A Critical Review of the Systolic Time Intervals

RICHARD P. LEWIS, M.D., STANLEY E. RITTGERS, M.S., WILBUR F. FORESTER, M.S., P.E., AND HARISIOS BOUDOULAS, M.D.

SYSTOLIC TIME INTERVALS (STI) have become one of the established "noninvasive" techniques of clinical cardiology. Indeed the term "noninvasive" was first used in connection with the STI. The STI were one of the first quantitative noninvasive tests of cardiac function and remain one of the simplest and most reliable to perform.

Most tests of ventricular performance deal with force and/or distance either alone or as a function of time. The STI are unique among these tests because time is the only variable. Hence, the validation of the STI has been a two stage process; first, to establish that external time measurements were adequate; and second, to correlate the STI with other parameters of ventricular function, none of which involve time as the primary variable. The first stage has been accomplished over the past ten years and work continues on the second stage.

The STI should not be considered competitive with other invasive or noninvasive studies. Indeed, no single noninvasive test provides all of the clinical information which is desired. The STI are less useful for differential diagnosis since the method is primarily a measure of left ventricular performance. As such, the STI provide a quantitative estimate of the effect (if any) of various cardiovascular disorders upon the left ventricle. Like all noninvasive techniques, the STI have the singular advantage that multiple observations can be performed. This allows study of the natural history of disorders and long-term effects of therapeutic interventions.

Since several recent reviews have extensively covered the historical background, pathophysiologic basis of the STI, and have summarized the changes in the STI which occur in disease states, this review will concentrate on three aspects: a critical evaluation of methodology, a summary of factors known to influence the STI, and the practical use of the STI for clinical decision-making.

Methodology

The three basic STI are the pre-ejection period (PEP), the left ventricular ejection time (LVET), and total electromechanical systole (QS) (fig. 1). The measurements are obtained from simultaneous high speed recordings (100 mm/sec) of an electrocardiographic lead best displaying the onset of left ventricular depolarization, a carotid pulse tracing, and a phonocardiogram best displaying the initial high frequency vibrations of the aortic closure sound. The patient is instructed to breathe quietly and at least 10 cardiac cycles are averaged to obtain the STI. Because there is a transmission delay (average 18.5 ± 8.2 [1 sd] msec) in the carotid pulse tracing, the PEP must be calculated by subtraction of the LVET from the QS.

It has long been appreciated that the STI vary inversely with heart rate. Thus, for deviations of the STI to be properly interpreted, correction must be made for variation related to differences in resting heart rate. This was an important conceptual advance for the clinical application of the STI. When the heart rate derived from the R-R interval is used, a simple linear equation best describes the relationship in the range of the resting heart rate. The regression equations of Weissler represent the largest population of normals and have generally been adopted (table 1). It is notable that the equations for males and females differ slightly. Different corrections are required for children until puberty. The STI steadily increase in duration from infancy to puberty (the PEP more than the LVET) and all are slightly prolonged in the elderly.

In applying the STI clinically, deviations from the normal regressions can be expressed in either of two ways: 1) subtraction of the actual value from the predicted normal for a given HR (\(\Delta\)PEP, \(\Delta\)LVET, \(\Delta\)QS), or 2) calculation of each STI as an "index" value. Clinical experience indicates the latter is the most useful approach. Calculation of the index value requires transposition of terms of the regression equation as shown in table 1. The normal index values, in fact, represent the expected normal value at zero heart rate. By calculation of the index value, an immediate estimate of the deviation from normal (not accountable by HR) is obtained. For example, a QS index (QS\(_I\)) of 506 msec in a male is easily recognized as being 40 msec shorter than the expected normal value of 546 msec.
Validation of the External Carotid Pulse

It is well known that the systemic pressure pulse undergoes a change in configuration as it passes down the arterial tree.\(^9\) It attains a higher peak pressure, becomes more smooth, and the incisural notch becomes less sharply defined (fig. 2).

In a recent study to determine the source of this distortion, micromanometer tip catheter measurements of aortic root pressure were compared to simultaneously recorded external carotid pulse waves employing an air-coupled Statham P23 Db strain gauge.\(^9\) Spectral analysis of the pulse waves was performed over a range of 0–100 Hz. Comparing the average amplitude at each frequency harmonic indicates that the aortic root and external carotid artery pulses have the same harmonic content and that frequencies beyond the fifteenth harmonic contain less than 2% of the fundamental amplitude (fig. 3). However, phase analysis of the two pulses showed a definite change in phase angle between the two pulses — the phase shift being most prominent at higher frequencies. The distortion in the carotid pulse is therefore not due to damping effects but rather to phase shifting of the pulse wave component frequencies causing a reshaping of the pulse wave.

This phase shift could affect the validity of the carotid pulse since the landmarks could be influenced.\(^6\) However, because of the short distance from the aortic root to the carotid artery, this error is negligible. Indeed, several investigations in which the LVET from the externally recorded carotid pulse has been compared to the LVET directly measured from a manometer tip catheter in the aortic root have shown no significant differences.\(^21\)–\(^24\) This phase shift could, however, produce significant distortion if the LVET is measured from more distal sites in the arterial tree.\(^9\)

**TABLE 1.** Calculation of STI Index Values from Resting Regression Equations\(^4\)

<table>
<thead>
<tr>
<th>Sex</th>
<th>Equation</th>
<th>Normal Index (ms)</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>QS(_2)I = 2.1 HR + QS(_2)</td>
<td>546</td>
<td>14</td>
</tr>
<tr>
<td>F</td>
<td>QS(_2)I = 2.0 HR + QS(_2)</td>
<td>549</td>
<td>14</td>
</tr>
<tr>
<td>M</td>
<td>LVETI = 1.7 HR + LVET</td>
<td>413</td>
<td>10</td>
</tr>
<tr>
<td>F</td>
<td>LVETI = 1.6 HR + LVET</td>
<td>418</td>
<td>11</td>
</tr>
<tr>
<td>M</td>
<td>PEP = 0.4 HR + PEP</td>
<td>131</td>
<td>10</td>
</tr>
<tr>
<td>F</td>
<td>PEP = 0.4 HR + PEP</td>
<td>133</td>
<td>10</td>
</tr>
</tbody>
</table>

Abbreviations: I = index; sd = standard deviation; M = male; F = female; HR = heart rate.

**Figure 1.** On the left is a schematic of the left ventricular events which comprise the STI. On the right is a recording of a phonocardiogram, external carotid pulse, and electrocardiogram at 100 mm/sec paper speed. The subintervals of the STI are indicated on both.

**Figure 2.** Comparison of a simultaneously recorded manometer tip catheter pressure pulse (Millar "Mikro-tip") in the aorta and an externally recorded carotid artery pressure pulse employing an air coupled Statham P23 Db strain gauge.
Validation of the QS₂

There is no absolute physiologic landmark for the end of systole which can be derived externally. The QS₂I interval, which ends with the initial high frequency vibrations of the aortic component of the second heart sound (A₂), represents an estimate in which easily identified physiologic landmarks are employed. Recent studies have demonstrated that the incisural notch and the initial high frequency vibrations of A₂ nearly coincide and follow aortic valve coaption by less than 5 msec.²⁶-²⁷ Aortic valve closure in turn normally follows left ventricular-aortic pressure crossover by 5-10 msec. It appears that this gap is relatively constant except in certain disease states (notably aortic valve disease).

The QS₂ could potentially be unreliable if there were a wide variability in the timing of the end-systolic left ventric-
ular-aortic pressure crossover. Although this has not been systematically investigated, studies of patients with atrial fibrillation and a wide variety of left ventricular systolic pressures show a remarkable constancy of the aortic and left ventricular pressure crossover at end-systole relative to peak aortic pressure.\textsuperscript{5, 19} Finally, the narrow range of normal for the QS\textsubscript{1} at all heart rates and pressures support the reliability of the QS\textsubscript{1} as a useful measure for the duration of systole.

Validation of the PEP

Recent catheter tip manometer studies in both experimental animals and man have validated the externally measured PEP.\textsuperscript{21, 22, 23} The PEP is in fact comprised of the electromechanical delay (Q to onset of pressure rise in the left ventricle) and the isovolumic contraction period. The electromechanical delay in normals is 30–40 msec\textsuperscript{5, 20, 21} and is minimally affected in disease unless left bundle branch block is present.\textsuperscript{5, 22–25} The electromechanical delay is prolonged by varying intervals in complete left bundle branch block. It has been shown that the upstroke of the apacardiogram offers a reliable measure of the onset of left ventricular pressure\textsuperscript{2, 21, 24, 25} and as such is useful in defining the electromechanical delay.

The first heart sound occurs 25–50 msec after left ventricular left atrial pressure crossover and as such is not a useful landmark for subdividing the PEP.\textsuperscript{20, 40} At present the clinical usefulness of defining the subintervals of the PEP is not conclusively established in patients in whom there is no left ventricular conduction delay.

Pulse Transducers

When considering a transducer system for pulse recordings, the following properties should be known: 1) time constant; 2) frequency response; 3) phase shift. A time constant which is too short will distort the pulse by poor representation of lower frequencies in the form of both amplitude loss and phase shift.\textsuperscript{41} A poor frequency response (which might well be caused by the connecting apparatus) causes poor definition of higher frequencies. It appears that a flat frequency response of from 0.1–30 Hz is required.\textsuperscript{18–20, 42} This allows faithful reproduction of the first 15 harmonics for heart rates up to 120 beats/min. Likewise, there should be no phase shift from 0.1–30 Hz. Phase distortion independent of the time constant predominately affects the higher frequencies and if present may also be due to the connecting apparatus. Of the above transducer inadequacies, poor amplitude frequency response will not affect the time events of the recorded pulse but may so distort the pulse configuration as to distort the landmarks. A phase shift on the other hand can alter the time events of the pulse.

From direct testing of several transducers in our laboratory and a review of the literature, it appears that nearly all pulse transducers have an adequate frequency response unless improper connecting apparatus is attached.\textsuperscript{43, 44} However, most, if not all, crystal devices have a short time constant (< 2 seconds). This distorts the pulse configuration and can efface the time landmarks\textsuperscript{41} (fig. 4). The ideal transducer has an infinite time constant.

Figure 5 shows the characteristics of the system employed in our laboratory. This involves a Statham P23 Db pressure transducer which is air coupled by attaching a 4" length of 1/8" inner diameter tygon tubing and a brass funnel 1 1/2" long with maximum and minimum inner diameter of 7/8" and 1/16", respectively. The transducer output is connected to a carrier preamplifier. The time constant of this device is infinite. Its frequency response and phase shift are flat (± 3 dB to 100 Hz).\textsuperscript{45} The distortion occurring at higher frequencies is due both to our connecting apparatus and the transducer itself.\textsuperscript{46} If a connecting apparatus different from the above is employed, it is imperative to establish that it allows a flat frequency response and phase shift to at least 30 Hz. Another transducer with similar excellent characteristics is the Hewlett-Packard Sanborn APT-16, which has no connecting apparatus.\textsuperscript{10, 43}

Optimum Paper Speed

The error incurred in reading a given STI can reflect two factors. One is due to misjudgment of the actual physiologic

\*Details of our testing system available upon request.
event desired. The second error is due to limitations of the observer's accuracy. This latter error is related to factors such as the spacing of the timelines, resolution of the observer's eye, thickness of timelines, etc. It has been suggested that a rapid paper speed minimizes this second error, although this contention has been disputed by the only direct study of the problem.44

In order to resolve this problem we have completed a study of seven carotid pulse waves obtained from seven patients. In each case the pulse wave was at least 4 cm in amplitude and judged to have distinct landmarks. The pulse waves were recorded on magnetic tape and re-recorded at 25, 50, and 100 mm/sec paper speed. The timelines were kept at 40 msec intervals for each paper speed. The pulses were electronically digitized using a Hewlett-Packard 9830A computer and digitizer. The computer-determined data were considered the most accurate estimate of the LVET against which to compare the technicians' measurements.

The results are illustrated in figure 6. The mean absolute deviations from the digitized value for five experienced STI technicians for each of seven pulses at each paper speed are shown. It is clear that there is significantly greater variability in the measurement at slower paper speeds. Of interest, when data from the previous study are analyzed in a similar manner, essentially identical results are obtained.44

In addition to greater measurement variation at slower paper speeds, this study also revealed that the LVET measured at 100 mm/sec paper speed was the most accurate. The mean LVET for the seven pulses obtained by electronic digitization was 236 msec. The mean value and average 1 SD for all seven patients at 25 mm/sec was 243 ± 7.1, at 50 mm/sec it was also 243 ± 5.2 and at 100 mm/sec it was 235 ± 3.6 (P < 0.05).

To determine the interobserver measurement error at 100 mm/sec paper speed, the mean calculated LVET for all seven pulses for each technician was compared to the mean electronically digitized LVET. The absolute mean errors were 3.0, 4.5, 3.6, 3.4, and 5.1 msec (average 3.9 msec).

To determine the intraobserver measurement error, the same five technicians measured the same pulse at 100 mm/sec paper speed on four separate occasions. The mean LVET from the four measurements for each observer was again compared to the electronically digitized value for that patient. The absolute mean errors were 5.0, 5.4, 3.5, 3.8, and 5.0 msec (average 4.5 msec).

These studies indicate that when the LVET is manually calculated at 100 mm/sec paper speed by trained technicians, there is a high degree of accuracy and precision, in each case to the nearest 5 msec or better. It should be noted that all of these studies were performed on a single pulse. In practice, ten pulses are measured and averaged thus reducing the measurement error even further.

In a similar manner the mean absolute error of the Q5 measurement was derived. The mean absolute error was 1.6 msec. Since the PEP is determined by subtraction of the LVET from the Q5, the error in the PEP is a function of the error in both primary variables. The same is true for the PEP/LVET. In order to estimate error in the measurement of the PEP/LVET a generalized equation was developed using the experimentally derived mean absolute error values of the LVET and Q5.45 This equation provides the maximum expected error (table 2). It is notable that the maximum error of the PEP/LVET is dependent on both the absolute value of the PEP/LVET and the HR, with the error being greatest at rapid heart rates when significant left ventricular dysfunction is present.

Several investigators have developed computer programs to measure the STI.46,47 Theoretically this should reduce systematic error. However, improper selection of landmarks by the computer may induce serious error so that the computer's selection of landmarks should be verified by a trained observer.

Other Technical Considerations

The carotid pulse should be as large as possible (4–5 cm) for optimal delineation of the upstroke and incisural notch (fig. 7). It is also useful to have thinning of the pulse line with sudden changes in direction. In general, only optical recorders provide these features. It is obvious that the paper speed must be accurate. At 100 mm/sec an error of 2% produces a 5 msec error. Thus, the recorder must be frequently calibrated. In our experience, many commercially available recording systems do not meet these requirements.

Other common, but important errors include: 1) failure to average ten consecutive cycles in order to minimize the influence of respiratory variation; 2) failure to employ the elec-

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*Detail of derivation of this equation available upon request.*
tetrocardiographic lead, which best defines the onset of electrical depolarization; 3) poor quality phonocardiograms which do not identify A2 precisely (sounds of frequencies less than 100 Hz must be effectively filtered). There are some patients in whom good carotid pulse tracings or phonocardiograms cannot be obtained. In such cases it is obvious that poor data should not be reported.

**Effect of Atrial Fibrillation and Other Dysrhythmias Upon Measurement of the STI**

This common dysrhythmia produces alterations in the usual relationship of the LVET and PEP to HR. There has been some controversy relating to the choice of either the preceding R-R interval per se or the HR calculated from the preceding R-R interval to correct the STI. Since HR and R-R are nonlinearly related, apparently different results are obtained from the two methods. In fact, it matters little which method is employed if the difference between the two is appreciated.

At slower HRs in atrial fibrillation the LVET does not lengthen as much as would be expected from the linear regression lines for normal subjects. This is most evident when the HR calculated from the preceding R-R interval is used rather than the actual R-R interval itself. This effect of R-R interval on LVET is mitigated when mitral stenosis (and impaired diastolic filling) is present.

In beats with a short preceding R-R interval there is diminished preload and a greater isovolumic pressure must be generated. As a consequence, the PEP following short cycle lengths is relatively prolonged. This is most striking at heart rates above 75 beats/min (R-R < 800 msec). Although an angiographic study has shown a high correlation between the PEP/LVET and left ventricular ejection fraction on a beat-to-beat basis, inclusion of many beats with short preceding R-R intervals can prove misleading. Indeed, if the PEP/LVET obtained from averaging 25 consecutive beats (which would likely include several beats with R-R intervals < 800 msec) and the PEP/LVET obtained from averaging only beats with R-R > 800 msec are compared to the PEP/LVET when sinus rhythm is restored, the former is significantly higher and the latter not different. Thus STI calculated by averaging all beats including those following short cycle lengths can underestimate potential left ventricular performance and this error can be minimized by measuring only those beats with an R-R > 800 msec.

Few studies of dysrhythmias other than atrial fibrillation have been reported. The STI have minimal clinical value in this setting and are best studied after the tachyarrhythmia is slowed or reverted.

Premature beats of any type may produce postextrasystolic potentiation and a decreased PEP/LVET in the following beat. In atrioventricular conduction disorders, beats with a properly timed atrial systole show a decreased PEP/LVET. Finally, pulsus alternans may produce marked beat-to-beat changes in the PEP/LVET. In all of these situations the beat-to-beat variations need to be considered when reporting the STI.

**Physiologic Variations of the STI**

Weissler’s original HR-STI regressions were based upon normal volunteers with no heart disease who were at rest in the supine position for one hour. In clinical use these conditions are not easily met; the patient is being sent for a “heart test” which could produce emotional arousal. For practical considerations in most busy laboratories the patient cannot be at rest more than a few minutes. However, if the 95% confidence intervals for Weissler’s data are considered, normal patients studied with only 5–10 min rest still fall into his normal range (fig. 8).

It is important to appreciate the day to day variation of the STI both in normal persons and in patients with stable chronic heart disease. This has been assessed in both groups (table 3). As might be expected, the mean one standard deviations of the STI for individuals are smaller than the one standard deviation values for the entire normal population (table 1), both for normals and abnormals. These small standard deviations indicate the remarkable consistency of the STI in both groups, although the variability is higher in patients with chronic heart disease.

**Factors Influencing the STI**

The factors known to influence the PEPI and LVET are listed in table 4. There have been several studies to determine the mechanism of STI abnormalities by direct correlation with other measurements of left ventricular performance. From these studies the following facts seem clear. When left ventricular failure occurs, regardless of cause, the PEPI lengthens and the LVET...

**Table 2. Maximum Error in Measurement of PEPI/LVET**

<table>
<thead>
<tr>
<th>PEPI/LVET</th>
<th>0.33</th>
<th>0.50</th>
<th>0.75</th>
</tr>
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<tbody>
<tr>
<td>HR 50</td>
<td>±0.021</td>
<td>±0.026</td>
<td>±0.034</td>
</tr>
<tr>
<td>(QS2 = 441 msec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR 75</td>
<td>±0.023</td>
<td>±0.028</td>
<td>±0.037</td>
</tr>
<tr>
<td>(QS2 = 400 msec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR 100</td>
<td>±0.028</td>
<td>±0.034</td>
<td>±0.045</td>
</tr>
<tr>
<td>(QS2 = 336 msec)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: HR = heart rate.*

**Figure 7. The effect of a low amplitude carotid pulse tracing upon the time landmarks of the LVET. The same patient was studied with the carotid tracing on high gain (left) and low gain (right). The landmarks of the low gain tracing are poorly delineated, producing a 17 msec error in the measurement of the LVET. Reproduced by permission from Grune & Stratton from “Systolic time intervals” in Noninvasive Cardiology, 1974.”*
shortens. The prolongation of the PEPI can be attributed almost entirely to a diminished rate of left ventricular pressure rise during isovolumic systole (LVdp/dt). Occasionally this can be masked (i.e., the PEPI is normal in the presence of a low rate of pressure rise) if the pressure developed during isovolumic contraction is low. This occurs in patients with a high left ventricular end-diastolic pressure and low systemic diastolic pressure.

Complete left bundle branch block usually delays activation of the left ventricle and therefore prolongs the PEPI (see earlier section). Lesser degrees of left ventricular conduction abnormality, however, seem to produce only a minimal delay in left ventricular activation. In chronic left ventricular disease associated with reduced diastolic compliance, the PEPI may also be prolonged if preload is inadequate. A similar phenomenon occurs with the diminished preload induced by upright tilt.

The shortening of the LVETI with heart failure is more complex to explain than the changes in the PEPI. A primary factor in the shortening of LVETI must be the relative lengthening of the PEP which induces a delayed onset of ejection. During ejection the velocity of fiber shortening is diminished when left ventricular failure is present, a condition which theoretically should produce a prolonged LVETI. However, the extent of fiber shortening is also reduced and this would tend to shorten the LVETI. It appears that the diminished extent of fiber shortening in left

**Table 3. Day-to-Day Variation of the STI²**

<table>
<thead>
<tr>
<th></th>
<th>QS₂</th>
<th>LVET</th>
<th>PEP</th>
<th>PEP/LVET</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normals (N = 33)</td>
<td>6.2*</td>
<td>5.2</td>
<td>4.3</td>
<td>0.015</td>
</tr>
<tr>
<td>II.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic stable LV disease (N = 17)</td>
<td>11.8</td>
<td>10.5</td>
<td>7.5</td>
<td>0.036</td>
</tr>
</tbody>
</table>

* = mean standard deviation.
LV = left ventricle.

**Table 4. Factors Influencing the Systolic Time Intervals**

<table>
<thead>
<tr>
<th></th>
<th>Increase (†)</th>
<th>Decrease (††)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) PEP</td>
<td>LV muscle failure</td>
<td>aortic valve disease</td>
</tr>
<tr>
<td></td>
<td>left bundle branch block</td>
<td>LV isovolumic pressure</td>
</tr>
<tr>
<td></td>
<td>▼ preload</td>
<td>positive inotropic agents</td>
</tr>
<tr>
<td></td>
<td>negative inotropic agents</td>
<td></td>
</tr>
<tr>
<td>2) LVET</td>
<td>aortic valve disease</td>
<td>LV muscle failure</td>
</tr>
<tr>
<td></td>
<td>▼ preload</td>
<td>positive inotropic agents</td>
</tr>
<tr>
<td></td>
<td>negative inotropic agents</td>
<td></td>
</tr>
<tr>
<td>3) QS₂</td>
<td>left bundle branch block</td>
<td>positive inotropic agents</td>
</tr>
<tr>
<td></td>
<td>aortic valve disease</td>
<td></td>
</tr>
</tbody>
</table>

Figure 8. Individual data on 31 female (left) and 26 male (right) patients who subsequently proved to have no heart disease. Ninety-five percent confidence intervals of the regression equations for 90 normal female and 121 normal male volunteers for each of the STI are superimposed. The patients were studied as part of a cardiac evaluation between 8:00 AM and 3:00 PM with only a five minute rest period. The values obtained under these circumstances were not statistically different from those of the normal volunteers. Permission for reproduction, see figure 7 legend.
ventricular decompensation usually predominates so that the net result is a shortened LVET. Of interest is the fact that the absolute size of the stroke volume per se does not determine the LVET.\(^4\) It is when stroke volume is small relative to end-diastolic volume that the LVET will be shortened. This can be observed in some patients with primary myocardial disease in whom a shortened LVET occurs when the left ventricular end-diastolic volume is increased, the ejection fraction reduced, and the stroke volume and cardiac output are normal.\(^3\)

Unlike the PEPI, which responds in an opposite manner to positive and negative inotropic agents, the LVETI is generally shortened by both. With negative inotropic drugs, the mechanism is similar to that which occurs with left ventricular failure.\(^69\) Positive inotropic agents can increase both the velocity and extent of fiber shortening. These changes have opposite effects on the duration of the LVETI. Generally the increased rate of shortening is the predominant effect so that the LVETI shortens or is unchanged.\(^73\) However, lengthening can occur when a marked hemodynamic response occurs (i.e., large increase in the stroke volume).\(^69\) Finally, diminished preload reduces the stroke volume and shortens the LVETI.\(^69\)

The duration of systole (QS\(_I\)) is one of the remarkable constants in the circulatory system. Although most types of heart disease may produce profound alterations in cardiac performance, manifest by directionally opposite changes in the PEPI and LVETI, the QS\(_I\) is unchanged from normal unless drug effects are present.

Since positive inotropic agents generally shorten both the LVET and PEPI, the QS\(_I\) is the most useful of the STI in judging the presence of positive inotropic stimulation. Indeed, studies have shown a strong correlation between urinary catecholamine excretion and the QS\(_I\) in acute myocardial infarction as well as a dose-related shortening of the QS\(_I\) in response to intravenously administered positive inotropic agents.\(^76\) This is a unique property of the STI. No other easily derived test of left ventricular function provides a measure of the inotropic state.

The diagnostic value of the STI for identification of left ventricular dysfunction can be enhanced by determination of the ratio of PEPI to LVETI. In the heart rate range below 110 beats/min this ratio is unrelated to heart rate since the PEPI and LVETI shorten proportionally as the heart rate increases. The PEPI/LVETI may identify left ventricular dysfunction when either (or both) the PEPI and LVETI are still within the normal range. Consequently, the PEPI/LVETI has become the single most useful measurement of left ventricular performance from the STI.

**Clinical Application**

**Evaluation of Left Ventricular Performance in Suspected Chronic Myocardial Disease**

This is the area in which the STI were first clinically evaluated. Early studies showed a strong correlation between the PEPI/LVETI and cardiac index.\(^4\)\(^5\) However, as more patients were studied, it became clear that while the STI were virtually always abnormal when the cardiac index was reduced, it was not uncommon to find an abnormal PEPI/LVETI in the face of a normal cardiac index.\(^2\) This was in accord with the longstanding observation that the cardiac index is one of the last parameters of left ventricular performance to become abnormal when disease is present.

Subsequently it was shown that of all direct parameters of left ventricular performance the PEPI/LVETI correlates best with the angiographic ejection fraction (EF) \((r = -0.90).\)\(^61\) This is true whether the underlying disease is myocarditis, cardiomyopathy, coronary artery disease with angina pectoris, hypertensive heart disease, mitral valve disease, congenital heart disease involving the left ventricle, or pericardial disease\(^64\) \(77\) \(81\) (unpublished observations). In myocardial infarction (both acute and chronic), pulmonary disease\(^82\) \(83\) and aortic valve disease, this relationship may be influenced by other factors but the same basic relationship persists (see later sections).

With the widespread use of modern potent oral diuretics the degree of congestive failure may relate poorly to the severity of underlying left ventricular muscle failure. It is no longer uncommon for patients with severe left ventricular dysfunction to be free of excessive fluid retention. In such instances the severity of the underlying muscle disease may be missed. Measurement of the STI can prevent this error. It is also not unusual for overdiuresis to occur in these patients.\(^66\) Worsening of the STI with therapy for congestive heart failure provides an early clue to this phenomenon.

There are several conditions in which circulatory congestion occurs on a basis other than left ventricular muscle failure. These include constrictive pericarditis, anemia, renal failure, cirrhosis with ascites, excessive fluid administration, cor pulmonale, and certain volume load lesions and shunts. In these patients the classic bedside signs of cardiomegaly, gallop rhythm, increased venous pressure, pulmonary rales and edema may not be reliable for assessing left ventricular function. The STI are highly useful to establish the role (if any) of left ventricular muscle dysfunction in these patients (unpublished observations). In other patients the presence of myocardial dysfunction may be relatively occult and is discovered only when the STI are measured.\(^79\) \(80\)

Among patients with chronic left ventricular disease there is a wide spectrum of severity of left ventricular dysfunction. In many of these disorders the long-term prognosis is strongly related to the severity of the performance abnormalities. Most standard bedside signs of heart failure are qualitative and do not consistently distinguish those with mild from those with severe dysfunction. The STI on the other hand do provide a quantitative estimate of left ventricular dysfunction.

**The STI in Acute Myocardial Infarction (AMI)**

The STI have been studied extensively in patients with acute myocardial infarction.\(^94\) \(96\) \(97\) \(94\) \(95\) Since left ventricular performance frequently changes during the course of the illness, serial measurements of the STI assume major importance. In the early stages of the AMI the STI provide a measure of the impact of the infarction on the left ventricle, while later studies are useful in assessing the long-term response to the healing process.

The most consistent (and unique) phenomenon noted in AMI is a marked abbreviation of the QS\(_I\). This has been shown to be a direct effect of increased adrenergic tone.\(^98\)
This factor is responsible for considerable confusion in the interpretation of the STI in AMI. In normal subjects with the high levels of adrenergic tone characteristic of the early stages of AMI, the PEPI should be shortened, the LVETI unchanged, and the PEPI/LVET low (0.20-0.25). Thus, a "normal" PEPI or PEPI/LVET actually represents left ventricular dysfunction when adrenergic tone is increased.

In spite of the above considerations, the directional changes in the PEPI and LVET with AMI are the same as in chronic disorders. In almost all instances, patients who are judged to have more severe left ventricular dysfunction clinically or by direct measurements with cardiac catheterization techniques have a more abnormal PEPI/LVET.

The mere presence of an acute MI need not necessarily produce an abnormal PEPI/LVET (although as noted above, these "normal" PEPI/LVET values are probably not normal). Since the STI are a test of performance and the spectrum of AMI size is large, a wide range of values for the PEPI/LVET is found when large groups of AMI patients are studied. Indeed, the same wide overlap with normal is found with other measures of ventricular performance, such as cardiac output, left ventricular dp/dt and echocardiographic measures.

If patients with AMI are divided into two groups according to the presence or absence of pre-existing disease (prior AMI, longstanding hypertension, primary myocardial dysfunction, then a striking (and expected) separation occurs (fig. 9). Those with no pre-existing disease have a normal PEPI/LVET throughout the acute phase and during the subsequent nine months of convalescence. Patients with prior left ventricular disease, on the other hand, have an abnormal PEPI/LVET throughout the acute phase and up to six months are required for final normalization of the PEPI/LVET. These results suggest that the STI may be useful for guiding the convalescence from an AMI and underscore the fact that patients with AMI are not a homogeneous population in terms of left ventricular performance.

The STI are probably of less value when cardiogenic shock is present. They often are technically difficult to obtain. The low isovolumic pressure and increased adrenergic tone may result in a normal PEPI in spite of a low left ventricular dp/dt. However, serial measurements of the LVETI may be useful. Recently, the PEPI has been combined with arterial and wedge pressure data to provide a contractility index that may also prove useful.

Assessment of Left Ventricular Function in Chronic Coronary Artery Disease (CAD)

The correlation between the PEPI/LVET and angiographic left ventricular ejection fraction is lower in CAD than for other types of chronic disease (fig. 10). The STI generally suggest better left ventricular performance than does the ejection fraction. Several phenomena unique to coronary artery disease appear to be responsible. These include a low isovolumic pressure (developed pressure < 40 mm Hg) due to a high LVEDP and low aortic diastolic pressure, underestimation of the ejection fraction by the single plane RAO view when localized contraction abnormalities are present, and the occurrence of transient myocardial ischemia during the left ventriculogram. It is clear that only one of these factors represents an error in the estimation of left ventricular performance by the STI.

In spite of the above considerations, inspection of figure 10 indicates that a PEPI/LVET of greater than 0.5 is associated with an ejection fraction of less than 40% in 95% of the cases. It can also be seen that the majority of patients with angina pectoris without prior AMI have normal STI and ejection fractions. Patients with prior AMI have either normal or abnormal STI depending on the size and number of prior infarctions. The STI are frequently abnormal in patients who have recovered from a previous myocardial infarction when all clinical and radiologic signs of cardiac disease are absent.

The STI have proved useful for assessing the effect of saphenous vein bypass upon left ventricular per-

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**Figure 9.** Serial changes in the PEPI/LVET after acute myocardial infarction. Patients with a previously normal left ventricle (LV) (N = 12) remain normal throughout while those with a previously abnormal LV (N = 13) have significant left ventricular dysfunction for at least three months. Asterisks indicate significant differences between the groups. bars represent 1 SEM, dashed line indicates upper limit of normal for PEPI/LVET. ADM = admission; DISCH = discharge; MO = months. Reproduced by permission from "Usefulness of systolic time intervals in coronary artery disease," in Am J Cardiol 37: 787, 1976.

**Figure 10.** Relationship between the angiographic left ventricular ejection fraction (RAO view) and PEPI/LVET in 127 patients with significant coronary artery disease. The symbols designate various categories. All patients with an isovolumic systolic pressure of less than 40 mm Hg had a prior myocardial infarction (MI). The dashed lines indicate 95% confidence intervals from a previous study. Permission for reproduction, see figure 9 legend.
formance. In many instances ischemic injury at the time of surgery causes postoperative ischemia of the PEP/LVET. This requires three months to return to preoperative baseline. Late deterioration of the STI suggests graft closure. Finally, these studies have demonstrated the role of excessive adrenergic tone in the early postoperative period which must be considered when comparing pre- and postoperative ventricular performance.

Patients with stable angina pectoris may also have increased adrenergic tone although this is not as marked or as common as in AMI. When patients with angina pectoris on no medication are compared to patients with chest pain and normal coronary arteries, the QS/I is significantly shorter in those with angina. Indeed, 16% of patients in our series had a QS/I less than 515 msec, the lower limit of normal. Thus, a QS/I of less than 515 msec in a patient with chest pain strongly suggests the pain reflects ischemic disease. Another study suggested that patients with shortened values of the QS/I have the most undeveloped collaterals.

Aortic Valve Disease

Recent studies have shown that prolongation of the LVETI is highly useful for identifying hemodynamically significant aortic stenosis. This is enhanced if also associated with a carotid peak dp/dt of less than 500 mm Hg/sec. Patients with significant aortic stenosis usually have an LVETI greater than 420 msec. Although the length of the LVETI does not correlate highly with the severity of the aortic stenosis, the combination of the LVETI and stroke volume provides a good estimate of the aortic valve area.

The mechanism of the prolonged LVETI is not completely clear. In part, it may reflect relative early opening and late closing of the aortic valve. There also appears to be a longer than normal delay of the incisura following left ventricular-aortic pressure crossover (fig. 11). This delay may be related to decreased aortic impedance resulting from poststenotic dilatation of the aorta and low aortic pressure. Occasionally this factor alone can prolong the LVETI even when the aortic stenosis is not critical. Whether actual prolongation of left ventricular systole is also a factor (it is in pulmonary stenosis) has not been established. Of interest, the prolonged LVETI almost always returns to normal after corrective surgery and often is shorter than normal if underlying left ventricular dysfunctions is present.

When left ventricular failure develops, the LVETI shortens as in other types of heart disease. However, it shortens to the normal range and almost never becomes shorter than two standard deviations of normal (< 398 msec) unless excessive adrenergic stimulation is present. The finding of a normal LVETI in a patient with congestive heart failure and clinical evidence of aortic stenosis strongly suggests the heart failure is associated with significant aortic stenosis. Conversely, a short LVETI, especially with a normal carotid dp/dt, strongly suggests aortic stenosis is not the cause of the heart failure. This is a common clinical problem in patients over age 50 years.

The PEPI is short in aortic stenosis due to the rapid dp/dt and low aortic diastolic pressure. However, the aortic closure sound is often absent or effaced when significant aortic stenosis is present so that neither the QS/I or PEPI can be determined.

Significant outflow obstruction also prolongs the LVETI in muscular subaortic stenosis and may be useful both for diagnosis and following therapy in this disorder. The LVETI is also prolonged by aortic regurgitation. The mechanisms are probably similar to aortic stenosis (i.e., early opening and late closing of the aortic valve, and delayed incisura) rather than to an increased stroke volume. The relationship of the duration of the LVETI to the magnitude of the regurgitant leak has not been precisely determined, but it appears that more severe regurgitation produces a greater prolongation of the LVETI. As is the case with aortic stenosis, left ventricular decompenation shortens the LVETI.

Mitral Valve Disease

The studies by Garrard and co-workers demonstrated that a linear relationship between the PEP/LVET and ejection fraction is retained in patients with mitral stenosis. If patients with mitral stenosis are compared to those with left ventricular disease (ischemic heart disease and primary myocardial disease) and similar levels of cardiac output, those with mitral stenosis have less severe abnormalities in STI and ejection fraction. Mitral stenosis thus appears unique in that a low cardiac index may be accompanied by a normal ejection fraction and normal STI. When the PEP/LVET ratio is significantly increased in patients with mitral stenosis, the ejection fraction is usually reduced.

In patients with mitral regurgitation, prolongation of the PEPI and shortening of the LVETI, with a consequent in-

![Figure 11](http://circ.ahajournals.org/)

**Figure 11.** Left ventricular (LV) and aortic (Ao) pressures and intracardiac (IC) phono obtained from two manometer tip catheters in a patient with significant aortic stenosis. Timelines are 40 msec. Note the 50 msec delay between LV-Ao pressure crossover and the dicrotic notch (DN). Permission for reproduction, see figure 7 legend.
crease in PEP/LVET, may result from either the dynamic effects of mitral regurgitation or the influence of diminished contractile performance of the left ventricle. Recent studies employing echocardiographic methods for assessing the contractile performance of the left ventricular chamber in patients with mitral regurgitation have demonstrated that prolongation of PEPI and shortening of LVETI is often observed when left ventricular chamber performance is within normal limits. These abnormalities in STI are accentuated when mitral regurgitation is accompanied by diminished left ventricular performance as reflected in the determination of the extent of minor axis diameter shortening. From these studies it appears that mitral regurgitation per se induces prolongation of PEPI and shortening of LVETI and that these changes are accentuated in the presence of left ventricular decompensation. The finding of a normal PEP/LVET in patients with mitral regurgitation provides evidence for well compensated contractile performance while an increase in PEP/LVET of 0.5 or greater favors the coexistence of mitral regurgitation and left ventricular decompensation.

Use of the STI in Clinical Pharmacology

Because of the extreme sensitivity of the test, the ease of its measurement, and the large body of existing literature, the STI are ideally suited for studying effects of pharmacologic agents upon the heart. Indeed, this may well represent a most useful future application of the technique. Most of the studies which have been performed have dealt with parameters of pharmacologic action such as the onset, magnitude, and duration of drug action, establishment of dose response relationships, and studies of the interplay of agonists and antagonists. With this class of drugs there are usually more striking hemodynamic changes than is the case with digitalis. Thus, caution must be exerted to ensure that pharmacologic effects on the peripheral circulation do not cloud the interpretation of the STI. This is particularly true when marked changes in arterial pressure occur.

The effect of negative inotropic agents upon the STI have been less extensively studied. In general, it appears that such agents induce the typical heart failure pattern of prolongation of the PEPI and shortening of the LVETI. Many antihypertensive drugs fall into this category but as yet there are no major studies of the effects of these agents upon the STI.

Only recently have studies appeared wherein the STI have been used as a routine clinical test to improve drug therapy. The STI appear to have great potential for evaluating therapy of thyroid disorders following patients receiving the cardiotoxic antineoplastic agent, adriamycin, and for assessing the effect of propranolol therapy for angina pectoris or acute myocardial infarction. In the case of propranolol therapy, the STI not only provide information concerning left ventricular function but also reflect the degree (if any) of excessive adrenergic tone which is present.

Summary

The theoretical basis for the use of the systolic time intervals has been largely established. The method has been validated by direct measures from within the circulatory system. Standards for equipment and technique have been defined. Numerous clinical studies have demonstrated the value of this quantitative noninvasive technique for assessing left ventricular performance. At present there is need for further studies of the clinical usefulness of the systolic time intervals to improve both diagnosis and therapy of various cardiovascular disorders.

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A critical review of the systolic time intervals.
R P Lewis, S E Rittogers, W F Froester and H Boudoulas

Circulation. 1977;56:146-158
doi: 10.1161/01.CIR.56.2.146

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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