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Single-Beat Estimation of End-Systolic Elastance Using Bilinearly Approximated Time-Varying Elastance Curve

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- **Background**—Although left ventricular end-systolic elastance (E_{es}) has often been used as an index of contractility, technical difficulties in measuring volume and in changing loading conditions have made its clinical application somewhat limited. By approximating the time-varying elastance curve by 2 linear functions (isovolumic contraction phase and ejection phase) and estimating the slope ratio of these, we developed a method to estimate E_{es} on a single-beat basis from pressure values, systolic time intervals, and stroke volume.
- *Methods and Results*—In 11 anesthetized dogs, we compared single-beat E_{es} with that obtained with caval occlusion. Although the decrease (but not the increase) in contractility (5.3 to 11.4 mm Hg/mL) and the change in loading conditions (3.7 to 34.0 mm Hg/mL) over wide ranges significantly altered the slope ratio, the estimation of E_{es} was reasonably accurate (y=0.97x+0.46, r=0.929, SEE=2.1 mm Hg/mL).
- *Conclusions*—E_{es} can be estimated on a single-beat basis from easily obtainable variables by approximating the time-varying elastance curve by a bilinear function. (*Circulation*. 2000;102:1983-1989.)

Key Words: contractility ■ elasticity ■ systole ■ ventricles ■ hemodynamics

The end-systolic elastance (E_{es}) , the slope of the end-system L tolic pressure-volume relationship (ESPVR), has been used as an index of cardiac contractility. Although recent studies challenged the initial concept^{1,2} of linear and loadinsensitive ESPVR by demonstrating contractility-dependent curvilinearity^{3,4} and load-dependence,^{5,6} E_{es} is still a powerful index to assess the inotropic state in experimental as well as clinical settings.7-10 The technical difficulties in measuring this index, however, prevent its widespread clinical acceptance. Difficulties include the need for a precise high-fidelity left ventricular (LV) volume curve as well as the need for multiple pressure-volume (P-V) loops under various loading conditions. Introduction of the conductance catheter9,11,12 and of the concept of a hydromotive pressure source^{13,14} for single-beat Ees estimation has partly solved these difficulties. Mirsky et al^{15,16} developed a single-beat method to assess myocardial contractility by fitting a model to late systolic data and estimating the unstressed state. They reconstructed ESPVR from this myocardial contractility. With all their efforts, however, simple, less invasive, single-beat methods that allow a precise E_{es} estimation are still required.

Senzaki et al¹⁰ developed a framework for estimating E_{es} that assumes a load insensitivity of the time-varying elastance waveform, E(t). The method offers advantages in E_{es} estimation not only of not requiring high-fidelity volume measurement but also of being applicable on a single-beat basis. In a

preliminary study, however, we found that the uniqueness of the elastance waveform could not be held when loading conditions or contractility was significantly changed. Such a limitation might be overcome if we could quantify the effects of contractility and loading conditions on the E(t) and incorporate them into the E_{es} estimation.

The purpose of this investigation, therefore, was to develop a framework for E_{es} estimation based on a characteristic E(t)while quantitatively incorporating its dependency on contractility and loading conditions. To this end, we approximated E(t) by 2 linear functions, one for the isovolumic contraction phase and the other for the ejection phase. We experimentally evaluated how changes in contractility and loading conditions affected the slope ratio of these 2 linear functions. The fact that the slope ratios were quantitatively correlated with contractility and loading conditions enabled us to estimate E_{es} over a wide range of contractility and loading conditions on a single-beat basis without instantaneous ventricular volume.

Methods

Theoretical Considerations: Single-Beat Estimation of E_{es}

To focus on the shape (but not amplitude) of the elastance curve, we normalized the elastance curve by both amplitude and time.^{1,2} As shown in Figure 1A, we approximated the time-varying elastance curve [E(t)] by a bilinear function: one for the isovolumic contraction

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Figure 1. A, Representative E(t) curve (solid line) and approximation by 2 linear functions (isovolumic contraction phase and ejection phase; dashed lines). B, Estimated end-systolic P-V relationship (solid line) from a single-beat P-V loop. Abbreviations as in text.

phase and the other for the ejection phase. We defined the ratio of the slope in the ejection phase to that in the isovolumic phase as α . Note that α is unaffected by both amplitude and time normalization and can be graphically illustrated with normalized elastance curves. By use of this approximation to the E(t) waveform, E_{es} is expressed as

(1)
$$E_{es} = E_{ad} + (E_{ad} - E_{ed})/PEP \cdot ET \cdot \alpha,$$

where E_{ad} is the elastance value at the end of the isovolumic contraction phase, E_{ed} is end-diastolic elastance, PEP is the preejection period, and ET is the ejection time.

Combining Equation 1 with the concept of the P-V relation (Appendix) yields

(2)
$$E_{es(SB)} = [P_{ad} + (P_{ad} - P_{ed})/PEP \cdot ET \cdot \alpha - P_{es}]/SV,$$

where $E_{es(SB)}$ is the single-beat estimation of E_{es}, P_{ad} is the pressure at the end of isovolumic contraction, P_{ed} is end-diastolic pressure, P_{es} is end-systolic pressure, and SV is stroke volume. Once E_{es} is estimated, the single-beat estimation $[V_{0(SB)}]$ of the volume-axis intercept of ESPVR (V_0) may be obtained by

$$\mathbf{V}_{0(\mathrm{SB})} = \mathbf{V}_{\mathrm{es}} - \mathbf{P}_{\mathrm{es}} / \mathbf{E}_{\mathrm{es}(\mathrm{SB})},$$

where V_{es} is end-systolic volume. Note that in this E_{es} estimation method, one requires only systolic time intervals, pressure values, V_{es} , and SV.

Preparation

The study conformed to the "Position of the American Heart Association on Research Animal Use" adopted November 11, 1984, by the American Heart Association. The study was performed in 11 mongrel dogs (16 to 20 kg) anesthetized with pentobarbital sodium (30 mg/kg IV) after premedication with ketamine hydrochloride (5 mg/kg IM). The dogs were ventilated with room air, and a 5F catheter was placed in the right femoral vein for administration of fluids and drugs. After a median sternotomy, the heart was suspended in a pericardial cradle. A catheter with 2 micromanometers (SPC-751, Millar Instruments) was introduced via the LV apex for simultaneous LV and aortic (1 to 2 cm above the aortic valve) pressure recording. An additional catheter was advanced to the main pulmonary artery for hypertonic saline injection for volume signal calibration. Snares made from capillary tubing were placed around the inferior and superior venae cavae for caval occlusion. A 6F 12-electrode conductance (volume) catheter (2-RH-216, Taisho Biomed Instruments) was also introduced into the LV through a second stab wound at the apex. This catheter was connected to a conductance volumetric system (Sigma 5 DF, Leycom). To minimize changes in parallel conductance deriving from noncardiac volume changes, we placed an insulator sheet between the heart and the lung.

A pair of pacing electrodes was fixed at the right atrial appendage for atrial pacing.

The ECG and instantaneous LV pressure and volume were digitized at 1000 Hz with 12-bit resolution [AD12-16D(98)H, Contec] and stored with a dedicated laboratory computer system (PC9821Ap, NEC) for subsequent analyses. During data acquisition, the action of the respirator was temporarily suspended at end expiration.

The volume signal was calibrated by use of the hypertonic saline technique as previously described in detail.^{11,12} In brief, saturated saline (1 to 2 mL) was rapidly injected into the main pulmonary artery to obtain the parallel conductance, the contribution of surrounding structures. The parallel conductance was repeatedly measured at the beginning of each protocol.

Experimental Protocols

Contractility Run (n=9)

After measurement of the baseline ESPVR, the bilateral cervical vagi were cut, and the sympathetic nerves were transected at the level of the stellate ganglia. A pair of electrodes was attached at the distal end of one of the left cardiac sympathetic nerves. We recorded ESPVR under enhanced contractility either by 1- to 2-Hz left cardiac sympathetic nerve stimulation (n=6) or by dobutamine administration (2 μ g · kg⁻¹ · min⁻¹, n=3) and under reduced contractility by propranolol administration (0.2 mg/kg).

Afterload Run (n=9)

ESPVR was recorded after pharmacological alterations in vascular resistance (afterload) with methoxamine (10 to 15 μ g · kg⁻¹ · min⁻¹) or sodium nitroprusside (3 to 10 μ g · kg⁻¹ · min⁻¹) infusion. Animals were pretreated with hexamethonium chloride (30 mg/kg) and atropine (0.1 mg/kg) to completely block autonomic reflexes.

Heart Rate Run (n=5)

We tested for the possible dependency of our estimation technique on heart rate by crushing the sinus node region and instituting atrial pacing to obtain ESPVR at different heart rates ($\pm 25\%$ of baseline heart rate).

ESPVR Determination From Multiple P-V Loops (True $E_{\mbox{\tiny es}})$

Conventional measurement ("gold standard") of E_{es} was made from serial LV P-V loops obtained during transient caval occlusions. The E_{es} and V_0 were calculated by an iterative linear regression method.^{17,18} We excluded the first 5 beats to avoid the possible effects of changes in parallel conductance associated with alterations in right ventricular volume.

	Heart Rate, bpm	E _{es} , mm Hg/mL	E _a , mm Hg/mL	α	n
Contractility run					
Baseline	136±25	13.2±3.3	9.1±2.5	0.61 ± 0.11	9
Enhanced contractility	150±17	22.3±5.9*	12.3±4.0*	$0.69{\pm}0.15$	9
Reduced contractility	126±22†	8.8±2.4*†	15.5±3.6*†	0.43±0.13*†	9
Afterload run					
Baseline	140 ± 16	9.1±2.6	14.6±6.3	$0.43{\pm}0.10$	9
Vasodilation	147±23	9.3±2.3	9.0±3.6*	$0.56 {\pm} 0.14^{*}$	9
Vasoconstriction	132±20	9.4±2.3	21.8±7.2*†	0.33±0.04*†	9
Heart rate run					
Baseline	140±18	11.1±1.8	11.4±3.5	$0.57 {\pm} 0.17$	5
Bradycardia	105±30*	9.7±2.6	11.3±2.4	$0.50{\pm}0.17$	5
Tachycardia	177±10*†	17.4±5.3†	14.1±4.1	$0.63{\pm}0.17$	5

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Data are shown as means ± SD.

*P<0.05 vs baseline.

+P < 0.05 vs enhanced contractility, vasodilation, or bradycardic conditions.

Estimation of PEP and ET

In this study, the early isovolumic point (t_{ed}) is defined as the moment when LV dP/dt exceeds 30% of positive dP/dt_{max} to focus the linear part of E(t) during the isovolumic contraction phase. The end of the isovolumic contraction phase (t_{ad}) is defined as the moment when the steep rise of the aortic pressure wave front begins. End-systole (t_{es}) is defined as the time when dP/dt decreases to 20% of dP/dt_{min}. Thus, PEP is obtained by subtracting t_{ed} from t_{ad} ; ET is obtained by subtracting t_{ad} from t_{es} .

Definition of Other Variables

We estimated effective arterial elastance (E_a) as an index of afterload. E_a was derived as the ratio of P_{es} to SV.¹⁹ We also calculated effective ejection fraction (EF_e) as the ratio of SV to stressed end-diastolic volume [end-diastolic volume (V_{ed})–V₀] as a measure of loading conditions. According to the framework of ventriculararterial coupling, EF_e approximates the ratio of E_{es} to E_{es}+E_a (Appendix).

Data Analysis

Estimated $E_{\rm es(SB)}$ and $V_{\rm 0(SB)}$ were both compared with their respective gold standards derived from multiple P-V loops. We also compared estimated $E_{\rm es(SB)}$ with the estimation obtained by the methods by Senzaki et al.^{10} We used the same normalized elastance curve as appears in their report. Agreement of ESPVR lines (SEE of ESPVR) was quantified by the root mean square of the $P_{\rm es}$ difference over the physiological volume range.

Data are presented as mean±SD. One-way repeated-measures ANOVA with the Newman-Keuls test was applied for multiple comparison under each run. Estimated and true E_{es} and V_0 were compared by linear regression analysis. Multiple regression analysis was used to determine the dependency of α on various indexes of contractility and loading conditions.

Results

Effect of Various Interventions on E_{es} and E_a

The Table summarizes the effects of various interventions on E_{es} as estimated by the standard method and on E_a . E_{es} and E_a values ranged between 5.3 and 28.8 mm Hg/mL and between 3.7 and 34.0 mm Hg/mL, respectively, for all interventions (total of 69 beats).

Contractility Run

 E_{es} increased with enhanced contractility (13.2±3.3 to 22.3±5.9 mm Hg/mL, *P*<0.05) and decreased with reduced contractility (8.8±2.4 mm Hg/mL, *P*<0.05). E_a increased with both enhanced (9.1±2.5 to 12.3±4.0 mm Hg/mL, *P*<0.05) and reduced (15.5±3.6 mm Hg/mL, *P*<0.05) contractility.

Afterload Run

 E_a decreased from 14.6±6.3 to 9.0±3.6 mm Hg/mL (P<0.05) with vasodilation and increased with vasoconstriction (21.8±7.2 mm Hg/mL, P<0.05). These interventions did not significantly alter E_{es} .

Heart Rate Run

Bradycardia decreased E_{es} nonsignificantly (11.1 to 9.7 mm Hg/mL, P=NS) with no sizable changes in E_a , suggesting concomitant alterations in arterial resistance. Vasoconstriction in response to decreased cardiac output might have counterbalanced the decrease in E_a . Tachycardia nonsignificantly increased E_{es} (17.4 mm Hg/mL, P=NS) and E_a (11.4 to 14.1 mm Hg/mL, P=NS). E_{es} was different between bradycardic and tachycardic conditions (P<0.05).

Effect of Interventions on Time-Varying Elastance Curve

Figure 2 shows examples of normalized E(t) curves (normalized by both amplitude and time) obtained in the same dog under baseline conditions and after administration of methoxamine under complete blockade of autonomic systems to increase afterload and reduce contractility, respectively. α was reduced from 0.6 under baseline conditions to 0.3 with depressed contractility and increased afterload. Similar differences in the E(t) curve were observed in all animals. As summarized in the Table, α was 0.61 ± 0.11 under baseline conditions, reaching values as low as 0.43 ± 0.13 (P<0.05) with reduced contractility. Enhancing contractility did not change α significantly. Vasodilation increased α from 0.43 ± 0.10 under baseline conditions to 0.56 ± 0.14 (P<0.05),



Figure 2. A, Representative LV elastance curves obtained at baseline (thick line) and after administration of methoxamine (thin line). B, Elastance curves normalized by amplitude and time for same data. Inset shows bilinear approximation of curves.

and vasoconstriction decreased α to 0.33±0.04 (*P*<0.05). Heart rate did not alter α significantly.

Determinants of α

We examined the dependence of α on various parameters, such as EF, EF_e, E_{es}, E_a, and PEP/(PEP+ET), by linear regression analysis. We selected these variables because α is likely to be sensitive to changes in contractility, loading conditions, and coupling between them. As shown in Figures 3A and 3B, α was tightly positively correlated with EF_e (r=0.900) and EF (r=0.858). α also correlated positively with E_{es} (r=0.657, Figure 3C) and negatively with E_a (r=-0.572, Figure 3D) and with PEP/(PEP+ET) (r=-0.393, Figure 3E). Correlations between α and vascular resistance, heart rate, V_{ed}, and P_{ed} were all poor (data not shown).

Estimation of α

As we show in Equation 2, our method requires the precise value of α . Although EF_e and E_{es} itself are good predictors of α , these values are unavailable beforehand. Instead, we used conventional EF to predict α (univariate model, α =0.022+1.171EF, r=0.858). α was also correlated with PEP/(PEP+ET), an index based on systolic time intervals. This index is directly coupled with an index of ventricular contractility (PEP/ET) that was used previously but is rarely used now. We also used both EF and PEP/(PEP+ET) to improve the accuracy of prediction of α [bivariate model, α =-0.210+1.348EF+0.682PEP/(PEP+ET), r=0.875]. Although both models predicted α reasonably well, the SEE was smaller in the latter model.

True Versus Estimated E_{es} and V₀

Figures 4A and 4B show scatterplots comparing $E_{es(SB)}$ with true E_{es} . Both models estimated E_{es} reasonably well. The slope and intercept were not significantly different from unity and zero, respectively, with either model for α . However, SEE was less with the bivariate model than with the univariate model (2.1 versus 2.4 mm Hg/mL).

Figures 4C and 4D show the scatterplots for the estimated versus true V_0 . The accuracy of prediction of V_0 was much less than that of E_{es} with either model for α .

Figure 5 shows the scatterplots for E_{es} and V_0 estimated by the method of Senzaki et al¹⁰ but with our data. The method of Senzaki et al produced a lower correlation between estimated and true values of E_{es} and V_0 (r=0.420 and 0.404, respectively) as well as a larger SEE (5.6 mm Hg/mL and 5.5 mL, respectively) than Figure 4.

On average, the SEE of ESPVR was 6.9, 6.8, and 10.1 mm Hg for our method with the univariate and bivariate models and the method of Senzaki et al, respectively.

Discussion

We found that the E(t) curve could be approximated by a bilinear function up to end systole, although the precise waveform of the E(t) was dependent on contractilities and loading conditions. The results indicated that E_{es} estimated by our method correlated well with conventional estimation over a wide range of cardiac contractilities and loading conditions.

Load Dependence of the Time-Varying Elastance Curve

A number of reports indicate that there are both positive and negative effects of ejection on E_{es} .²⁰ Length-dependent changes in the affinity of contractile proteins for calcium ions²¹ or in the amount of calcium release²² have a positive inotropic effect, whereas the uncoupling effects of shortening, viscoelastic properties, or length-dependent changes in transsarcolemmal kinetics of calcium have a negative inotropic effect.^{23–26} Thus, the time course of the elastance curve could also be modulated when the loading condition is altered over a wide range.

Sagawa et al²⁵ showed in excised, cross-circulated, bloodperfused canine hearts that the instantaneous E(t) curve depended on loading conditions and thus on the methods of defining E(t). Other investigators also reported differences between isovolumic and ejecting contractions on the shape of E(t),⁶ indicating that afterload significantly influenced the time course of contraction and relaxation of the LV. Our data further demonstrated that the shape of the E(t) curve was dependent on loading conditions even in in situ hearts.





Senzaki et al¹⁰ assumed constancy in the shape of the E(t) curve in examining data recorded from humans. Although they include data from patients with various diseases, we speculate that a lack of data obtained under pharmacological interventions on their part is what prevented them from observing significant variability in the shape of the E(t) curve.

Technical Advantages of Our Method

Although the E_{es} provides a load-insensitive index of contractile state, its clinical application has been limited for various reasons. Our method has the advantage of removing 2 major hindrances to clinical application of the E_{es} concept. First, our method needs only V_{ed} and V_{es} but not "instantaneous" LV volume. We have shown that with V_{ed} and V_{es} obtained by conductance catheter, our method is capable of estimating E_{es} and V_0 with an accuracy similar to that of the multiple-loop method. Second, one need not alter loading conditions. This is of tremendous benefit because changing loading conditions could lead to reflex-mediated change in hemodynamics. Our method, moreover, can be applied to studying rapid changes in contractility, such as occur with arrhythmias.

Comparison With Other Methods

Both our method and that of Senzaki et al¹⁰ have the advantage that neither instantaneous LV volume measurements nor manipulation of loading conditions is needed. They are different in that we have introduced the load dependence of the E(t) curve. We tested whether this load dependence would improve the accuracy of E_{es} and V_0 estimation by examining the wider range of coupling conditions. We have demonstrated that at least in normal dogs, we successfully improved the accuracy of E_{es} and V_0 estimation. This advantage becomes evident only if we study the ranges of coupling conditions wider than the physiological range. Although we studied a wider range of coupling conditions, our study has the limitation that we did not study normal or diseased human hearts.

Applications of This Method

As already stated, we believe that this method greatly enhances the use of E_{es} in the clinical as well as in the experimental setting. Clinically, in the catheterization laboratory, it is relatively easy to register high-fidelity pressures as well as V_{ed} and V_{es} for estimating the single-beat E_{es} . In the



Figure 4. Summary scatterplots of relationships between true and estimated E_{es} (A and B) and true and estimated V_0 (C and D). A and C were obtained by using EF only in estimating α and B and D using both EF and systolic time intervals. Solid line and dashed curves indicate linear regression and its 95% confidence limits.

experimental setting, there has been a growing need for methods to estimate a load-independent index of contractility in small animals (rats and mice), because these species are especially useful in genetic engineering to produce cardio-



Figure 5. Summary scatterplots of relationship between true and estimated E_{es} (A) and true and estimated V_0 (B) based on our data but using method of Senzaki et al.¹⁰ Solid line and dashed curves indicate linear regression and its 95% confidence limits.

vascular disease models. Because of the advantages stated in the previous section, our method is especially suited for the estimation of contractility in small animals.

Limitations

Some investigators have observed in dogs that ESPVR is not necessarily linear but rather shows a curvilinearity that is dependent on contractility.^{3,4} We found, in the present data, that ESPVR was predominantly linear and that nonlinearity accounted for only 2% of the variance (data not shown). Because of this apparent linearity, we reasoned that curvilinearity was not a factor compromising our estimation accuracy. Our method thus seems to be able to estimate the apparent linear slope of ESPVR determined between V_{ed} and V_{es} . However, interpretations of the estimated V_0 should be made with caution, because the V_0 values were obtained by a linear extrapolation outside of the operating volume.

We imposed a wide range of contractilities and loading conditions. The dynamic afterload properties, arterial compliance, and characteristic impedance were not explicitly altered. Indeed, when characteristic impedance is effectively increased, as in aortic stenosis or hypertrophic obstructive cardiomyopathy, it is known that the shape of the E(t) curve changes.²⁵ Obviously, we need to further investigate whether E(t) can be approximated by a bilinear function and whether the estimation of α holds even in such conditions.

Finally, our way of defining early isovolumic point and end systole from the pressure wave was somewhat arbitrary. We distinguished end systole (time with maximal elastance) from end ejection. Indeed, end systole is earlier than the end of ejection.¹⁷ Kono et al¹⁷ observed that E_{es} would be overestimated if end-ejection criteria were used, although the differ-

ence was small. We purposely defined early isovolumic point at the moment when dP/dt reached 30% of its maximum rather than 10%. This effectively extracted the linear part of the elastance curve during the isovolumic contraction phase and thereby improved the accuracy of bilinear approximation of E(t) curves. To apply this method to noninvasively obtained data, further investigation is needed on how the definitions of early isovolumic point and end systole affect the accuracy.

Summary

Identifying the load dependence of the waveform of E(t) and using its approximation by a bilinear function, we developed a method for estimating E_{es} and V_0 on a single-beat basis without need for instantaneous LV volume or changes in loading conditions. This method proved itself capable of estimating E_{es} and V_0 with reasonable accuracy over a wide range of contractilities and loading conditions. We conclude that this technique is useful in the quantitative assessment of LV contractility in experimental studies and is worth studying further in the clinical setting.

Appendix

As shown in Figure 1B, E_{ad} , E_{ed} , and E_{es} will be approximated by P_{ad} , P_{ed} , and putative peak pressure when there is no ejection (P_{max}) according to the relations

 $P_{ad} = E_{ad} \cdot (V_{ed} - V_0),$

(3)

$$\mathbf{P}_{ed} = \mathbf{E}_{ed} \cdot (\mathbf{V}_{ed} - \mathbf{V}_0),$$

and

$$P_{max} = E_{es} \cdot (V_{ed} - V_0)$$

Multiplying Equation 1 on both sides by $(V_{ed} - V_0)$ and substituting Equation 3 into the result yields

(4)
$$P_{max} = P_{ad} + (P_{ad} - P_{ed})/PEP \cdot ET \cdot \alpha.$$

 $E_{\rm es}$ can be estimated from $P_{\rm max},\,P_{\rm es},$ and SV13,14 as

(5)
$$E_{es} = (P_{max} - P_{es})/SV.$$

Substituting P_{max} in Equation 5 with Equation 4 yields Equation 2. According to the framework of ventricular-arterial coupling using the ESPVR,¹⁹ SV is derived as

$$SV = E_{es}/(E_{es} + E_a)(V_{ed} - V_0).$$

Dividing SV by V_{ed}-V₀ yields

$$EF_e = E_{es}/(E_{es} + E_a).$$

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