Systolic Time Intervals as Measures of the Contractile State of the Left Ventricular Myocardium in Man

By S. Sultan Ahmed, M.D., Gilbert E. Levinson, M.D., Carl J. Schwartz, M.D., and Philip O. Ettinger, M.D.

SUMMARY

Previous studies relating systolic time intervals and measures of cardiac performance have suggested that the time intervals may be useful indices of myocardial contractility. To explore this possibility, systolic times and left ventricular (LV) performance and contractility were measured nearly simultaneously in 14 normal subjects and 56 patients with cardiac disease. Pre-ejection period (PEP) and the ratio of PEP to LV ejection time (LVET) changed significantly with acute inotropic influences (exercise and isoproterenol), were normal in patients with right or left ventricular overloads in whom cardiac index and ejection fraction were depressed but contractile element velocity at peak dP/dt and the Frank-Levinson contractility index were normal, and were significantly abnormal in patients with either clinically evident or occult LV decompensation in whom the measures of contractility were reduced. Correlations of PEP and PEP/LVET with measures of both performance and contractility were insignificant for patients with valvular disease, shunts, or cor pulmonale and significant but weak for the entire series. However, in subjects with either normal left ventricles or cardiac disease confined to the left ventricle, PEF and PEP/LVET exhibited good correlations with measures of pump function and excellent correlations with measures of contractility. These results indicate that the systolic times are a valid measure of contractility which should prove useful in comparing patients with cardiac pathology confined to the LV myocardium and in following patients with extramyocardial hemodynamic lesions of constant severity.

Additional Indexing Words:
Heart failure Phonocardiography Carotid pulse Myocardiopathy

The durations of the phases of cardiac activity have long been of interest to physiologists and clinicians.1−8 Recently, Weissler and his associates9−11 have popularized the technic, described by Katz and Feil,12 of defining the phases of systole from simultaneous electrocardiogram, phonocardiogram, and central arterial pulse tracing. These noninvasive measurements have proved useful investigatively13−18 and clinically.19−23 Clearly, the systolic time intervals are parameters of cardiac pump function, specifically of the performance of the left ventricle (LV). Recently, it has been suggested that these intervals may also be useful parameters of cardiac tissue function, i.e., of the contractile state of the LV myocardium.24−29

Studies of isolated papillary muscle have shown that the reciprocal relation between force and velocity of contraction, reported by
Hill\textsuperscript{30} to be a fundamental mechanical property of skeletal muscle, may also characterize the contractile state of heart muscle.\textsuperscript{31-33} The applicability of the force-velocity-length relation to cardiac tissue has been confirmed by studies performed on the intact hearts of anesthetized animals\textsuperscript{34, 35} and in human subjects in whom roentgen-opaque markers had been sutured to the ventricles during cardiac surgery.\textsuperscript{36} Several indices of contractility have been described using data obtained by left heart catheterization in intact human subjects.\textsuperscript{37-41}

The present study was undertaken to determine the relationships, in normal and diseased hearts, between systolic time intervals and direct measurements of myocardial contractility obtained by invasive technics.

\textbf{Methods}

Seventy subjects, grouped as shown in table 1 on the basis of clinical and hemodynamic findings, were studied by right and left heart catheterization in the basal, postabsorptive state under mild barbiturate sedation and local procaine analgesia. Clinically essential medications, including digitalis, were not discontinued. All subjects were studied at rest and some during supine bicycle exercise or intravenous isoproterenol administration.

Catheters were positioned in main pulmonary artery, LV apex, and aortic root. The LV was entered by the transseptal technic (not used in normal subjects) or by retrograde catheterization via the right brachial artery (6F or 7F NIH catheters, 80 cm long). The aortic catheter was either a polyethylene catheter (id 1.13 mm, 70 cm long) introduced through the left brachial artery by the Stille-Seldinger technic or an NIH catheter introduced via right brachial arteriotomy. Its tip was advanced into the LV and then withdrawn into the aortic root 1-2 cm above the valve. Pressures were recorded simultaneously from LV and aorta using Statham strain gauges and an oscillographic recorder. Because of its high-frequency response, the Statham P23Gb gauge was used for recording the LV pulse. The LV dP/dt was obtained using a resistance-capacitance differentiating circuit (time constant 1.1 msec) connected to the output of the pressure channel. The maximum error of the differentiator is approximately 0.9% when summing the fundamental with the 10th harmonic.\textsuperscript{39} Knopp, Rahimtoola, and Swan have demonstrated that conventional catheter systems and a circuit of this type provide a satisfactory method for recording the derivative within the physiologic range of man.\textsuperscript{42}

The LV ejection fraction was measured by indicator dilution.\textsuperscript{43} Indocyanine green dye (Cardio-Green, Hynson, Westcott, and Dunning, Inc.) was introduced into the LV by sudden injection, and blood was sampled at a rate of 2.0 ml/sec through the aortic catheter and a Gilford densitometer by means of a Harvard withdrawal pump. The sampling dead space ranged from 1.0 to 1.5 ml, and the 90% response time for the catheter-densimeter system was approximately 0.6 sec. For these curves, concentration was plotted semilogarithmically as a function of stroke number. Except for the initial one or two beats on some curves, concentrations uniformly fell on a single slope of exponential decay. From this slope, the ejection fraction, which is the ratio of stroke volume to end-diastolic volume, was calculated. The results of two or more measurements of

\textbf{Table 1}

Diagnoses and Numbers of Subjects Studied

\begin{tabular}{lll}
\hline
Group & Abnormality & Subjects (no.) & Total (no.) \\
\hline
I & None & 14 & 14 \\
II & Right ventricular overload: & & \\
& a. Pure mitral stenosis & 9 & 23 \\
& b. Cor pulmonale & 9 & \\
& c. Uncomplicated atrial septal defect & 5 & \\
III & Left ventricular disease, compensated: & & \\
& a. Aortic valve disease & 10 & 21 \\
& b. Cardiomyopathy (alcoholic or idiopathic) & 6 & \\
& c. Hypertensive heart disease & 5 & \\
IV & Left ventricular dysfunction, decompensated: & & \\
& a. Aortic valve disease & 7 & \\
& b. Cardiomyopathy & 5 & \\
\hline
\end{tabular}

\textit{Circulation, Volume XLVI, September 1972}
SYSTOLIC TIME INTERVALS

Mean Values at Rest (± SEM)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEP/LVET (msec)</td>
<td>0.379 ± 0.015</td>
<td>0.414 ± 0.018</td>
<td>0.460* ± 0.020</td>
<td>0.513* ± 0.037</td>
</tr>
<tr>
<td>PEP (msec)</td>
<td>107 ± 5</td>
<td>109 ± 4</td>
<td>122* ± 4</td>
<td>141† ± 12</td>
</tr>
<tr>
<td>LVET (msec)</td>
<td>284 ± 12</td>
<td>267 ± 6</td>
<td>271 ± 8</td>
<td>299 ± 12</td>
</tr>
<tr>
<td>Cylx (liters/min/m²)</td>
<td>1.29 ± 0.04</td>
<td>1.30 ± 0.05</td>
<td>1.20 ± 0.08</td>
<td>0.73‡ ± 0.07</td>
</tr>
<tr>
<td>VCE (cm/sec)</td>
<td>25.8 ± 0.9</td>
<td>25.0 ± 1.0</td>
<td>23.6 ± 2.0</td>
<td>17.31‡ ± 1.6</td>
</tr>
<tr>
<td>CI (liters/min/m²)</td>
<td>3.48 ± 0.19</td>
<td>2.75† ± 0.12</td>
<td>2.71* ± 0.18</td>
<td>2.09‡ ± 0.12</td>
</tr>
<tr>
<td>EF (%)</td>
<td>53.2 ± 1.8</td>
<td>41.2‡ ± 3.4</td>
<td>35.2‡ ± 2.4</td>
<td>20.0‡ ± 1.0</td>
</tr>
</tbody>
</table>

Abbreviations: PEP = preejection period; LVET = left ventricular ejection time; Cylx = the Frank-Levinson index of contractility; VCE = contractile element velocity at peak dP/dt; CI = cardiac index; EF = left ventricular ejection fraction.

*†‡ Statistically significant differences from the mean values of group I: * = P < 0.05; † = P < 0.01; and ‡ = P < 0.001.

Table 2

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ejection fraction were averaged in each subject for each state.

Cardiac output, except in patients with atrial septal defect, was measured from indocyanine green dilution curves sampled from the aortic root after pulmonary artery or right atrial injection. For these curves, concentration was plotted semilogarithmically as a function of time and extrapolated to 1% of peak concentration. Areas were obtained by summation of the concentrations, and forward flow was calculated by the method of Kinsman, Moore, and Hamilton. Mean stroke volume was obtained as the average from two or more such curves in each state. In patients with atrial septal defect, stroke volume was obtained from aortic dilution curves during continuous infusions of dye into the LV. This technique has been shown to yield accurate measurements of minute flow. End-diastolic volume was calculated as the ratio of mean stroke volume to mean ejection fraction. In the case of aortic regurgitation the appropriate ratio is that of forward stroke volume to ejection fraction, knowledge of regurgitant and total stroke volumes being required only for the calculation of end-systolic and not of end-diastolic volume. LV radius was calculated on the assumption that the chamber was a sphere at the end of the isovolumetric period, and the circumferential fiber length was calculated as 2πr.

Assuming a uniform series elastic constant, the velocity of the contractile element (VCE) at peak dP/dt was calculated as the ratio of dP/dtmax (the maximum rate of LV pressure rise) in mm Hg/sec to simultaneous LV pressure, in accordance with Levine et al. The Frank-Levinson index of contractility (Cylx) was calculated as (dP/dtmax/MIP)/2πr, where MIP is the maximum isovolumic (aortic diastolic) pressure and r is the end-diastolic radius of the LV.

Systolic time intervals were obtained from the intravascular aortic pulse tracings and the electrocardiogram. The time from the Q wave to the incisura of the aortic pulse is the duration of total electromechanical systole. LV ejection time (LVET) was measured from onset to incisura of the aortic pulse. The preejection period (PEP) was obtained by subtracting LVET from the duration of total electromechanical systole. The PEP/LVET ratio was calculated in each instance.

Statistical analyses were performed using conventional methods for small samples. Differences between groups were evaluated by Student's t test. Correlations were measured using the correlation coefficient r.

Results

Differences Between the Groups

The mean values for all data for all groups at rest are shown in table 2. It will be noted that PEP and PEP/LVET did not differ significantly from normal in patients with RV overloads (group II) but were significantly
Table 3

Mean Values at Rest (± SEM) for Normal Subjects and those with Compensated Left Ventricular Disease

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group I</th>
<th>Group IIa</th>
<th>Group IIb</th>
<th>Group IIc</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEP/LVET (msec)</td>
<td>0.379</td>
<td>0.420</td>
<td>0.491*</td>
<td>0.503‡</td>
</tr>
<tr>
<td>±0.015</td>
<td>±0.029</td>
<td>±0.05</td>
<td>±0.027</td>
<td></td>
</tr>
<tr>
<td>PEP (msec)</td>
<td>107</td>
<td>120</td>
<td>124</td>
<td>125*</td>
</tr>
<tr>
<td>±5</td>
<td>±6</td>
<td>±11</td>
<td>±8</td>
<td></td>
</tr>
<tr>
<td>LVET (msec)</td>
<td>284</td>
<td>290</td>
<td>258</td>
<td>250</td>
</tr>
<tr>
<td>±12</td>
<td>±13</td>
<td>±16</td>
<td>±8</td>
<td></td>
</tr>
<tr>
<td>Cylx</td>
<td>1.29</td>
<td>1.5*</td>
<td>0.93†</td>
<td>0.91†</td>
</tr>
<tr>
<td>±0.04</td>
<td>±0.09</td>
<td>±0.10</td>
<td>±0.09</td>
<td></td>
</tr>
<tr>
<td>Vce</td>
<td>25.8</td>
<td>29.1</td>
<td>18.9†</td>
<td>18.2‡</td>
</tr>
<tr>
<td>±0.9</td>
<td>±3.0</td>
<td>±2.40</td>
<td>±1.89</td>
<td></td>
</tr>
<tr>
<td>CI (liters/min/m²)</td>
<td>3.48</td>
<td>2.51†</td>
<td>2.42*</td>
<td>3.27</td>
</tr>
<tr>
<td>±0.19</td>
<td>±0.20</td>
<td>±0.43</td>
<td>±0.36</td>
<td></td>
</tr>
<tr>
<td>EF (%)</td>
<td>53.2</td>
<td>31.1‡</td>
<td>34.3†</td>
<td>42.7*</td>
</tr>
<tr>
<td>±1.8</td>
<td>±3.2</td>
<td>±6.3</td>
<td>±3.2</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations and symbols as in table 2.

Increased in the presence of LV disease whether compensated (group III) or decompensated (group IV), and were more markedly elevated in the latter group. LVET played no role in the increased PEP/LVET since it was not significantly altered in any of these groups. The mean values for the Frank-Levinson index of contractility and the contractile element velocity at peak dP/dt were normal in patients without LV disease (group II) and in those with clinically compensated LV disease (group III) but were significantly depressed in clinically decompensated LV disease. In contrast, mean cardiac index and ejection fraction were significantly below the normal mean values in all patient groups with or without LV disease and with or without clinical decompensation. Thus, it is seen from the data of groups II and III that, with normal contractility and comparable deficits in

Table 4

Responses to Inotropic Stimuli

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Exercise (N = 29)</th>
<th>Isoproterenol (N = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cont</td>
<td>Expt</td>
</tr>
<tr>
<td>PEP/LVET (msec)</td>
<td>0.439</td>
<td>0.391</td>
</tr>
<tr>
<td>±0.020</td>
<td>±0.018</td>
<td>±1.5</td>
</tr>
<tr>
<td>PEP (msec)</td>
<td>119</td>
<td>100</td>
</tr>
<tr>
<td>±4</td>
<td>±4</td>
<td>±2.2</td>
</tr>
<tr>
<td>LVET (msec)</td>
<td>276</td>
<td>257</td>
</tr>
<tr>
<td>±6</td>
<td>±6</td>
<td>±1.6</td>
</tr>
<tr>
<td>Cylx</td>
<td>1.17</td>
<td>1.44</td>
</tr>
<tr>
<td>±0.06</td>
<td>±0.08</td>
<td>±3.9</td>
</tr>
<tr>
<td>Vce</td>
<td>23.1</td>
<td>29.1</td>
</tr>
<tr>
<td>±1.1</td>
<td>±1.5</td>
<td>±4.6</td>
</tr>
<tr>
<td>CI (liters/min/m²)</td>
<td>2.79</td>
<td>4.31</td>
</tr>
<tr>
<td>±0.12</td>
<td>±0.22</td>
<td>±5.7</td>
</tr>
<tr>
<td>EF (%)</td>
<td>41.0</td>
<td>44.0</td>
</tr>
<tr>
<td>±2.5</td>
<td>±2.6</td>
<td>±3.0</td>
</tr>
</tbody>
</table>

Abbreviations: Cont = control data before exercise or isoproterenol; Expt = experimental data during exercise or isoproterenol. Other abbreviations and symbols as in tables 2 and 3.
performance (CI and EF), PEP/LVET may be either normal (group II) or significantly increased (group III) and, from the data of groups III and IV, that PEP/LVET may be increased in the presence of either normal (group III) or depressed (group IV) contractility.

There were no differences among the three subgroups of group II or between the two subgroups of group IV but within group III there were disparities among the three subgroups (table 3). The patients with aortic valve disease (group IIIa), with significant depression in CI and EF but with normal VCE and slightly but significantly elevated Cylx, exhibited no significant alteration in PEP/LVET. However, those with myocardiopathy (group IIIb), who had comparable depressions in systemic performance characteristics but also a deficit in contractility, exhibited a significant elevation in PEP/LVET. Moreover, the patients with hypertensive heart disease (group IIIc) also showed significant elevation in PEP/LVET in association with depressed contractility in the presence of normal CI and only slightly reduced EF.

Responses to Inotropic Stimuli
Twenty-nine subjects, including eight normal, were exercised (table 4). It will be noted that PEP/LVET, PEP, and LVET decreased significantly while Cylx, VCE, CI, and EF exhibited significant increases. The principal change in systolic times was a shortening of PEP. The Cylx and VCE showed increases of comparable magnitude. The rise in CI was due chiefly to a 33% mean acceleration of heart rate and partly to a 16% mean augmentation of stroke volume.

Seven patients were studied during isoproterenol infusion. Responses were similar to

### Table 5
Correlations among Contractility Measures, Performance Characteristics, and Systolic Time Intervals

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PEP/LVET vs PEP</td>
<td>0.89†</td>
<td>0.91‡</td>
<td>0.92‡</td>
<td>0.92‡</td>
<td>0.93‡</td>
</tr>
<tr>
<td>LVET</td>
<td>-0.40†</td>
<td>-0.28*</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Cylx</td>
<td>-0.51‡</td>
<td>-0.70‡</td>
<td>-0.72‡</td>
<td>-0.77‡</td>
<td>-0.86‡</td>
</tr>
<tr>
<td>VCE</td>
<td>-0.51‡</td>
<td>-0.67‡</td>
<td>-0.68‡</td>
<td>-0.74‡</td>
<td>-0.83‡</td>
</tr>
<tr>
<td>EF</td>
<td>-0.35†</td>
<td>-0.61‡</td>
<td>-0.62‡</td>
<td>-0.65‡</td>
<td>-0.73‡</td>
</tr>
<tr>
<td>CI</td>
<td>-0.24*</td>
<td>-0.42‡</td>
<td>-0.39†</td>
<td>-0.43†</td>
<td>-0.53†</td>
</tr>
<tr>
<td>PEP vs LVET</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Cylx</td>
<td>-0.51‡</td>
<td>-0.66‡</td>
<td>-0.70‡</td>
<td>-0.73‡</td>
<td>-0.82‡</td>
</tr>
<tr>
<td>VCE</td>
<td>-0.45‡</td>
<td>-0.65‡</td>
<td>-0.68‡</td>
<td>-0.71‡</td>
<td>-0.79‡</td>
</tr>
<tr>
<td>EF</td>
<td>-0.33</td>
<td>-0.47‡</td>
<td>-0.53‡</td>
<td>-0.54‡</td>
<td>-0.67‡</td>
</tr>
<tr>
<td>CI</td>
<td>-0.29*</td>
<td>-0.46‡</td>
<td>-0.47†</td>
<td>-0.51‡</td>
<td>-0.62‡</td>
</tr>
<tr>
<td>LVET vs Cylx</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>VCE</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>EF</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>CI</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Cylx vs VCE</td>
<td>0.82‡</td>
<td>0.95‡</td>
<td>0.96‡</td>
<td>0.97‡</td>
<td>0.96‡</td>
</tr>
<tr>
<td>EF</td>
<td>0.40‡</td>
<td>0.55‡</td>
<td>0.57‡</td>
<td>0.59‡</td>
<td>0.73‡</td>
</tr>
<tr>
<td>CI</td>
<td>NS</td>
<td>0.31*</td>
<td>0.31*</td>
<td>0.39*</td>
<td>0.52†</td>
</tr>
<tr>
<td>VCE vs EF</td>
<td>0.33‡</td>
<td>0.51‡</td>
<td>0.51‡</td>
<td>0.50‡</td>
<td>0.64‡</td>
</tr>
<tr>
<td>CI</td>
<td>0.32†</td>
<td>0.43‡</td>
<td>0.42‡</td>
<td>0.43‡</td>
<td>0.57†</td>
</tr>
<tr>
<td>EF vs CI</td>
<td>0.57‡</td>
<td>0.55‡</td>
<td>0.33‡</td>
<td>0.32†</td>
<td>0.52†</td>
</tr>
</tbody>
</table>

*P < 0.05.
†P < 0.01.
‡P < 0.001.
§This analysis excluded groups II, IIIa, and IVa, and also two patients of IIIc whose hypertensive heart disease was accompanied by mild mitral stenosis.

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those with exercise but changes in contractility were more marked than those in systolic times and in pump performance. Increase in systemic flow was again due principally to cardioacceleration (mean 37%) and in lesser part to increased stroke volume (mean 21%).

**Correlations among the Various Measurements**

The correlations for all pairs of variables are shown in table 5. For the entire series of 70 subjects, PEP/LVET exhibited significant correlations with all of the other variables. These correlations, except for that between PEP/LVET and LVET, were due predominantly to relations of the several contractility and performance measures with PEP since none exhibited a significant correlation with LVET. However, except for the correlations of PEP/LVET with PEP and of Cylx with VE, all of the correlations are weak as shown by the low values for $r^2$ (the "coefficient of determination") indicating that only a small fraction of the observed variability in one parameter is attributable to variation in the other.

Serial reanalyses, with various groups and subgroups deleted singly and in combinations, showed that all exclusions, except of groups I, IIb, IIIc, and IVb, revealed increasingly close relations of PEP and PEP/LVET with

![Correlation graph](image-url)

Figure 1

Correlations between PEP/LVET and the contractility index for the entire series and for all subjects without valve disease, shunts, or pulmonary heart disease.
the contractility and performance measures. For example, as shown in table 5, the exclusion of the 17 patients with aortic valve disease (groups IIIa and IVa) from the analysis considerably improved the correlations of PEP/LVET and PEP with CyIx, VCE, EF, and CI.

Deletion of the patients with mitral stenosis in group IIa plus two patients in IIIc whose hypertensive heart disease was accompanied by mild mitral stenosis with valve areas > 1.8 cm²) also revealed improved correlations of PEP/LVET and PEP with CyIx, VCE, EF, and CI. Exclusion of patients with either cor pulmonale (IIb) or atrial septal defect (IIc) produced a similar result. Table 5 shows the results of analyses after deleting patients, first with aortic valve disease, then with either aortic or mitral valve disease, then with either valve disease or atrial septal defect, and finally with valve disease, atrial septal defect, or cor pulmonale. In the last group deleted (42 patients with either aortic stenosis, aortic regurgitation, mitral stenosis, atrial septal defect, or pulmonary heart disease), there were no significant correlations between any of the systolic time intervals and any other variable. However, as shown in the last column of table 5 and in figures 1–3, in the 28 patients remaining, with either normal left ventricles or LV disease, compensated or decompensated, due to cardiomyopathy or

![Figure 2](http://circ.ahajournals.org/)

**Figure 2**

Correlations between PEP/LVET and ejection fraction.

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Correlations between PEP/LVET and cardiac index.

Discussion

In almost all cardiac lesions, the state of the muscle may be the critical factor determining disability, responsiveness to medical or surgical therapy, and prognosis for life. This is true not only in pathology affecting the myocardium primarily as, for example, toxic myocardopathy, infectious myocarditis, and hypertensive heart disease, but also in rheumatic valvular lesions, coronary artery disease, and congenital volume or pressure overloads. Clearly, a means of assessing the functional state of the myocardium is a clinical necessity.

A measure of LV contractility should: (1) detect the contractile deficit of the LV which is in clinically manifest failure; (2) yield normal values in cardiac diseases which do not affect LV contractility; (3) exhibit appropriate changes with positive and negative inotropic influences; (4) reflect the
state of LV inotropy uninfluenced by pump-function alterations due solely to altered preload, afterload, or other factors; (5) be sensitive to contractile deficits which may exist in the absence of clinically overt failure; and (6) exhibit close correlations with selected, validated, independent measures of contractility.

The present study demonstrates (table 2) that PEP is significantly prolonged and PEP/LVET significantly increased in patients with clinically evident LV decompensation and clear-cut depression of both LV function and contractility (first criterion). Moreover, it shows that, in patients with lesions burdening the right ventricle but not the left, in whom LV function was depressed but LV contractility normal (table 2), systolic times were not significantly altered (second criterion). In addition, with isoproterenol or exercise (table 4), the increased pump function was associated with augmented contractility, shortened PEP, and diminished PEP/LVET (third criterion). In patients with compensated aortic valve disease (table 3), where significant reduction in pump function was not associated with altered contractility, PEP and PEP/LVET were not significantly different from normal (fourth criterion). Sensitivity to subtle contractile deficits is indicated by the prolongation of PEP and increase of PEP/LVET in patient groups (IIb and IIIc in table 3) in whom contractile element velocity and contractility index were reduced but LV decompensation had not been clinically evident (fifth criterion). Finally, PEP and PEP/LVET exhibited statistically significant correlations (table 5) both with measures of pump performance, as has also been shown by others,46, 47 and with the two measures of contractility studied (sixth criterion).

Thus it would appear that the systolic time intervals have fulfilled the stipulated criteria. However, certain reservations must be acknowledged on both empiric and theoretic grounds. In the first place, the patients with RV overloads (group II) did, in fact, exhibit an elevated mean PEP/LVET and, although the difference from the normal mean was not significant with the numbers of patients available in this study, it would have achieved statistical significance if a larger group with comparable variance had been studied. Such a finding would be consistent with the presumption that, since increases in stroke volume due to enhanced LV filling are accompanied by lengthening of LVET and shortening of PEP, decreases in stroke volume due to diminished diastolic filling would be associated with prolonged PEP and abbreviated LVET. Indeed, in all three subgroups of group II, stroke volumes and cardiac indices significantly below normal were observed in conjunction with statistically insignificant but suggestive shortening of LVET and, in the subgroups with mitral stenosis or atrial septal defect, with insignificant but suggestive lengthening of PEP. As with the total group, each subgroup exhibited normal contractility. Thus, in any individual patient or subgroup with RV overload, alterations in systolic time intervals may be observed which are consistent with reductions in pump function characterized by subnormal ejection fraction, stroke volume, and cardiac index but are not a manifestation of depressed LV contractility.

In the second place, in patients with clinically compensated aortic valve disease, it has been shown46, 47 that Q-S₂ and LVET are lengthened (consistent with the retarded ejection rate in aortic stenosis and the augmented total stroke in aortic regurgitation) and that PEP is abbreviated; with LV decompensation, PEP lengthens and LVET shortens. Thus, in the course of the disease, with possible concomitant alterations in severity of the valve lesions and in myocardial damage, single observations of PEP, LVET, and PEP/LVET may all lie in, above, or below the normal range without any useful correspondence with the state of the myocardium.

Finally, the correlations of PEP and PEP/LVET with the measures of contractility (table 5), although statistically significant, are not good. This is not surprising since the influences on PEP and LVET noted above, of such factors as pathologically altered preload,
stroke volume, and resistance to ejection, would tend to obfuscate any relationship between the systolic time intervals and the contractile state.

In view of these considerations, it is understandable that, in the 42 patients in whom extramyocardial factors are major determinants of performance and of systolic times, there were no significant correlations between any systolic time interval and any other variable, and that serial exclusion of these patients yielded progressive improvement in correlations between systolic time intervals and the measures of both performance and contractility. In the patients free of these systematic and pathologic extramyocardial influences on systolic times, an intimate relation is discerned between contractility and both PEP and PEP/LVET. For PEP/LVET and Cylx, for example, the coefficient of determination \( r^2 = 0.746 \) shows that almost three fourths of the variability in measured PEP/LVET was attributable to variations in contractility and only one fourth to other factors. In this connection, it is also of interest that the weak relation \( r = 0.4 \) between Cylx and EF for the entire series was considerably strengthened by confining analysis to patients without valve disease, shunts, and pulmonary heart disease. Thus, it is clear that, in a heterogeneous sample, most of the variability in EF (1–0.4\(^2\), or about five sixths, in the present study) is attributable to variation in factors other than contractility but that, in patients in whom LV performance characteristics are not constrained by valvular lesions, shunts, impaired right heart function, or pulmonary vascular disease, much of the variability in EF (one half in the present series) is a reflection of differences in contractility.

There being no correlations between LVET and any other variable, it is clear that PEP is responsible for the relations between PEP/LVET and the performance and contractility measures. That slightly higher correlations were calculated with Cylx, \( V_{\text{cylx}} \), and EF using PEP/LVET rather than PEP almost certainly reflects the fact that the ratio is only minimally influenced by heart rate as Weissler et al. have shown.\(^{11}\) The same phenomenon underlies the fact that cardiac index was better related to PEP than to PEP/LVET since PEP is correlated with both of the variables (stroke volume and heart rate) which determine cardiac index while the ratio is relatively insensitive to rate.

It is of interest that the measures of contractility correlate more closely with PEP and PEP/LVET than with measures of performance. This is consistent with the contractile state being the predominant influence on the duration of the prejection period, lesser determinants being activation time and diastolic filling (preload), while performance, although also a function of contractility, is influenced in relatively larger measure by its other determinants: preload, afterload, and, in the case of minute flow, heart rate. It follows that PEP and PEP/LVET should more intimately relate to measures of contractility than of performance, as was, indeed, the case. It follows also that isovolumic contraction time (ICT), obtained by subtracting activation time from PEP, should correlate even more closely than PEP with measures of contractility.

These results and conclusions are consonant with those of studies in the anesthetized dog. Talley, Meyer, and McNay found correlations between PEP and several indices of contractility (time to maximal \( dP/dt \) and the ratio of maximal \( dP/dt \) to simultaneous LV pressure) over a wide range of induced changes in inotropy.\(^{48}\) Metzger et al., also using acute interventions, observed an inverse relation between maximum LV \( dP/dt \) and true (i.e. internally measured) ICT.\(^{49}\) The latter has been shown by Martin et al. in man to exhibit good correlations with external measurements of both ICT and PEP.\(^{50}\) During acute interventions in their study, conduction time did not change and changes in PEP and internal ICT not only showed excellent correlation but were alike in absolute value. Since ICT is necessarily shorter than PEP (by the electrical-mechanical delay), the similarity in absolute values for the induced changes
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indicates a greater percentage change (i.e. a greater sensitivity to change) for the ICT.

It appears from these studies that ICT is the interval most intimately related to contractility but that, in the experimental animal, PEP is an index of the contractile state and, in both the experimental animal and man, changes in PEP satisfactorily reflect acute changes in inotropy. From the present study, it is clear that both PEP and PEP/LVET can serve as indices of the contractile state in clinical heart disease. However, our results show that comparisons among patients or groups of patients are valid only in the absence of extramyocardial influences on PEP and LVET such as occur with valvular, pulmonary, and shunt lesions. This is not to say that the systolic times are useless in evaluating contractility in such lesions. If the severity of an extramyocardial lesion, such as aortic stenosis, can be either demonstrated or reasonably assumed to be constant, and unchanging QRST intervals indicate constancy of activation time, then clear-cut changes in PEP or PEP/LVET during the clinical course indicate that the contractile state of the myocardium is changing.

It should be appreciated that systolic times in our study were obtained from the electrocardiogram and an intraaortic pulse recording. Since our purpose was to evaluate, under optimal circumstances, relations between systolic times and direct measures of contractility and performance, we chose not to use external recording technics with which technical difficulties (e.g. in identification of the first high-frequency components of S₂) might obscure or impair significant relationships. However, available evidence indicates that measurements obtained with external recordings should exhibit the same relationships, clinical utility, and limitations as were observed in the present study. Comparison of data obtained from electrocardiogram, phonocardiogram, and carotid pulse tracing with data obtained from electrocardiogram and high-fidelity, manometer-tip, intraaortic catheters has shown that the external recordings yield accurate measurements of systolic time intervals.49,51

We conclude, therefore, that the noninvasive measurement of these intervals should provide a valid assessment of the contractile state of the left ventricular myocardium in man, suitable for comparing patients or groups of patients in whom cardiac pathology is confined to the myocardium and for following the clinical course of patients with extramyocardial hemodynamic lesions of constant severity.

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