The Evaluation of Left Ventricular Function in Man

A Comparison of Methods

By Thomas H. Kreulen, M.D., Alfred A. Bove, M.D., Ph.D., Michael T. McDonough, M.D., Milton J. Sands, M.D., and James F. Spann, M.D.

SUMMARY

Comparisons of the sensitivities of parameters for assessing left ventricular performance in man were made in 38 patients. The parameters compared were the ejection fraction, ventriculographic contraction patterns, the left ventricular end-diastolic pressure, and the contractile indices including the contractile element velocity at 10 mm Hg (Vce 10) and maximal contractile element velocity (Vmax). The contractile indices were obtained by catheter tip manometry, utilizing developed pressure (DP) to calculate the velocity of contractile element shortening (Vce) from the formula: 
\[
\text{dp/dt}_{32} \text{ DP}
\]
Vce 10 was measured directly and Vmax was derived by linear manual extrapolation of the pressure-velocity plot to 0 mm Hg. Vmax values derived from linear manual extrapolation were compared with values obtained by computer least squares fitting of the Vce and developed pressure data points to single and double exponential equations. The Vce and developed pressure data points fit the single exponential equation better than the double exponential equation but the use of either equation resulted in slightly higher values for Vmax than obtained with linear manual extrapolation. The effect of heart rate on myocardial contractility was eliminated by making comparisons at both a basal and an atrial paced rate of 100. Utilizing all methods, 24 patients were identified to have ventricular dysfunction. The contractile indices were significantly less sensitive than any other parameter (P < 0.05) and identified seven patients while the left ventricular end-diastolic pressure, ejection fraction, and presence of asynery identified 15, 15, and 12 patients, respectively. The use of a common atrial paced rate of 100 did not increase the sensitivity of the contractile indices. Since there was only partial overlapping between parameters in the identification of left ventricular dysfunction, the combination of different parameters was more sensitive than any single parameter alone. It is concluded that several methods are required to identify all patients with left ventricular dysfunction and that the contractile indices are the least sensitive indicator of left ventricular dysfunction.

Additional Indexing Words:
Myocardial contractility
Ventriculography
Ventricular pressure
Force-velocity relations
Atrial pacing

EVALUATION of left ventricular function in man by invasive means presently is accomplished by two major techniques: first, the recording of left ventricular pressure and second, the performance of left ventriculography. While some of the parameters derived from these techniques assess characteristics of left ventricular pump performance and others are based upon current concepts of myocardial muscle mechanics, all methods have both theoretical and practical limitations. Nevertheless, the clinical usefulness of any parameter may be evaluated by assessing one or more characteristics which the ideal parameter of left ventricular function should possess. These characteristics include high sensitivity, high specificity, reproducibility, ease of performance, ability to assess regional function, independence of preload and afterload, possession of quantitative as well as qualitative value, and the ability to give prognostic information. This study compares the sensitivity of several parameters of left ventricular function derived from the analysis of left ventricular pressure recordings and the left ventriculogram. The parameters derived from the analysis of left ventricular pressure recordings are the left ventricular end-diastolic pressure and the contractile indices. The contractile indices which were measured are the contractile element velocity at 10 mm Hg developed pressure, or Vce 10, and the maximal contractile element velocity at 0 mm Hg developed pressure, or Vmax. An analysis of regional wall motion and the
ejection fraction are the parameters obtained from the left ventriculogram.

Methods

Patient Groups

Thirty-eight patients were studied during diagnostic cardiac catheterization. Seven of the 38 patients were studied because of recurrent episodes of atypical chest pain. These patients had normal resting electrocardiograms. Two of the seven underwent Master two-step tests which were negative. These seven patients were found to be normal and had normal intracardiac pressures, a normal left ventricular end-diastolic pressure measuring less than 13 mm Hg, no valvular gradients, a normal cardiac index measuring greater than 2.5 L/min/m², a normal left ventriculogram with a normal ejection fraction measuring greater than 50%, normal regional wall motion and normal coronary cineangiograms. The normal ranges of values for Vce 10 and Vmax were derived from this group of seven normal patients.

Thirty-one of the 38 patients had various forms of congenital, valvular, myocardial and coronary artery diseases. These patients were defined to have diseased hearts whether their left ventricular function was normal or abnormal. Patients with mitral or aortic insufficiency were excluded from the study since the calculation of the contractile indices assumes that early systole is isovolumic. All patients were in normal sinus rhythm at the time of catheterization.

Data Acquisition

All patients were studied in the fasting state while mildly sedated with diazepam (Valium). Right and left heart catheterizations were performed via a right antecubital cut-down. A short teflon catheter was placed percutaneously into the left brachial artery. Standard pressures were measured using Statham P23 Db transducers. Pressures were referenced to atmospheric pressure at 5 cm below the sternal angle. The left ventricular end-diastolic pressure was measured following the A wave and averaged over one respiratory cycle. In every patient, prior to and within 10 min of the left ventriculogram, left ventricular pressure was also measured using a catheter tip manometer (Statham Model SF-1 or Millar Mikro-Tip Model PC-471) and recorded at a paper speed of 200 mm/second. The first derivative of left ventricular pressure was measured with a resistance-capacitance differentiating circuit having a time constant of 2.5 msec. This provided differentiation without phase distortion to 125 Hz. Left ventricular pressure and its first derivative were recorded at the basal heart rate and following two minutes of atrial pacing at a heart rate of 100.

A single plane left cineventriculogram was accomplished in the 30° right anterior oblique projection using a Siemens 10-6 inch image intensifier system. A power injection into the left ventricle utilizing 30-55 ml of Renografin 76 was made through a multiholed catheter passed retrogradely across the aortic valve. Cine films were recorded at 60 frames/sec using 35 mm film. Calibration of the ventricular image size was made with a 10 cm grid filmed at the level of the left ventricle with the same tube-to-image intensifier distance as used during ventriculography. Selective coronary cineangiograms were recorded in multiple projections.

Data Analysis

Left ventricular pressure and its first derivative (dp/dt) were measured every five msec during isovolumic systole (fig. 1). These measurements were made using .02 sec time lines on the recording paper and a transparent grid which identified the three paired simultaneous points on the left ventricular pressure and dp/dt trace between the time lines. Systole was considered to be isovolumic until the left ventricular pressure equaled arterial diastolic pressure. Using developed pressures (total left ventricular pressure minus left ventricular end-diastolic pressure) above 10 mm Hg, the velocity of the contractile element shortening (Vce) was calculated from the formula: \[ \frac{dp}{dt} = \frac{32}{P} \] where P is the developed pressure and 32 is the series elastic constant.

Determinations of Vce were made from three consecutive beats and were plotted against left ventricular developed pressure (fig. 2). It was found in all patients that the values of Vce derived from different beats fell along the same pressure-velocity curve. Using the determinations from all three beats, the maximal velocity of contractile element shortening (Vmax or Vce at 0 pressure) was determined by visual straight line extrapolation through the steepest portion of the descending limb of the pressure-velocity curve and is expressed in muscle lengths (ML) per second. Vce at 10 mm Hg, termed Vce, 10, was used as an additional index of contractility since it avoids the problem of extrapolation to zero pressure.

In order to evaluate and eliminate potential errors in the linear manual extrapolation to Vmax, Vmax was also derived by fitting the values of Vce and developed pressure to single exponential \[ Vce = Vmax - A (e^{C} - 1) \] and double exponential \[ Vce = Vmax \cdot e^{B} - A \cdot e^{C} - 1 \] equations using the least squares method. The solution for the best fit curve was obtained using a digital computer (Digital Equipment Corporation PDP 9) and gave the mean and standard error for each parameter of the equation (Vmax, A, B, C) where Vmax, A, B, and C are the derived constants for the best fit equation. The use of these exponential equations to derive Vmax is empiric and is based upon several observations. Although the force-velocity curve as described by Hill is hyperbolic, curve fitting of these data to the Hill equation using nonlinear regression produced unacceptable.
METHODS OF EVALUATING LV FUNCTION IN MAN

results with large standard errors for all equation parameters. Since exponential curves are similar in form to hyperbolic curves, they were used empirically to derive Vmax. This technique has also been used by other investigators.1-10

Left ventricular volumes and the ejection fraction were calculated from end-diastolic and end-systolic silhouettes using the right anterior oblique projection and the single plane area length method.11 Each ventriculogram was analyzed for the presence of regional wall motion abnormalities (asynergy) by the method of Herman et al.12 All premature contractions and immediately successive beats were excluded from analysis.

The sensitivities of the different parameters of left ventricular performance were compared by statistical methods as described in the appendix.

Results

The diagnosis, and hemodynamic, ventriculographic, and contractility data for each of the 38 patients are presented in table 1.

Comparison of Linear Manual Extrapolation and Exponential Curve Fitting for Derivation of Vmax

Vce and developed pressure data points from the basal and atrial paced rate of 100 were used from 38 patients, resulting in the analysis of a total of 76 pressure-velocity curves each of which used data points from three consecutive beats. Using a standard error of less than 15% of the derived Vmax value as a criterion for acceptance, 61 of 76 curves gave acceptable values for Vmax using the single exponential equation and 43 of 76 curves gave acceptable values for Vmax using the double exponential equation. Thus, it appears that the single exponential equation is a better approximation of the pressure-velocity curve than the double exponential equation. The values of Vmax derived by single and double exponential equations were compared to those derived by linear manual extrapolation and yielded correlation coefficients of .76 and .74, respectively. The mean of the 61 acceptable Vmax values using the single exponential equation was greater than the mean obtained by using linear manual extrapolation of the corresponding pressure-velocity curves, measuring $2.90 \pm .17 \text{ (SEM)}$ ML/sec and $2.54 \pm .07$ ML/sec, respectively ($P < 0.001$). The mean of the 43 acceptable Vmax values using the double exponential equation was also significantly greater than the mean obtained by using linear manual extrapolation of the corresponding pressure-velocity curves, measuring $2.69 \pm .17$ ML/sec and $2.50 \pm .10$ ML/sec, respectively ($P < 0.001$). Therefore, the use of single or double exponential extrapolation results in a Vmax value which corresponds closely to the value obtained by linear manual extrapolation but is greater in magnitude.

Effect of Heart Rate on Vmax (fig. 3)

For the entire group of patients the mean basal heart rate was 68 beats/min. With atrial pacing at a heart rate of 100 there was a small but significant increase in Vmax from $2.4 \pm .08$ to $2.7 \pm .11$ ML/sec ($P < 0.001$). There was considerable individual variation in the response to atrial pacing, however, which did not correlate with the presence or absence of heart disease. Vmax increased by $0.40 \pm .13$ ML/sec in patients with normal hearts and by $0.29 \pm .13$ ML/sec in patients with diseased hearts.

Contractile Indices in Normal and Diseased Hearts (fig. 4)

Vce 10 and Vmax, both in the basal state and at an atrial paced rate of 100, were compared in patients with normal hearts, patients with diseased hearts with an ejection fraction greater than .50, and patients with diseased hearts with an ejection fraction less than .50. Figure 4A illustrates that there was no significant difference in the mean basal Vce 10 values of patients with normal hearts (1.91 $\pm .12$ ML/sec) and those with diseased hearts and an ejection fraction greater than .50 (2.03 $\pm .09$ ML/sec), while patients with diseased hearts and an ejection fraction less than .50 had a significantly depressed basal mean Vce 10 value (1.53 $\pm .08$ ML/sec; $P < 0.05$). One of 16 patients with diseased hearts and an ejection fraction greater than .50 and five of 15 patients with diseased hearts and an ejection fraction less than .50 were identified as having left ventricular dysfunction by a depressed basal Vce 10 value below the normal range of 1.5 to 2.4 ML/sec. Figure 4B illustrates a similar comparison.
Table 1

Diagnosis and the Hemodynamic, Ventriculographic and Contractility Data for the 38 Patients

<table>
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<tr>
<th>Patient</th>
<th>Basal heart rate</th>
<th>Basal Vmax</th>
<th>Basal Vve 0</th>
<th>Basal Vmax</th>
<th>Basal Vve 0</th>
<th>Paced Vmax</th>
<th>Paced Vve 0</th>
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<th>EF</th>
<th>Asynergy</th>
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<td>2.23</td>
<td>2.76</td>
<td>6.8</td>
<td>.67</td>
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</table>

Group with normal hearts and an EF > .50

| MB      | 62               | 2.3        | 2.9        | 2.1        | 3.0        | 16         | .80        |       |    | No       | PMD       |
| HB      | 75               | 2.5        | 3.1        | 2.4        | 2.7        | 10         | .51        |       |    | Yes      | CAD       |
| JBo     | 68               | 1.8        | 2.1        | 4.3        | 5.2        | 34         | .71        |       |    | No       | AS        |
| JBu     | 100              | 1.2        | 1.3        | 1.2        | 1.3        | 10         | .50        |       |    | No       | ASD       |
| WE      | 61               | 2.1        | 3.4        | —          | —          | 12         | .54        |       |    | No       | Hypertension |
| HH      | 86               | 2.7        | 3.4        | 2.4        | 2.9        | 3          | .62        |       |    | No       | CAD       |
| WH      | 62               | 2.1        | 2.6        | 2.4        | 2.9        | 18         | .56        |       |    | Yes      | CAD       |
| DK      | 79               | 2.0        | 2.4        | 2.3        | 2.5        | 8          | .86        |       |    | No       | AS        |
| LK      | 79               | 1.6        | 2.3        | 2.0        | 2.6        | 7          | .63        |       |    | Yes      | CAD       |
| TL      | 71               | 2.3        | 2.9        | 2.3        | 2.9        | 6          | .68        |       |    | No       | CAD       |
| LM      | 91               | 2.2        | 2.9        | 2.4        | 2.9        | 22         | .68        |       |    | No       | PMD       |
| JP      | 73               | 1.8        | 2.3        | —          | —          | 9          | .64        |       |    | No       | CAD       |
| BR      | 61               | 1.6        | 2.4        | 2.3        | 3.0        | 14         | .68        |       |    | Yes      | CAD       |
| DS      | 88               | 2.1        | 2.6        | 2.1        | 2.6        | 2          | .62        |       |    | No       | MS        |
| RS      | 68               | 2.4        | 3.4        | 2.6        | 3.4        | 10         | .72        |       |    | No       | AS        |
| CW      | 59               | 1.8        | 2.6        | 2.0        | 2.4        | 8          | .60        |       |    | Yes      | CAD       |
| Mean    | 2.03             | 2.66       | 2.34       | 2.87       | 11.8       | .65        |           |       |    |          |           |

Group with diseased hearts and an EF < .50

| WCa     | 100              | 1.3        | 1.5        | 1.3        | 1.5        | 18         | .21        |       |    | Yes      | CAD       |
| WCh     | 45               | 1.5        | 2.1        | 1.8        | 2.6        | 6          | .45        |       |    | No       | PMD       |
| AD      | 68               | 1.3        | 1.6        | 1.4        | 1.7        | 16         | .25        |       |    | Yes      | CAD       |
| FD      | 65               | 1.9        | 2.3        | 2.3        | 3.0        | 20         | .39        |       |    | No       | CAD       |
| LD      | 57               | 1.2        | 2.0        | —          | —          | 18         | .34        |       |    | No       | PMID      |
| JDe     | 107              | 1.1        | 1.5        | 1.1        | 1.5        | 23         | .25        |       |    | Yes      | AS        |
| JF      | 56               | 1.9        | 2.5        | 1.7        | 2.3        | 18         | .25        |       |    | Yes      | CAD       |
| JG      | 91               | 1.6        | 2.2        | 1.6        | 2.2        | 29         | .17        |       |    | No       | PMD       |
| GH      | 60               | 1.5        | 2.4        | 1.8        | 2.5        | 6          | .33        |       |    | Yes      | PMD       |
| RH      | 71               | 2.0        | 2.5        | 2.4        | 3.0        | 18         | .39        |       |    | Yes      | CAD       |
| RMeK    | 70               | 1.5        | 1.8        | 2.0        | 2.4        | 7          | .31        |       |    | Yes      | CAD       |
| CK      | 53               | 1.9        | 2.5        | 2.2        | 2.6        | 8          | .32        |       |    | No       | AS        |
| HM      | 70               | 1.7        | 2.2        | 2.2        | 3.1        | 37         | .31        |       |    | No       | CAD       |
| RN      | 75               | 1.6        | 2.0        | 1.6        | 2.0        | 28         | .30        |       |    | No       | PMD       |
| JN      | 66               | 1.0        | 1.4        | 1.4        | 1.6        | 6          | .21        |       |    | No       | PMD       |
| Mean    | 1.53             | 2.03       | 1.77       | 2.28       | 17.2       | .29        |           |       |    |          |           |

and sem

| WCa     | ±.08             | ±.10       | ±.10       | ±.14       | ±.24       | ±.01       |           |       |    |          |           |

Abbreviations: PMD = primary myocardial disease; CAD = coronary artery disease; AS = aortic stenosis; ASD = atrial septal defect; LVEDP = left ventricular end-diastolic pressure; EF = ejection fraction; MS = mitral stenosis.

for basal Vmax values showing no significant difference in the mean values of patients with normal hearts (2.37 ± .12 ML/sec) and patients with diseased hearts and an ejection fraction greater than .50 (2.66 ± .13 ML/sec), while patients with diseased hearts and an ejection fraction less than .50 had a significantly depressed value (2.03 ± .10 ML/sec; P < 0.05). One of 16 patients with diseased hearts and
an ejection fraction greater than .50 and four of 15 patients with diseased hearts and an ejection fraction less than .50 had depressed basal Vmax values below the normal range of 1.8 to 2.7 ML/sec. Combining the basal values of both Vce 10 and Vmax, a total of six patients were identified as having left ventricular dysfunction.

Figure 4C illustrates that the values of Vce 10 at an atrial paced rate of 100 show no significant difference between the mean values of patients with normal hearts (2.23 ± .14 ML/sec) and those with depressed hearts and an ejection fraction greater than .50 (2.34 ± .17 ML/sec), while patients with diseased hearts and an ejection fraction less than .50 had a significantly depressed value (1.77 ± .10 ML/sec; P < 0.05). One of 14 patients with depressed hearts and an ejection fraction greater than .50 had values below the normal range of 1.7 to 2.6 ML/sec. Figure 4D illustrates that the values of Vmax at an atrial paced rate of 100 show no significant difference between the mean values of patients with normal hearts (2.76 ± .15 ML/sec) and those with depressed hearts and an ejection fraction greater than .50 (2.87 ± .21 ML/sec), while patients with diseased hearts and an ejection fraction less than .50 had a significantly depressed value (2.28 ± .14 ML/sec; P < 0.05). One of 14 patients with depressed hearts and an ejection fraction greater than .50 and six of 14 patients with diseased hearts and an ejection fraction less than .50 had values below the normal range of 2.3 to 3.1 ML/sec. Thus, the use of Vce 10 and Vmax at an atrial paced rate of 100 identified seven patients as having left ventricular dysfunction, only one more patient than was identified in the basal state. In addition, when plots similar to the above were made using Vmax values derived from single and double exponential equations, no abnormal left ventricles were detected that were not detected by linear manual extrapolation.

Relationships Between the Contractile Indices, Left Ventricular End-diastolic Pressure, Ejection Fraction, and Asynergy (fig. 5)

In figure 5, the left ventricular end-diastolic pressure of all 38 patients is plotted on the ordinate with the horizontal dashed line separating patients with normal and elevated left ventricular end-diastolic pressures using 13 mm Hg as the upper limit of normal. The ejection fraction is plotted on the abscissa with the vertical dashed line separating patients with normal and reduced ejection fractions using .50 as the lower limit of normal. There was no relation between the left ventricular end-diastolic pressure and ejection fraction. Based upon the left ventricular end-diastolic pressure and ejection fraction alone, patients in the lower right quadrant have a normal left ventricular end-diastolic pressure and ejection fraction while patients in the other three quadrants have left ventricular dysfunction. In this lower right quadrant, the presence of asynergy identified abnormal left ventricular function in three patients and depressed contractile indices identified abnormal left ventricular function in one patient. Nine patients had only a single abnormality of left ventricular function: three with asynergy, three with an elevated left ventricular end-diastolic pressure, two with a reduced ejection fraction and one with depressed contractile indices. Of the seven patients with depressed contractile indices, six had an ejection fraction less than .30 and five had an elevated left ventricular end-diastolic pressure. Of the 12 patients with asynergy, contractile indices were below the normal range in only three.

Sensitivity of Methods for Detecting Left Ventricular Dysfunction (table 2)

Combining all methods, 24 of the 38 patients were identified to have left ventricular dysfunction. Utilizing analysis of left ventricular pressure (contractile indices and the left ventricular end-diastolic pressure), 17 of these 24 patients were identified while ventriculography (ejection fraction and regional wall motion) identified 20 of the 24 patients. Although there is partial overlap between these two techniques, there was no statistical difference in the sensitivity between the use of ventricular pressure analysis and ventriculography. As pointed out above, only seven patients had depressed contractile indices. The con-

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**Figure 3**

*Effect of heart rate on Vmax. The mean basal Vmax value of 2.4 ± .08 ML/sec increased to 2.7 ± .11 ML/sec. Note the marked individual variation in the response to the increased heart rate.*
Figure 4

Contractile indices in normal and diseased hearts. The individual and mean values with their standard errors for patients with normal hearts, patients with diseased hearts and an ejection fraction greater than .50, and patients with diseased hearts and an ejection fraction less than .50 for each group are given in order in muscle lengths per second. A) Basal Vce 10: $1.91 \pm 0.12$, $2.03 \pm 0.09$, $1.53 \pm 0.08$. B) Basal Vmax: $2.37 \pm 0.12$, $2.66 \pm 0.13$, $2.03 \pm 0.10$. C) Atrial paced Vce 10 at 100: $2.23 \pm 0.14$, $2.34 \pm 0.17$, $1.77 \pm 0.10$. D) Atrial paced Vmax at 100: $2.76 \pm 0.15$, $2.87 \pm 0.21$, $2.28 \pm 0.14$.

Table 2

Number of Patients Detected to Have Left Ventricular Dysfunction

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<td>Pressure methods</td>
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<tr>
<td>Contractile indices</td>
<td>7</td>
</tr>
<tr>
<td>End-diastolic pressure</td>
<td>15</td>
</tr>
<tr>
<td>Contractile indices + end-diastolic pressure</td>
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<tr>
<td>Ventriculography</td>
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<tr>
<td>Ejection fraction</td>
<td>15</td>
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<tr>
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Contractile indices were significantly less sensitive than left ventricular end-diastolic pressure, ejection fraction or the presence of asynergy in detecting left ventricular dysfunction ($P < 0.05$). Only one patient was identified by the use of contractile indices that was not identified by any other method. The left ventricular end-diastolic pressure, ejection fraction, and presence of asynergy identified approximately equal numbers of patients with left ventricular dysfunction and were not significantly different from each other in their sensitivity. However, since there was only a partial overlapping of patients identified to have left ventricular dysfunction by different parameters, the co-

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bination of parameters improved the ability to identify left ventricular dysfunction over any single parameter used alone. The combined analyses of regional wall motion and the measurement of the ejection fraction was 16% more sensitive than measurement of the ejection fraction alone (P < 0.05). Analysis of left ventricular pressure in addition to analysis of the left ventriculogram was 17% more sensitive than analysis of the left ventriculogram alone (P < 0.05). Conversely, the analysis of the left ventriculogram in addition to analysis of left ventricular pressure was 29% more sensitive than the analysis of left ventricular pressure alone (P < 0.05).

Discussion

This study compares the sensitivity of several methods for assessing left ventricular function in man and demonstrates that several parameters are required to identify all patients with left ventricular dysfunction. Any single parameter is equally sensitive to any other except for the contractile indices which are predominantly sensitive only to advanced stages of left ventricular dysfunction. Calculation of the ejection fraction, analysis of regional wall motion, and measurement of the end-diastolic pressure, identify the majority of patients with left ventricular dysfunction.

There are at least five factors which might have contributed to the insensitivity of the contractile indices. In the current study, these factors were identified and avoided. First, although the use of fluid-filled catheters has been advocated to make measurements of left ventricular pressure and its first derivative,13 possible errors inherent in these techniques which could decrease the frequency response of the system were eliminated by the use of transducer tip catheters in every patient. Second, measurements of myocardial contractility in both isolated and intact heart prepa-

Figure 5

Relationships between the contractile indices, left ventricular end-diastolic pressure, ejection fraction, and the presence of asynergy.

Rations have been shown to be rate dependent14-17 due to the treppe phenomenon of Bowditch.18 A common atrial paced rate of 100 was used in an attempt to avoid rate-dependent differences in contractility between patients, but this did not produce a significant increase in the sensitivity of the contractile indices. Third, the extrapolation of Vce to zero pressure (Vmax) has been criticized on both theoretical and practical grounds.18, 20 Although this is more of a problem when using total rather than developed pressure to derive Vmax, the results of linear manual extrapolation were compared to computer curve fitting utilizing both single and double exponential equations. Although the Vmax values obtained by exponential curve fitting gave higher values for Vmax, they corresponded closely to the values derived by linear manual extrapolation and did not alter the ability of this method to detect left ventricular dysfunction. In addition, the problem of extrapolation was avoided by the use of Vce 10 which is a directly measured point on the pressure-velocity curve. Fourth, patients with mitral or aortic regurgitation were excluded since the absence of an isovolumic period invalidates the assumption made to calculate Vce. Finally, a major problem in evaluating the sensitivity of any method is the availability of suitable control data. Inclusion of patients with undetected left ventricular dysfunction into a control group could falsely broaden the range for normal values of any index and reduce the apparent sensitivity of the method. The rigid definition of a normal heart in the current study, which requires the absence of any known congenital or acquired heart disease, normal hemodynamic and ventriculographic findings, and a normal coronary arteriogram, excludes as thoroughly as possible patients with heart disease and undetected left ventricular dysfunction. Thus, the low sensitivity of the contractile indices should not be related to a false lower limit of the normal values. Few additional control data are available in the literature for the range of contractile indices using developed pressure in adult patients with normal hearts. Graham et al. calculated Vmax in 20 children with congenital heart disease and no apparent left ventricular dysfunction.9 They found a mean of 3.3 ML/sec as compared to our seven normal patients who had a mean of 2.37 ML/sec. However, their data are not comparable to the current study since their data were from young children with faster basal heart rates, a series elastic constant of 28 was used, an exponential extrapolation to 0 pressure was used, and the effect of associated congenital lesions on left ventricular function is incompletely understood. The data of Peterson et al. are more comparable to the present data even though they used a series elastic constant of 28 to calculate
Vce. In 22 patients with normal left ventricular function, they found a range of Vmax values from 1.32 to 2.93 ML/sec, which is similar to the present study.

Other factors which may decrease the sensitivity of the contractile indices could not be avoided. The muscle model utilized is only an approximation and may be a source of some error. We chose developed pressure to calculate the contractile element velocity since the use of total pressure has been shown to give values for Vmax which are preload dependent. Since an elevated left ventricular end-diastolic pressure can in itself depress the value obtained for Vmax when total pressure is used, the calculation of Vmax utilizing total pressure would seem to offer little advantage over the simpler measurement of the left ventricular end-diastolic pressure. The use of a common series elastic constant in all patients may also be a serious problem. The series elastic constant and the effect of disease states on this constant have not been measured in man. It has been shown in animals, however, that the series elastic constant is unchanged from the normal value in animals with hypertrophy or congestive heart failure. The use of the contractile indices in the presence of asynergy may be criticized. It is certainly true that the values of Vce 10 and Vmax obtained in these patients represent an average value for the total heart. However, this does not detract from their potential use as an empiric means of identifying abnormal left ventricular function in these patients. Nevertheless, it should be emphasized that left ventricular dysfunction was not detected by the use of contractile indices in 9 of 12 patients with asynergy or in 9 of 15 patients with reduced ejection fractions.

The demonstration of the insensitivity of the contractile indices is consistent with several previous studies (table 3). Simon et al. found that the value of maximum Vce using total pressure (termed Vmax in their study) was significantly depressed in patients who had a left ventricular end-diastolic pressure greater than 14 mm Hg. Levine et al. studied 12 patients with aortic stenosis and calculated Vmax from estimations of aortic flow as well as dp/dt / P using total pressure. They found depressed Vmax values in four of these 12 patients and all four had overt congestive heart failure with mean left ventricular diastolic pressures greater than 10 mm Hg. Graber et al. studied 18 patients and noted a wide scatter of basal Vmax values (.6 to 4 ML/sec) with significant depression of basal Vmax values in only three patients, all of whom had a marked reduction of their ejection fraction (.27 or less) and an elevation of their left ven-

Table 3
Summary of Studies Which Compare the Sensitivity of the Isovolumic Indices to Conventional Parameters of Left Ventricular Function

<table>
<thead>
<tr>
<th>Author</th>
<th>Isovolumic index</th>
<th>Derivation of index</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simon et al.</td>
<td>Peak Vce</td>
<td>Total pressure</td>
<td>LVEDP as sensitive to LV dysfunction as peak Vce.</td>
</tr>
<tr>
<td>Levine et al.</td>
<td>Vmax</td>
<td>Total pressure</td>
<td>LVEDP as sensitive to LV dysfunction as Vmax.</td>
</tr>
<tr>
<td>Graber et al.</td>
<td>Vmax</td>
<td>Total pressure</td>
<td>LVEDP and EF as sensitive to LV dysfunction as Vmax. Large reduction of EF before Vmax is depressed.</td>
</tr>
<tr>
<td>Parmley et al.</td>
<td>Vce 5</td>
<td>Developed pressure</td>
<td>LV stroke work index and LVEDP better predictors of survival than Vce 5 in patients with acute myocardial infarction.</td>
</tr>
<tr>
<td>Hugenbolt et al.</td>
<td>Vmax</td>
<td>Stress-velocity data</td>
<td>Considerable overlap of Vmax values between patients who had normal and abnormal LV function as determined by conventional criteria.</td>
</tr>
<tr>
<td>Mason et al.</td>
<td>Vmax</td>
<td>Total pressure</td>
<td>Overlap of Vmax values between patients who were normal, had LV hypertrophy, and those who had congestive heart failure.</td>
</tr>
<tr>
<td>Krayenbuel et al.</td>
<td>Vmax</td>
<td>Total pressure</td>
<td>Basal Vmax an insensitive indicator of LV dysfunction. Stress (isometric exercise) required to identify patients with LV dysfunction.</td>
</tr>
<tr>
<td>Falsetti et al.</td>
<td>Vmax</td>
<td>Total pressure (fluid filled catheters)</td>
<td>Vmax more sensitive than EF.</td>
</tr>
<tr>
<td>Peterson et al.</td>
<td>Vmax, peak dp/dt, Vce 5, Vee 10, Vee 40</td>
<td>Total and developed pressure</td>
<td>Ejection phase (EF, Vef) indices more sensitive than isovolumic indices.</td>
</tr>
<tr>
<td>Graham et al.</td>
<td>Vmax</td>
<td>Total and developed pressure</td>
<td>Patients with hypertrophied left ventricles may have a depressed Vmax only when total pressure is used.</td>
</tr>
</tbody>
</table>

Abbreviations: LVEDP = left ventricular end-diastolic pressure; LV = left ventricle; EF = ejection fraction.

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tricular end-diastolic pressure. They found that conventional techniques of pump performance (left ventricular stroke work index and left ventricular end-diastolic pressure) were more sensitive than Vce at 5 mm Hg developed pressure. Hugenholz et al. studied 33 children and compared conventional criteria of left ventricular function (end-diastolic volume, ejection fraction, left ventricular end-diastolic pressure) with Vmax derived from stress-velocity data. There was considerable overlap of Vmax values between patients who were normal or abnormal based on the conventional criteria. Although they concluded that Vmax gave additional information regarding the functional state of the left ventricle, the overlap of Vmax values between patients with normal and abnormal conventional criteria as well as the lack of a suitable control group, makes their conclusions uncertain. Mason et al. calculated Vmax using total pressure in 18 patients with apparent left ventricular disease, in 17 patients with left ventricular hypertrophy, and in 9 patients with overt congestive heart failure. Even though these patients could be separated as groups, the range of normal values was not defined so that identification of ventricular dysfunction on the basis of Vmax in a single patient remains uncertain. Krayerbuehl et al. studied 110 patients using total pressure to calculate Vce. It was found that in the basal state, Vmax was an insensitive indicator of left ventricular dysfunction and that measurement of Vmax in a stressed state (isometric exercise in their study) was necessary to identify individual patients with left ventricular dysfunction. Falsetti et al. compared several indices of left ventricular performance in a group of 45 patients including 19 patients with either mitral or aortic regurgitant lesions. They calculated Vce from pressures measured with fluid-filled catheters and suggested that Vmax, based upon total pressure, was more sensitive than the ejection fraction. These conclusions do not seem warranted since many of these patients had significant valvular regurgitant lesions which violates the assumption of an isovolumic period needed to calculate Vce, valvular lesions may produce congestive heart failure in spite of unaltered myocardial function, there was a lack of a clearly defined control group, and uncertainties in the reliability of an adequate frequency response may be introduced by the use of fluid-filled catheters. More recently, Peterson et al. found that ejection phase indices were more sensitive to left ventricular dysfunction than isovolumic indices.

All but two of the above studies utilized total pressure to calculate Vce and some of the low values of Vmax may be explained by the depressed Vmax values in patients with elevated left ventricular end-diastolic pressures when total pressure is used to calculate Vce. This possibility is emphasized by Graham et al. who calculated Vmax in 20 children with congenital heart disease associated with apparently normal left ventricular function, and in 15 children with a left ventricular pressure overload associated with left ventricular hypertrophy. They showed that a significant difference in Vmax values between the two groups existed only when total pressure was used.

In addition to being sensitive, the ideal parameter for assessing left ventricular function should be specific, easily performed, reproducible, have the ability to assess regional function, be preload and afterload independent, have quantitative value, and give prognostic information. The current study suggests that the contractile indices, although insensitive, are specific for advanced stages of left ventricular dysfunction. They are also reproducible from beat to beat and may be independent of preload and afterload when developed pressure is used to calculate Vce. However, they are not easily derived, particularly without the aid of a computer, and cannot assess regional function. The measurement of the left ventricular end-diastolic pressure is certainly easily performed and reproducible but has limitations.

The uncertainty of the proper positioning of the external pressure transducer and relating ventricular pressure to atmospheric rather than intrapacardial pressure, may introduce significant errors. It is a poor predictor of end-diastolic volume in both normal and disease states. It is not a direct measure of left ventricular performance and gives little quantitative information regarding the state of left ventricular performance. This is particularly true within the normal range of pressures where large volume changes which produce significant changes in left ventricular performance may result in small changes in left ventricular end-diastolic pressure. Further evidence of this phenomenon may be seen in patients with an increased afterload, increased left ventricular mass, or both since these patients may have an elevated end-diastolic pressure without apparent alteration of contractile performance. Furthermore, patients with circulatory congestion from other causes may have elevations of end-diastolic pressure without ventricular dysfunction. Nevertheless, since these measurements are made in the clinical setting usually under conditions where intravascular volumes are normal, elevations of the left ventricular end-diastolic pressure are most often related to impaired left ventricular performance or a change in the normal ventricular pressure-volume relationships. Thus, in spite
of these limitations, an elevated left ventricular end-diastolic pressure serves as a useful and simple index which identifies a left ventricular abnormality. The nature and extent of this abnormality must then be defined by other techniques.

Dimensional analysis of the left ventriculogram, so that the ejection fraction and a qualitative analysis of regional wall motion are obtained, is the single most useful technique presently available for assessing left ventricular performance. It is the only method which can identify the presence of asynergy, which may be an important determinant of over-all left ventricular function.\textsuperscript{12} Under basal conditions the ejection fraction appears to be quite specific even in the presence of valvular heart disease,\textsuperscript{31} has quantitative value, and has been shown to have prognostic value in determining both the natural history and results of surgery in patients with coronary artery disease,\textsuperscript{35, 37} primary myocardial disease,\textsuperscript{38, 39} and valvular heart disease.\textsuperscript{40} The ejection fraction is reproducible\textsuperscript{41} except in the presence of atrial fibrillation where considerable beat-to-beat variation may occur.\textsuperscript{42} This variation of the ejection fraction is probably related to its dependence on acute changes in preload and afterload.\textsuperscript{43, 44} However, chronic changes in preload and afterload do not appear to alter the ejection fraction as much, so that it remains a useful index of left ventricular performance.\textsuperscript{45} This method requires detailed analysis of only two cine frames. It does have problems in mathematic modeling, precision of border definition, particularly in end-systole, and the difficulties of repeated injections of contrast material involved in repeated measurements.\textsuperscript{2} The single plane method, while less sensitive than the biplane method,\textsuperscript{46} still retains considerable sensitivity as shown by the present study.

There is also information available from the ventriculogram which has not been analyzed in this study. This includes the determination of left ventricular mass,\textsuperscript{47} fiber shortening rates (Vcf, both instantaneous and mean)\textsuperscript{48, 49} and an analysis of ventricular shape changes.\textsuperscript{38} The simultaneous measurement of pressure and volume is now becoming more feasible with the advances in the technical design of appropriate catheters. This will allow the assessment of the instantaneous relations between stress, velocity, and length on a more routine basis which may give additional useful information concerning left ventricular function in the clinical setting.

### Appendix

The comparisons of the sensitivities of the parameters of left ventricular function were carried out in the following manner.\textsuperscript{50} For a large sample, the sensitivity of a given test (parameter) is defined as the ability of that test to detect an abnormality when left ventricular dysfunction is truly present. This study defines a left ventricle to have normal function if all parameters of left ventricular function included in the study are normal and to have abnormal function if any single parameter is abnormal.

The sensitivities of any two tests are defined as (table 4):

\[
sensitivity \text{ of test } x = \frac{a + c}{N}
\]

\[
sensitivity \text{ of test } y = \frac{a + b}{N}
\]

The sensitivity of test \( x \) can be compared with the sensitivity of test \( y \) by a nonparametric Chi-square test using the following formula:

\[
x^2 = \frac{[|b - c| - 1]^2}{b + c}
\]

If \( x^2 \) (observed) is greater than \( x^2 \) from the Chi-square table using 1 degree of freedom at the 0.05 level of significance, then test \( x \) is statistically more sensitive than test \( y \) (\( P < 0.05 \)).

However, while comparing the sensitivity of a combination of tests with the sensitivity of one of the tests singly, it is necessary to evaluate the improvement due to the combination of tests over the single test. When comparing test \( C \) (the combination of \( x \) and \( y \)) with test \( x \), the improvement of \( C \) over \( x \) is conditional upon the number of cases detected as normal by \( x \) or the improvement of \( C \) over \( x \) can be expressed by the ratio:

\[
\frac{\text{abnormals in } C \text{ undetected by } x \text{ observed normals in } x}{\text{normals in } x}
\]

and the percent improvement (\( P \)) of \( C \) over \( x \) is:

\[
P = \frac{\text{abnormals in } C - \text{abnormals in } x}{\text{normals in } x} \times 100
\]

The hypothesis of no improvement was tested by using the \( z \) test which is defined as:

\[
z = \sqrt{\frac{P - p_0}{p_0(1 - p_0)}}
\]

where \( P = \text{calculated (actual) percentage improvement of } C \text{ over } x \), \( p_0 = \text{hypothetical percentage improvement of } C \text{ over } x \) against which the actual percentage improvement is tested, and \( N_0 = \text{number of normals observed in test } x \).

This hypothesis was tested at the 0.05 level of significance.

### Table 4

<table>
<thead>
<tr>
<th>Test x</th>
<th>Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>a + b</td>
<td>a + c</td>
<td>b + d</td>
</tr>
</tbody>
</table>

**Abbreviations:** \( a, b, c, \) and \( d \) = the number of patients in each of four groups defined as normal or abnormal by tests \( x \) and \( y \); \( N = \text{the total number of patients examined.} \)
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Circulation, Volume 51, April 1973


Correction

The correct authorship of Acute Myocardial Infarction in Toxic Cardiomyopathy without Coronary Obstruction (Circulation 51: 453, 1975) is:
Timothy J. Regan, M.D., Chia F. Wu, M.D., Allen B. Weisse, M.D., Christos B. Moschos, M.D., S. Sultan Ahmed, M.D., Michael M. Lyons, M.D., and Bunyad Haider, M.D.

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T H Kreulen, A A Bove, M T McDonough, M J Sands and J F Spann

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