Single-beat Estimation of Ventricular End-systolic Elastance–Effective Arterial Elastance as an Index of Ventricular Mechanoenergetic Performance

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Background: The ratio of ventricular end-systolic elastance (Ees) to effective arterial elastance (Ea) is known to reflect not only ventricular mechanical performance but also energetic performance. Despite these useful features, technical difficulties associated with estimating Ees make the clinical application of Ees/Ea impractical. We developed a framework to estimate Ees/Ea without measuring ventricular volume or altering the loading condition.

Methods: To achieve this goal, we approximated the ventricular time-varying elastance curve with two straight lines, one for the isovolumic phase and the other for the ejection phase, and characterized the curve with the slope ratio, k, of these two straight lines. Using the concept of the pressure-volume relationship, Ees/Ea is algebraically expressed as

\[ \frac{E_{es}}{E_a} = \frac{P_{es}}{P_{ad}} \left( 1 + k \cdot \frac{ET}{PEP} \right) - 1, \]

where P es is end-systolic pressure, P ad is aortic diastolic pressure, ET is ejection time, and PEP is pre-ejection period. In 11 anesthetized dogs, we recorded arterial and ventricular pressures and ventricular volume and estimated Ees and Ea under various contractile states and loading conditions.

Results: An empirical relation between k and Ees/Ea was found as k = 0.53 (Ees/Ea)0.51. Simultaneous solution of these two equations yielded Ees/Ea as a function of PEPEP and ET/PEP. The estimated Ees/Ea values correlated well with the measured Ees/Ea values (r = 0.925, SEE = 0.051).

Conclusions: The proposed framework is capable of estimating Ees/Ea from ventricular and aortic pressure. (Key words: End-systolic elastance; end-systolic pressure–volume relationship; ventricular–arterial coupling.)

It has been well established that ventricular performance (e.g., ejection fraction, stroke volume, cardiac output) depends on ventricular–arterial coupling. 1-6 Ventricular–arterial coupling is also related to efficiency of mechanical energetic transfer from the heart to the arteries and that of conversion of metabolic energy to mechanical energy. 4-7 Therefore, clinical estimates of one of the most direct index of ventricular–arterial coupling (Ees/Ea), the ratio of left ventricular end-systolic elastance (Ees) to effective arterial elastance (Ea), 8,9 would be useful if difficulties associated with Ees measurements are circumvented.

To circumvent problems in measuring Ees/Ea, we developed a framework to estimate Ees/Ea directly from ventricular and aortic pressure without estimating Ees, measuring ventricular volume, or altering loading condition. Although estimation of Ees/Ea with only peripheral arterial pressure is desirable from the clinical viewpoint, at this early stage, we have designed this study to determine whether we can estimate Ees/Ea from ventricular and aortic pressures only. For this purpose, we approximated the waveform of the ventricular time-varying elastance curve with two straight lines, one for the isovolumic phase and the other for the ejection phase. Theoretical analysis based on the concept of end-systolic pressure–volume relationship (ESPVR) indicated that Ees/Ea is a unique function of the slope ratio of these two
straight lines, systolic time intervals and aortic pressure.

In a preliminary study, \( k \) was considerably altered with changes in the contractile state and/or loading condition. In the present study we first determined the empirical relationship between \( k \) and the contractile states and/or loading condition, and then incorporated it into the estimation of \( E_{JE} \). The results indicated that the proposed framework is capable of estimating \( E_{JE} \) from ventricular and aortic pressure.

Materials and Methods

Theoretical Consideration

The time-varying elastance curve of the left ventricle has a distinctive waveform both in animals and in humans as described by Suga et al.\(^{11}\) and Senzaki et al.,\(^{12}\) respectively. We approximated the elastance curve with two straight lines as shown in figure 1, one for the isovolumic phase with a slope of \( \tan \theta _1 \), and the other for the ejection phase with a slope of \( \tan \theta _2 \). Because elastance is proportional to pressure for a given constant volume,

\[
\frac{E_{cs} - E_{ad}}{E_{ad}} = \frac{P_{max} - P_{ad}}{P_{ad}}
\]

where \( E_{cs} \) and \( E_{ad} \) are the elastance at end-systole and at the onset of ejection, respectively, and \( P_{max} \) and \( P_{ad} \) are the putative isovolumic pressure and the left ventricular pressure at the onset of ejection, respectively. Based on this, the ratio of the slopes, \( k \), is expressed as

\[
k = \frac{\tan \theta _2}{\tan \theta _1} = \frac{[E_{cs} - E_{ad}] / [E_{ad} / PEP]}{[(P_{cs} - P_{ad}) / P_{ad}] \cdot (PEP / ET)}
\]

where PEP is the pre-ejection period and ET is the ejection time. Rearranging the equation for \( P_{max} \) yields

\[
P_{max} = P_{ad} + P_{ad} \cdot k \cdot ET / PEP
\]

Since both the decrease in ventricular pressure from \( P_{max} \) to the actual end-systolic pressure \( (P_{cs}) \) and the increase in arterial pressure from zero to \( P_{ad} \) result from the same ventricular ejection, the ratio of \( E_{cs} \) to \( E_{ad} \) is expressed as

\[
E_{cs} / E_{ad} = (P_{max} - P_{cs}) / P_{cs}
\]

Substituting \( P_{max} \) in equation 3 with equation 2 yields

\[
E_{cs} / E_{ad} = P_{ad} / P_{cs} (1 + k \cdot ET / PEP) - 1
\]

Thus, after determining the \( k \) values, \( E_{cs} / E_{ad} \) can be calculated from ventricular and aortic pressures.

Although changes in contractile states and loading conditions reportedly have minimal effects on the normalized left ventricular elastance curve,\(^{11,12}\) our preliminary study indicated that the aforementioned variables change the waveform and thus the slope ratio, \( k \), considerably. To determine the empirical relationship between \( k \) and other variables, we extensively altered heart rate, contractility, and afterload and observed the effects on \( k \). \( E_{cs} / E_{ad} \) can be calculated with equation 4 once the dependence of \( k \) on other variables is empirically formulated.

Surgical Preparations

Animal care was conducted in accordance with the guidelines of the Physiologic Society of Japan and the Guiding Principles in the Care and Use of Animals as approved by the Council of the American Physiologic Society. Eleven dogs (20.0 ± 3.0 [SD] kg) were anesthetized with intravenously administered pentobarbital sodium (30 mg/kg) and ventilated with room air. The chest was opened mid sternally, and a 6-French 12-electrode conductance catheter (2RH-216; Taisho Biomed Instruments, Osaka, Japan) was inserted into the left ventricle from the apex to measure ventricular volume (Sigma 5DF; Leycom, Oegstgeest, The Netherlands). The heart was wrapped with a thin vinyl sheet to minimize the influence of adjacent structures, such as the lung, on conductance volumetry. One catheter-tipped micromanometer (PC-751; Millar Instruments, Houston, TX) was inserted into the left ventricle from the apex to deter-
mine left ventricular pressure, and another catheter-tipped micromanometer was inserted into the proximal ascending aorta through the right carotid artery for aortic pressure measurement (fig. 2A). To measure parallel conductance for volume signal calibration, a saturated NaCl solution was injected through an 18-gauge catheter placed in the pulmonary artery. Drugs were administered through a catheter inserted in the right femoral vein. Cardiac preload was altered through a pair of occluders made of thin polyethylene tubes that were placed around the inferior and superior caval veins. The proximal branches of the bilateral stellate ganglia were cut to block central sympathetic outflow to the heart. The distal branches of the left cardiac sympathetic nerve were isolated for electrical stimulation. The vagus nerves were bilaterally cut. The sinus node was mechanically crushed, and pacing electrodes were sutured on the right atrium.

**Protocols**

Before each measurement, we determined parallel conductance by the hypertonic saline technique. Under control conditions, we reduced preload by simultaneously occluding the vena cava superior and vena cava inferior for approximately 10 s. Multiple pressure-volume loops were obtained during vena cava occlusion to determine the ESPVR (fig. 2B). The respirator was stopped at the end-expiration during each measurement. After the control run, we examined the effects of heart rate, ventricular contractility, and afterload on time-varying elastance by repeating vena cava occlusions at each condition.

**Heart Rate Run** (n = 7). Pacing rate was altered from 60 to 180 beats/min. At each level of pacing rate, we waited approximately 5 min to allow hemodynamics to reach a steady state. We recorded the pressure-volume loops and estimated ESPVR.

**Contractility Run** (n = 7). We increased ventricular contractility by bilaterally stimulating the cardiac sympathetic nerves at frequencies of 1, 2, and 5 Hz with an amplitude of 1.0 volts and a duration of 2 ms. Propranolol (2 mg/kg) was injected to attenuate contractility. At each level of contractility, we recorded pressure-volume loops and estimated ESPVR.

**Afterload Run** (n = 7). We abolished the sympathetically mediated reflex with a ganglionic blocker (hexamethonium, 30 mg/kg intravenously) and then infused methoxamine (10–15 mg ⋅ kg⁻¹ ⋅ min⁻¹ intravenously) or nitroprusside (3–10 mg ⋅ kg⁻¹ ⋅ min⁻¹ intravenously) to increase and decrease the afterload, respectively. In each afterload condition, we recorded pressure-volume loops and estimated ESPVR.

**Measurement and Analysis**

Left ventricular pressure, volume, and aortic pressure were digitized at 1 kHz by means of a 12-bit analog-to-digital converter (AD12-16D(98)H; Contec, Osaka, Japan) and stored on the hard disk of a dedicated laboratory computer system (PC-9821; NEC, Tokyo, Japan).

The slope (Ees) and the volume axis intercept (V0) of ESPVR were determined from multiple pressure-volume loops obtained during bicaval occlusion with the algorithm reported by Kono et al.¹⁵ Ees was defined as the ratio of Pes to stroke volume. The ratio of measured Ees
to $E_a$ served as the reference to examine the accuracy of the estimated $E_{es}/E_a$ values by the proposed framework. The time-varying elastance curve was determined as the instantaneous ratio of ventricular pressure to volume in excess of $V_o$.

\[ \dot{E}(t) = \frac{P(t)}{V(t) - V_o} \]

where $E(t)$, $P(t)$, and $V(t)$ are instantaneous ventricular elastance, pressure, and volume, respectively. $E(t)$ was approximated by two straight lines, one for the isovolumic phase and the other for the ejection phase. The ratio of the slopes of these straight lines was defined as $k$ (fig. 2A, bottom).

We numerically estimated the time derivative of left ventricular pressure (dP/dt). We defined the onset of ventricular contraction as the moment at which left ventricular dP/dt reached 10% of its maximum. The onset of ejection and the ejection time (ET) were determined from the aortic pressure curve. The interval between the onset of contraction and that of ejection was defined the pre-ejection period (PEP). Aortic pressure at the onset of ejection was defined as $P_{ae}$ and that at the end of ejection as $P_{es}$. We assumed that $P_{es}$ determined from aortic pressure approximated that from ventricular pressure. From these variables we derived ET/PEP and $P_{ae}/P_{es}$ (fig. 2A).

**Results**

**Ranges of Changes in Heart Rate, Contractility, and Afterload**

Figure 3 shows the effects of changes in heart rate, contractility ($E_{es}$), and afterload ($E_a$) on the $k$ value. Each solid line connects data points obtained from the same animal. As can be seen in the left panel (heart rate run), varying the heart rate between 60 and 180 beats/min resulted in $k$ values between 0.27 and 0.75. The $k$ values tended to increase with heart rate ($r = 0.20$, NS). In the contractility run, shown in the middle panel, $E_{es}$ varied between 3.6 to 28.3 mmHg/ml. The $k$ values were between 0.27 and 0.84 and were coupled with $E_{es}$ ($r = 0.89; P < 0.0001$). In the afterload run, shown in the right panel, $E_a$ varied between 6.3 and 24.3 mmHg/ml. The resultant $k$ values were between 0.27 and 0.64 and were negatively correlated with $E_a$ ($r = 0.75; P = 0.001$).

**Determinants of the Slope Ratio, $k$**

To determine the effects on the slope ratio, $k$, we plotted the $k$ value as a function of $E_{es}/E_a$, $P_{ae}/P_{es}$, and ET/PEP (figure 4). In the heart rate run (left panels), the $k$ value closely correlated with $E_{es}/E_a$ ($r = 0.88; P < 0.0001$; RMSE = 0.055), marginally correlated with $P_{ae}/P_{es}$ ($r = 0.57; P = 0.039$; RMSE = 0.047), and did not correlate with ET/PEP ($r = 0.16$, NS). In the contractility run, shown in the middle panels, $k$ correlated with $E_{es}/E_a$ ($r = 0.92; P < 0.0001$; RMSE = 0.0225), ET/PEP ($r = 0.71; P = 0.0003$; RMSE = 0.056), and $P_{ae}/P_{es}$ ($r = 0.57; P = 0.0075$; RMSE = 0.803). In the afterload run, shown in the right panels, $k$ highly correlated with $E_{es}/E_a$ ($r =
0.96; \( P = < 0.0001; \text{RMSE} = 0.021 \) and weakly correlated with ET/PEP (\( r = 0.535; \ P = 0.0125; \text{RMSE} = 0.052 \)). No correlation was seen between \( k \) and \( \frac{P_{ad}}{P_{es}} \) (\( r = 0.17, \text{NS} \)).

Because the \( k \) value best correlated with \( \frac{E_{es}}{E_a} \) under all experimental conditions, we pooled the \( \frac{E_{es}}{E_a} \) data from all animals and examined whether a single empirical formula is capable of estimating the \( k \) value from \( \frac{E_{es}}{E_a} \). As shown in figure 5, \( k \) is highly correlated with \( \frac{E_{es}}{E_a} \). Using a power function, \( k \) is expressed as

\[
k = 0.53 \left( \frac{E_{es}}{E_a} \right)^{0.51}
\]

(5)

The correlation coefficient \( r \) was 0.8933 with RMSE of 0.0044 (\( P < 0.001 \)). Therefore, one can estimate the \( k \) value with equation 5 for a given \( \frac{E_{es}}{E_a} \) value with reasonable accuracy.

**Evaluation of the Estimation of \( \frac{E_{es}}{E_a} \)**

We derived \( \frac{E_{es}}{E_a} \) values by simultaneously solving equations 4 and 5 with the Newton’s iteration method.\(^{14}\) We derived \( \frac{E_{es}}{E_a} \) values for all measurements but four. In the four measurements in which \( \frac{E_{es}}{E_a} \) values could not be estimated, the measured \( \frac{E_{es}}{E_a} \) values were 0.415, 0.347, 0.297, and 0.352 (0.383 ± 0.0445, mean ± SD). As shown in figure 6, the estimated \( \frac{E_{es}}{E_a} \) values correlated well with measured \( \frac{E_{es}}{E_a} \) values (\( \text{measured } \frac{E_{es}}{E_a} = 0.96 \text{ [estimated } \frac{E_{es}}{E_a} + 0.098; \ r = 0.925; \text{RMSE} = 0.051 \text{ mmHg/ml} \)). Therefore, \( \frac{E_{es}}{E_a} \) can be estimated reasonably well from arterial and ventricular pressure curves without measuring ventricular volume or load manipulation.

**Discussion**

**Advantage of the Proposed Method To Estimate \( \frac{E_{es}}{E_a} \)**

The purpose of this investigation was to develop a framework to evaluate \( \frac{E_{es}}{E_a} \) that avoided the necessity to measure ventricular volume and used variables that were readily accessible in a clinical setting. To achieve this aim, \( \frac{E_{es}}{E_a} \) was determined directly rather from individually measured \( E_{es} \) and \( E_a \) values. We made use of the characteristic waveform of ventricular time-varying elastance curve and approximated it with a bilinear func-
Fig. 5. Relation between slope ratio (k) and E\textsubscript{es}/E\textsubscript{a}. A simple power function best described the relation.

Fig. 6. Relation between the measured E\textsubscript{es}/E\textsubscript{a} and estimated one. Estimated E\textsubscript{es}/E\textsubscript{a} correlated well with measured E\textsubscript{es}/E\textsubscript{a}.

Fig. 7. Nomograph to estimate E\textsubscript{es}/E\textsubscript{a} from ET/PEP and P\textsubscript{ad}/P\textsubscript{es}. In this nomograph, we used PEP/ET rather than ET/PEP, because the former is more commonly used. Note that E\textsubscript{es}/E\textsubscript{a} cannot be reliably determined when E\textsubscript{es}/E\textsubscript{a} values are extremely low (shaded area).

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Although we could estimate E\textsubscript{es}/E\textsubscript{a} with simultaneous solution of the two equations, finding the root is a rather complex procedure. To simplify this procedure, we plotted the solutions of all sets of P\textsubscript{ad}/P\textsubscript{es} and ET/PEP over the realistic range of respective variables as a nomogram (fig. 7). The shaded area represents extremely low E\textsubscript{es}/E\textsubscript{a} values that indicate severely compromised ventricular coupling with the arterial system. Under such conditions, no simultaneous solutions can satisfy the two equations. Indeed, in 4 of 63 measurements, we could not find solutions. In these conditions, the measured E\textsubscript{es}/E\textsubscript{a} was 0.383 ± 0.0445. This is to say that E\textsubscript{es}/E\textsubscript{a} values in these conditions were too low to be reliably estimated by the proposed framework. Nevertheless, this is not a serious impediment of the present method, because it provides an accurate estimate of E\textsubscript{es}/E\textsubscript{a} over most pathophysiologic ranges. Inability to measure E\textsubscript{es}/E\textsubscript{a} by the present method indicates that E\textsubscript{es}/E\textsubscript{a} is extremely low.

E\textsubscript{es}/E\textsubscript{a} as an Index of Ventricular Mechanoenergetic Performance

In comparison with the simple measurement of blood pressure, estimation of E\textsubscript{es}/E\textsubscript{a} provides more detailed information regarding hemodynamics. Even if the hemodynamic state is compromised for various reasons, arterial pressure might hardly change due to stabilizing mechanisms. However, changes in hemodynamics might be detected through the measurement of E\textsubscript{es}/E\textsubscript{a}. In fact, changes in E\textsubscript{es}/E\textsubscript{a} might reflect the operation of these pressure-stabilizing mechanisms. It is conceivable that
changes in $E_{cv}/E_a$ could precede hypotension. Therefore, the continuous monitoring of $E_{cv}/E_a$ may be useful in predicting hypotension. If a decrease in blood pressure is detected, the cases with preserved contractility but low afterload can be differentiated from those with low contractility but high afterload by estimating $E_{cv}/E_a$.

The estimation of $E_{cv}/E_a$ allowed us to estimate energetic efficiency of ventricular contraction. Mechanical efficiency is defined as the ratio of stroke work to ventricular pressure-volume area, and metabolic efficiency as the ratio of stroke work to myocardial oxygen consumption per beat. Because $E_{cv}/E_a$ is the major determinant of both of these efficiencies, \(^\text{15}\) one can estimate these efficiencies from $E_{cv}/E_a$ as well.

**Afterload Dependence of the Time-varying Elastance Curve**

Independence of the elastance curve waveform from loading conditions and ventricular contractility has often been described.\(^\text{12,11}\) However, various studies have described the load dependence of the pressure-volume relationship. Some of the load dependence has been explained by uncoupling effects, shortening deactivation, or internal ventricular resistance.\(^\text{16,17}\) We speculated that the slope ratio of the elastance curve, which is usually less than unity, might represent the negative effects of ejection on ventricular contractility. If this is the case, the coupling state of the ventricle with the arterial systems should affect the waveform.

**Limitations**

We used end-ejection pressure as a substitute of end-systolic pressure. Left ventricular ejection continues after end-systole; thus, end-systolic pressure does not exactly coincide with end-ejection pressure. In addition, we used aortic pressure curve to define the onset and the end of ejection, and we substituted left ventricular pressure with aortic pressure when measuring end-systolic and end-isovolumic pressures. These small differences in pressure measurements might influence the accuracy of the estimated $E_{cv}/E_a$. However, the fact that the estimated $E_{cv}/E_a$ agreed reasonably well with measured $E_{cv}/E_a$ values suggests that these approximations were reasonable. Because ventricular and aortic pressure measurements are more invasive than peripheral arterial pressure measurement, and not performed in most clinical settings, further studies are needed to examine the usefulness of the less invasive methods using, e.g., electrocardiography and echocardiography. Although $E_{cv}/E_a$ cannot be obtained by this method for very low $E_{cv}/E_a$ (i.e., high PEP/ET and low $P_{as}/P_{cv}$), refinement of the empirical relation between $k$ and $E_{cv}/E_a$ might resolve this.

**Conclusions**

We developed a simple method to estimate $E_{cv}/E_a$, an index of ventricular-arterial coupling, from ventricular and aortic pressure curves. This method used an approximation of time-varying elastance curve with two straight lines, \(i.e.,\) a bilinear function. The slope ratio of these two lines quantitatively depended on the ventricular arterial coupling state. Using this approximation, $E_{cv}/E_a$ can be estimated from ventricular and aortic pressure, and systolic time interval over wide ranges of contractility and loading conditions.

**References**


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