Serial Measurements of Systolic Time Intervals: Effects of Propranolol Alone and Combined with Other Agents in Hypertensive Patients

MARY C. KYLE, M.S., AND EDWARD D. FREIS, M.D.

SUMMARY  Systolic time intervals (STI) were recorded serially before and during 1 year of treatment in 367 hypertensive men. The patients were randomly assigned, double-blind, to one of the following regimens: propranolol alone (P), propranolol plus hydrochlorothiazide (P + T), propranolol plus hydralazine (P + H), propranolol plus hydrochlorothiazide plus hydralazine (P + T + H), or reserpine plus hydrochlorothiazide (R + T). Systolic time intervals were calculated by a computer pattern-recognition and measurement program. Diastolic blood pressure and heart rate (HR) decreased with each treatment regimen. The pre-ejection period (PEP) was prolonged following P alone. The left ventricular ejection time (LVET), after correction for HR, was shortened with P + T and R + T and prolonged after P + H. The PEP/LVET was reduced with P + H. The prolongation of PEP during long-term administration of P is comparable with previous studies of its acute effects and suggests a moderate decrease in left ventricular performance. Calculation of STI also appears to be a useful method for showing the effects of adding other antihypertensive agents.

(Hypertension 2: 111-117, 1980)

KEY WORDS  • propranolol  • reserpine  • hydrochlorothiazide  • hydralazine  • systolic time intervals

SYSTOLIC time intervals (STI) have provided useful information on the clinical pharmacology of digitalis glycosides, catecholamines, β-adrenergic blocking agents, and other drugs.¹ Most studies have focused on the effects of acute interventions, however, and few on the long-term effects of pharmacological agents on STI using serial measurements during continuous treatment.

The purpose of this study was to utilize serial measurements of STI to determine the long-term effects of propranolol, alone and in combination with hydralazine and/or hydrochlorothiazide, on the left ventricular performance of hypertensive patients. A group of patients receiving reserpine in combination with hydrochlorothiazide was also included. Measurement of the various indices was performed by computer pattern-recognition and measurement programs.²

Methods

Subjects

The STI of 367 hypertensive patients were recorded during the Veterans Administration cooperative study on the therapeutic efficacy of propranolol alone and in various combinations with other drugs. (Details of the study have been published previously.²) The patients were men without clinical evidence of congestive heart failure between the ages of 18 and 59 years (mean age, 48) who exhibited diastolic blood pressures (DBP) ranging between 90–114 mm Hg. The regimens under evaluation were propranolol alone (P), propranolol plus hydrochlorothiazide (P + T), propranolol plus...
hydralazine (P + H), and propranolol plus hydrochlorothiazide plus hydralazine (P + T + H); these were compared with the standard regimen, reserpine plus hydrochlorothiazide (R + T). The dose of propranolol in each regimen could be titrated over a range of 60 to 480 mg per day.

The STI of 199 normal men that had been previously recorded in the central laboratory were used as normal control data (see Appendix).

Equipment and Recording Procedure

The STI was calculated from simultaneous tape recordings of the electrocardiogram, phonocardiogram, and the external carotid arterial pulse wave made while the patient was in the supine position. Serial STI recordings for each patient were made at approximately the same time of day to avoid the effects of diurnal variation. 1 During the prerandomization period, the STI was recorded on two separate visits when all patients were receiving only a placebo; during the postrandomization period, it was recorded at 3, 6, and 12 months of treatment, with one of the above therapeutic regimens administered double-blind. Recordings were made within 1 to 5 hours after the patient had taken his medication. Blood pressure readings were taken with the patient in the sitting position using a standard mercury sphygmomanometer at the time of randomization and at the 6- and 12-month postrandomization visits.

Lead V₃ of the electrocardiogram was recorded using a Hewlett Packard Bioelectric Amplifier. The phonocardiogram was recorded with a Hewlett Packard Heart Sound Amplifier and a model 21050A transducer. A lower cutoff frequency of 100 Hz and a slope of 12 db per octave were used. The carotid arterial pulse wave was recorded with a special-purpose low-gain amplifier and a pulse-wave transducer. The transducer consists of a Pitran pressure-sensitive transducer (model PT-H2, Stow Laboratories, Inc., Hudson, MA) mounted in a water-filled plexiglass housing covered with a plastic membrane. The data were monitored on a four-channel oscilloscope and recorded on a Hewlett Packard 3960 four-channel instrumentation tape recorder. Tapes were sent to the central laboratory where each recording was visually inspected on an oscilloscope, 20 seconds of data selected from it and converted to digital form at a sampling rate of 250 points/sec, and analyzed by computer.

Measurements and Statistical Analysis

The computer program for measuring STI² uses the digitized data and a pattern recognition algorithm to identify points in the electrocardiogram, phonocardiogram, and carotid pulse wave. The program then calculates the pre-ejection period (PEP), the left ventricular ejection time (LVET), the total electromechanical systole (QS₃), and the ratio PEP/LVET. 1 The accuracy of the computer program was previously evaluated by comparison of measurement values calculated from visual inspection with those calculated by computer for the primary variables QS₃ and LVET. In the 142 cases compared, all LVET and all but two QS₃ measurements agreed within 4 msec.²

Since LVET and QS₃ vary inversely with heart rate (HR),¹ 4 these variables were adjusted for HR using the normal regression equations relating HR and the intervals given in the Appendix. This adjustment was made by calculating the deviation from the normal regression line as the difference between the observed value and predicted normal value for a given HR (Δ LVET and Δ QS₃). The PEP and PEP/LVET were not adjusted for HR because of the small correlation coefficient observed between PEP and HR in our normal subjects (see Appendix) and those of Fabian et al, ³ and because of evidence from acute studies indicating that PEP should not be adjusted for HR.⁴⁵

To determine whether the two prerandomization values for the STI could be averaged, they were tested for significant differences between the first and second prerandomization values, using Student's t-test for paired observations; no significant differences were found. The average of the prerandomization values was therefore used for later comparison with the postrandomization data. To determine whether averaging also could be used for the postrandomization data, regression lines were fitted through the values for the STI obtained at 3, 6, and 12 months. Since these variables did not reveal any significant trends during the postrandomization period, the data at 3, 6, and 12 months were averaged. These prerandomization and postrandomization average values were then used to test the significance of the changes after each therapeutic regimen, using Student's t test for paired observations.

To determine if the STI changes varied according to DBP response, the data in each treatment group were also subdivided according to the patients' blood pressure response. The responders were defined as those whose postrandomization DBP fell below 90 mm Hg and was at least 5 mm Hg less than the prerandomization DBP. Responders and non-responders were analyzed separately to test the significance of the difference between prerandomization and postrandomization STI in these two subgroups. A similar subdivision was made with respect to dosage, the low-dosage patients being defined as those taking 120 mg or less of P daily as opposed to the high-dosage group who received 240 to 480 mg of P daily.

Results

The postrandomization changes presented in Table 1 and figure 1 indicated that both DBP and HR decreased significantly (p < 0.001) in all treatment groups. The most important STI changes included the following: 1) PEP was significantly prolonged following P alone (p < 0.001) (although when these patients were divided into low- and high-dosage groups, the...
Table 1. Prerandomization Mean Values and Mean Changes Postrandomization

<table>
<thead>
<tr>
<th>Measurement</th>
<th>P Group (n = 78)</th>
<th>P + T Group (n = 73)</th>
<th>P + H Group (n = 74)</th>
<th>P + T + H Group (n = 72)</th>
<th>R + T Group (n = 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBP (mm Hg)</td>
<td>Prerand. mean</td>
<td>Postrand. change</td>
<td>Prerand. mean</td>
<td>Postrand. change</td>
<td>Prerand. mean</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>70</td>
<td>-11*</td>
<td>70</td>
<td>-8*</td>
<td>71</td>
</tr>
<tr>
<td>Δ Qs (msec)</td>
<td>18</td>
<td>+3</td>
<td>18</td>
<td>-9*</td>
<td>19</td>
</tr>
<tr>
<td>Δ LVET (msec)</td>
<td>-2</td>
<td>0</td>
<td>-3</td>
<td>-7*</td>
<td>0</td>
</tr>
<tr>
<td>PEP (msec)</td>
<td>117</td>
<td>+7*</td>
<td>118</td>
<td>+1</td>
<td>117</td>
</tr>
<tr>
<td>PEP/LVET</td>
<td>0.42</td>
<td>0.00</td>
<td>0.42</td>
<td>0.00</td>
<td>0.42</td>
</tr>
</tbody>
</table>

*Difference of prerandomization and postrandomization means is significant with p < 0.001 using two-tailed test.
†Difference of prerandomization and postrandomization means is significant with p < 0.01 using two-tailed test.

Abbreviations: DBP = diastolic blood pressure; H = hydralazine; HR = heart rate; Δ LVET = left ventricular ejection time adjusted for HR; P = propranolol; PEP = pre-ejection period; PEP/LVET = ratio of pre-ejection period to left ventricular ejection time; Δ Qs = total electromechanical systole adjusted for HR; R = reserpine; T = hydrochlorothiazide.

Discussion

Systolic time intervals have been used extensively as clinical indices of left ventricular function, cardiac output, and cardiac neural activity. Most studies have been concerned with the effects of acute interventions on STI. In our study, STI was evaluated as a method for assessing the effects on left ventricular performance of long-term administration of P alone or in combination with hydralazine and/or hydrochlorothiazide in hypertensive subjects. Such long-term assessment seemed indicated because of the striking contrast between the immediate and long-term hemodynamic effects of β-adrenergic blockade in hypertension.

For many years STI has been used to assess the acute effects of adrenergic influences on the heart. Wiggers was the first to document shortening of STI in animals in response to epinephrine. Others have shown that isoproterenol and epinephrine infusions both cause a shortening of PEP and LVET. Epinephrine infusion, however, causes no shortening of LVET when it is corrected for HR. Also, when HR is held constant by atrial pacing, infusion of isoproterenol does not change the LVET in patients with heart disease. These findings indicate that the shortening of LVET observed with isoproterenol or epinephrine is secondary to HR changes rather than to inotropic effects produced by these agents. By contrast, the shortening of PEP after β-adrenergic stimulation with isoproterenol is not prevented by atrial
pacing, indicating that its response is dependent on contractility changes. Acute intravenous administration of P in normal subjects and hypertensive patients is associated with a slight lengthening of PEP, which probably reflects a decrease in the inotropic activity of the myocardium. Therefore, PEP seems to provide a more reliable indication of inotropic activity than LVET.

Two factors may influence the prolongation of PEP observed in many hypertensive patients in the pretreatment period as compared to the normal controls: 1) diminished left ventricular performance; and 2) the elevated level of DBP (i.e., the pressure in the left ventricle must be raised to a higher level than normal to open the aortic valve). On the other hand, increased adrenergic activity would shorten PEP and could account for the normal values found in some of our patients. The large spread of pretreatment PEP values (fig. 2) is consistent with the results reported by Tarazi et al., who divided hypertensive patients into three groups and found that those with fixed essential hypertension had a prolonged PEP. Shortened and normal values were observed in patients with borderline and hyperkinetic essential hypertension respectively. The level of sympathetic activity could also account for the inverse relationship between the initial value of PEP and its change after β-adrenergic blockade; that is, the patients with increased

---

**FIGURE 1.** Bar graph showing mean postrandomization changes. H = hydralazine; ΔLVET = left ventricular ejection time adjusted for heart rate; P = propranolol; PEP = pre-ejection period; PEP/LVET = ratio of pre-ejection period to left ventricular ejection time; R = reserpine; T = hydrochlorothiazide.

**FIGURE 2.** Scatter diagrams showing the relationships between PEP prerandomization and the change in PEP after P alone (upper) and between PEP/LVET prerandomization and the change in PEP/LVET after P+H (lower). H = hydralazine; P = propranolol; PEP = pre-ejection period; PEP/LVET = ratio of pre-ejection period to left ventricular ejection time.
adrenergic activity would have shorter initial values of PEP and show the greatest increases in PEP following P.

In the pretreatment period, PEP/LVET, which is regarded as an index of left ventricular function, was also significantly increased. This was due to a lengthening of PEP, however, rather than a shortening of LVET. The observed increase in PEP/LVET may reflect decreased left ventricular performance but it also may be the result of the increased DBP.

If other influences remain unaltered, a rise of DBP should increase the isovolumic contraction time and hence PEP, while a fall in DBP should shorten PEP. Shaver et al. reported the values of PEP and DBP before and after methoxamine infusion when stroke volume, HR, and inotropic state were held constant. Their data show a significant correlation between the rise in DBP and the increase in PEP following methoxamine. Similarly, when other factors are equal, a reduction in DBP should result in a decrease in PEP.

In our study, PEP increased in the patients who received P alone despite no change or a fall in DBP, although the extent of the increase was greater in the nonresponders. This indicates that the observed prolongation of PEP after P was the result of some change other than DBP, the most likely being a decrease in left ventricular performance resulting from the β-adrenergic blockade. Since the change was small, however, the increase in PEP did not suggest a clinically important reduction in the performance of the left ventricle.

The change in PEP was significant only with the regimen containing P alone, and it occurred predominantly in patients taking higher doses of P (240-480 mg/day). The lack of significant prolongation of PEP in the patients receiving lower doses did not appear to be related to either DBP or HR changes following P since there was no significant difference in either of these variables between the low- and high-dosage groups.

It is also possible that the change in PEP observed after treatment with P could be influenced by the baseline level of PEP. Figure 2 demonstrates the inverse relationship between the prerandomization level of PEP and the change after P: the greater the duration of PEP prerandomization, the less the increase during treatment. Tarazi et al. have previously described a similar relationship after acute administration of P in hypertensive patients. They also found that the prolongation of PEP was inversely related to the control values of PEP. Although there is a fairly large scatter in figure 2, the relationship suggests that, in general, patients with greater left ventricular dysfunction before treatment exhibit less change in left ventricular chamber performance after chronic treatment with P alone. The reason for this relationship is not clear. A possible explanation is that some hypertensive patients maintain relatively normal values of PEP through the mechanism of increased β-adrenergic activity. If such is the case, they would be expected to show a greater increase in PEP following P than those with less β-adrenergic activity, and, hence, initially greater values of PEP.

There was no apparent reduction in left ventricular performance when P alone was combined with hydralazine or thiazide. The reason for this is also not apparent. Possible explanations include the higher doses of P required in the P alone regimen or neutralization of the inhibiting effects of P by hydralazine, which could increase preload and possibly result in some reflex myocardial stimulation in the presence of incomplete β-adrenergic blockade.

Following acute intravenous administration of P in hypertensive patients, a significant shortening of LVET when corrected for HR has been reported. In our study, Δ LVET (LVET adjusted for HR) was unchanged after chronic oral administration of P. This agrees with the observations of Frohlich et al. who studied the long-term hemodynamic effects of P in hypertensive patients. When LVET was adjusted for HR there was no significant difference before and during treatment with P. They further observed a decrease in cardiac output, which was due entirely to a reduction in HR while stroke volume remained unchanged.

There was a significant increase in Δ LVET in the P+H group. The reason for this increase was not clear since P should suppress the chronotropic and inotropic effects of reflex sympathetic cardiac stimulation produced by P. As mentioned above, however, the β-adrenergic inhibition may have been incomplete. Another explanation is that cardiac output could remain elevated because of the reduction in total peripheral resistance produced by the arteriolar vasodilatation. The significant fall in diastolic blood pressure would lower ventricular outflow impedance, thereby permitting an increased stroke output and thus a longer Δ LVET. Also, right heart pressures rise after hydralazine due to arteriolar dilatation without venous dilatation, which could increase preload. This also may explain the reduction in PEP/LVET following P+H. As seen in figure 2, the patients with higher prerandomization values of PEP/LVET tended to have the greater decreases after treatment with P+H. Since the prerandomization mean of PEP/LVET was significantly above that of the normotensive controls, the decrease with P+H represents a return toward normal. The lack of significant change with the other regimens may indicate that there was no reduction in the performance of the left ventricle caused by these combinations of drugs.

The Δ LVET decreased with P+T and also with R+T: a possible explanation might be that both regimens contained hydrochlorothiazide. Changes in Δ QS in general tended to be similar to those observed with Δ LVET with significant reductions in all of the groups receiving hydrochlorothiazide.

Our patients showed mild pretreatment elevations in DBP and relatively small changes in blood pressure following drug therapy. Whether a more dramatic change in the ST1 would be observed in patients with higher initial arterial pressure levels or with higher dose levels of drugs remains unanswered. These serial
studies of the long-term effects of P on STI showed that the increase in PEP following P alone, although small, was consistent with the effects observed after acute administration of the drug.\textsuperscript{6}–\textsuperscript{17}

The present automated method, which facilitates analysis of repeated recordings in large numbers of patients, appears useful in demonstrating subtle changes in left ventricular chamber performance that might not be revealed in small-scale studies of STI. Furthermore, this method appears able to differentiate the effects of adding other agents. Our study therefore demonstrates that STI, which is readily measured by computer techniques, provides a useful method for identifying functional cardiac changes associated with antihypertensive drug treatment, particularly in large-scale studies.

Acknowledgments

We are very grateful to Hubert V. Pipherger, M.D., for the use of his computer facilities, and to Ibrahim Khatri, M.D., for his helpful suggestions. The participation of the following nurse specialists in hypertension in obtaining the systolic-time-interval recordings is also gratefully acknowledged: Susan Saydak, R.N., Geri Aldrich, R.N., Carol Wigley, R.N., Margie J. Bowen, R.N., Alba Hernandez, R.N., Mary Smith, R.N., Karen Maddock, R.N., Brenda Thornhill, R.N., Maria H. Natal, R.N., and Jean M. DaMore, R.N.

The authors also wish to acknowledge, with gratitude, the contributions of the following persons:

Principal Investigators
J. R. Thomas, M.D., Veterans Administration Hospital, Memphis, Tennessee (Chairman)
Leo Elson, M.D., (deceased), Veterans Administration Hospital, Jackson, Mississippi
Arthur S. Gear, Jr., M.D., Veterans Administration Hospital, Richmond, Virginia
James R. Oster, M.D., Veterans Administration Hospital, Miami, Florida
Elia A. Ramirez, M.D., Veterans Administration Hospital, San Juan, Puerto Rico
Frederick N. Talmers, M.D., Veterans Administration Hospital, Allen Park, Michigan

Operations Committee
Sibley W. Hoobler, M.D., Cleveland, Ohio (Chairman)
C. Morton Hawkins, Sc.D., Houston, Texas (Member)
W. McFate Smith, M.D., San Francisco, California (Member)

Veterans Administration Cooperative Studies Program Coordinating Center
Kenneth E. James, Ph.D., Veterans Administration, Edward Hines, Jr. Hospital, Hines, Illinois (Chief)
Jack Becktel, Veterans Administration, Edward Hines, Jr. Hospital, Hines, Illinois (Biostatistician)
Arthur F. Johnson, Ph.D., Veterans Administration, Edward Hines, Jr. Hospital, Hines, Illinois (Biostatistician)

Consultants
Harold W. Schnaper, M.D., Birmingham, Alabama
Lawrence W. Shaw, Biostatistician, Washington, D.C.
Barry J. Paterson, M.D., Veterans Administration Hospital, Miami, Florida

Veterans Administration Cooperative Studies Program
James A. Hagan, M.D., Ph.D., Veterans Administration Central Office, Washington, D.C. (Chief)

National Heart, Lung, and Blood Institute
Thomas P. Blaszkowski, Ph.D., Bethesda, Maryland (Representative)

References

12. Wiggers CJ: Studies on the consecutive phases of the cardiac cycle. II. The laws governing the relative durations of ventricular systole and diastole. Am J Physiol 56: 439, 1921

Appendix

Due to the linear relationship of STI and HR,\textsuperscript{1} it is customary to correct the STI for this influence of HR using regression equations. Linear regression equations relating
STI and HR were calculated from computer measurements of STI recorded on 199 normal male subjects. Ages ranged from 20 through 78 years (mean, 45) and HR from 52 through 105 beats/min (mean, 72). All intervals are expressed in milliseconds.

In Table A-1, regression equations for QS, and LVET were used to adjust for HR. The PEP and PEP/LVET were not adjusted for HR. The small \( r \) value for the correlation of these variables with HR indicates that an adjustment for HR is not appropriate. For PEP, the value of \( r^2 \), which is 0.07, indicates that only 7% of the proportion of the PEP variance can be attributed to its linear regression on HR while 93% of the variation is not explainable through the relation of PEP with HR.

### Table A-1. Systolic Time Intervals in Normal Males: Statistics

<table>
<thead>
<tr>
<th>Variable (Y)</th>
<th>Mean ± sd</th>
<th>Regression equation</th>
<th>( s_{r,x} )</th>
<th>( r )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>QS</td>
<td>379 ± 25</td>
<td>( Y = 518 - 1.9 ) HR</td>
<td>16</td>
<td>-0.77</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVET</td>
<td>283 ± 21</td>
<td>( Y = 394 - 1.5 ) HR</td>
<td>14</td>
<td>-0.75</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PEP</td>
<td>97 ± 15</td>
<td>( Y = 126 - 0.4 ) HR</td>
<td>15</td>
<td>-0.27</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PEP/LVET</td>
<td>0.35 ± 0.06</td>
<td>( Y = 0.32 + 0.0004 ) HR</td>
<td>0.06</td>
<td>-0.07</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Abbreviations: \( sd \) = standard deviation; \( s_{r,x} \) = sample standard deviation from regression in milliseconds; \( r \) = correlation coefficient; \( p \) = probability for the two-tailed test of significance that the regression coefficient equals zero; \( QS \) = total electromechanical systole; LVET = left ventricular ejection time; PEP = pre-ejection period, PEP/LVET = ratio of PEP to LVET; HR = heart rate; n.s. = not significant.
Serial measurements of systolic time intervals: effects of propranolol alone and combined with other agents in hypertensive patients.
M C Kyle and E D Freis

Hypertension. 1980;2:111-117
doi: 10.1161/01.HYP.2.1.111

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1980 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/2/1/111