured from Figure 6A of Takaoka et al. In particular note the equality of the values of $m$ for $E_{\text{max}}/e_{\text{am}} = 1/3$ and 3, or for $E_{\text{max}}/e_{\text{am}} = 1/2$ and 2, that results by applying Eq. (8), and the equalities of the corresponding values of $SW$ as shown in Table II and verified by the corresponding values of $SW$ in Figure 6A of Takaoka et al. Here again, Eq. (7) and the results of Table II suggest that the linear dependence of $SW$ on $V_{\text{ed}}$ given by Eq. (9) is an approximation.

Other areas appearing under ESPVR are $CW$ and $PE$. $CW$ seems to be related to the energy absorbed in the contraction of myocardium (see appendix A of Shoucri). The area $PE$ appears to be related to the energy absorbed by the internal metabolism of the heart. For example Takaoka et al. observed that the area $PE$ increases in cardiomyopathy cases. Variations of areas $SW/TW$, $CW/TW$, $PE/TW$, with $E_{\text{max}}/e_{\text{am}}$ based on previous theoretical relations are shown in Figure 4. Experimental verification of these curves can be found in Figure 5 of Shoucri. The curve for $SW/TW$ is similar to Figure 2 of Little and Cheng, Figure 7 of Fourie et al, and Figure 4 of Takaoka et al. The interrelation between these different areas comes from the fact that $SW/TW + CW/TW + PE/TW = 1$. No experimental investigation of this interrelation has yet been undertaken.

### Table II. Verification of Equations (7) and (8) from Simulation Data

<table>
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<tr>
<th>$V_{\text{am}}$ (ml)</th>
<th>$E_{\text{max}}$ (mmHg/ml)</th>
<th>$E_{\text{max}}/e_{\text{am}}$</th>
<th>$m$ (mmHg/ml)</th>
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$V_{\text{am}}$ = intercept of ESPVR with volume axis; $V_{\text{ed}}$ = end-diastolic volume; $E_{\text{max}}$ = maximum slope of ESPVR; $e_{\text{am}}$ = corresponding arterial elastance. Values for $V_{\text{am}}$, $V_{\text{ed}}$, $E_{\text{max}}$, $E_{\text{max}}/e_{\text{am}}$ are taken from Figure 6A of Takaoka et al with an obvious change in the notation.
CONCLUSION

Important features of this study are as follows:

a) The inclusion of the radial active force of the myocardium $\vec{D}h$ in the mathematical formalism describing ESPVR;

b) The possibility of using the ratio $E_{\text{max}}/e_{\text{am}}$ to distinguish between normal ($E_{\text{max}}/e_{\text{am}} = 2$), mildly depressed ($E_{\text{max}}/e_{\text{am}} = 1$) (maximum $SW$), and severely depressed states of the heart ($E_{\text{max}}/e_{\text{am}} \ll 1$);

c) It is suggested that the interrelation between different areas under ESPVR (summarized in Figures 3 and 4) plays a fundamental role in understanding cardiac mechanics. The linear equation Eq. (9) for $SW_1$ for instance does not represent a fundamental aspect of cardiac contraction, but rather appears simply to be an isolated approximation. Figure 4 shows that there is a need for an integrated approach for the modelling of different areas under ESVPR. For instance in Figure 2, the study of the area $V_{ed} d_2 d_4 V_m$ (or by symmetry $V_{ed} d_3 d_1 V_m$) which represents the work of the active force $\vec{D}h$, when $\vec{D}h$ moves from $d_2$ to $d_4$, has not received any attention.

d) An important aspect of this interrelation between different areas under ESPVR, not discussed in this study, is the relation between oxygen consumption and the different areas of $PE$, $SW$, $CW$ under ESPVR. This problem has been discussed\textsuperscript{11,12} and requires further experimental as well as theoretical study.

The possibility of non-invasive implementation of the results of this study for clinical work using M-mode echocardiography for example is another challenge for experimentalists and has been discussed.\textsuperscript{12} Finally, it should be mentioned that an interesting review of cardiac mechanics based on PVR has been given by Suga.\textsuperscript{19}

REFERENCES