Assessment of the end-systolic pressure-volume relationship in human beings with the use of a time-varying elastance model

RAYMOND G. MCKAY, M.D., JULIAN M. AROESTY, M.D., GARY V. HELLER, M.D., PH.D., HENRY D. ROYAL, M.D., SANFORD E. WARREN, M.D., AND WILLIAM GROSSMAN, M.D.

ABSTRACT The analysis of left ventricular end-systolic pressure-volume relationships in human beings has been hindered by the lack of a practical method of serial volume assessment and by an imprecise definition of end-systole. Modifications of the end-systolic relationship that have been used to circumvent these problems have included the use of single-point end-systolic pressure-volume ratios, the use of peak systolic pressure/minimum ventricular volume points for end-systolic points, and the use of end-ejection as a marker for end-systole. To assess the correlation between the parameters generated by these modifications with the slope (E$_{max}$) and volume intercept (V$_o$) of the end-systolic line as defined by Sagawa’s model of time-varying elastance, simultaneous measurement of left ventricular pressure and gated radionuclide volume was made in 26 patients under various loading conditions and pressure-volume diagrams were constructed for each loading condition from 32 simultaneous pressure-volume coordinates. Two pressure-volume diagrams were recorded in 14 patients and three pressure-volume diagrams were recorded in 12 patients. E$_{max}$ and V$_o$ were determined in all patients from the slope and volume intercept of the isochronous pressure-volume line with the maximum time-varying elastance as described by Sagawa’s model and were designated true E$_{max}$ and true V$_o$, respectively. True E$_{max}$ was subsequently correlated with three estimates of E$_{max}$ computed from a single-point end-systolic ratio (r = .76, SEE = 1.53, p < .001), from peak systolic pressure/minimum systolic volume points (r = .87, SEE = 0.67, p < .001), and from end-ejection pressure-volume points marked by peak negative dP/dt (r = .91, SEE = 0.57, p < .001). It is concluded that the parameters E$_{max}$ and V$_o$ of a time-varying elastance model of the end-systolic pressure-volume relationship can be constructed for man with the use of simultaneous left ventricular pressure measurements and gated radionuclide ventriculography, and that true E$_{max}$ calculated by this method is reasonably approximated by single-point pressure-volume ratios and peak systolic and end-ejection measurements.


CONSIDERABLE EVIDENCE from both animal and human studies has suggested that the end-systolic pressure-volume relationship is linear over a physiologic range of loading conditions and is a sensitive indicator of left ventricular contractile function.$^{1,3}$ As originally described,.$^{1,2}$ this relationship may be derived from a model of time-varying elastance, as described by the equation

\[ E(t) = P(t) / (V(t) - V_o(t)) \]

where E = elastance; t = time; P = instantaneous pressure; V = instantaneous volume; V$_o$ = volume intercept of the end-systolic line. According to this model, the slope of the regression line connecting isochronous pressure-volume coordinates from multiple pressure-volume loops over a range of loading conditions is represented by E or elastance, and increases progressively throughout isovolumetric contraction and left ventricular ejection, and then subsequently decreases during isovolumetric relaxation. The maximum elastance that is achieved, E$_{max}$, represents the slope of the end-systolic line, and has been shown to correlate well with measures of basal contractility and to be sensitive to inotropic modulation.

In spite of the theoretical appeal of end-systolic contractile indexes, this approach to the analysis of myo-
cardiac function in humans has been hindered by two basic impediments. First, by definition, to measure the $E_{max}$ and $V_o$ of the end-systolic pressure-volume relationship, it is necessary to obtain pressure-volume data in a given subject under multiple left ventricular loading conditions while maintaining constant contractility. However, the serial assessment of pressure-volume relationships under changing loading conditions with standard techniques of volume measurement is difficult. As a result, several investigators have attempted to obviate load alteration by using only a single end-systolic pressure-volume point from a given patient to estimate $E_{max}$.\(^5\)–\(^12\)

A second major difficulty has been the precise identification of end-systole. Sagawa has defined end-systole as the point at which the active contractile process has reached a maximum and has identified this point as the time of maximum elastance. However, many clinical investigators have substituted end-ejection for end-systole and used either the aortic pressure dicrotic notch or peak negative dP/dt to determine end-systolic pressure-volume data points.\(^5\)–\(^7\),\(^13\) Still other investigators have assumed no significant difference between peak and end-systolic pressure and have substituted peak-systolic pressure/minimum ventricular volume for end-systolic pressure-volume plots.\(^14\),\(^15\)

Although there have been multiple reports on the practical utility of the contractile indexes derived from modifications of the end-systolic pressure-volume relationship,\(^4\)–\(^7\) there has been no study examining the relationship of these indexes and true $E_{max}$ as defined by the Sagawa time-varying elastance model. Accordingly, the purpose of the present study was to analyze the end-systolic pressure-volume relationship in patients according to a time-varying elastance model with the use of a recently developed approach to ventricular pressure-volume analysis,\(^16\),\(^17\) and to examine the relationship between true $E_{max}$ generated from this model and contractile indexes derived from the use of single-point end-systolic pressure-volume ratios and peak-systolic and end-ejection models.

Methods

Study group. End-systolic pressure-volume relationships were assessed in 26 patients from data collected at the time of cardiac catheterization. The study group consisted of 17 men and nine women with a mean age of 60 years. All patients were referred for evaluation of chest pain, and were being treated with a combination of long-acting nitrates (18/26), $\beta$-blockers (21/26), and/or calcium blockers (10/26). At the time of the study none of the patients had evidence of acute myocardial infarction, unstable angina pectoris, uncompensated congestive heart failure, ventricular ectopy, valvular pathologies, or cardiomyopathy. After approval of the research study by the Beth Israel Committee on Human Research, each patient gave informed consent after being informed of the nature, purpose, and potential risks involved. There were no complications as a result of this study.

Cardiac catheterization and coronary angiography. Right heart catheterization was performed on all patients with a flow-directed Swan-Ganz thermodilution catheter that was inserted percutaneously into the right femoral vein and advanced to the pulmonary artery. Coronary angiography was performed in all patients by a standard technique. Left ventriculography was performed via a pigtail catheter with simultaneous biplane cine recordings in the right and left anterior oblique projections. After routine catheterization, the left ventricular and thermodilution catheters were left in place and radionuclide studies were subsequently performed.

Left ventricular pressures were measured with a fluid-filled catheter in 16 patients and with a high-fidelity micromanometer Millar catheter in 10 patients. Pressures in fluid-filled catheters were measured with a P-50 Micron pressure transducer attached directly to a manifold that was connected to the proximal hub of the intracardiac catheter without intervening tubing. This system has excellent frequency response (flat $\pm 5\%$ to $> 20$ Hz) and has been described previously in a report from our laboratory.\(^20\) Recordings were inscribed with a Honeywell-Electronics for Medicine recorder (VR-12).

Gated blood pool scintigraphy

Acquisition. As in our previous study,\(^19\) after routine catheterization, a gated radionuclide ventriculogram was obtained at baseline and after pharmacologic manipulation to change left ventricular loading conditions (see below). Acquisition of radionuclide studies was begun approximately 30 min after the contrast ventriculographic examination. In all patients, heart rate, left ventricular pressure, and pulmonary capillary wedge pressure had returned to their precontrast levels. Each patient was injected with 0.75 GBq (20 mCi) of $^{99m}$Tc-labeled autologous red blood cells. Labeling was by a technique in vitro.\(^21\)

All radionuclide studies were acquired with the patients in the supine position and with use of a mobile Anger camera computer system (Technicare 410 with on board VIP computer system). Each gated cardiac blood pool study was obtained with a 30 degree slant-hole collimator to obtain cephalic angulation in the modified left anterior oblique (mLAO) view. The degree of obliquity was between 35 and 45 degrees and was individualized in each patient to best visualize the septum. Neither the patient nor the camera were moved between studies in the multiplex-study protocol.

The gated cardiac blood scans were obtained with use of a $64 \times 64$ matrix for the full field of view (200 cm). Thirty-two frames per RR interval were acquired. Minimum acquisition time was 3 min, although most studies were acquired over 5 min. The time of each gated study was recorded and a blood sample was obtained at the midpoint of each study.

Analysis. For each mLAO scan that was obtained, a left ventricular count rate (volume) vs time curve was obtained with an operator-drawn, fixed left ventricular region of interest and computer-generated background regions of interest. Background was assumed to be constant both spatially and temporally. The operator used the end-diastolic image to identify the septal border of the ventricle and the stroke volume image to identify the atrioventricular and free wall borders of the heart. In patients with severe left ventricular dysfunction, the end-diastolic image was used to confirm the boundaries of the free wall of the ventricle.

Since multiple left ventricular volume-time curves were obtained in each patient, the relative change in end-diastolic volume between studies was determined by correcting the end-diastolic counts in each curve for acquisition time, physical decay, and biological clearance. Acquisition time for each end-
diastolic frame was calculated by multiplying the frame duration (RR interval/number of frames) by the number of cardiac cycles collected. Loss of counts due to physical decay was calculated by checking the time at which each study was acquired. Biological clearance of the tracer was calculated by measuring, in a well counter, the changes in the counts in a 100 μl sample of blood obtained at the midpoint of each study.

A square wave that indicated the time at which the gamma camera’s computer system detected the patient’s R wave on an electrocardiogram was output to the Electronics for Medicine recorder to synchronize the radionuclide volumes with the left ventricular pressure tracings (see below).

Changes in left ventricular loading conditions. In all patients, changes in left ventricular loading conditions were effected by pharmacologic intervention. All patients were either on β-blockers or pretreated with 1 mg of intravenous atropine to avoid changes in heart rate with preload and/or afterload manipulation. Before any change in loading conditions, a mLAO scan was obtained in each patient with simultaneous recording of left ventricular pressure at a rapid paper speed midway through the scan. Subsequently, 18 patients received intravenous nitroglycerin, five received intravenous nitropressure, and three received intravenous phenylephrine. Nitroglycerin was begun at 25 μg/min, nitropressure was begun at 3 μg/min, and phenylephrine was begun at 10 μg/min. Increasing doses of the medications were administered until an approximate 20 mm Hg decrease in systolic blood pressure had been achieved with nitroglycerin or nitropressure, or a similar increase in systolic blood pressure had been achieved with phenylephrine. When a steady state had been achieved, a repeat mLAO scan was obtained with repeat measurement of left ventricular pressure.

A further change in loading conditions was effected in four patients receiving nitroglycerin, seven receiving nitropressure, and one patient receiving phenylephrine with increases in doses of these medications to achieve an additional 20 mm Hg decrease in systolic blood pressure with nitroglycerin or nitropressure, and an additional 20 mm Hg increase in blood pressure with phenylephrine. When a steady state had again been achieved, an mLAO scan and left ventricular pressure were again obtained.

Generation of pressure-volume diagrams. Pressure-volume diagrams were constructed for each patient by the method illustrated in figure 1 at baseline and after changes in left ventricular loading conditions. First, the time-activity curve obtained from each mLAO scan was digitized by a Tektronix 4956 computer into 32 volume points. Second, at least six left ventricular pressures tracings obtained midway through the mLAO scan were digitized and averaged into 32 pressure points. Finally, the time-activity volume points and the average left ventricular pressure points were synchronized to end-diastolic and pressure-volume diagrams were then plotted from 32 simultaneous pressure-volume coordinates throughout the cardiac cycle. Absolute volumes were assigned to each patient’s baseline pressure-volume diagrams by assigning the angiographically determined end-diastolic volume to the loop. Absolute volumes for subsequent pressure-volume diagrams were determined on the basis of relative changes in end-diastolic counts and radionuclide ejection fraction.

Two pressure-volume diagrams were obtained from 14 patients who were examined under two different loading conditions, and three diagrams were constructed for 12 patients who were examined under three different loading conditions.

Calculation of $E_{\text{max}}$ and $V_O$ according to time-varying elastance. Pressure-volume loops for all patients were analyzed according to the time-varying elastance model illustrated in figure 2. For each patient, linear regression was applied for isochronic (every 60 msec) pressure-volume coordinates over the range of loading conditions that were recorded. A slope and volume intercept were subsequently recorded for each isochronic pressure-volume line. The maximum slope that was recorded was designated as $E_{\text{max}}$ of the end-systolic line, with the volume intercept of that line being defined as $V_O$. $E_{\text{max}}$ and $V_O$ defined

**FIGURE 1.** Method used for construction of pressure-volume diagrams. The left ventricular time-activity curve from an mLAO scan is digitized into 32 volume points. Next, six left ventricular pressure tracings taken at the midpoint of the radionuclide scan are averaged and digitized by computer into 32 pressure points. Finally, pressure-volume loops are plotted from 32 pressure-volume coordinates throughout the cardiac cycle.
by this method were subsequently called true $E_{\text{max}}$ and true $V_0$, respectively.

**Calculation of contractile indexes from modifications of the end-systolic relationship.** For each patient, a single end-systolic pressure-volume point was obtained from the initial radionuclide pressure-volume diagram before any change was induced in loading by identifying the point at which the ratio of left ventricular pressure/volume reached a maximum and the subsequent ratio was called $E_{\text{max}}$—single point. By definition, the volume intercept calculated with this modification is considered to be zero.

In all patients, estimates of $E_{\text{max}}$ and $V_0$ were also calculated from the left ventricular peak systolic pressure/minimum ventricular volume ratio from each pressure-volume diagram. Coordinates were fitted to a straight line and the slope of this line was called $E_{\text{max}}$—peak systole and its volume intercept was called $V_0$—peak systole.

For 10 patients in whom left ventricular pressure was measured with a high-fidelity micromanometer Millar catheter, estimates of $E_{\text{max}}$ and $V_0$ were calculated from end-ejection determinants of end-systole by fitting left ventricular pressure-volume coordinates occurring at peak negative dP/dt to a straight line. The slope and volume intercept of the end-systolic line calculated by this method were termed $E_{\text{max}}$—end-ejection and $V_0$—end-ejection, respectively.

**Statistics.** Left ventricular end-diastolic and end-systolic volumes were determined from each patient’s contrast ventriculogram with use of the Wayne modification of the formula of Dodge and Sandler for single-plane angiography.

All correlations between true $E_{\text{max}}$ and true $V_0$ with contractile indexes derived from modifications of the end-systolic relationship were performed by linear regression analysis. Radionuclide scans were analyzed by two observers without knowledge of ventricular function or change in loading conditions and volume measurements were averaged. Interobserver and intraobserver variability both yielded a r value of .96.

**Results**

Left ventriculography and coronary angiography. Of the 26 patients that were studied, five patients had normal coronary arteries and the remaining 21 had significant coronary artery disease (five had one-vessel disease, two had two-vessel disease, and nine had three-vessel disease). Eleven patients had evidence of prior myocardial infarction. Left ventricular ejection fraction ranged between 21% and 88%. No patient had any valvular abnormality. Angiographic data and clinical characteristics are recorded in table 1.

The calculation of end-systolic contractile indexes according to the time-varying elastance model. In all patients, isochronic pressure-volume lines increased in slope throughout isovolumetric contraction and the left ventricular ejection period to a maximum value and then decreased during isovolumetric relaxation. Figure 2 illustrates three pressure-volume diagrams, in which true $E_{\text{max}}$ is designated as the maximum slope that is achieved, from a representative patient.

Notably, as originally described by Sagawa, the volume intercepts of the isochronic pressure-volume lines should have a constant volume intercept after approximately 0.08 sec into systole. As shown in figure 2, we found considerable variation in the volume intercepts of isochronic lines; a similar variation was found in all patients.

**Correlation of true $E_{\text{max}}$ with modifications of the end-systolic relationship.** True $E_{\text{max}}$ correlated with $E_{\text{max}}$—single point with an r = .76 ($y = 1.47x - 1.31$, SEE = 1.53, p < .001), with $E_{\text{max}}$—peak systole with an r = .87, ($y = 0.89x - 0.05$, SEE = 0.67, p < .001), and with $E_{\text{max}}$—end-ejection with an r = .91 ($y = 1.43x - 0.62$, SEE = 0.57, p < .001). These correlations are diagrammed in figures 3 through 5.

**Correlations of true $V_0$ with modifications of the end-systolic relationship.** True $V_0$ correlated with $V_0$—peak systole with an r = .78 ($y = 1.17x - 15.1$, SEE = 42.8, p < .001) and with $V_0$—end-ejection with an r =
.98 (y = 1.59x + 4.79, SEE = 21.8, p < .001).

Relationship between E_max and left ventricular ejection fraction. True E_max, E_max—single point, and E_max—peak systole all correlated significantly with left ventricular ejection fraction determined by contrast ventriculography (true E_max: r = .67, SEE = 1.22, p < .001; E_max—single point: r = .72, SEE = 1.65, p < .001; E_max—peak systole: r = .59, SEE = 1.19, p < .002). E_max—end-ejection did not correlate significantly with ejection fraction (r = .42, SEE = 1.46, p = NS).

Relationship between V_o and left ventricular ejection fraction. Unlike E_max, V_o generated either from Sagawa's model or any modification of the end-systolic relationship demonstrated no significant relationship to left ventricular ejection fraction. True V_o correlated with ejection fraction with an r = .16, SEE = 71.4, p = NS. V_o—peak systole correlated with ejection fraction with an r = .17, SEE = 83, p = NS. V_o—end-
ejection correlated with ejection fraction with r = .17, SEE = 131, p = NS.

Discussion
In 1981, Sagawa summarized the present state of the art for analysis of end-systolic pressure-volume relationships. In particular, he noted both the difficulty in obtaining pressure-volume data during changing loading conditions without provoking reflex changes in contractility and the difficulties in a precise definition of end-systole. He described modifications of the end-systolic relationship that various investigators had employed and wrote that “with this popularity, the original meanings of the end-systolic pressure-volume relations and its parameters have become ambiguous.”

He also questioned the meaning of the volume intercept of the end-systolic line and noted the variation in results that different investigators had reported. More-

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over, he believed that at that time there was no method that would allow for accurate and repeated measurements of ventricular volume that could be used to “close the gap of information between (canine) excised heart data and information on diseased hearts in man.”

The present study was designed to address some of the problems identified by Sagawa. In particular, this study has shown that a time-varying elastance model can be evaluated in intact man in the clinical setting and that true $E_{\text{max}}$, calculated from this model can be estimated moderately well from modifications of the end-systolic relationship that are in current use. While ejection fraction can at best be considered a crude estimate of contractile state, true $E_{\text{max}}$ shows a positive correlation with this parameter, supporting the notion that $E_{\text{max}}$ can be used as a measure of contractile function. Notably, however, our findings suggest that the volume intercept of the end-systolic relationship is not a useful measure of contractile performance.

Modifications of the end-systolic pressure-volume relationship. Sagawa has suggested that all attempts to use modifications of the end-systolic relationship be encouraged in an attempt to make end-systolic indexes more easily obtainable and perhaps develop a noninvasive method of deriving them. A number of theoretical objections need to be considered, however, concerning the modifications in current use.

In terms of single-point end-systolic ratios, perhaps the most important criticism that has been raised is that this model assumes that the volume intercept is equal to zero for all hearts. Although there has not been uniform agreement on the derivation and meaning of the volume intercept, there is at least some evidence that in chronically diseased hearts the volume intercept increases markedly. Thus, if $V_0$ is assumed to be zero for all patients and a single pressure-volume point is joined to the origin, the resultant slope value (e.g., $E_{\text{max}}$-single point) could be substantially different from the true end-systolic slope.

In terms of an end-ejection model for assessment of end-systolic relationships, Sagawa has pointed out that “the simultaneity of end-ejection and end-systole is...
purely coincidental.” For example, with respect to right ventricular pressure-volume relationships, Maughan et al.23 have noted that right ventricular ejection extends far beyond end-systole, presumably because of the relative low pulmonary vascular resistance. Other investigators have likewise shown that end-systole does not necessarily coincide with end of ejection.24, 25 A similar situation could potentially exist in the left ventricle when mitral regurgitation is present.

In terms of peak-systolic models, a number of investigators have noted that potentially wide differences exist between peak-systolic and end-systolic pressure. The difference seems to be most pronounced in patients with low systemic vascular resistance.26

In spite of the theoretical objections enumerated above, in the present study we have found that all three of these modifications reasonably approximate true E\text{max} as determined from time-varying elastance measurements.

**E\text{max} as an indicator of contractile function.** The positive correlations between true E\text{max} and the modifications of true E\text{max} calculated with left ventricular ejection fraction reported above are suggestive of the fact that E\text{max} can be used as an indicator of contractile function. However, an important factor limiting our understanding of E\text{max} as a contractile index is that at present we have no simple marker of ventricular function that can be used as a completely load-dependent measure of contractile state for comparison. In particular, the afterload dependency of ejection fraction makes this at best a poor standard of comparison for E\text{max}. This point is well illustrated in figure 2: the patient’s three pressure-volume diagrams indicate ejection fractions of 87%, 73%, and 61%. The only possible conclusion that can be drawn is that ejection fraction is not as useful an index of contractility as E\text{max}.

**The meaning of the volume intercept.** The physiologic meaning of the volume intercept of the end-systolic relationship is uncertain. Some data4, 5 suggest there may be an inverse relationship between V\text{o} and myocardial contractility, although this has not been widely substantiated by other investigators.22 There are several possible explanations for this apparent discrepancy. First, the volume intercept may have little relationship to contractile function. A second possibility is that the volume intercept cannot be accurately approximated from the limited end-systolic pressure-volume data that are obtained. A third and related possibility, supported by some experimental studies,28, 29 is that the end-systolic relationship is not linear in the region of the volume intercept. Notably, recent work by Maughan et al.29 has shown that V\text{o} is highly affected by changes in afterload.

**Potential utility of radionuclide end-systolic pressure-volume relationships.** The theoretical appeal of end-systolic pressure-volume contractile indexes lies in the fact that these indexes are load independent and can presumably be used to assess basal contractility and inotropic modulation. Use of these indexes could potentially improve our assessment of left ventricular pump function in a wide variety of pathophysiologic states. Until recently, however, derivation of these indexes has been difficult. Angiographic methods are hindered by the limited number of cardiac cycles that can be analyzed, a high incidence of ventricular arrhythmias, the presence of regional wall motion abnormalities that make geometric assumptions for volume calculations inaccurate, the effect of iodinated contrast on ventricular function, and the risk to the patient from multiple contrast injections.30 Similarly, echocardiographic methods are limited by difficulties with echo visualization in many patients and regional wall motion abnormalities that adversely affect geometric volume calculations.31 In contrast, radionuclide methods can be used to analyze a large number of cycles, are less affected by regional wall abnormalities, and can be repeated as often as needed to assess pressure-volume relationships under changing loading conditions without risk to the patient or effect on ventricular function. Absolute volumes can be obtained by calibrating radionuclide volumes to baseline contrast angiographic measurements, as was done in this study. Alternatively, absolute radionuclide volumes can also be obtained directly from radionuclide ventriculography by several previously described techniques.19

**Limitations of the present study.** Certain limitations of the present study need to be emphasized. First, linearity of the end-systolic relationship was assumed in all patients and was approximated by examining pressure-volume relationships over a limited range of loading conditions (e.g., over only a 20 mm Hg pressure range in 14 of the 26 patients). While the end-systolic relationship has been shown to be linear, a larger range of loading conditions with at least three pressure-volume diagrams would be more appropriate for the accurate measurement of end-systolic indexes. A second limitation of this study is the necessity of the assumption of a constant inotropic state at baseline and after pharmacologic manipulation with nitroglycerin, nitroprusside, or phenylephrine. Since there was no significant change in either heart rate or in dP/dt in the study group under different loading conditions, it seems reasonable to presume that contractile state remained constant.
However, the possibility of small centrally mediated reflex changes in contractility cannot be ruled out completely. Finally, this study has not examined end-systolic relationships in patients with valvular abnormalities. The definition of end-systole may be very different, for example, in patients with either mitral regurgitation or aortic insufficiency. As a result, the correlation between end-systolic contractile indexes determined from a time-varying elastance model and those determined from modifications of this model could be substantially different.

In conclusion, in this study we examined, in human beings, left ventricular end-systolic pressure-volume relationships using a model of time-varying elastance and a radionuclide approach to serial volume assessment. Our data suggest that $E_{\text{max}}$, determined with this approach is a useful index of myocardial contractile function, while $V_0$ bears little relationship to inotropic state. In addition, our results suggest a reasonable correlation between $E_{\text{max}}$ calculated according to Sagawa’s model and $E_{\text{max}}$ determined from modifications of the end-systolic relationship in current use.

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Circulation. 1986;74:97-104
doi: 10.1161/01.CIR.74.1.97

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