Noninvasive Determination of Left Ventricular End-systolic Stress: Validation of the Method and Initial Application

NATHANIEL REICHEK, M.D., JOHN WILSON, M.D., MARTIN ST. JOHN SUTTON, M.B.,

THEODORE A. PLAPPERT, SHELDON GOLDBERG, M.D., AND JOHN W. HIRSHFELD, M.D.

SUMMARY   End-systolic left ventricular (LV) meridional wall stress is a quantitative index of true myocardial afterload that can be plotted against LV end-systolic diameter to give an index of contractility independent of loading conditions. We developed a noninvasive method for estimating end-systolic LV meridional wall stress based on M-mode LV echographic end-systolic diameter (LVID) and posterior wall thickness (PWT) and cuff systolic arterial pressure and compared it to simultaneous invasive LV wall stress derived from micromanometer LV pressure recordings and continuously digitized echograms in 12 subjects (four with atypical chest pain, six with severe aortic regurgitation (AR) and two with congestive cardiomyopathy), before and after load manipulation with nitroprusside, nitroglycerin, phenylephrine or saline. Cuff systolic pressure correlated well with end-systolic LV micromanometer pressure ($r = 0.89$, $n = 31$, range 96–160 mm Hg) and noninvasive end-systolic stress (0.334 P(LVID)/PWT $[1 + $ PWT/LVID$]$) correlated extremely well with invasive stress ($r = 0.97$, $n = 31$, range 36–213×10^3 dyn/cm^2). Invasive and noninvasive slopes ($r = 0.91$, $n = 7$) and LVID intercepts ($r = 0.89$, $n = 7$) of the stress-diameter plots also correlated well. Noninvasive stress-diameter plots in nine normal subjects showed a range of slopes of 50–93×10^3 dyn/cm and intercepts of 1.8–2.8 cm. Mean basal end-systolic noninvasive stress in 22 normal subjects ($64.8 \pm 19.5 \times 10^3$ dyn/cm^2) and 14 treated hypertensives ($56.3 \pm 26.7 \times 10^3$ dyn/cm^2) was significantly lower than in nine patients with symptomatic aortic regurgitation who had reduced ejection fraction ($142.2 \pm 53.2 \times 10^3$ dyn/cm^2, $p < 0.01$) or four patients with congestive cardiomyopathy ($187.3 \pm 49.8 \times 10^3$ dyn/cm^2, $p < 0.01$), while a mild elevation of stress in symptomatic aortic regurgitation with normal ejection fraction was not statistically significant ($91.1 \pm 20.7 \times 10^3$ dyn/cm^2, $n = 6$). Thus, afterload excess contributed to ejection fraction reduction. We conclude that end-systolic stress may be determined noninvasively and may be a useful approach to quantitation of LV afterload and contractility.

LEFT VENTRICULAR (LV) systolic function is the product of the interaction of four variables: myocardial contractile state, end-diastolic myocardial length, afterload and LV myocardial mass.[1] Clinical ejection phase indexes, such as ejection fraction or velocity of circumferential fiber shortening, cannot determine the relative contribution of each of these variables to LV pump dysfunction in a given heart. Therefore, methods are needed to quantitate each of the fundamental variables using noninvasive techniques. There are well-characterized noninvasive methods for estimating LV diameter, wall thickness, chamber volume and myocardial mass,[2-6] but quantitation of afterload and contractility remain a challenge.

Recent studies have examined the use of the end-systolic force-length relationship to characterize myocardial contractility.[7-11] This relationship can be plotted using LV end-systolic pressure or wall stress as the force measurement and end-systolic LV volume, circumference or diameter as the length measurement. When force is expressed as wall stress, the myocardial afterload and contractile state can be readily compared in ventricles of different sizes and wall thicknesses, because these variables are included in the stress calculation. Several echocardiographic methods for noninvasive estimation of peak and end-systolic wall stress have been described.[12-15] However, further validation is required. In particular, the effects on the reliability of noninvasive estimates of LV end-systolic pressure and wall stress of disorders and pharmacologic agents that alter ejection impedance, and may alter left ventricular pressure contour, must be assessed. Among these are aortic regurgitation, vasodilators, α-adrenergic agents and changes in inotropic state. Moreover, descriptive data on end-systolic stress in normal and abnormal left ventricles are limited. Therefore, the present study was designed to provide a more extensive assessment of noninvasive end-systolic stress compared with simultaneous invasive data before and after afterload modification; to characterize the normal range of noninvasive end-systolic stress and the normal stress-length relationship; and to examine the range of end-systolic stress in normal, pressure-overloaded, volume-overloaded and myopathic left ventricles.

Methods

Population

Simultaneous invasive and noninvasive wall stress studies were performed in 12 subjects who underwent

cardiac catheterization. Four had atypical chest pain without evidence of heart disease, six had severe aortic regurgitation and two had congestive cardio-myopathy. Subjects with segmental LV contraction abnormalities were excluded, because the end-systolic force-length analysis assumes homogeneous myo-cardial function. Subjects with significant mitral regurgitation were also excluded because end-systole is not isovolumic, and may be difficult to define ac-curately, in mitral regurgitation. The relationship of micromanometer peak and end-systolic pressure to cuff blood pressure were also examined in 14 ad-ditional subjects, of whom two had significant mitral regurgitation.

Noninvasive studies were performed in 22 normal persons; 14 treated hypertensives without clinical or echocardiographic evidence of LV dysfunction or ischemic heart disease; six subjects with severe aortic regurgitation and symptoms of congestive heart failure with normal angiographic ejection fraction; nine with severe aortic regurgitation, symptoms of congestive heart failure and abnormal angiographic ejection fraction; and four with heart failure due to congestive cardiomyopathy.

Invasive Studies

LV pressure was recorded with Millar micro-manometer catheters inserted through a sheath by the percutaneous femoral approach. Catheters were balanced and calibrated both electronically and physically during each study. After baseline echo-cardiographic and pressure data were recorded, hemo-dynamic load was altered with nitroprusside infusion in eight subjects, phenylephrine infusion in two, saline infusion in one subject and sublingual nitroglycerin in one subject, while LV pressure and LV echogram were continuously recorded on an Irex system 2 strip-chart recorder at 50- and 100-mm/sec paper speeds, using an amplifier that had a flat frequency response from 0–100 Hz. At intervals before and after load altera-tion, duplicate cuff arterial pressures were determined

in the subject's left arm by an observer who could not see the LV pressure recording. Time of cuff pressure and values reported were noted on the strip chart using an event marker. LV echograms were recorded at the high chordal level after long-axis and transverse scans were performed. The transducer was kept in place throughout the study and the echogram was continu-ously observed to assure that all recordings came from the same level in the ventricle. An illustrative echo recording is shown in figure 1.

To determine invasive meridional wall stress, records were calibrated and digitized on a Hewlett-Packard minicomputer and digitizer and stored at 10-msec intervals on a floppy disc. Meridional LV wall stress was determined using the angiographically validated method of Grossman and co-workers[16]: $(0.334 \ P/(LVID)/PWT \ [1 + PWT/LVID])$ where P = LV pressure, LVID = LV diameter and PWT = LV posterior wall thickness.

Unsmoothed data were subsequently printed and plotted (fig. 2). End-systole was identified as the time of initial appearance of the smallest LVID registered, and end-systolic P, LVID and PWT were noted. Peak micromanometer systolic LV pressure was also noted for each cycle. Data were analyzed as the mean of three to five cardiac cycles.

To determine noninvasive end-systolic stress, the same stress equation was used, with substitution of the mean of duplicate cuff arterial systolic pressures for LV micromanometer pressure and manual identifica-tion of end-systole as the time of smallest LVID, with a straight edge and calipers. Actual measurements of end-systolic LVID and PWT were determined on the digitizer. Stress was calculated from the same three to five cycles used for the invasive stress value.

Noninvasive Studies

Echograms for noninvasive studies were obtained and analyzed in a manner identical to that described for the noninvasive aspect of invasive-noninvasive comparisons. In nine normal subjects, sublingual
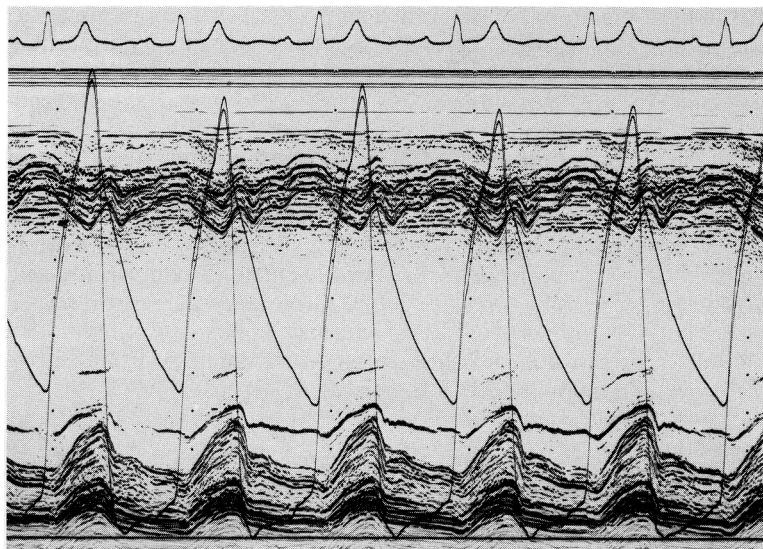

Figure 1. *Simultaneous recording of the left ventricular echocardiogram, ECG and micromanometer aortic root and left ven-tricular pressure in a subject with aortic regurgitation.*
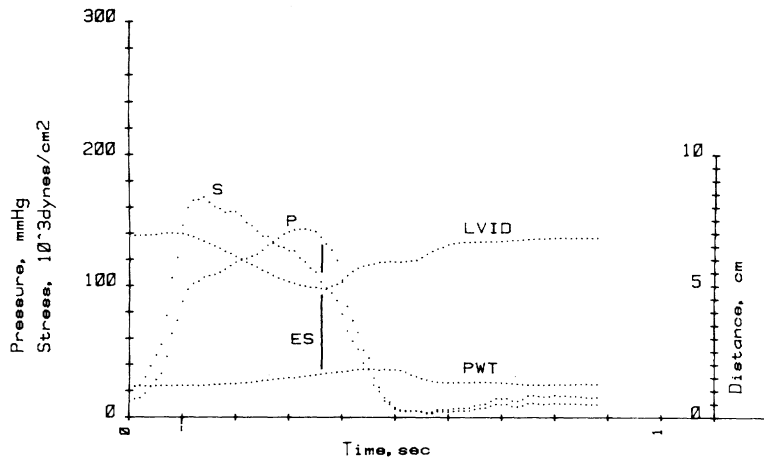
FIGURE 2. *Unsmoothed plot of digitized data from a single cardiac cycle showing left ventricular dimension (LVID) and posterior wall thickness (PWT) derived from the echocardiogram, left ventricular pressure (P) and calculated LV meridional wall stress (S). At end-systole (ES), P is very similar to peak P.*

nitroglycerin was then administered and serial LV echograms and cuff systolic pressures were recorded to define the normal noninvasive end-systolic stress-length relationship.

Statistical Methods

Simultaneous invasive and noninvasive pressure and end-systolic stress values were compared by standard linear regression.[17] Linearity of the end-systolic stress-length relationship for both invasive and noninvasive data was also assessed by linear regression. Linear regression plots were computer drawn, with extension of the regression line to its y intercept for ease of visual interpretation. However, the regressions are validated only for the range of actual data points obtained. Comparison of noninvasive data from the five clinical groups studied was done by analysis of variance.

Results

Validation of Noninvasive End-systolic Pressure and Stress

Thirty-one simultaneous sets of invasive and noninvasive end-systolic stress data were suitable for analysis. Both before and after load manipulation, end-systolic micromanometer pressure correlated extremely well with peak systolic micromanometer pressure in each record (figs. 2 and 3) (r = 0.97), with a regression equation of end-systolic P = 0.89 peak P + 8 mm Hg.

Because of the close correlation of peak and end-systolic pressure, end-systolic pressure and noninvasive cuff systolic pressure also correlated well (r = 0.89 over a range of 96–160 mm Hg [fig. 3B]). The regression equation was: noninvasive P = 1.07 end-systolic P + 0.8 mm Hg. Further micromanometer recordings in an additional 12 subjects without mitral regurgitation confirmed these observations, but in two subjects with severe mitral regurgitation, end-systolic micromanometer pressure was substantially less than peak pressure and cuff systolic pressure was a poor estimate of end-systolic pressure.

Noninvasive end-systolic LV meridional stress and invasive stress (fig. 4) correlated even more closely (r = 0.97, slope of 1.1 and y intercept of 1.4 × 10³ dyn/cm² over a range of 35–213 × 10³ dyn/cm²).

Validation of Noninvasive Stress-Length Plots

In seven subjects, enough data were obtained with load manipulation to generate both invasive and noninvasive stress-length plots. The mean pressure range was 22 mm Hg and heart rate varied no more than 10 beats/min in any subject. An invasive end-systolic stress-length plot and the corresponding noninvasive plot are shown in figure 5. Both are linear (r = 0.91 invasive, 0.91 noninvasive) and slopes and LVID intercepts are similar. For all seven subjects, invasive and noninvasive slopes and LVID intercepts correlated well (r = 0.91 and 0.89, respectively) (fig. 6). The slope of each regression was close to unity, but the standard errors were large, in part because of the small number of comparisons. In two subjects, invasive data on postpremature beats demonstrated enhanced contractility due to postextrasystolic potentiation, associated with stress-length values shifted to the left from the stress-length line in the basal contractile state (fig. 7). Unfortunately, coupling intervals could not be matched at multiple loads to permit determination of a postpremature slope.

Noninvasive Studies

The mean value for end-systolic meridional stress in normal subjects was 64.8 ± 19.5 × 10³ dyn/cm² (fig. 8) and did not differ significantly from the value of 56.3 ± 26.7 × 10³ dyn/cm² in treated hypertensives. End-systolic stress in six subjects with aortic regurgitation with symptoms of congestive heart failure and normal ejection fraction was 91.1 ± 20.7 × 10³ dyn/cm², but was not statistically different from normal. In contrast, stress was markedly elevated in aortic regurgitation with symptoms of congestive heart failure and decreased ejection fraction (142.2 ± 53.2 × 10³ dyn/cm²) and even higher in patients with congestive cardiomyopathy (187.3 ± 49.8 × 10³ dyn/cm²). Both of these groups differed significantly from normal (p < 0.01).

A representative noninvasive stress-length line in a normal subject obtained before and after sublingual nitroglycerin is shown in figure 9. Normal slopes ranged from 50–93 × 10³ dyn/cm² and diameter intercepts ranged from 1.8–2.8 cm (fig. 10). Correlation coefficients ranged from 0.78–0.95, with the lower
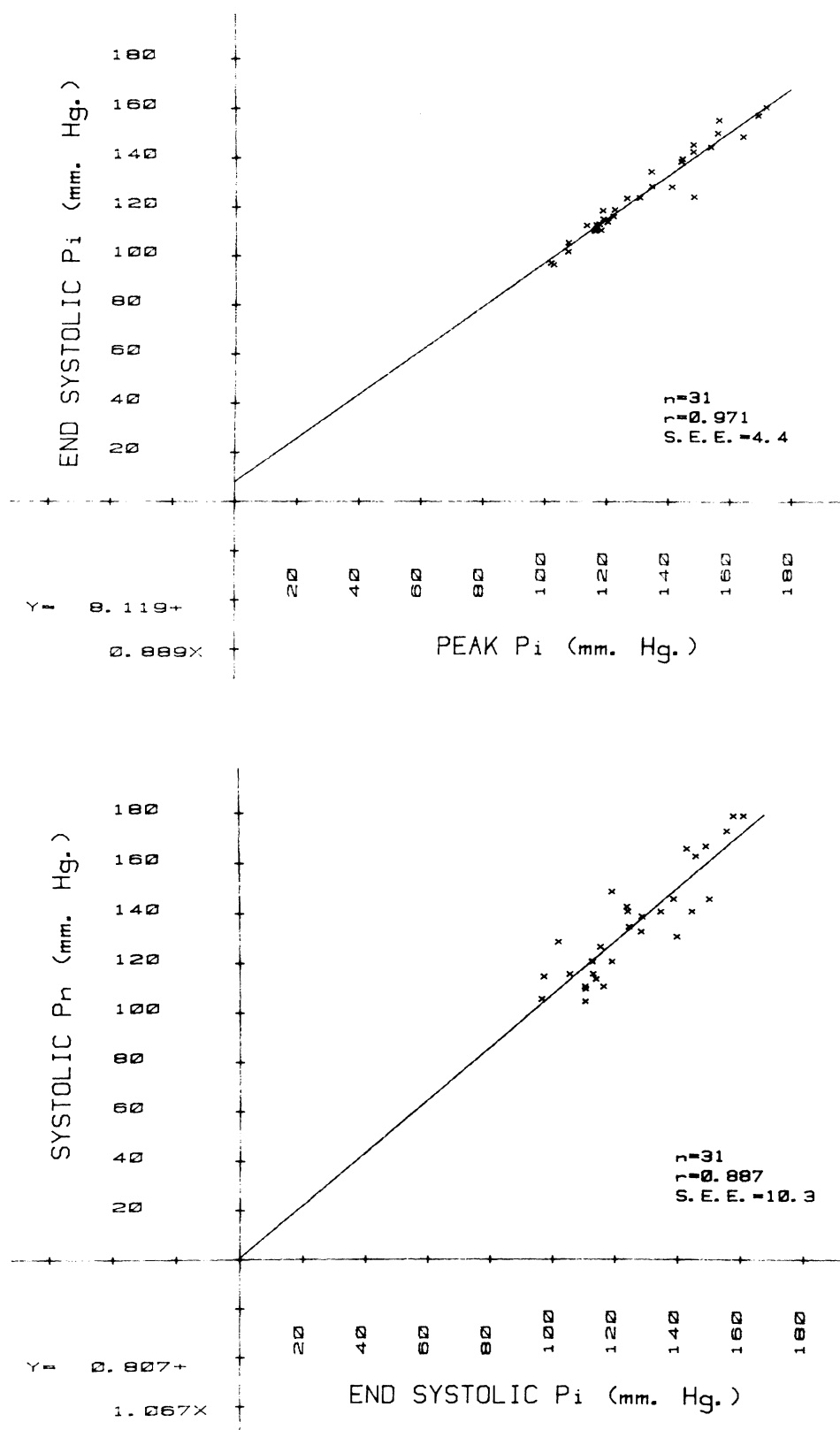
FIGURE 3. (A) Micromanometer end-systolic LV pressure (End-systolic Pi) corresponds closely to micromanometer peak systolic pressure (peak Pi) before and after load manipulation (r = 0.97, slope = 0.89, intercept = 8 mm Hg). (B) Noninvasive cuff systolic pressure (Pn) correlates well with invasive micromanometer end-systolic left ventricular pressure (Pi) (r = 0.89, slope = 1.07, intercept = 0.8 mm Hg).
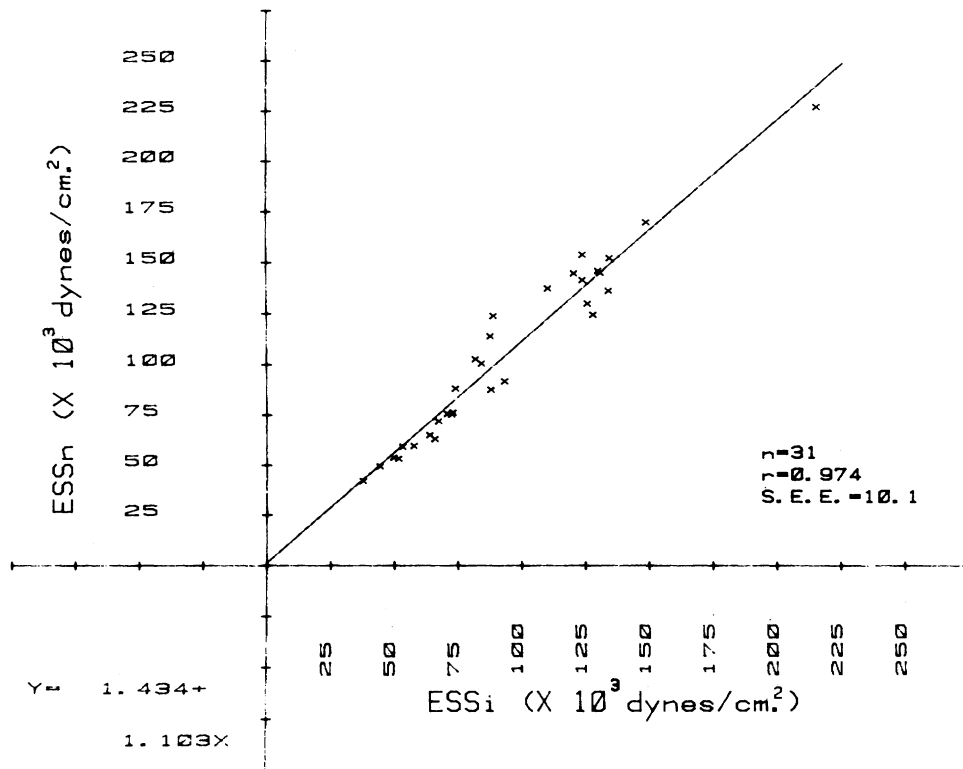
FIGURE 4. *Noninvasive end-systolic stress (ESSn) correlates extremely well with simultaneous invasive end-systolic stress (ESSi) (r = 0.97, slope = 1.1, intercept = 1.4).*

values occurring in subjects in whom the pressure range obtained was relatively small. The regression line constructed by pooling single baseline stress-length points from each subject in the entire group (dashed line, fig. 10) was not similar in slope to the mean of the individual stress-length lines, but was considerably flatter. Therefore, pooled single-point data from a population cannot be used to describe the mean stress-length relationship of the population as a whole.

Discussion

This study demonstrates the reliability of a simple, noninvasive method for determining end-systolic LV meridional stress. The method is successful because the dimensional data needed for stress calculation are readily identified manually from the M-mode echo-cardiogram, and because a close relationship exists between cuff systolic blood pressure and end-systolic micromanometer LV pressure. This pressure relationship is impaired in severe mitral regurgitation, in which LV pressure decreases in late systole, but it is not impaired by severe aortic regurgitation or by administration of either vasodilators or a vasoconstrictor in doses that alter LV end-systolic pressure enough to permit generation of stress-length lines. These are fairly severe tests. However, end-systolic pressure is a function of many variables, including vascular resistance, LV stroke volume and ejection rate. Whether more marked alterations in these variables would impair the reliability of the method remains to be determined.

Marsh and co-workers described an analogous method for noninvasive end-systolic meridional stress, based on estimation of dicrotic notch pressure.[13] They have also shown linearity of end-systolic stress-length in normal hearts, demonstrated the effect of enhanced contractility with postextrasystolic potentiation and shown close invasive-noninvasive correlations using intraarterial pressure recordings from fluid-filled catheters. However, reliance on dicrotic notch pressure might exclude application of the method in aortic regurgitation, in which identification of dicrotic notch on external pulse recordings may be difficult. Furthermore, our data demonstrate that high-fidelity LV end-systolic pressure at echocardiographic end-ejection correlates well with peak LV pressure and with systolic cuff pressure, which are much higher than estimated dicrotic notch pressure. This result is in agreement with observations in isolated working heart and the intact circulation in dogs.[7, 10] Therefore, use of cuff systolic pressure may be preferable to use of dicrotic notch pressure for this purpose.

Noninvasive end-systolic stress may provide a more appropriate method for characterizing afterload. LV systolic pressure and systemic vascular resistance are often used as afterload indexes. However, the relationship between LV systolic pressure and true myocardial afterload is mediated by the LaPlace relationship, while systemic vascular resistance is a derived mean expression of peripheral pressure-flow relationships, not a physical load seen by the left ventricle. True LV afterload is best expressed as systolic wall
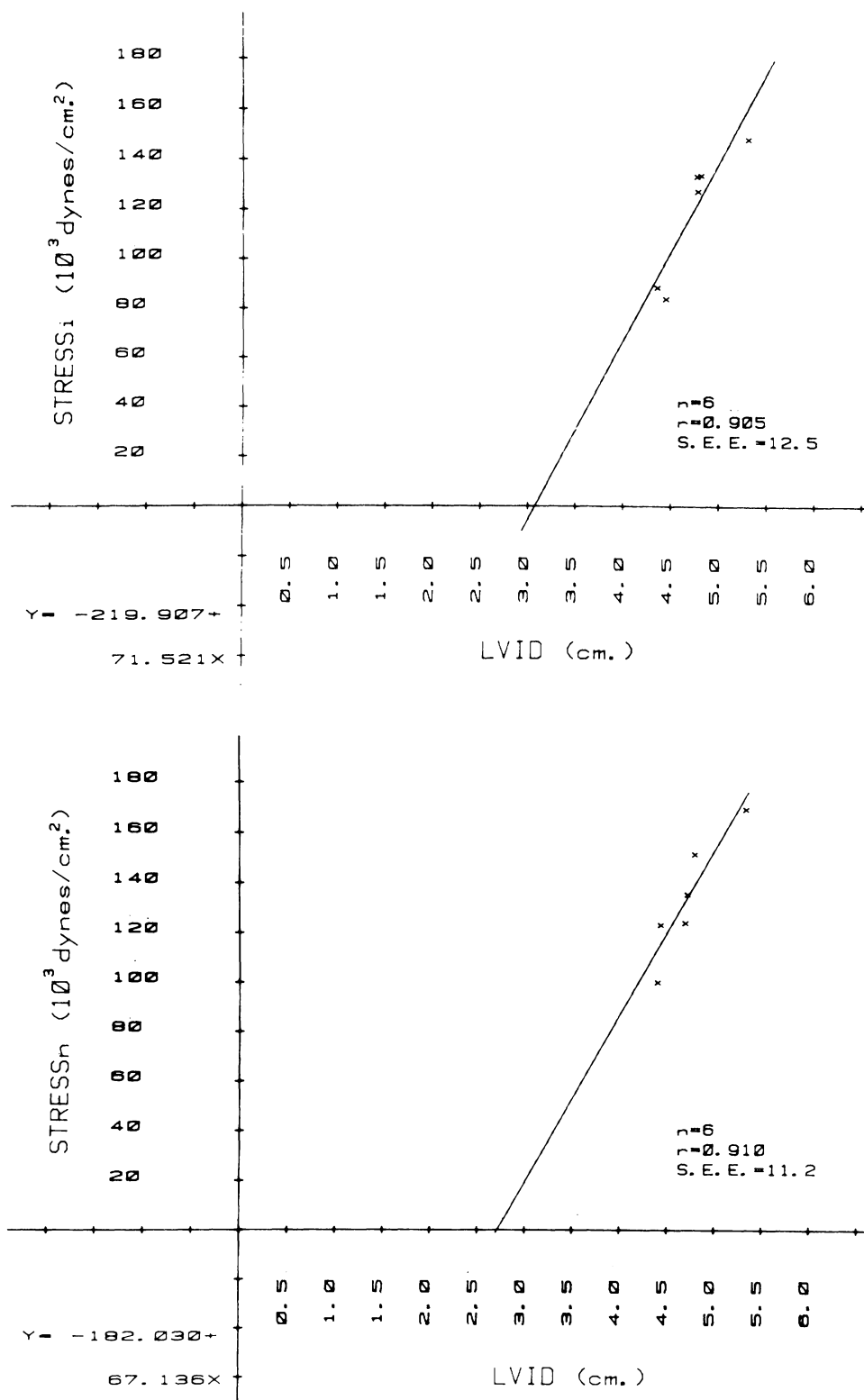
FIGURE 5. *(A) The end-systolic stress-length relationship expressed as a plot of invasive end-systolic stress (ESSi) vs left ventricular end-systolic diameter (LVIDs) before and after i.v. nitroprusside in a patient with aortic regurgitation. The relationship is linear (r = 0.91, slope = 71.5 × 10³ dyn/cm and extrapolated LVID intercept = 3.1 cm). (B) Noninvasive end-systolic stress-length relationship determined simultaneously with invasive plot in A, plots noninvasive end-systolic stress (ESSn) against LVIDs (r = 0.91). The slope of 67.1 × 10³ dyn/cm and extrapolated LVID intercept of 2.7 cm are quite similar to those obtained from invasive data.*
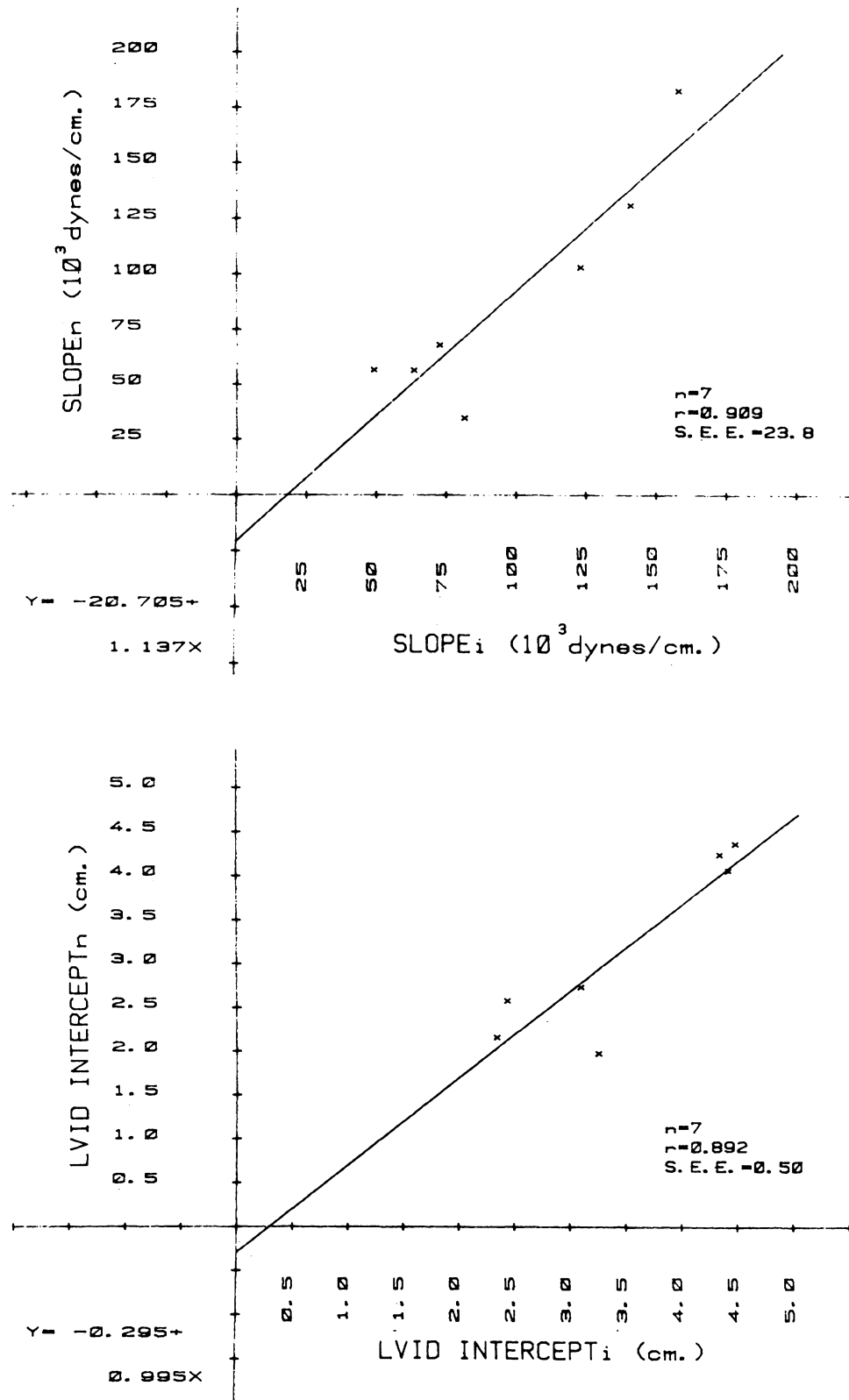
FIGURE 6. *(A) Noninvasive end-systolic stress-length slope (Slope_n) correlates well with invasive end-systolic stress-length slope (Slope_i) (r = 0.91, slope = 1.1, intercept = −20.7.) (B) Noninvasive left ventricular dimension (LVID) intercept correlates well with invasive LVID intercept (r = 0.89, slope = 0.995, intercept = −0.3 cm).*
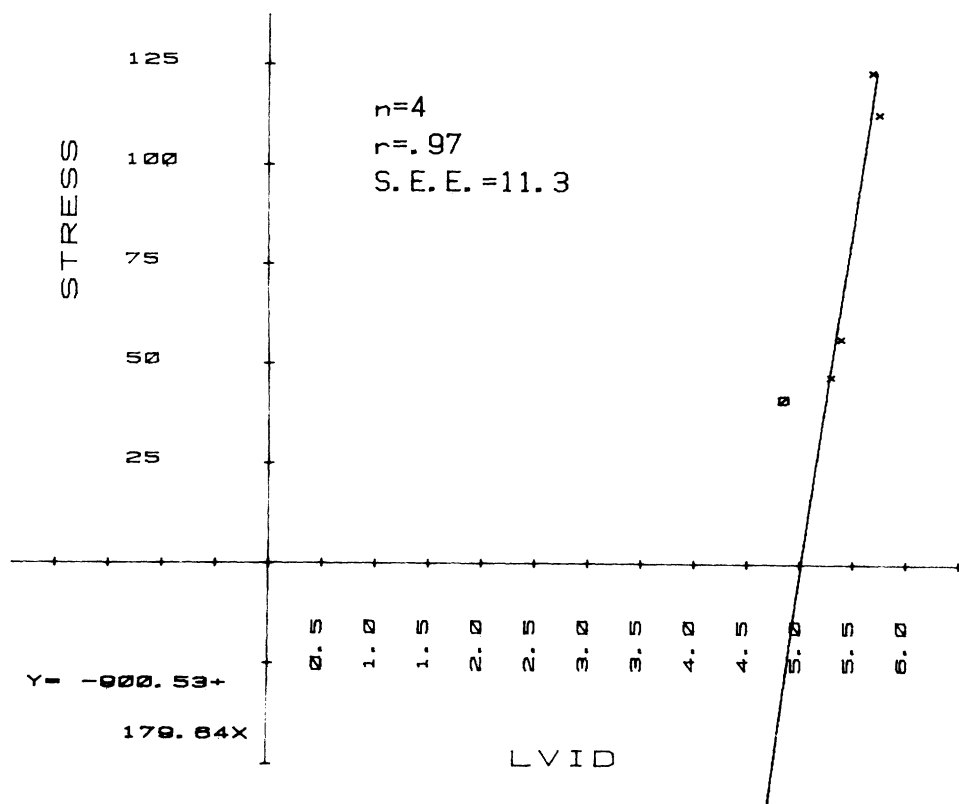
FIGURE 7. *End-systolic invasive stress-length plot in a subject with aortic regurgitation. A postpremature beat (circle) is displaced to the left from the basal stress-length line owing to enhanced contractility. LVID = left ventricular dimension.*

tension,[9] which has a complex relationship to LV pressure and only an indirect relationship to systemic vascular resistance. Moreover, since LV wall thickness and diameter differ greatly among hearts, com-

parisons of systolic tension must be normalized to tension per unit cross-sectional area of myocardium, or wall stress, to permit comparisons between hearts. Furthermore, in the intact circulation, LV wall stress varies continuously throughout systole (fig. 2), so that instantaneous afterload is continuously changing. Carabello et al.[18] proposed the use of mean systolic stress as an afterload index. However, end-systolic stress may have a special conceptual value as an after-
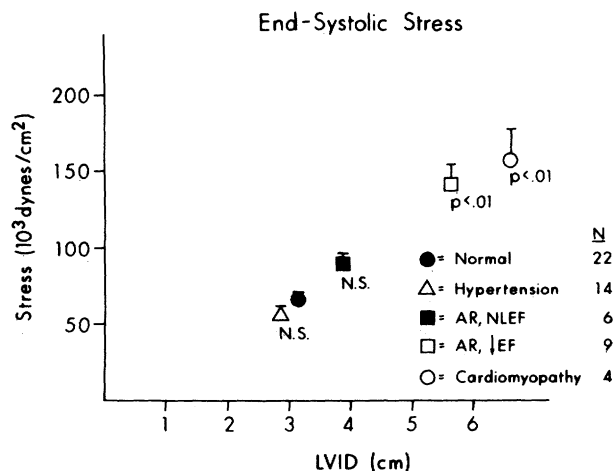

FIGURE 8. *Noninvasive end-systolic stress in normal subjects, treated hypertensives and patients with symptomatic aortic regurgitation with normal ejection fraction (AR nl EF) are similar, while end-systolic stress in symptomatic aortic regurgitation with decreased ejection fraction (AR decreased EF) and congestive cardiomyopathy (open circle) are significantly elevated. Cross-bars represent the standard error of the mean.*
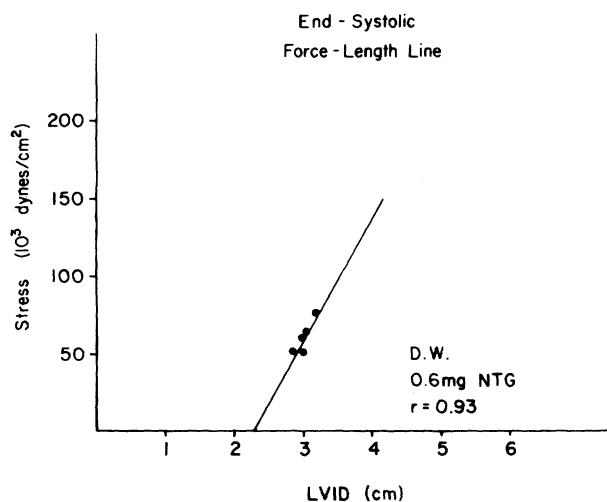

FIGURE 9. *Noninvasive end-systolic stress-length line in a normal subject before and after sublingual nitroglycerin.*
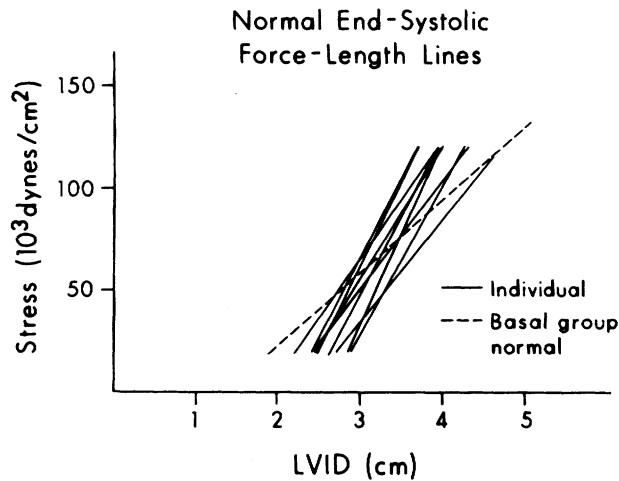
FIGURE 10. *Noninvasive end-systolic stress-length lines in nine normal subjects are shown (solid lines). The dashed line represents the data before nitroglycerin for the entire group in the basal state.*

load marker. As shown in isolated heart by Weber et al.[8] and Suga and Sagawa,[7] ejection ends when instantaneous myocardial force (wall tension, stress or pressure) reaches the maximal, or isometric, value for the existing instantaneous myocardial length or ventricular volume. Thus, end-systolic stress is literally the afterload that limits ejection. Whatever the time course of stress earlier in systole, only a reduction in end-systolic stress can result in an increase in systolic emptying of the ventricle in a given contractile state.[8]

The descriptive value of end-systolic stress is indicated by our noninvasive group data. Treated hypertensives had normal end-systolic stress, presumably because of a combination of compensatory hypertrophy and load reduction by antihypertensive agents. In contrast, subjects with reduced ejection fraction due to either aortic regurgitation or congestive cardiomyopathy had markedly elevated end-systolic stress. Thus, while myocardial contractile state may have been abnormal in these subjects, afterload excess also contributed to manifest LV pump dysfunction.

In the present study, a mild elevation of end-systolic stress in subjects with aortic regurgitation who had normal ejection fraction and symptoms of congestive failure was not significant. However, we have shown, using slightly more normal subjects and subjects with aortic regurgitation in a simpler two-way statistical comparison, that a similar mild stress elevation was significant in asymptomatic aortic regurgitation with normal ejection fraction and could be normalized by nitroglycerin.[16] Despite afterload excess, the end-systolic stress-length slope was normal in asymptomatic aortic regurgitation with normal ejection fraction, suggesting that intrinsic contractile state was normal. We believe that in the present study, the group with a normal ejection fraction and symptomatic aortic regurgitation was not statistically different from normal, because of the small number studied and the large number of intergroup comparisons made. Mean values for noninvasive end-

systolic stress in normal subjects and in patients with aortic regurgitation with normal ejection fraction were quite similar in this and in the previous study (normal subjects 65 vs 63 $\times$ 10^3 dyn/cm^2; aortic regurgitation 91 vs 80 $\times$ 10^3 dyn/cm^2, respectively).

A second potential application of noninvasive LV wall stress is for determining the end-systolic stress-length relationship, used as an index of intrinsic contractility. We observed a good correlation between invasive and noninvasive slopes and intercepts in simultaneous comparisons. The response to post-extrasystolic potentiation in our study and that of Marsh and co-workers demonstrate the sensitivity of the stress-length relationship to acute increases in contractile state. The noninvasive stress-length data in normal subjects demonstrates the normal range for slope and intercept. These data also indicate that it may be misleading to attempt to use single data points obtained in many different subjects to construct a group force-length relationship, because the line obtained is markedly different from the mean of individual lines.

A potential problem in using the end-systolic force-length relationship for assessing contractility in the intact circulation is that large perturbations in pressure may evoke reflex changes, particularly adrenergic discharge related to the baroreceptor response, which could alter inotropic state during data collection. An advantage of using wall stress rather than pressure as the force measurement in this analysis is that small pressure changes, like the 10–20 mm Hg changes commonly obtained with nitroglycerin or nitroprusside or phenylephrine in this study, combined with concomitant changes in LV diameter and wall thickness, result in a wide range of wall stress. Consequently, the baroreceptor response may be minimized, as suggested by the small changes in heart rate evoked in our subjects. In turn, since use of wall stress rather than pressure requires only small pressure changes, the effect of large alterations in aortic impedence on the relationship of cuff and LV end-systolic pressure may not be of practical importance.

Important limitations to the method must be noted. As with all mechanics methods that have been used clinically, it assumes a uniform contractile state. Hence, it should not be applied in subjects with ischemic heart disease and segmental variations in myocardial performance. Second, the analysis requires a discrete isovolumic isometric point at end-systole. Hence, it cannot be applied in the presence of significant mitral regurgitation, in which isometric conditions may not obtain and identification of end-systole is ambiguous. Because meridional stress is calculated without reference to LV length, no assumptions about LV minor-to-major axis ratio are required. However, as with many M-mode echocardiographic methods, this one assumes that the line of information sampled is representative of that around the circumference of the ventricle at that level. Because the method is easily extended to use cross-sectional echocardiographic information, however, M-mode sampling errors may not be critical.[19]

A further conceptual problem is use of the M-mode LVID as the myocardial length measurement for meridional stress-length analysis. Because meridional stress is exerted in a plane perpendicular to LVID, LV apex-to-base length is the appropriate length measurement. Quinones and co-workers used M-mode echocardiographic data to calculate circumferential stress, which is appropriately plotted against LVID, but this requires an assumed ratio of LVID to LV length.[14] Our data and those of Marsh and co-workers indicate that the meridional stress-LVID plot behaves like other force-length plots with respect to linearity and response to acute inotropic changes.[13] Moreover, only a change in the LVID/length ratio in a given heart at different end-systolic loads would result in erroneous conclusions from such plots. In any event, the issue does not affect the reliability of noninvasive meridional stress per se.

A final problem is that the ratio of meridional to circumferential stress varies with LV shape, and comparison of afterload in ventricles of different shape should include both. Again, two-dimensional echocardiography to measure LV length can obviate the problem.[20]

In summary, end-systolic LV meridional wall stress can be estimated simply and accurately from totally noninvasive data. The information derived can be used to identify the presence of "afterload excess" as a component of LV dysfunction and, with load manipulation, to provide a contractility index that is independent of load.

Acknowledgment

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