Is Standardization of Left Ventricular Chamber Elastance Necessary?

Henry H. Hsia, MD, and Mark R. Starling, MD

Because of the relation between left ventricular (LV) chamber elastance and heart size, it has been hypothesized that maximum time-varying elastance (E_max) must be standardized to differentiate between preserved and depressed LV systolic performance. To test this hypothesis, we studied 66 patients, of whom 25 had a normal LV, 20 had aortic regurgitation, 14 had mitral regurgitation, and seven had cardiomyopathy, with micromanometer-determined LV pressures and radionuclide angiograms during multiple LV loading conditions. Multiple regression analysis established that E_max was independently related to LV end-diastolic volume (r=-0.69). When the E_max and LV end-diastolic volume (EDV) data from all patients were plotted, a curvilinear relation was evident. Data transformation to the base e identified two distinct linear relations, one in the normal patients of InE_max = -0.60 (lnEDV) + 4.34 (r = -0.67, p<0.001); and one in the patients with cardiac pathology of InE_max = -1.06(lnEDV) + 6.12 (r = -0.73, p<0.001), which differed from each other (p<0.01). When a mathematical standardization was applied to these data to eliminate the independent contribution of heart size to the reduction in lnE_max, the normal patients had a standardized InE_max versus lnEDV slope of 0, whereas that in the patients with cardiac pathology remained negative and continued to differ from that in the normal patients (p<0.001). Dichotomization of patients with cardiac pathology into those with preserved and depressed LV chamber elastance by lnE_max or standardized InE_max provided highly concordant data (k=0.73, p<0.001). Moreover, the estimated contribution of LVEDV to the reduction in E_max in patients with cardiac pathology averaged only 14±7%. We conclude from these data that LV chamber elastance calculated with radionuclide angiography has an independent relation with LVEDV, that a mathematical standardization of E_max for heart size does not significantly alter the dichotomization of patients with cardiac pathology into those with preserved and depressed LV systolic performance, and that heart size makes a relatively small contribution to the reduction in this index of LV systolic performance. Thus, standardization for heart size may not be necessary to identify whether preserved or depressed LV chamber elastance exists in an individual adult patient with cardiac pathology compared with normal adult patients. (Circulation 1990;81:1826-1836)

The time-varying elastance concept has been shown to be relatively independent of alterations in left ventricular (LV) loading conditions but sensitive to pharmacological changes in LV contractility.1-3 Multiple studies in various animal preparations4-9 and humans10-16 have supported the use of the time-varying elastance or end-systolic pressure-volume (E_s) relations for the evaluation of LV systolic performance. However, because of the potential influence of body and heart size on the LV chamber elastance calculation, Sagawa3 suggested that standardization of maximum time-varying elastance (E_max) may be necessary to eliminate this possible confounding influence and, thus, to enable a comparison of LV systolic performance between individuals. Belcher et al8 demonstrated a reduction in the variance of E_s after regression equation adjustment for body and LV weights in dogs. Berko et al7 also demonstrated the need to standardize E_s for end-diastolic volume (EDV) in dogs to define whether changes in LV contractility had occurred after the production of acute mitral regurgitation. Insufficient data are available in humans to define the
proper standardization process and, more importantly, to define whether standardization of \( E_{\text{max}} \) or \( E_a \) alters the discrimination between preserved or depressed LV chamber elastance in individual adult patients with a variety of pathological conditions. Accordingly, the purpose of this investigation was to use a mathematical method for standardizing \( E_{\text{max}} \) to determine whether it is necessary to standardize \( E_{\text{max}} \) to dichotomize individual adult patients into those with preserved and depressed LV systolic performance.

**Methods**

**Patients**

The study population consisted of 66 patients, of whom 25 had atypical chest pain, who constituted the normal patient population, 20 had aortic regurgitation, 14 had mitral regurgitation, and seven had cardiomyopathy. The cardiomyopathy group consisted of two patients with LV dysfunction and interventricular conduction defects of unknown etiology, two patients with idiopathic dilated congestive cardiomyopathy, and three patients with hypertensive heart disease manifest by a history of hypertension, an increase in LV wall thickness according to echocardiography, and LV hypertrophy according to electrocardiography. This latter group, therefore, represents a hybrid group consisting of patients with either hypertrophic or dilated cardiomyopathic heart disease. There were 59 men and seven women whose ages ranged from 23 to 76 years with a mean age of 52±10 (SD) years for the normal patients and 54±14 years for the patients with cardiac pathology. A cardiac catheterization was performed to evaluate atypical chest pain or to define the extent of hemodynamic impairment in the patients with valvular or cardiomyopathic heart disease. Each patient gave written, informed consent for this investigation on forms approved by the human studies committees at the University of Michigan or VA Medical Center, Ann Arbor. All patients were in normal sinus rhythm, and no patient had experienced a prior myocardial infarction or had electrocardiographic evidence of a prior myocardial infarction. Administration of all diuretics, \( \beta \)-adrenergic blocking agents, and vasoactive agents was stopped 24–48 hours before the catheterization, and administration of nitrate preparations was stopped 12 hours before the catheterization.

**Protocol**

A diagnostic right and left heart catheterization documented intracardiac pressures, cardiac outputs, and normal coronary anatomy in each patient; and, in addition, normal LV size, performance, and wall motion in the normal patients and grade 3+ or 4+ angiographic regurgitation in the patients with aortic or mitral regurgitation. Each patient was then entered into the protocol, which consisted of the simultaneous acquisition of micromanometer-derived LV and ascending aortic pressures and radionuclide angiograms under control conditions and during methoxamine or nitroprusside infusions. The infusion rates were adjusted in each patient to increase LV pressure by approximately 50 mm Hg with the vasconstrictor and to decrease LV pressure by approximately 30 mm Hg with the vasodilator.

**Hemodynamics**

The hemodynamic data acquisitions have been described in detail elsewhere.\(^{14,16,17}\) Briefly, a right atrial pacing catheter was placed to maintain a constant heart rate throughout the protocol. A micromanometer catheter (VPC 780C or VPC 684D, Millar Instruments, Houston, Texas) was positioned to measure LV pressures (50- and 200-mm Hg scale) and ascending aortic pressure (200-mm Hg scale). These pressures were recorded simultaneously with two electrocardiographic leads by a physiological recorder (VR-12, Electronics for Medicine, Pleasantville, New York; Micor Siemens, Iseland, New Jersey) at 100 mm/sec for 10–20 cardiac cycles at the beginning, middle, and end of each radionuclide acquisition. These pressure waveforms were manually averaged, and the average LV pressure waveforms were hand digitalized with an inductance digitizing surface (Calcomp 9100, Anaheim, California) interfaced to a PC (IBM, Armonk, New York). A program developed in this laboratory yields instantaneous LV pressure and the first derivative of LV pressure (\( \text{dP/dt} \)) at a sampling frequency of 200 Hz from the peak of the R wave.

**Echocardiographic Measurements**

All patients underwent M-mode echocardiography of the LV performed at the level of the chordae tendineae. The LV dimension and wall thickness measurements were made according to American Society of Echocardiography standards.\(^{16}\) Then, LV mass was calculated as \( 1.1 \left[ \text{LVEDD} + \text{PWth} + \text{IVSth} \right]^3 - (\text{LVEDD})^3, \) where LVEDD is LV end-diastolic diameter, PWth is posterior wall thickness, and IVSth is interventricular septal thickness.\(^{19}\) These echocardiographic LV mass calculations correlate with those obtained from biplane contrast cineangiography in this laboratory (\( n=19, r=0.84, p<0.001 \)).

**Radionuclide Angiography**

Gated equilibrium radionuclide angiograms were acquired after in vivo red blood cell labeling with 30 mCi technetium-99m for 30-msec frames throughout the cardiac cycle for 500 cardiac cycles. During the midportion of each radionuclide acquisition, a 2-ml blood sample was drawn. The blood samples were later counted for 2 minutes, and the time delay between acquisition and counting of the blood samples was recorded. At the end of the protocol, distance measurements were made for attenuation correction. Attenuation-corrected radionuclide LV volumes were calculated frame-by-frame with background subtracted hand-drawn region-of-interest LV count data, decay-corrected blood sample counts,
and attenuation correction as previously validated in this laboratory.16,20,21

Calculation of LV Chamber Elastance

The corresponding micromanometer LV pressures and radionuclide LV volumes for each loading condition were plotted to obtain pressure-volume loops.16 The isochronal, instantaneous pressure-volume data points obtained during each loading condition were subjected to linear regression analysis beginning at the peak of the R wave every 30 msec for 20 sequential frames. The maximum slope was defined as \( E_{\text{max}} \) which represents a relatively load-independent measure of LV systolic performance.1–3 Validation of this radionuclide approach to calculating LV chamber elastance compared with that obtained from biplane contrast cineangiography and a representative example of the radionuclide pressure-volume loops and resultant isochrones from a normal patient have been previously published.16

Data Analysis

Methods of standardizing LV chamber elastance have been proposed.7,8,14,22,23 To determine the optimal variable to be used in the standardization process, a stepwise multiple regression analysis was performed in the normal patients with \( E_{\text{max}} \) and the input variables of body surface area, radionuclide LVEDV, body weight, and echocardiographic LV mass.

After establishing the optimal variable for standardizing \( E_{\text{max}} \), we then applied a mathematical method to adjust the measured \( E_{\text{max}} \) to obtain a standardized \( E_{\text{max}} \). Standardized \( E_{\text{max}} \) = mean \( E_{\text{max}} \) + \( \Delta E_{\text{max}} \), where \( \Delta E_{\text{max}} \) is the deviation of the measured \( E_{\text{max}} \) from the predicted \( E_{\text{max}} \), and the predicted \( E_{\text{max}} \) is obtained from \( E_{\text{max}} = \text{m} \times X + b \). This regression equation is specified by the relation between \( E_{\text{max}} \) and the optimal standardizing variable in the normal patients. This mathematical method, therefore, corrects for the variation in the measured \( E_{\text{max}} \) that can be attributed to the variation in X, which is the optimal standardizing variable of body or heart size.7,24

In an attempt to separate patients with depressed from preserved LV chamber elastance with the use of \( E_{\text{max}} \) and to establish whether the standardization procedure alters this dichotomization, the measured \( \ln E_{\text{max}} \) and standardized \( \ln E_{\text{max}} \) in each patient were determined to represent depressed LV systolic performance when their LV chamber elastance fell 2 SD below the mean \( \ln E_{\text{max}} \) in our 25 normal patients. A Cohen’s kappa test25 was then used to establish the degree of concordance between the two dichotomization procedures. In addition, a McNemar’s test was used to determine whether a dissociation occurred between indexes used to identify abnormal LV systolic performance.26

All data are presented as mean \pm 1 SD. The hemodynamic data were analyzed with a repeated-measures analysis of variance. When a significant \( F \) statistic was obtained, multiple-range tests were used to identify where differences occurred. A probability value of 0.05 or less was considered significant.

Results

Hemodynamics

The baseline hemodynamic data for each of the 25 normal patients and the mean baseline hemodynamic data for the four patient groups are shown in Tables 1 and 2, respectively. There was no difference between their mean heart rates. The mean LV systolic pressure in the patients with aortic regurgitation was greater than that in the normal patients \((p<0.05)\). In the patients with mitral regurgitation, it was less than that in the patients with aortic regurgitation \((p<0.05)\). Moreover, the mean LV end-diastolic pressure in the patients with aortic regurgitation was higher than that in the normal patients \((p<0.05)\). In contrast, the mean (+)dP/dt\text{max} values did not differ significantly between the four patient groups. The mean LVEDV and LV end-systolic volumes (ESV) in the patients with aortic and mitral regurgitation were larger than those in the normal patients \((p<0.05\) for all comparisons), and the mean LVEDV in the patients with cardiomyopathy was less than that in the patients with aortic regurgitation \((p<0.05)\). In the patients with aortic regurgitation, the mean ejection fraction was less than that in the normal patients \((p<0.05)\); in the patients with cardiomyopathy, it was less than that in the normal patients and patients with aortic and mitral regurgitation \((p<0.05\) for all comparisons).

LV Chamber Elastance

In each patient, there was a progressive increase in the time-varying elastance throughout systole until \( E_{\text{max}} \) was reached.16 The correlation coefficients for \( E_{\text{max}} \) ranged from 0.84 to 1.00 with a mean of 0.97 \pm 0.03. The individual \( E_{\text{max}} \) values ranged from 0.18 to 7.46 mm Hg/ml. The mean \( E_{\text{max}} \) for each patient group is shown in Table 2. The mean \( E_{\text{max}} \) for the patients with aortic and mitral regurgitation and cardiomyopathy were all less than those in the normal patients \((p<0.05\) for all comparisons). Moreover, the mean \( E_{\text{max}} \) values for the normal patients and all patients with cardiac pathologies of 5.01 \pm 1.52 and 1.89 \pm 1.41 mm Hg/ml, respectively, differed \((p<0.001)\). In contrast, the extrapolated volume-axis intercepts \((V_0)\) in the normal patients and all patients with cardiac pathologies of 22 \pm 18 and 40 \pm 82, respectively, did not differ because of the wide range of values, primarily in the latter group of patients. Only one of the 25 normal patients and eight of the 41 patients with cardiac pathology had negative \( V_0 \) values.

Relation Between \( E_{\text{max}} \) and Body and Heart Size

From previous studies in animals and humans, a relation between \( E_{\text{max}} \) or \( E_{cs} \) and body or LV weight,8 EDV,7,14 or LV mass14 has been shown. With a univariate analysis in the normal patients, \( E_{\text{max}} \) correlated with radionuclide LVEDV and body surface
Table 1. Baseline Hemodynamic Data in Normal Patients

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n=25 patients.

HR, heart rate; LVP, left ventricular pressure; LVEDP, left ventricular end-diastolic pressure; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; E_{max}, time-varying elastance; V_{0}, volume-axis intercept.

**Standardization of E_{max}**

Because of the large range of radionuclide LVEDV values in the normal patients and patients with LV volume overload and cardiomyopathy, a curvilinear relation existed between E_{max} and LVEDV in the total population (Figure 1). To compensate for this curvilinear relation, these data were transformed to the base e to convert this curvilinear relation to a log linear relation of lnE_{max} versus lnEDV. Two distinct linear relations were specified, one for the normal patients and another for the patients with cardiac pathology (Figure 2). For the normal patients, it was lnE_{max} = -0.60(lnEDV) + 4.34 (r = -0.67, p < 0.001); and for the patients with cardiac pathology, it was lnE_{max} = -1.06(lnEDV) + 6.12

Table 2. Baseline Hemodynamic Data

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*p<0.05 vs. Normal, †p<0.05 vs. AR, ‡p<0.05 vs. MR.

HR, heart rate; LVP, left ventricular pressure; LVEDP, left ventricular end-diastolic pressure; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; E_{max}, time-varying elastance; V_{0}, volume-axis intercept; AR, patients with aortic regurgitation (n=20); MR, patients with mitral regurgitation (n=14); CM, patients with hypertrophic or dilated cardiomyopathy (n=7).
(r = -0.73, p < 0.001). A Z test for parallelism established that the slopes of the relation between lnE\text{max} and lnEDV differed in these two patient groups (p < 0.01). The mean lnE\text{max} for the normal patients was 1.56 ± 0.33.

To eliminate the specific influence of heart size, as measured by radionuclide LVEDV, on these two relations, a mathematical method was used to standardize the individual lnE\text{max} values as described in “Methods.” Consequently, standardized lnE\text{max} values were obtained by adding to the mean lnE\text{max} the deviation of the measured lnE\text{max} from the predicted lnE\text{max} in each patient, where the predicted lnE\text{max} = -0.60(lnEDV) + 4.34, which is specified by the relation between lnE\text{max} and lnEDV in the normal patients. This process removes the variation in lnE\text{max} that can be attributed to the variation in lnEDV.

As shown in Figure 3, after this mathematical standardization, the normal patients had a standardized lnE\text{max} versus lnEDV slope of zero and a mean lnE\text{max} of 1.56 ± 0.24, implying that all normal patients had preserved LV chamber elastance, which fell within 2 SD of 1.56, regardless of their LVEDV. The slope of the regression line shifted upward from −1.06 to −0.46 in the patients with cardiac pathology. Nevertheless, it remained negative and continued to differ from the zero slope obtained in the normal patients (p < 0.001). This suggests that residual factors existed in determining the individual...
ln$E_{\text{max}}$ values after the influence of heart size was removed in the patients with cardiac pathology.

**Dichotomization of LV Chamber Elastance**

To determine whether standardization of ln$E_{\text{max}}$ for heart size altered the identification of patients with cardiac pathology, who had depressed LV chamber elastance, we dichotomized these patients based on the ln$E_{\text{max}}$ values obtained in the normal patient group. Depressed LV chamber elastance was defined as an ln$E_{\text{max}}$ that was 2 SD below the mean ln$E_{\text{max}}$ in the normal patients, whereas preserved LV chamber elastance was defined as an ln$E_{\text{max}}$ that remained within 2 SD of the mean ln$E_{\text{max}}$ in the normal patients. Consequently, for ln$E_{\text{max}}$ depressed LV chamber elastance was specified by an ln$E_{\text{max}}$ that fell below $1.56 - 2 \cdot 0.33$, or an ln$E_{\text{max}}$ of less than 0.90; for standardized ln$E_{\text{max}}$, depressed LV chamber elastance was defined by a standardized ln$E_{\text{max}}$ that fell below $1.56 - 2 \cdot 0.23$, or a standardized ln$E_{\text{max}}$ of less than 1.08. Separation of individual patients with preserved and depressed LV chamber elastance by either the measured or standardized ln$E_{\text{max}}$ yielded highly concordant data ($k=0.73$, $p<0.001$, Figure 4). Only four patients moved from depressed to preserved and one patient from preserved to depressed LV chamber elastance after standardization of ln$E_{\text{max}}$, suggesting that the measured ln$E_{\text{max}}$ and standardized ln$E_{\text{max}}$ values have similar discriminatory power for identifying individual patients with cardiac pathology who have depressed LV systolic performance.

The dichotomization of patients with aortic regurgitation, mitral regurgitation, or cardiomyopathy into those with and without depressed LV systolic performance by the use of $E_{\text{max}}$ (<1.97 mm Hg/ml), radionuclide LVESV (>82 ml) and ejection fraction (<45%), and (+)dP/dt$\text{max}$ (<1,000 mm Hg/sec) demonstrated, in general, the ability of $E_{\text{max}}$ to identify a greater number of patients with abnormal LV systolic performance than these other more commonly used indexes of LV systolic performance (Figure 5). In patients with aortic regurgitation, 50%, 55%, 25%, and 10% ($p<0.05$ vs. $E_{\text{max}}$ and ESV) were abnormal; in patients with mitral regurgitation, 64%, 50%, 14% ($p<0.05$ vs. $E_{\text{max}}$), and 14% ($p<0.05$ vs. $E_{\text{max}}$) were abnormal; and in patients with cardiomyopathy, 71%, 28%, 43%, and 43% were abnormal. Only in patients with aortic regurgitation were the $E_{\text{max}}$ and radionuclide LVESV as frequently abnormal. In contrast, in patients with mitral regurgitation or cardiomyopathy, $E_{\text{max}}$ was more commonly abnormal than radionuclide LVESV. The $E_{\text{max}}$ values were more frequently abnormal in all patient groups than were the radionuclide LV ejection fraction or (+)dP/dt$\text{max}$ values.

**Figure 3. Graph showing relation between standardized $E_{\text{max}}$ and EDV. ln$E_{\text{max}}$ values were standardized for the variation in lnEDV. As a result, the slope relating the standardized ln$E_{\text{max}}$ to lnEDV was zero in the normal patients, suggesting that these patients all had normal left ventricular chamber elastance, irrespective of their heart size; whereas in the patients with cardiac pathology, it remained negative and different from that in the normal patients ($p<0.001$). This suggests that additional factors provided a significant contribution to the reduction in the standardized ln$E_{\text{max}}$ in the patients with cardiac pathology. $E_{\text{max}}$, time-varying elastance; EDV, end-diastolic volume.**

**Figure 4. Scheme depicting dichotomization of patients with cardiac pathology into those with preserved or depressed left ventricular chamber elastance with measured ln$E_{\text{max}}$ or standardized ln$E_{\text{max}}$ is shown. There is a high degree of concordance, with only four patients changing from depressed to preserved and one patient from preserved to depressed left ventricular chamber elastance after standardization of ln$E_{\text{max}}$. $E_{\text{max}}$, time-varying elastance.**
Abnormal LV Performance

Percentage of Depression in the
\( E_{\text{max}} \) Slope Due to Heart Size

To further elucidate the relative contribution of LVEDV to a depressed \( E_{\text{max}} \), we estimated the percentage of decrease in \( \ln E_{\text{max}} \) and standardized \( \ln E_{\text{max}} \) that could be attributed to heart size. The inverse of the natural logarithm was used to assure that no negative values were involved in the calculation. For all patients with cardiac pathology and an \( \ln E_{\text{max}} \) of less than 0.90, the percentage of depression was equal to \( (e^{1.56} - e^{\ln E_{\text{max}}})/e^{1.56} \), for all patients with cardiac pathology and a standardized \( \ln E_{\text{max}} \) of less than 1.08, the percentage of depression was equal to \( (e^{1.56} - e^{\ln E_{\text{max}}})/e^{1.56} \). Thus, the percentage of depression in \( \ln E_{\text{max}} \) due to LVEDV was the percentage depression of \( \ln E_{\text{max}} \) in these patients from the mean \( \ln E_{\text{max}} \) of 1.56 in the normal patients minus the percentage depression of the standardized \( \ln E_{\text{max}} \) from the same mean. This analysis revealed that only 14 ± 7% of the depression in \( E_{\text{max}} \) in the patients with cardiac pathology and depressed LV chamber elastance could be attributed to heart size.

Discussion

In physiological terms, it has been accepted that some kind of standardization for body or heart size is necessary to compare time-varying elastance determinations from mammalian species of markedly different sizes, such as rat with dog, dog with human, and human with whale, and within the same species, such as child with adult. This is because LV pressure is relatively invariable compared with LV size and stroke volume. In contrast, whether standardization of the maximum time-varying elastance (\( E_{\text{max}} \)) is necessary in adult cardiology to discriminate between preserved and depressed LV systolic performance in adult patients with cardiac pathology compared with normal adult patients is not known. Furthermore, an understanding of the specific purpose for standardizing \( E_{\text{max}} \) is an important prerequisite. If a measure of only net LV systolic performance is desired, then \( E_{\text{max}} \) does not need to be standardized; but if knowledge of whether LV systolic performance is adequate for a given heart or body size is desired, then standardization of \( E_{\text{max}} \) for heart or body size must be considered.

The data from the present investigation address this latter issue in adult patients with and without cardiac pathology. They indicate that \( E_{\text{max}} \) calculated with radionuclide angiography has an independent relation with LVEDV in normal patients. A transformation of the \( E_{\text{max}} \) and LVEDV data to the base e made this relation linear and provided two distinctly different relations: one for the normal patients and another for the patients with cardiac pathology, which differed significantly. After a mathematical standardization, which removed the variation in \( \ln E_{\text{max}} \) that could be accounted for by the variation in \( \ln \text{EDV} \), the relation between the standardized \( \ln E_{\text{max}} \) and heart size in the two patient groups continued to differ significantly. The dichotomization of individual patients with cardiac pathology into those with preserved and depressed LV chamber elastance by use of either the measured \( \ln E_{\text{max}} \) or standardized \( \ln E_{\text{max}} \) yielded highly concordant results. Furthermore, only 14% of the total decrease in \( \ln E_{\text{max}} \) in the patients with cardiac pathology and depressed LV chamber elastance could be attributed to heart size. Moreover, irrespective of whether \( E_{\text{max}} \) was standardized or not, it, in general, identified a greater proportion of patients with abnormal LV systolic performance in the three patient groups with cardiac pathology than did more commonly used indexes of LV systolic performance.

The time-varying elastance concept described by Sagawa et al1 and Sagawa,2,3 in the excised and
supported LV, has been shown in animals\textsuperscript{4-6,9} and humans\textsuperscript{10,11,28} to be a useful index for assessing changes in LV contractility. The time-varying elastance is described by a slope ($E_{es}$), a volume-axis intercept ($V_0$), and a time ($T_{max}$). Also, $E_{max}$ is relatively independent of preload and afterload,\textsuperscript{3} which makes it an especially attractive index of LV systolic performance compared with isovolumic and ejection phase indexes, which are variably affected by LV loading conditions.\textsuperscript{28-31} Although changes in $E_{max}$ within a given subject may reflect changes in LV contractility,\textsuperscript{10,11,28,31} the use of $E_{max}$ to identify depressed LV systolic performance in individual patients may be difficult, because heart size may introduce considerable overlap in the individual $E_{max}$ values.\textsuperscript{3,8}

Initial studies in humans attempted to index $E_{es}$ to body surface area,\textsuperscript{10,11} but the validity of such an approach has been questioned,\textsuperscript{3} and better relations between $E_{max}$ and $E_{es}$ and LV mass and LVEDV have been reported in normal patients.\textsuperscript{14} Consequently, other methods of standardizing $E_{max}$ and $E_{es}$ have been suggested. Belcher et al.\textsuperscript{8} demonstrated that $E_{es}$ was related to body and LV weights and that $E_{es}$ could be better standardized by regression equation adjustment than by indexing. They demonstrated that a regression equation adjustment provided a better fit of these data and a reduction in the variance of the slopes, irrespective of LV contractility. Subsequently, Berko et al.\textsuperscript{17} demonstrated that an inverse relation existed between $E_{es}$ and LVEDV in animals under control conditions and after the production of acute mitral regurgitation. Moreover, although the LVEDV and ejection phase indexes increased after the creation of acute mitral regurgitation, $E_{es}$ declined significantly. When $E_{es}$ was mathematically standardized for the change in heart size, the mean standardized $E_{es}$ obtained after acute mitral regurgitation was similar to that obtained under control conditions. These data suggest that when comparisons are made before and after an intervention, which concomitantly alters heart size significantly, a standardization of this index of LV systolic performance should be performed to allow appropriate conclusions to be drawn regarding alterations in LV contractility.

Whether a similar correction is necessary to dichotomize individual patients with variable LV sizes and cardiac pathology into those with preserved and depressed LV systolic performance has not been clearly delineated. In prior studies\textsuperscript{22,23} and the present investigation, different approaches have been tried for standardizing $E_{max}$ and $E_{es}$ in patients with and without cardiac pathology. Originally, Suga et al.\textsuperscript{22} established, in the excised supported LV, that a relation existed between $E_{es}$ and the extrapolated volume-axis intercept, $V_d$, but not myocardial mass volume. They proposed that the simple product of $E_{es}$ and $V_d$ might be a reasonable first approach to standardizing this index of LV contractility. Subsequently, Mirsky et al.\textsuperscript{23} attempted to standardize $E_{es}$ derived from the stress-strain relations of a single beat by multiplying $E_{es}$ by either $V_0$ or LV mass volume. When they standardized $E_{max}$ using $V_0$ or LV mass, the derived parameters were found to vary between patient groups. In contrast, only four patients had a change from depressed to preserved and one patient from preserved to depressed LV chamber elastance when measured ln$E_{max}$ values were compared with the standardized ln$E_{max}$ values in the present investigation. Our data suggest that, in adult cardiology, alterations in LV systolic performance relative to heart size can be detected with the measured $E_{max}$ because the effect of heart size on $E_{max}$ in patients with cardiac pathology is small.

There may be several possible explanations for these divergent observations. First, after an examination of the data reported by Grossman et al.\textsuperscript{10} Suga et al.\textsuperscript{22} noted that negative $V_0$ values were common in humans, which would make the multiplication of $E_{es}$ by these $V_0$ values uninterpretable. The potential also existed in patients with large $V_0$ and low $E_{es}$ values that a simple multiplication might normalize this index in patients who clearly had depressed LV systolic performance. Moreover, if this approach is to be used, it requires that the $V_0$ value be accurately determined. Several investigators have questioned the validity of a simple extrapolation to the volume-axis intercept because of the estimation error that may result\textsuperscript{22} and the potential for nonlinearity of the $E_{es}$ relation.\textsuperscript{23} Finally, in an LV, which has been altered by transient ischemia or infarction, the index of $E_{es}$ multiplied by $V_0$ may not reflect the contractile state of the residual normal myocardium.\textsuperscript{22} Suga et al.\textsuperscript{22} concluded, therefore, that this simple approach to standardization was only a first approximation and that other methods may, indeed, be necessary in humans. Accordingly, a mathematical method of standardizing $E_{max}$ was used in the present investigation as a possible alternative.

The mathematical standardization of $E_{es}$ used by Berko et al.\textsuperscript{22} and of $E_{max}$ in the present investigation uses the linear relation between $E_{es}$ or $E_{max}$ and a measure of heart size to correct these slopes for the variation that can be attributed to heart size in the normal animal or human heart. This procedure corrects only the slopes and, therefore, does not depend on an extrapolation to obtain $V_0$. In the present investigation, $E_{max}$ was principally related to LVEDV, and, thus, this measure of heart size was used in the mathematical standardization. When the $E_{max}$ values were standardized, no significant change occurred in the determination of whether preserved or depressed LV chamber performance was present in an individual patient with cardiac pathology. Moreover, heart size, as measured by LVEDV, contributed only 14% to the reduction in $E_{max}$ in the patients with cardiac pathology and depressed LV chamber elastance. The reduction in $E_{es}$ reported after the production of acute mitral regurgitation in the animals studied by Berko et al.\textsuperscript{17} was approximately 20%, which is similar to that for $E_{max}$ in the patients with chronic valvular or cardiomyopathic heart disease in the present
The rightward shift in the $E_{\text{max}}$ relation reported by Berko et al.\textsuperscript{7} may have been a result of ventricular dilatation and remodeling and not necessarily a change in LV contractility, because the standardized $E_{\text{max}}$ values were unchanged after the creation of acute mitral regurgitation. In our patients with cardiac pathology, the effects of chronic LV volume overload and cardiomyopathy may have overwhelmed these processes by producing significant depression in LV systolic performance. Consequently, in adult patients with chronic disease processes, which affect LV size and contractility, the effect of these pathophysiological processes on LV chamber elastance is substantially greater than that of heart size.

The radionuclide approach used in this investigation to calculate LV volumes and chamber elastance requires discussion. Although several methods for calculating radionuclide LV volumes have been proposed, an attenuation correction technique like that used in this investigation has been reported to provide the most accurate determination of LV volumes.\textsuperscript{21,34,35} The radionuclide LV volume technique used in this investigation has provided LVEDV and LVESV that have correlated highly with those obtained with biplane contrast cineangiography.\textsuperscript{20,21} Moreover, it has produced comparable mean LV volumes on a frame-by-frame basis throughout the cardiac cycle to those obtained with biplane contrast cineangiography under control conditions and after alterations in LV loading conditions produced by methoxamine or nitroprusside.\textsuperscript{16} These data also show that despite the time-averaged nature and the reduced spatial and temporal resolution of radionuclide angiography compared with biplane contrast cineangiography that comparable calculations of LV chamber elastance can be obtained.\textsuperscript{16} Thus, because the radionuclide approach does not alter LV hemodynamics, volumes, or contractility during data acquisition and because multiple acquisitions can be performed, it represents a reasonable technique for obtaining multiple pressure-volume data points to calculate LV chamber elastance in humans.

We used M-mode echocardiographic determinations of LV mass to establish the optimal measure to be used in the mathematical standardization process. We used American Society of Echocardiography criteria to measure LV dimensions and wall thicknesses in our patients, which may not be the optimal approach for calculating LV mass.\textsuperscript{19} The biplane contrast cineangiographic calculations of LV mass used in this investigation have been previously reported to be nearly identical over a wide range of mass values to those determined at necropsy in the nonhuman primate.\textsuperscript{36} We compared our American Society of Echocardiography and University of Pennsylvania (PENN) convention\textsuperscript{19} calculations of LV mass to these cineangiographic LV masses in patients with a wide range of LV mass calculations and found comparable correlation coefficients and similar standard errors. Despite comparable slopes in the regression equations, the $y$ axis intercepts differed. Consequently, at least in this laboratory, we assumed that an appropriate correction of either the American Society of Echocardiography or PENN convention LV mass calculations would be satisfactory for the purposes of this investigation.

We also assumed that the LV chamber elastance slopes were linear. This assumption is consistent with previous observations in animals\textsuperscript{1–6,9} and humans.\textsuperscript{10–15} Nevertheless, there is data to suggest that end-systolic pressure-volume relations may have a saturation effect in that they may plateau at high arterial pressures,\textsuperscript{37,38} they may become curvilinear toward the volume-axis intercept below a critical coronary perfusion pressure,\textsuperscript{39} or they may demonstrate contractile-dependent curvilinearity.\textsuperscript{40,41} In this investigation, we did not lower arterial pressure below that reported by Sunagawa et al.\textsuperscript{39} to cause curvilinearity toward the volume-axis intercept. Saturation and contractile-dependent curvilinearity have not been demonstrated to occur in humans, probably because of insufficient data points. Without a greater number of data points to establish under what circumstances curvilinearity may exist in humans, it is probably reasonable, at least within the contractile ranges observed in this investigation, to assume that within the operational pressure-volume range of these LVs that the $E_{\text{max}}$ relation is linear.\textsuperscript{10–15,42}

Finally, we altered LV loading conditions by steady-state infusions of methoxamine or nitroprusside with intact autonomic reflexes. To eliminate the effects of reflex changes in heart rate on LV contractility, we used right atrial pacing throughout the protocol in each patient. Although we cannot completely exclude the possibility of reflex changes in LV contractility, previous data from this laboratory would suggest that, although modest changes in catecholamines may occur, there is no significant effect on LV contractility as measured with isovolumic indexes.\textsuperscript{43} This is consistent with animal data, which suggest that greater changes in catecholamines are necessary to produce an effect on LV contractility.\textsuperscript{44,45} Thus, within the modest range of loading conditions used in this investigation to calculate LV chamber elastance, there was probably little effect on basal LV contractility.

We conclude from these data that LV chamber elastance calculated with radionuclide angiography may not require standardization for heart size to establish whether LV systolic performance is preserved or depressed in an individual adult patient with LV volume overload or cardiomyopathy compared with normal adult patients. Presumably, this is because these pathological processes have a far more substantial effect on LV systolic performance than heart size, because only 14% of the reduction in $E_{\text{max}}$ in the patients with cardiac pathology and depressed LV chamber elastance in this investigation could be attributed to heart size. It would, however, appear that standardization will be necessary to determine whether an intervention significantly affects $E_{\text{max}}$ or
E_{es}, particularly when the intervention also has a significant effect on heart size. Moreover, it should not be concluded from the data in this investigation that a standardization of LV chamber elastance is not required to compare LV systolic performance between species.

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Is standardization of left ventricular chamber elastance necessary?
H H Hsia and M R Starling

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