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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 (E_{es}) to effective arterial elastance (E_a) is known to reflect not only ventricular mechanical performance but also energetic performance. Despite these useful features, technical difficulties associated with estimating E_{es} make the clinical application of E_{es}/E_a impractical. We developed a framework to estimate E_{es}/E_a 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, E_{es}/E_a is algebraically expressed as $E_{es}/E_a = P_{ad}/P_{es}(1 + k \cdot ET/PEP) - 1$, where P_{es} is end-systolic pressure, P_{ad} is aortic diastolic pressure, ET is ejection time, and PEP is preejection period. In 11 anesthetized dogs, we recorded arterial and ventricular pressures and ventricular volume and estimated E_{es} and E_a under various contractile states and loading conditions.**

Results: **An empirical relation between k and E_{es}/E_a was found as $k = 0.53 (E_{es}/E_a)^{0.51}$. Simultaneous solution of these two equations yielded E_{es}/E_a as a function of P_{ad}/P_{es} and ET/PEP. The estimated E_{es}/E_a values correlated well with the measured E_{es}/E_a values ([Measured E_{es}/E_a] = 0.96 [Estimated E_{es}/E_a] + 0.098, r = 0.925, SEE = 0.051).**

Conclusions: **The proposed framework is capable of estimating E_{es}/E_a 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.[1-3] 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 (E_{es}/E_a), the ratio of left ventricular end-systolic elastance (E_{es}) to effective arterial elastance (E_a),[8,9] would be useful if difficulties associated with E_{es} measurements are circumvented.

To circumvent problems in measuring E_{es}/E_a, we developed a framework to estimate E_{es}/E_a directly from ventricular and aortic pressure without estimating E_{es}, measuring ventricular volume, or altering loading condition. Although estimation of E_{es}/E_a 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 E_{es}/E_a 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 E_{es}/E_a is a unique function of the slope ratio of these two

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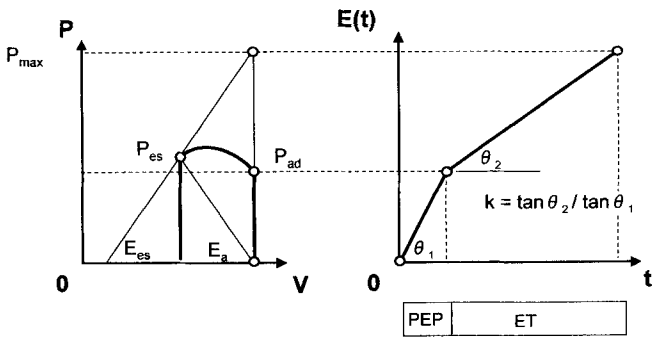

Fig. 1. Schematic drawing of a pressure–volume loop, end-systolic pressure–volume relationship (with a slope of end-systolic elastance [E_{es}]), arterial pressure–volume relationship (with a negative slope of effective arterial elastance [E_a]), end-systolic pressure (P_{es}), ventricular pressure at which the ventricle begins to eject (P_{ad}), and putative isovolumic pressure (P_{max}) (*left*). Also shown are bilinearly approximated time-varying elastance curve, E(t), slope ratio ($k = \tan\theta_2/\tan\theta_1$), pre-ejection period (PEP), and ejection time (ET) (*right*). The horizontal dashed lines indicate the proportionality of elastance and pressure for a constant volume. See text for details.

straight lines, systolic time intervals and aortic pressure. In a preliminary study,[10] we found that the slope ratio, 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_{es}/E_a. The results indicated that the proposed framework is capable of estimating E_{es}/E_a 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 ventricular volume,

$$(E_{es} - E_{ad})/E_{ad} = (P_{max} - P_{ad})/P_{ad}$$

where E_{es} 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

$$k = \tan\theta_2/\tan\theta_1 = [(E_{es} - E_{ad})/ET]/(E_{ad}/PEP) = [(P_{es} - P_{ad})/P_{ad}] \cdot (PEP/ET) \quad (1)$$

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

$$P_{max} = P_{ad} + P_{ad} \cdot k \cdot ET/PEP \quad (2)$$

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

$$E_{es}/E_a = (P_{max} - P_{es})/P_{es} \quad (3)$$

Substituting P_{max} in equation 3 with equation 2 yields

$$E_{es}/E_a = P_{ad}/P_{es}(1 + k \cdot ET/PEP) - 1 \quad (4)$$

Thus, after determining the k values, E_{es}/E_a 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_{es}/E_a 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 midsternally, and a 6-French 12-electrode conductance catheter (2-RH-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-

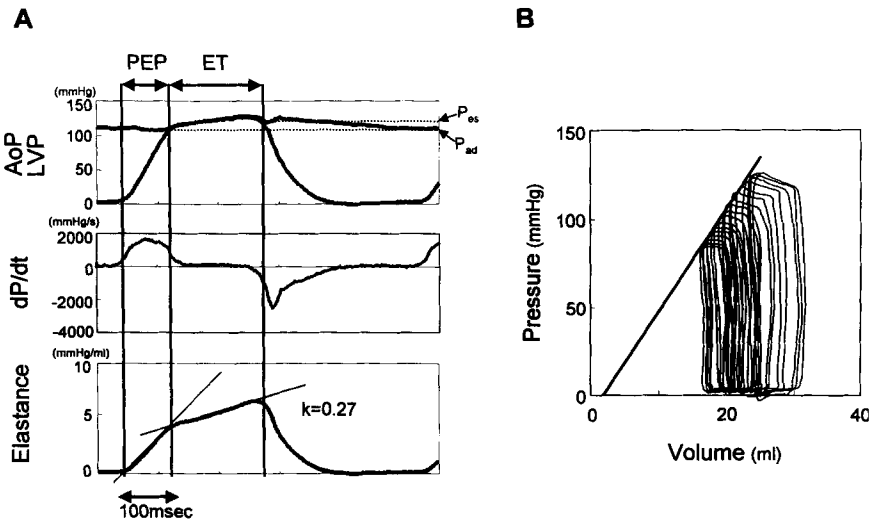

Fig. 2. Representative data showing left ventricular pressure (LVP) and aortic pressure (AoP), time derivative of LVP (dP/dt), and elastance curve from top to bottom. (*A*) Bilinear approximation of elastance curve, its slope ratio (k), pre-ejection period (PEP), ejection time (ET), pressure at the onset of ejection (P_{ad}), and that at end-systole (P_{es}) are also indicated. (*B*) The method to estimate E_{es} from multiple pressure–volume loops during vena cava occlusion.

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 ganglions 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 (E_{es}) and the volume axis intercept (V_0) of ESPVR were determined from multiple pressure-volume loops obtained during bicaval occlusion with the algorithm reported by Kono *et al.*[13] E_a was defined as the ratio of P_{es} to stroke volume. The ratio of measured E_{es}

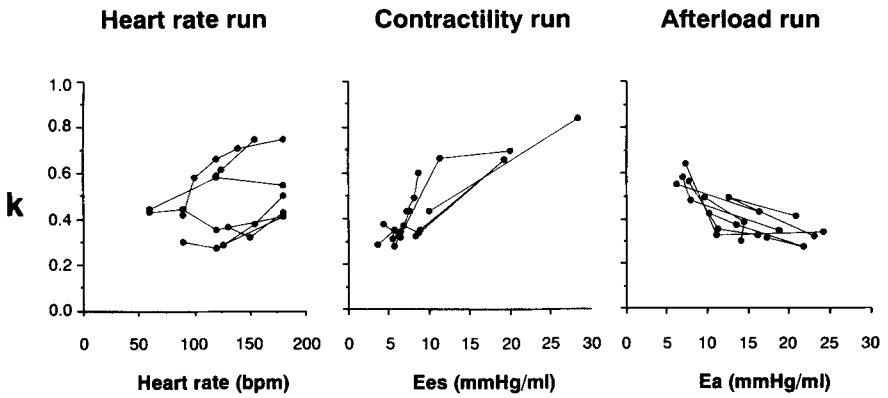

Fig. 3. Effects of changes in heart rate, end-systolic elastance (E_{es}), and effective arterial elastance (E_a) on slope ratio (k).

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_0.

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

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_{ad} 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_{ad}/P_{es} (fig. 2A).

Statistical Analysis

We evaluated the effects of hemodynamic variables on k using a standard linear regression analysis. The empirical relationship between k and E_{es}/E_a was formulated with a monoexponential curve. The values of E_{es}/E_a directly measured from pressure-volume loops were compared with the estimated E_{es}/E_a values. The accuracy of the estimated E_{es}/E_a was assessed by root mean square of errors (RMSE). $P < 0.05$ was considered statistically significant.

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_{ad}/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 = 0.035), marginally correlated with P_{ad}/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_{ad}/P_{es} (r = 0.57; $P = 0.0073$; RMSE = 0.803). In the afterload run, shown in the right panels, k highly correlated with E_{es}/E_a (r =

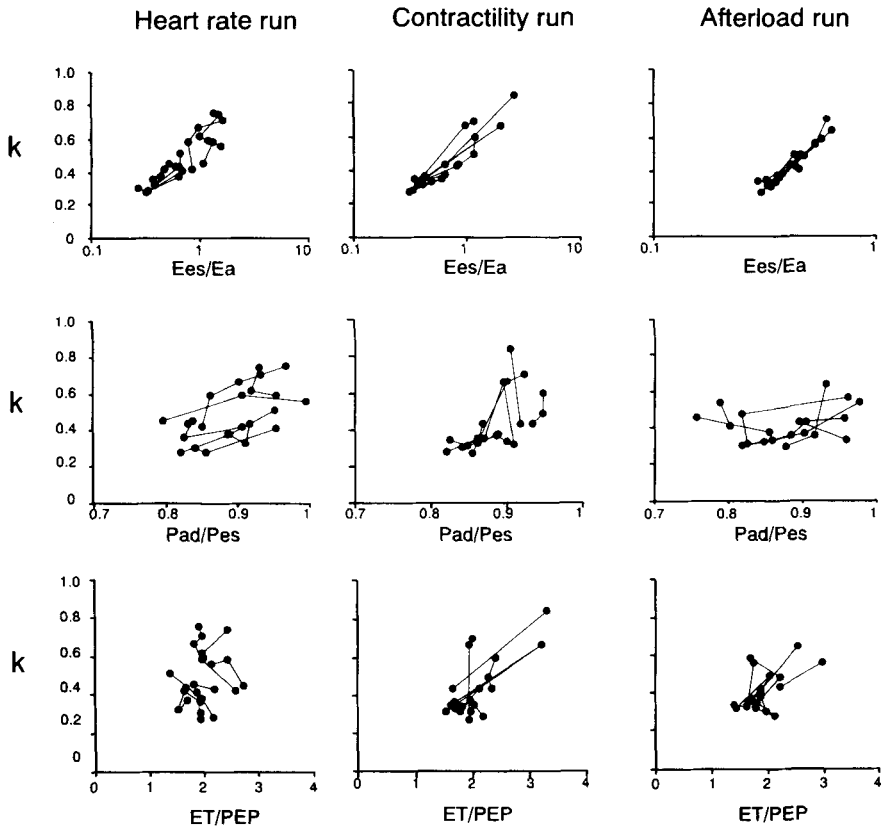

Fig. 4. Relation between slope ratio (k) and E_{es}/E_a (*upper*), P_{ad}/P_{es} (*middle*), and ET/PEP (*lower*) in each protocol.

0.96; $P = < 0.0001$; RMSE = 0.021) and weakly correlated with ET/PEP (r = 0.535; $P = 0.0125$; RMSE = 0.052). No correlation was seen between k and P_{ad}/P_{es} (r = 0.17, NS).

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

$$k = 0.53(E_{es}/E_a)^{0.51} \quad (5)$$

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 E_{es}/E_a value with reasonable accuracy.

Evaluation of the Estimation of E_{es}/E_a

We derived E_{es}/E_a values by simultaneously solving equations 4 and 5 with the Newton's iteration method.[14] We derived E_{es}/E_a values for all measurements but four. In the four measurements in which E_{es}/E_a values could not be estimated, the measured 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 E_{es}/E_a values correlated well with measured E_{es}/E_a values ([measured E_{es}/E_a] = 0.96 [estimated E_{es}/E_a] + 0.098; r = 0.925; RMSE = 0.051 mmHg/ml). Therefore, 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 E_{es}/E_a

The purpose of this investigation was to develop a framework to evaluate 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, 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-

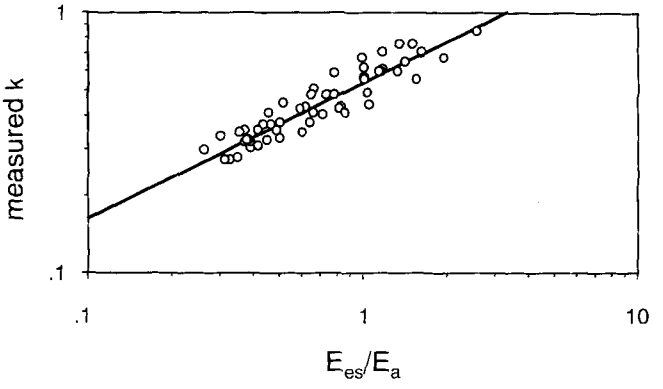

Fig. 5. Relation between slope ratio (k) and E_{es}/E_a. A simple power function best described the relation.

tion. This approximation resulted in a simple equation for E_{es}/E_a that consisted of systolic time intervals, arterial pressure, and the slope ratio, k (equation 4). In addition, we obtained, through animal experiments, an empirical relationship between k and E_{es}/E_a (equation 5). Because these relationships indicate that k and E_{es}/E_a are mutually dependent on each other, the simultaneous solution of equations 4 and 5 enabled us to estimate E_{es}/E_a. This framework allowed us to estimate E_{es}/E_a without volumetry or load manipulation.

Although we could estimate E_{es}/E_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_{ad}/P_{es} and ET/PEP over

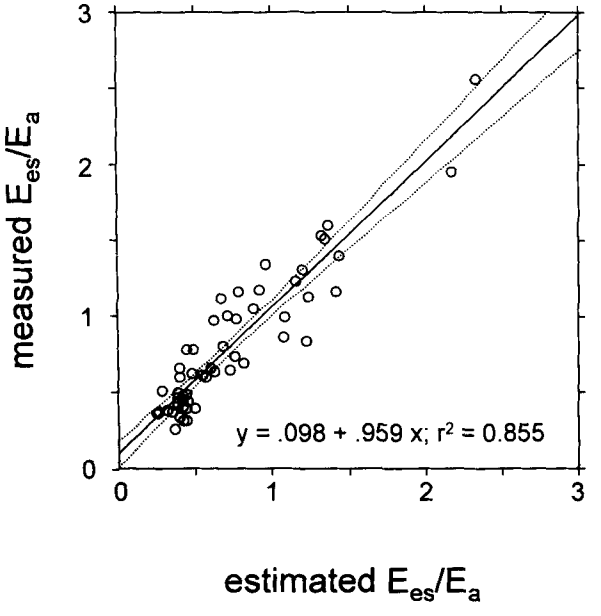

Fig. 6. Relation between the measured E_{es}/E_a and estimated one. Estimated E_{es}/E_a correlated well with measured E_{es}/E_a.

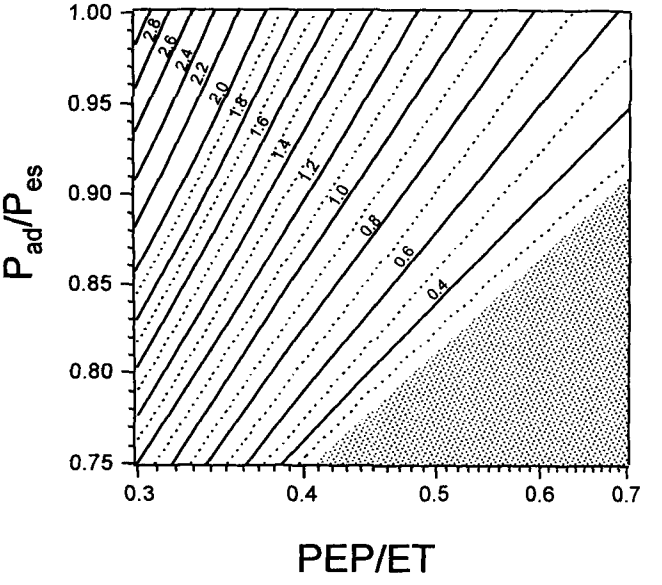

Fig. 7. Nomograph to estimate E_{es}/E_a from ET/PEP and P_{ad}/P_{es}. In this nomograph, we used PEP/ET rather than ET/PEP, because the former is more commonly used. Note that E_{es}/E_a cannot be reliably determined when E_{es}/E_a values are extremely low (shaded area).

the realistic range of respective variables as a nomogram (fig. 7). The shaded area represents extremely low E_{es}/E_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_{es}/E_a was 0.383 ± 0.0445. This is to say that E_{es}/E_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_{es}/E_a over most pathophysiologic ranges. Inability to measure E_{es}/E_a by the present method indicates that E_{es}/E_a is extremely low.

E_{es}/E_a as an Index of Ventricular Mechanoenergetic Performance

In comparison with the simple measurement of blood pressure, estimation of E_{es}/E_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_{es}/E_a. In fact, changes in E_{es}/E_a might reflect the operation of these pressure-stabilizing mechanisms. It is conceivable that

changes in E_{es}/E_a could precede hypotension. Therefore, the continuous monitoring of E_{es}/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_{es}/E_a.

The estimation of E_{es}/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_{es}/E_a is the major determinant of both of these efficiencies,[15] one can estimate these efficiencies from E_{es}/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.[11,12] 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.[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_{es}/E_a. However, the fact that the estimated E_{es}/E_a agreed reasonably well with measured E_{es}/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_{es}/E_a cannot be obtained by this method for very low E_{es}/E_a (*i.e.*, high PEP/ET and low P_{ad}/P_{es}), refinement of the empirical relation between k and E_{es}/E_a might resolve this.

Conclusions

We developed a simple method to estimate E_{es}/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_{es}/E_a can be estimated from ventricular and aortic pressure, and systolic time interval over wide ranges of contractility and loading conditions.

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