New Methods

Noninvasive Single-Beat Determination of Left Ventricular End-Systolic Elastance in Humans

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OBJECTIVES	The goal of this study was to develop and validate a method to estimate left ventricular end-systolic elastance (E_{es}) in humans from noninvasive single-beat parameters.
BACKGROUND	Left ventricular end-systolic elastance is a major determinant of cardiac systolic function and ventricular-arterial interaction. However, its use in heart failure assessment and management is limited by lack of a simple means to measure it noninvasively. This study presents a new noninvasive method and validates it against invasively measured E_{es}.
METHODS	Left ventricular end-systolic elastance was calculated by a modified single-beat method employing systolic (P_s) and diastolic (P_d) arm-cuff pressures, echo-Doppler stroke volume (SV), echo-derived ejection fraction and an estimated normalized ventricular elastance at arterial end-diastole (E_{Nd}): $E_{es(sb)} = [P_d - (E_{Nd(est)} \times P_s \times 0.9)]/(E_{Nd(est)} \times SV)$. The E_{Nd} was estimated from a group-averaged value adjusted for individual contractile/loading effects; $E_{es(sb)}$ estimates were compared with invasively measured values in 43 patients with varying cardiovascular disorders, with additional data recorded after inotropic stimulation (n = 18, dobutamine 5 to 10 μg/kg per min). Investigators performing noninvasive analysis were blinded to the invasive results.
RESULTS	Combined baseline and dobutamine-stimulated E_{es} ranged 0.4 to 8.4 mm Hg/ml and was well predicted by $E_{es(sb)}$ over the full range: $E_{es} = 0.86 \times E_{es(sb)} + 0.40$ (r = 0.91, SEE = 0.64, p < 0.00001, n = 72). Absolute change in $E_{es(sb)}$ before and after dobutamine also correlated well with invasive measures: $E_{es(sb)}$: $\Delta E_{es} = 0.86 \times \Delta E_{es(sb)} + 0.67$ (r = 0.88, p < 0.00001). Repeated measures of $E_{es(sb)}$ over two months in a separate group of patients (n = 7) yielded a coefficient of variation of 20.3 ± 6%.
CONCLUSIONS	The E_{es} can be reliably estimated from simple noninvasive measurements. This approach should broaden the clinical applicability of this useful parameter for assessing systolic function, therapeutic response and ventricular-arterial interaction. (J Am Coll Cardiol 2001;38:2028–34) © 2001 by the American College of Cardiology

The effectiveness of chronic heart failure therapy depends upon an accurate assessment of the underlying pathophysiology, accompanied by close patient monitoring and tailored treatment (1–3). Such comprehensive management approaches stabilize acute exacerbations, reduce readmissions, enhance quality of life and improve survival (1–3). However, variability of disease presentation and its response to treatment (3–5) and a growing complexity of therapeutic options have increased the need for more specific and better measures of cardiac performance.

Routine approaches for assessing left ventricular (LV) function are based largely on image-analysis or right-heart monitoring. Both are useful yet provide limited information specific to the LV, and neither indexes ventricular-arterial interactions, which can be crucial for optimizing chronic therapy (6–9). The end-systolic pressure-volume relation

(ESPVR) and its slope (E_{es}) have proven very useful in this regard since E_{es} is a major determinant of LV systolic performance and heart interaction with the systemic vasculature (8–13). However, E_{es} determination has generally required invasively measured LV pressure and volumes recorded over a range of cardiac loading. This has hampered the broader application of this parameter to clinical heart failure diagnosis and management.

Several approaches have been proposed for estimating E_{es} without loading interventions (14–16), and these are generally referred to as single-beat methods ($E_{es(sb)}$). For example, based on similarities between the amplitude and time-normalized human LV time-varying elastance curves during early isovolumic contraction, we reported that E_{es} could be estimated from steady-state data (15). This approach has been since applied to other species as well (17). Subsequent studies (16) improved on this approach by individually adjusting the normalized elastance curve to compensate for load and contractility dependencies.

A strength of these particular methods (14,16) is their potential to be used noninvasively. While this has already been attempted (18), there are no data validating the noninvasive approach by comparing it with directly mea-

Abbreviations and Acronyms

E_d = left ventricular end-diastolic elastance
E_{es} = left ventricular end-systolic elastance
$E_{es(sb)}$ = left ventricular elastance at end-systole derived by single-beat technique
EF = ejection fraction
$E_{Nd(avg)}$ = group-averaged normalized left ventricular elastance at the onset of ejection
$E_{Nd(est)}$ = noninvasive estimated normalized left ventricular elastance at the onset of ejection
ESPVR = end-systolic pressure volume relation
LV = left ventricle or left ventricular
P_d = diastolic arterial pressure
P_{es} = left ventricular end-systolic pressure
P_s = systolic arterial pressure
SV = stroke volume
V_d = left ventricular volume at the onset of ejection
V_{ed} = left ventricular end-diastolic volume
V_{es} = left ventricular end-systolic volume
V_0 = volume axis intercept of the end-systolic pressure volume relation

sured (multiple-cycle derived) invasive E_{es}. In this study, we developed a modified noninvasive method for $E_{es(sb)}$ and verified this method by comparisons with results obtained from invasive (multiple-beat) analysis.

METHODS

Study population. The primary study group consisted of 43 patients studied in the cardiac catheterization laboratories of the Johns Hopkins Hospital (n = 11) or Taipei Veterans General Hospital, Taiwan (n = 32). Invasive and noninvasive pressure-volume data were measured simultaneously at the first center and within 1 to 2 h of each other at the latter center. For simultaneous studies, a custom light-weight radio-lucent horizontal tilt-table was attached to the catheterization table to position patients for echo-Doppler recording. Thirty-four men and nine women were studied, with a mean age of 62 ± 12 years. Primary indications for cardiac catheterization were chest pain (n = 26) or heart failure (n = 17). Clinical diagnoses included noncardiac disease (normal coronary artery anatomy and LV systolic function, n = 13), coronary artery disease (n = 13), hypertensive cardiac disease (n = 8), dilated cardiomyopathy (n = 5), hypertrophic cardiomyopathy (n = 1), constrictive pericarditis (n = 1) and heart transplantation (n = 2). Ejection fraction (EF) ranged from 17% to 88% (mean: 69 ± 15%).

Additional studies were obtained by noninvasive method in seven subjects with vascular stiffening and normal heart function (placebo arm of pharmacologic study) to test measurement reproducibility over time. All patients provided informed consent, and the relevant institutional review board for each respective institution approved the protocol(s).

Study protocol. Patients underwent routine coronary angiography, left ventriculography and right heart catheteriza-

tion. A 7F multielectrode conductance/micromanometer catheter was then placed into the LV, with the pigtail tip advanced to the ventricular apex. Left ventricular volumes were recorded using a stimulator-microprocessor (Sigma V, CardioDynamics, the Netherlands) and calibrated to match thermodilution-derived stroke volume (SV) and contrast ventriculogram-derived EF. Echocardiograms were performed (Sonos-5500, Agilent, Palo Alto, California) using a wide-band frequency-fusion phase-array transducer. Brachial systolic (P_s) and diastolic (P_d) blood pressures were obtained with an oscillometric blood pressure monitor. End-systolic pressure (P_{es}) was estimated from $P_s \times 0.9$ (19). This was further tested in 17 subjects in whom concomitant brachial cuff pressure and invasive data were measured, yielding a linear relation with slope 1.01, p < 0.0001, r = 0.75. Left ventricular outflow tract diameter was measured at the base of the aortic leaflets in a parasternal long-axis view from which cross-sectional area was determined. Stroke volume was measured from proximal aorta pulse-wave Doppler-flow (apical five-chamber view) and aortic cross-sectional area (20). A standard method was used to calculate LV EF from two-dimensional guided M-mode echocardiographic data (21).

In addition to rest data, noninvasive and invasive assessments were made in 18 patients before and after varying contractility by dobutamine (5 to 10 μg/kg per min, intravenous). Comparisons were simultaneous in five studies and sequential (separated by 1 to 2 h) in the others. A total of 29 pre/post dobutamine comparisons were obtained (two doses in most patients).

$E_{es(sb)}$ estimation algorithm. The algorithm for $E_{es(sb)}$ assumed a linear end-systolic pressure-volume relation in the measured data range and a constant volume axis intercept of the end-systolic pressure volume relation (V_0). Using pressures and volumes determined at times during midisovolumic contraction (t_d) and at end-systole (t_{es}), two values of LV elastance were derived: $E_d = P_d/(V_d - V_0)$ and $E_{es} = P_{es}/(V_{es} - V_0)$. Their ratio E_{Nd} (E_d/E_{es}) was the time and amplitude normalized time varying elastance at time t_d. We found that values of E_{Nd} were conserved during the isovolumic period in humans despite diverse cardiac disease, heart function and arterial load. Thus, knowledge of t_d meant that E_{Nd} and, thereby, E_{es} and V_0 could be derived (14).

The prior study of Senzaki et al. (14) sampled pressures and volumes at several time points during isovolumic contraction (i.e., multiple values of t_d). This was easily achieved since both signals were measured invasively, and the final E_{es} estimate averaged separate calculations. For noninvasive analysis, however, a single pressure-volume point is used, timed at the onset of ejection (end of the isovolumic period). By substituting arterial diastolic pressure for end-isovolumic LV pressure and arterial systolic pressure for LV end-systolic pressure, one obtains (see Appendix for details):

$$E_{es(sb)} = [P_d - (E_{Nd} \times P_s \times 0.9)]/[(V_{ed} - V_{es}) \times E_{Nd}]$$

$$= [P_d - (E_{Nd} \times P_s \times 0.9)]/[SV \times E_{Nd}] \qquad [1]$$

where V_{ed} and V_{es} are end-diastolic and end-systolic volumes, SV is stroke volume, E_{Nd} is the normalized elastance value at the onset of ejection and P_d and P_s are arterial diastolic and systolic pressures, respectively.

The accuracy of equation 1 is dependent on the reliability of the measured data and the value chosen for E_{Nd}. Our prior study employed high-fidelity pressure/volume signals to yield accurate timing for E_{Nd} determination and early isovolumic contraction data to minimize intrapatient variability about the group-averaged normalized LV elastance at the onset of ejection ($E_{Nd(avg)}$) value. For noninvasive application, E_{Nd} occurs at the onset of ejection, increasing individual load/contractile-dependent deviations from the population average. To reduce this variance, we developed an approach similar to that of Shishido et al. (16) using a regression model to improve the individual noninvasive estimated normalized LV elastance at the onset of ejection ($E_{Nd(est)}$) for each patient, based on noninvasive measures of systolic function (EF) and arterial load (ratio of arterial diastolic to systolic pressure).

The $E_{Nd(est)}$ regression-model was based on data obtained in 23 completely separate and previously recorded studies in which invasive aortic pressure and LV pressure-volume data were concomitantly measured. An individual time-varying elastance function was calculated from rest steady-state data, with V_0 in this calculation based on multicycle ESPVR analysis as previously described (14). This curve was normalized by amplitude and time, and its value at the upstroke of aortic pressure determined. This served as the "gold standard" value for E_{Nd}. The $E_{Nd(est)}$ was obtained from a group-averaged normalized elastance curve value at this same time t_d ($E_{Nd(avg)}$), baseline EF and the ratio of arterial diastolic to systolic pressure (P_d/P_{es}), given by:

$$E_{Nd(est)} = 0.0275 - 0.165 \times EF + 0.3656 \times (P_d/P_{es})$$
$$+ 0.515 \times E_{Nd(avg)} \qquad [2]$$

where $E_{Nd(avg)}$ is given by a seven-term polynomial function:

$$E_{Nd(avg)} = \sum_{i=0} a_i \times t_{Nd}^{\ i}$$

where a_i are (0.35695, −7.2266, 74.249, −307.39, 684.54, −856.92, 571.95, −159.1) for i = 0 to 7, respectively. The value of t_{Nd} was determined by the ratio of pre-ejection period (R wave $\rightarrow$ flow-onset) to total systolic period (R-wave $\rightarrow$ end-flow), with the time at onset and termination of flow defined noninvasively from the aortic Doppler waveform. Each factor in equation 2 was a significant independent contributor to the regression. Figure 1 compares $E_{Nd(est)}$ with directly measured E_{Nd}. The regression yielded an overall r = 0.88 and p < 0.00001, with a SEE about 10% the mean. The $E_{es(sb)}$ was then derived by combining equations 1 and 2:
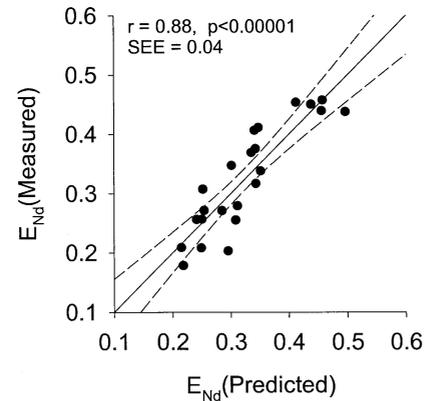

Figure 1. Estimation of normalized time-varying elastance value at the onset of ejection for individual subjects. The estimate is based on the group-averaged value (14), resting ejection fraction and the ratio of diastolic to systolic arterial pressure (equation 2). Plot shows correlation between predicted normalized left ventricular elastance at the onset of ejection (E_{Nd}) and directly measured value.

$$E_{es(sb)} = [P_d - (E_{Nd(est)} \times P_s \times 0.9)]/[SV \times E_{Nd(est)}]$$

$$[3]$$

Statistical methods. Results are expressed as mean ± SD. Univariate linear regression was performed to test the agreement between noninvasively estimated and invasively measured E_{es} values at rest and changes in E_{es} induced by dobutamine. Bland-Altman analysis was employed to assess for systematic bias in the correlation.

RESULTS

Estimation of E_{es} by $E_{es(sb)}$ Figure 2A displays typical pressure-volume loop data used to derive invasive E_{es}. The ESPVRs were generally linear over the observed data range. Figure 2B shows the corresponding noninvasive analysis displayed as two pressure-volume points (solid and open circles). From these points, equations 1 and 2 were used to determine $E_{es(sb)}$. Figure 2C and 2D show similar examples before and after dobutamine infusion. The plots demonstrate a generally good correlation between directly measured E_{es} and the noninvasive estimate.

Figure 3A displays group regression results for 43 baseline comparisons between invasive E_{es} and the single-beat noninvasive $E_{es(sb)}$ estimate. The regression equation was: $E_{es} = 0.78 \times E_{es(sb)} + 0.55$ (r = 0.81, SEE = 0.50, p < 0.0001). The mean difference was 0.03 mm Hg/ml (95% confidence interval: −0.14 $\rightarrow$ 0.19), that is, no systematic bias, and 80% of the estimate errors fell below 0.6 mm Hg. Figure 3C shows combined baseline and postdobutamine data, extending the range of E_{es} comparisons nearly twofold and improving the strength of the overall correlation. The regression SEE was 0.64, with the mean error of 0.43 ± 0.5 (again with no bias) and with about 75% of the estimates falling within 0.6 mm Hg/ml of the measured value.
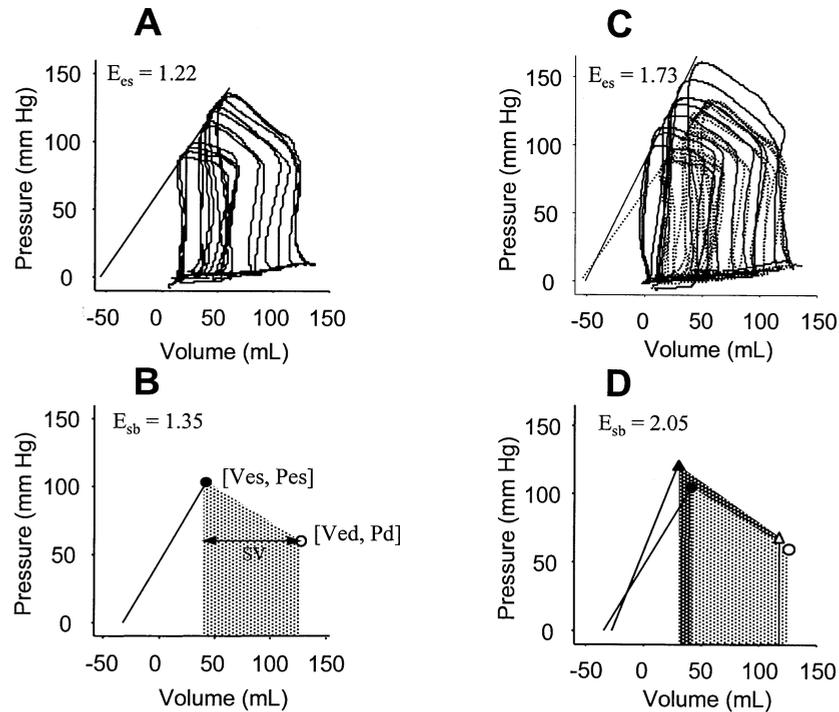
Figure 2. **(A)** Invasive pressure-volume loops and analysis used to derive (E_{es}). Multiple beats are recorded before and during transient obstruction of the inferior vena cava. **(B)** Noninvasive assessment of ($E_{es(sb)}$) displayed in pressure-volume plane from the same example. Two sets of (volume, pressure) data points are measured and used to predict $E_{es(sb)}$. The **dotted area** represents a schematic pressure-volume loop based on these points. From these data, $E_{es(sb)}$ is estimated using equation 4. **(C)** Example of pressure-volume data at rest and after dobutamine stimulation. **(D)** Corresponding noninvasive $E_{es(sb)}$ for the same example displayed in **C**. **Light and darkened dotted areas** are schematic loops from the two points. Pd = diastolic arterial pressure at the onset of ejection; Pes = left ventricular end-systolic pressure; SV = stroke volume; Ved = left ventricular end-diastolic pressure; Ves = left ventricular end-systolic volume.

Relative changes in E_{es} by dobutamine. To further test the robustness of the noninvasive method, the estimated change in E_{es} induced by dobutamine in each patient was compared with the directly measured change based on invasive loop analysis (Fig. 3C and 3D) . The results (Fig. 4) revealed a good correlation given by: ΔE_{es} = 0.86 × $\Delta E_{es(sb)}$ + 0.29 (r = 0.88, SEE = 0.67, p < 0.0001).

Comparison with P_{es}/V_{es} ratio. The steady-state ratio of end-systolic pressure to end-systolic volume (P_{es}/V_{es}) is the most commonly employed approximation for E_{es}, particularly for noninvasive use. It makes a simple assumption that the volume axis intercept of the ESPVR is zero. To determine if the $E_{es(sb)}$ provided additional accuracy over this more easily measured ratio, we compared P_{es}/V_{es} to invasive E_{es}. The results shown in Figure 5 demonstrate that P_{es}/V_{es} was less well-correlated with E_{es} (r = 0.56) compared with $E_{es(sb)}$ and consistently overestimated E_{es}, particularly at higher values. The residuals (Fig. 5B) were significantly different from zero, averaging 2.2 mm Hg/ml. This result contrasts with that for $E_{es(sb)}$, which yielded a relation closer to the identity line.

Reproducibility of $E_{es(sb)}$. To test the chronic reproducibility of $E_{es(sb)}$ measurements, the noninvasive parameter was measured over three successive months in seven subjects with systolic hypertension enrolled in a randomized placebo-controlled trial of a novel antihypertension agent.

These patients were those subsequently found to be on placebo. Data were obtained at baseline and monthly for two months, each measured in a fasting state in the morning. Mean $E_{es(sb)}$ was 3.3 ± 0.94, 3.6 ± 1.3 and 3.1 ± 1.1 at the three observation points, with an average coefficient of variation of 20 ± 6%. Variability of $E_{es(sb)}$ was primarily related to that of SV (cov [coefficient of variation] = 14 ± 6.6%).

DISCUSSION

We developed and tested a novel fully noninvasive method for estimating E_{es}. The method requires five easily measured parameters obtained from noninvasive arm-cuff blood pressures, echo-Doppler cardiography and the electrocardiogram. This is the only study to date to directly verify a fully noninvasive estimation method against invasive multiple cycle-derived pressure-volume relations in humans.

The correlations between measured and estimated $E_{es(sb)}$ values at rest and with acute contractility change were generally good, and there was reasonable repeated-measurement reproducibility over time. It is important in this regard to consider the accuracy of the new estimation method relative to likely clinical applications. The majority (between 75% to 80%) of absolute discrepancies between $E_{es(sb)}$ and the invasive "goal-standard" value were smaller
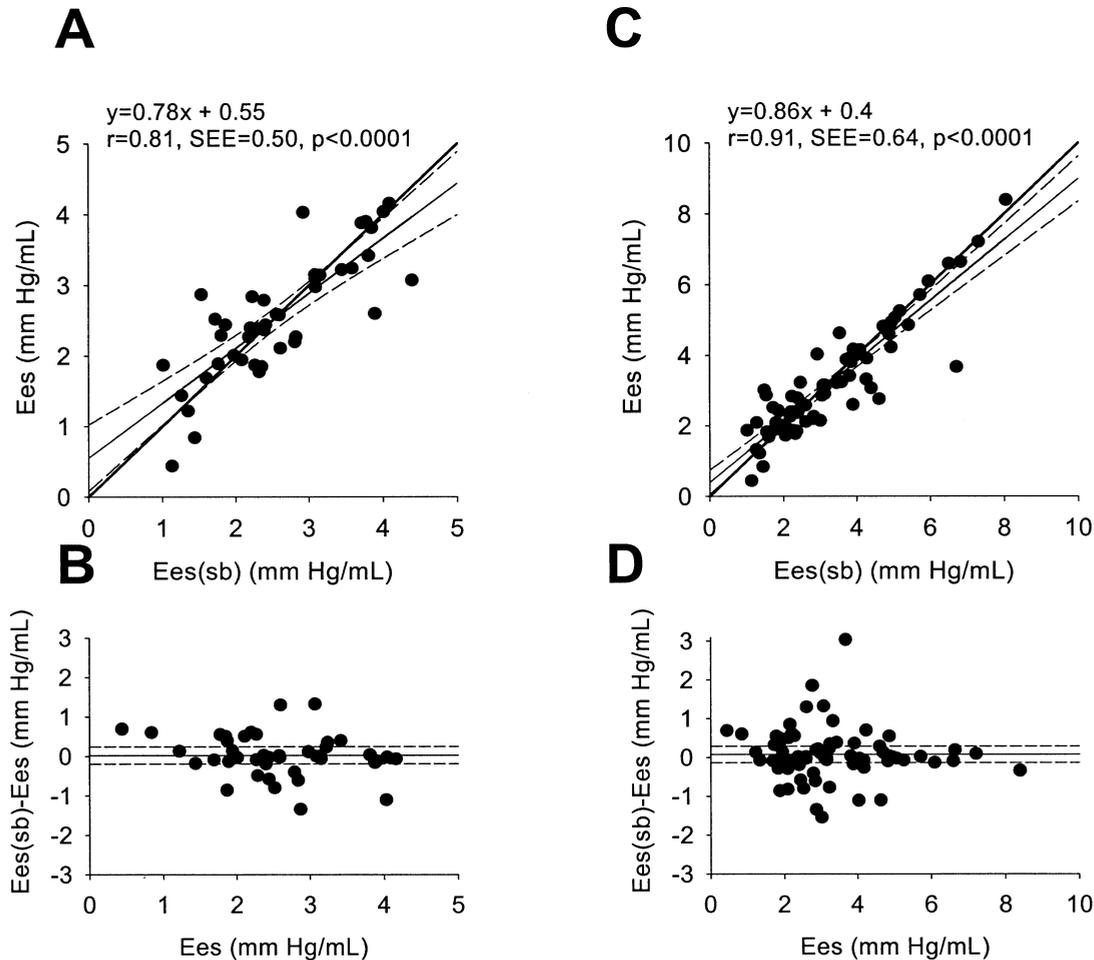
Figure 3. **(A)** Linear regression **(solid line)** and 95% confidence intervals **(dotted lines)** comparing noninvasive left ventricular elastance at end-systole derived by single-beat technique ($E_{es(sb)}$) and invasive (multi-beat) left ventricular end-systolic elastance (E_{es}) at baseline for 43 subjects. **(B)** Bland-Altman plot of $E_{es(sb)}$-E_{es} difference versus mean value. Mean and 99% confidence interval of the mean difference is shown. **(C and D)** Same analysis as in **A and B** but including data after dobutamine stimulation, which expanded the range of E_{es} comparisons. The correlation between measurements is very good and falls along the line of identity.

than 0.6 mm Hg/ml (consistent with SEE from regression analysis). The E_{es} typically ranges near 2.0 mm Hg/ml in normal hearts (13), <1.0 mm Hg/ml in dilated failing hearts (12) and about 4.0 mm Hg/ml in hypertrophied hearts (22). Thus, an absolute error of 0.6 mm Hg/ml should be adequate to correctly identify most patients within these populations. The 20% variability observed with repeated measures suggests that $E_{es(sb)}$ estimates are unlikely to cross between disease groups by pure chance. However, it also indicates that moderate changes are likely needed for the new method to detect real alterations in $E_{es(sb)}$ over time or with interventions.

Comparison with other single-beat analysis methods. Several prior studies have reported methods for estimating E_{es} from single-beat data. Most commonly, the P_{es}/V_{es} ratio is calculated. However, the assumption that the ESPVR passes through the origin in humans results in consistent overestimation of true E_{es} and substantially greater prediction variance (Fig. 5) (14). Kameyama et al. (9) used a more complex noninvasive analysis to estimate E_{es}

based on pressure-cuff calibrated subclavian artery pulse tracings, echocardiography imaging and load interventions. This approach, and recent adaptations employing acoustic quantification methodology (23), remain limited by a need for varying load, which can result in unreliable image quantitation during the loading change. Other efforts to assess E_{es} involve curve fitting to the pressure waveform (15), an approach that seems less reliable than the $E_{es(sb)}$ method (14) and is not translatable to noninvasive analysis.

Recently, Shishido et al. (16) proposed a bilinear approximation to the normalized time varying elastance curve (rising phase only) and found this simple fit provided a reliable estimate of E_{es} in anesthetized dogs. Central to their determination was individual estimation of the point at which the first linear approximation to rising elastance transited to the second, an inflection occurring at or near the onset of ejection. Rather than being independent of loading or contractile conditions, the inflection point had sensitivities that could be predicted from EF. Lack of a stable inflection point might seem to counter our prior clinical
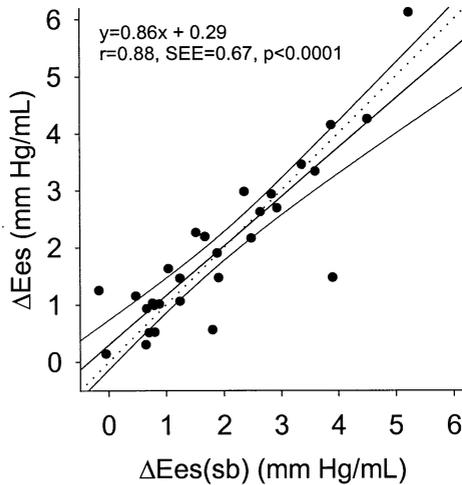
Figure 4. Paired comparison of change in left ventricular end-systolic elastance (ΔE_{es}) induced by dobutamine determined by noninvasive estimation versus the directly assessed value derived from invasive pressure-volume loops. The noninvasive method provided a good estimate of ΔE_{es} (n = 29, r = 0.88, p < 0.0001, with a regression slope and intercept that were not statistically different from 1.0 and 0, respectively. $\Delta E_{es(sb)}$ = change in left ventricular end-systolic elastance by single-beat technique.

study (14) in which the elastance waveform was fairly well conserved during early systole. However, this earlier invasive analysis relied on data measured during the pre-ejection isovolumic period, when load and contractile effects on the elastance curve were minimal. In contrast, the method of Shishido et al. (16) as well as the present method relied on data measured solely at the onset of ejection, where these factors are more influential. Equation 2 in this study was developed independently yet concurrently with the approach of Shishido et al. (16) and serves the same purpose as their regression model to individualize a bilinear elastance. One noteworthy difference was that the present study developed the model from an independent patient group and then applied this to a separate study population.

The new $E_{es(sb)}$ method should also be contrasted to a recently described single-beat determination of preload recruitable stroke work (24). Preload recruitable stroke work is a useful systolic parameter that typically displays greater stability to varying loading over E_{es} and other indexes, and the recent study by Karunanithi and Feneley (24) extended this index to single-beat analysis. However, determination required invasive pressure and volume data, and it is unclear how easily or well this can be extended to noninvasive testing. Furthermore, it is more difficult to assess ventricular-arterial interaction with preload recruitable stroke work as opposed to E_{es}, which is an advantage for the latter in predicting systemic pressure responses to afterload or preload reduction therapy (11,13).

Study limitations. Technical limitations in the catheterization laboratory precluded simultaneous noninvasive/invasive analysis in many subjects, and those studies in which this was achieved still may not have optimized echo-Doppler imaging. However, this should have intro-
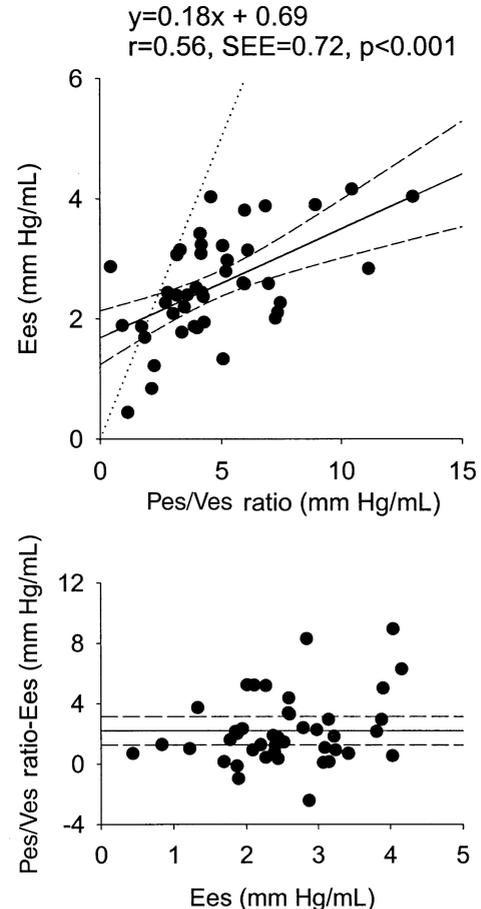

Figure 5. Comparison of resting end-systolic pressure/volume ratio (P_{es}/V_{es}) as an estimate of elastance to directly measured left ventricular end-systolic elastance (E_{es}) by invasive analysis. Unlike $E_{es(sb)}$ (Fig. 3B), the pressure-volume ratio consistently overestimated directly measured E_{es}, and the regression had a non-zero bias (2.2 mm Hg/ml) as demonstrated in the lower Bland-Altman plot.

duced greater scatter in our comparison data, not less. This study also did not evaluate the load-sensitivity of $E_{es(sb)}$ but, rather, focused on the correlation between this parameter and directly measured invasive data. Prior invasive investigations of the $E_{es(sb)}$ method have demonstrated the lack of loading influences (14).

As with many prior studies, the current invasive analysis frequently yielded an apparent negative V_0 intercept for the ESPVR measured in the physiologic data range. This is not a unique feature of conductance catheter analysis, as similar findings have been reported in various mammalian species regardless of the volume method used. As previously discussed (14), this is mostly related to nonlinear behavior of the ESPVR at highly reduced load. Importantly, the behavior of the ESVPR in the physiologic loading range defines the relevant hemodynamic responses; so E_{es} assessed in this range is most important. The new noninvasive algorithm was designed to estimate this operational E_{es} value, regardless of whether it predicted a negative (i.e., nonphysiologic) V_0 based on a purely linear extrapolation.

Conclusions. Left ventricular end-systolic elastance can be estimated from easily obtained noninvasive parameters, and the values obtained are generally well correlated with directly measured data. Besides its implications regarding contractile strength, E_{es} values also help clarify integrated cardiovascular responses to altered vascular loading (8,11–13,25). In this important sense, it should be useful for assessing the efficacy of heart failure therapies and targeting the type of treatment most likely to prove beneficial.

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REFERENCES

1. Stevenson LW, Massie BM, Francis GS. Optimizing therapy for complex or refractory heart failure: a management algorithm. Am Heart J 1998;135:293–309.
2. Fonarow GC, Stevenson LW, Walden JA, et al. Impact of a comprehensive heart failure management program on hospital readmission and functional status of patients with advanced heart failure. J Am Coll Cardiol 1997;30:725–32.
3. Steimle AE, Stevenson LW, Chelimsky-Fallick C, et al. Sustained hemodynamic efficacy of therapy tailored to reduce filling pressures in survivors with advanced heart failure. Circulation 1997;96:1165–72.
4. Senni M, Tribouilloy CM, Rodeheffer RJ, et al. Congestive heart failure in the community: trends in incidence and survival in a 10-year period. Arch Intern Med 1999;159:29–34.
5. Vasan RS, Benjamin EJ, Levy D. Congestive heart failure with normal left ventricular systolic function: clinical approaches to the diagnosis and treatment of diastolic heart failure. Ann Intern Med 1996;156:146–57.
6. Asanoi H, Kameyama T, Ishizaka S, Nozawa T, Inoue H. Energetically optimal left ventricular pressure for the failing human heart. Circulation 1996;93:67–73.
7. Binkley PF, VanFossen DB, Nunziata E, Unverferth DV, Leier CV. Influence of positive inotropic therapy of pulsatile hydraulic load and ventricular-vascular coupling in congestive heart failure. J Am Coll Cardiol 1990;15:1127–35.
8. Ishihara H, Yokota M, Sobue T, Saito H. Relation between ventriculoarterial coupling and myocardial energetics in patients with idiopathic dilated cardiomyopathy. J Am Coll Cardiol 1994;23:406–16.
9. Kameyama T, Asanoi H, Ishizaka S, Sasayama S. Ventricular load optimization by unloading therapy in patients with heart failure. J Am Coll Cardiol 1991;17:199–207.
10. Suga H, Sagawa K. Instantaneous pressure-volume relationships and their ratio in the exercised, supported canine left ventricle. Circ Res 1974;35:117–26.
11. Kass DA, Maughan WL. From "Emax" to pressure-volume relations: a broader view. Circulation 1988;77:1203–12.
12. Feldman MD, Pak PH, Wu CC, et al. Acute cardiovascular effects of OPC-18790 in patients with congestive heart failure. Circulation 1996;93:474–83.
13. Chen CH, Nakayama M, Nevo E, Fetics BJ, Maughan WL, Kass DA. Coupled systolic-ventricular and vascular stiffening with age implications for pressure regulation and cardiac reserve in the elderly. J Am Coll Cardiol 1998;32:1221–7.
14. Senzaki H, Chen CH, Kass DA. Single-beat estimation of end-systolic pressure-volume relation in humans: a new method with the potential for noninvasive application. Circulation 1996;94:2497–506.
15. Takeuchi M, Igarash Y, Tomimoto S, et al. Single-beat estimation of the slope of the end-systolic pressure-volume relation in the human left ventricle. Circulation 1991;83:202–12.
16. Shishido T, Hayashi K, Shigemi K, Sato T, Sugimachi M, Sunagawa K. Single-beat estimation of end-systolic elastance using bilinearly approximated time-varying elastance curve (in process citation). Circulation 2000;102:1983–9.
17. Setser R, Henson RE, Allen JS, Fischer SE, Wickline SA, Loren CH. Left ventricular contractility is impaired following myocardial infarction in the pig and rat: assessment by the end systolic pressure-volume relation using a single-beat estimation technique and cine magnetic resonance imaging. Ann Biomed Eng 2000;28:484–94.
18. Lee DS, Kim KM, Kim SK, et al. Development of a method for measuring myocardial contractility with gated myocardial SPECT and arterial tonometry. J Nucl Cardiol 1999;6:657–63.
19. Kelly RP, Ting CT, Yang TM, et al. Effective arterial elastance as index of arterial vascular load in humans. Circulation 1992;86:513–21.
20. Dubin J, Wallerson DC, Cody RJ, Devereux RB. Comparative accuracy of Doppler echocardiographic methods for clinical stroke volume determination. Am Heart J 1990;120:116–23.
21. Teichholz LE, Kreulen T, Herman MV, Gorlin R. Problems in echocardiographic volume determination: echocardiographic-angiographic correlations in the presence or absence of asynergy. Am J Cardiol 1976;37:7–12.
22. Pak PH, Maughan WLM, Baughman KL, Kieval RS, Kass DA. Mechanisms of acute mechanical benefit from VDD pacing in hypertrophic heart disease. Circulation 1998;98:242–8.
23. Chen CH, Nevo E, Fetics B, et al. Comparison of continuous left ventricular volumes by transthoracic two-dimensional digital echo-quantification with simultaneous conductance catheter measurement in patients with cardiac diseases. Am J Cardiol 1997;80:756–61.
24. Karunanithi MK, Feneley MP. Single-beat determination of preload recruitable stroke work relationship: derivation and evaluation in conscious dogs. J Am Coll Cardiol 2000;35:502–13.
25. Kass DA. Clinical Evaluation of left heart function by conductance catheter technique. Eur Heart J 1992;13 Suppl E:57–64.

APPENDIX

The ventricular elastance model for the end-systolic point is:

$$E_{es} = P_{es}/(V_{es} - V_0) \qquad [A1]$$

and for the onset of ventricular ejection point is:

$$E_d = P_d/(V_d - V_0) \qquad [A2]$$

Since by definition, $E_{Nd} \times E_{es} = E_d$, equation A2 can be rewritten as:

$$V_d - V_0 = (P_d/E_{Nd})/E_{es} \qquad [A3]$$

Rearranging equation A1 and combining it with equation A3 yields:

$$V_d - V_{es} = (P_d/E_{Nd} - P_{es})/E_{es}$$
$$= [P_d - (E_{Nd} \times P_s)]/[E_{Nd} \times E_{es}] \qquad [A4]$$

which is then solved for E_{es}:

$$E_{es} = [P_d - (E_{Nd} \times P_{es})]/[(V_d - V_{es}) \times E_{Nd}] \qquad [A5]$$

Left ventricular volume at the onset of ejection (V_d) is very close to the LV end-diastolic volume, so stroke volume (SV) can substitute for ($V_d - V_{es}$). The P_{es} is approximated by the product of brachial systolic pressure $P_s \times 0.9$. Substitution of these variables in equation A5 yields equation 1 in the Methods section.