Systolic Time Intervals as Possible Predictors of Pressure Response to Sustained Beta-Adrenergic Blockade in Arterial Hypertension

A Within-Patient, Placebo-Controlled Study

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SUMMARY Systolic time intervals (STI) were recorded at rest and during isometric exercise (IHG) in 20 hypertensive outpatients, WHO Stage 1 or 2. In a double-blind crossover study, slow-release metoprolol 200 mg once daily and matched placebo were given for 4 weeks each, at the end of a 2-week placebo washout. Blood pressure and STI were taken in the last day of washout and of either crossover period. Treatment decreased blood pressure and heart rate values at rest and on peak IHG; it didn't modify prejection period index (PEPI), left ventricular ejection time index (LVETI), and their ratio at rest, but decreased the ratio between diastolic blood pressure and PEPI (DBP/PEPI ratio) at rest and on peak IHG and lengthened the PEPI at peak IHG. Resting PEPI values on placebo treatment showed a negative correlation with systolic (r = — 0.72) as well as diastolic (r = — 0.90) pressure reduction on slow-release metoprolol as compared with placebo treatment. The PEPI/LVETI ratio at rest on placebo treatment showed a negative correlation with systolic (r = — 0.78) as well as diastolic (r = — 0.82) pressure reduction at rest on metoprolol compared with placebo treatment. Patients with a resting PEP/LVETI ratio less than 0.43 showed a reduction in both systolic and diastolic pressure approximating or exceeding 20 mm Hg, whereas patients with a PEP/LVETI ratio greater than 0.47 showed a decrease in systolic and diastolic blood pressure of less than 10 mm Hg. In patients with a PEP/LVETI ratio of 0.43 to 0.47 (50% of the trial population), STI didn't show any correlation with the pressure response to /3-blockade. A positive correlation was found between the DBP/PEPI ratio at rest on placebo treatment and systolic (r = 0.56) as well as diastolic (r = 0.76) pressure reduction at rest on slow-release metoprolol compared with placebo treatment. Thus, STI appeared as promising predictors of the magnitude of blood pressure response to sustained /3-blocking therapy in mild-to-moderate essential hypertension, mostly in patients with a resting PEP/LVETI ratio less than 0.43 or greater than 0.47. (Hypertension 5: 140-146, 1983)

KEY Words • hypertension • systolic time intervals • metoprolol • beta-blockers • isometric exercise

THE mechanisms by which /3-adrenergic blocking agents reduce blood pressure levels in essential hypertension are still incompletely defined. Factors such as renin levels, age, and cardiac output have been proposed as useful predictors of the pressure response to the β-adrenergic blockade, but too many conflicting data seem to limit the acceptance of their predictive role and of the consequent implications about the β-blocker's mode of action.

Sympathetic nervous activity, as revealed by plasma catecholamine levels, has been suggested as another possible predictor of the antihypertensive effect of a sustained β-adrenoceptor blocker. On the other hand, systolic time intervals (STI) have been shown to correlate with plasma catecholamine levels in essential arterial hypertension; moreover, the long-term antihypertensive response to β-adrenergic blockade appears predictable by pretreatment values of STI, as reported in a large open trial.

The aim of the present study was to ascertain, according to a double-blind within-patient design, the possible usefulness of the STI in the prediction of the pressure response to a sustained oral treatment of mild-to-moderate arterial hypertension with a recently developed slow-release formulation of metoprolol.

Materials and Methods

Study Design

The study was designed as a formal multicenter double-blind crossover comparison between slow-release metoprolol and placebo in outpatients with essential arterial hypertension WHO Stage I or II (fig. 1). Pa-
patients with clinical evidence of heart failure, second- and third-degree heart block, bronchial asthma, or diabetes mellitus requiring insulin were excluded.

At the end of a 2-week placebo washout period, preceded by gradual discontinuation of previous antihypertensive treatment, patients with resting lying diastolic blood pressure above 90 mm Hg were given slow-release metoprolol, 200 mg (1 tablet), in single morning daily doses and matched placebo for 4 weeks each, according to a randomized within-patient design. The eligibility criteria were thus applied prior to randomization, which was done by a random-number table taken from the Fisher and Yates's textbook. Clinical visits were scheduled for the last day of the washout period and of each cross-over period, always at the same time of the day (11 a.m.), approximately 3 hours after the morning drug intake. All patients, as well as the physicians involved (the authors of this paper), remained unaware of the treatment both before and during the study period. All patients gave their written informed consent to be included in the study, which was approved by the local Ethics Committee.

**Experimental Procedures**

Exposure to cold, exertion, and eating were avoided for at least 2 hours before performing the experimental procedures. After 120 minutes' rest in a comfortable semirecumbent position, systolic and diastolic blood pressure, heart rate, and STI were recorded. Without changing body position, the subject performed an isometric hand-grip exercise test (IHG) using a Vigorimeter Martin cuff manometer, according to the standard protocol, consisting in the maintenance of 30% maximal voluntary contraction while breathing normally. Systolic and diastolic blood pressure, heart rate, and STI were measured in the last 15 to 20 seconds of the IHG, which lasted 3 minutes in all.

**Equipment and Measurements**

Blood pressure was taken by a standard mercury sphygmomanometer. Systolic pressure was recorded at the appearance of the brachial artery sounds, and diastolic pressure at the disappearance of the sounds (Korotkoff Phase 5). On each occasion, the third of three consecutive readings was registered for both systolic and diastolic pressure. The heart rate was counted from an electrocardiogram (ECG) strip, and averaged from six consecutive R-R intervals.

The STI were recorded from a simultaneous high-speed recording (100 mm/sec) of an ECG 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 mean of at least 10 cardiac cycles was taken to obtain STI values. The linear regression equation reported by Weissler et al. was used to correct STI for the heart rate values.

In both centers participating in the trial, STI were recorded by means of a Siemens Mingograph polygraph with four writing channels. The tracings from both centers were read by one observer, unaware of the origin of the patients, only after all patients had completed the study and before opening the medication code.

**Statistical Analysis**

Analysis of variance and nonparametric tests were used to check the homogeneity of patient distribution.

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**Figure 1.** Flow chart of the study. BP = blood pressure; HR = heart rate; STI = systolic time interval; SR = slow release.
between the two centers as well as between the two treatment sequences as regards age, sex, WHO stage, and both baseline and exercise values of heart rate, blood pressure, and STI, all recorded at the end of the placebo washout. Differences between the placebo washout and placebo treatment periods were analyzed by analysis of variance for randomized block design. Analysis of variance according to a crossover design was used to compare slow-release metoprolol with placebo treatment with regards to hemodynamic values and STI.

Correlation coefficients, regression lines with 95% confidence limits for predicted y values, and limits of the slope of the regression lines with 95% confidence were calculated according to standard techniques.

Finally, a χ² test was used to compare slow-release metoprolol with placebo treatment on the percentage of patients attaining satisfactory blood pressure control. Significance levels less than 5% were assumed significant.

Results

Trial Population

Twenty hypertensive outpatients participated in the study; they were 14 men and six women aged 31 to 58 years (mean ± SD = 44.2 ± 8 years), 19 in WHO Stage I, and one in WHO Stage II.17

All had normal sinus rhythm, and none had defects of atrioventricular conduction. Before, two patients were receiving β-blockers, two diuretics, and one a fixed combination, without attaining satisfactory blood pressure control (defined as a supine diastolic blood pressure at rest of less than 90 mm Hg).

After the placebo washout period, all patients were eligible to enter the crossover phase of the trial. According to the randomization, 11 patients followed the sequence metoprolol-placebo and nine the inverse sequence. A homogeneity check for patient distribution between the centers as well as between the two treatment sequences, regardless of the center (table 1), as regards to age, sex, WHO stage, and resting as well as exercise values recorded at the end of the washout period did not show any statistical differences between the two groups.

Compliance and Withdrawals

Patient compliance, based on count of the tablets remaining on the days of the clinical visits, was 100% in each patient, on both slow-release metoprolol and placebo treatment. None of the patients discontinued the study.

Antihypertensive Effect

Compared with the washout period, placebo treatment caused small changes in both blood pressure and heart rate at rest and on peak exercise (table 2). None of these changes reached statistical significance.

Slow-release metoprolol reduced systolic blood pressure, diastolic blood pressure, and heart rate at rest by 9.7% (15.6 ± 7 mm Hg, p < 0.01), 16.7% (16.4 ± 7 mm Hg, p < 0.01), and 19.1% (13.1 ± 6 beats/min, p < 0.01) respectively, as compared with placebo treatment values.

Systolic blood pressure was below 150 mm Hg in 11 of 20 patients during β-blockade and in three of 20 during placebo treatment (p < 0.01). On slow-release metoprolol treatment, diastolic blood pressure was below 90 mm Hg in eight of 20 patients (40%) and ranged between 90 and 95 mm Hg in nine patients (45%). In the remaining three patients, diastolic blood pressure approximated 100 mm Hg. On placebo treatment, diastolic blood pressure exceeded 90 mm Hg in all patients (p < 0.01) and ranged between 90 and 95 mm Hg in two (p < 0.01).

In comparison with placebo treatment, slow-release metoprolol also reduced peak IHG values of systolic and diastolic blood pressure and of heart rate by 9.9% (19.3 ± 8 mm Hg, p < 0.01), 11.6% (15.5 ± 8 mm Hg, p < 0.01) and 22.9% (19.4 ± 7 mm Hg, p < 0.01) respectively. Neither blood pressure nor heart rate showed any changes, both at rest and on peak IHG, between the two study periods regardless of the treatment, as well as between the two treatment sequences.

Prediction of Pressure Response

A negative correlation was found between resting values of PEPI/LVET ratio on placebo treatment and

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sequence 1</th>
<th>Sequence 2</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>45.3 ± 8</td>
<td>42.8 ± 7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sex</td>
<td>7 M, 4 F</td>
<td>7 M, 2 F</td>
<td>n.s.</td>
</tr>
<tr>
<td>Stage WHO</td>
<td>10, 1, 1</td>
<td>9, 1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Resting data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>66.2 ± 8</td>
<td>66.2 ± 5</td>
<td>n.s.</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>171.8 ± 15</td>
<td>160.0 ± 12</td>
<td>n.s.</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>110.0 ± 11</td>
<td>105.5 ± 6</td>
<td>n.s.</td>
</tr>
<tr>
<td>PEPI (msec)</td>
<td>145.0 ± 18</td>
<td>143.7 ± 16</td>
<td>n.s.</td>
</tr>
<tr>
<td>LVETI (msec)</td>
<td>402.2 ± 26</td>
<td>401.3 ± 24</td>
<td>n.s.</td>
</tr>
<tr>
<td>PEP/LVET ratio</td>
<td>0.396 ± 0.06</td>
<td>0.413 ± 0.04</td>
<td>n.s.</td>
</tr>
<tr>
<td>DBP/PEPI ratio</td>
<td>0.74 ± 0.07</td>
<td>0.72 ± 0.06</td>
<td>n.s.</td>
</tr>
<tr>
<td>IHG data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>75.7 ± 8</td>
<td>81.4 ± 10</td>
<td>n.s.</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>196.8 ± 27</td>
<td>191.1 ± 24</td>
<td>n.s.</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>123.1 ± 18</td>
<td>123.8 ± 13</td>
<td>n.s.</td>
</tr>
<tr>
<td>PEPI (msec)</td>
<td>139.5 ± 16</td>
<td>143.5 ± 17</td>
<td>n.s.</td>
</tr>
<tr>
<td>LVETI (msec)</td>
<td>408.6 ± 27</td>
<td>413.9 ± 29</td>
<td>n.s.</td>
</tr>
<tr>
<td>PEP/LVET ratio</td>
<td>0.365 ± 0.05</td>
<td>0.383 ± 0.03</td>
<td>n.s.</td>
</tr>
<tr>
<td>DBP/PEPI ratio</td>
<td>0.87 ± 0.08</td>
<td>0.85 ± 0.07</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

WHO = World Health Organization; HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; PEPI = prejection period index; LVETI = left ventricular ejection time index; IHG = isometric handgrip exercise.
systolic ($r = -0.78, p < 0.01$) as well as diastolic ($r = -0.82, p < 0.01$) pressure reduction at rest induced by slow-release metoprolol (figs. 2 and 3).

Patients with a resting PEP/LVET ratio less than 0.43 showed a reduction in both systolic and diastolic pressure approximating or exceeding 20 mm Hg. On the other hand, patients with a resting PEP/LVET ratio exceeding 0.47 failed to respond to slow-release metoprolol. A negative correlation was also found between resting values of PEP/LVET ratio and diastolic pressure ($r = 0.01$ and $-0.12$ respectively). Also, the changes in PEPI, PEP/LVET ratio, and DBP/PEPI ratio produced by IHG in patients on placebo treatment did not show any significant relationship with pressure reduction at rest induced by slow-release metoprolol.

**Unwanted Effects**

On $\beta$-blockade, all patients maintained their normal sinus rhythm. The P-R segment remained below 0.20 msec in all patients. One patient complained of moderate asthenia and vivid dreams on metoprolol but not on placebo treatment, whereas two patients complained of mild headache and dizziness only on placebo.

**Discussion**

This is the first placebo-controlled double-blind study to substantiate the possible predictive value of STI on the magnitude of the antihypertensive response to sustained $\beta$-adrenergic blocking therapy in arterial hypertension. In fact, the pressure response to slow-release metoprolol significantly correlated with PEPI, PEP/LVET ratio, and DBP/PEPI ratio measured at rest in the absence of $\beta$-blockade at the end of placebo treatment period.

About 61%, 52%, and 31% of total variance of systolic pressure reduction proved to be accounted for comparison with placebo washout, nor between the two study periods, regardless of the treatment.

In comparison with placebo treatment, slow-release metoprolol caused a slight lengthening of PEPI at rest $145 \pm 14$ to $147 \pm 12$ msec, n.s.) and on IHG $142 \pm 12$ to $150 \pm 12, p < 0.01$, as well as of LVETI values at rest $399 \pm 28$ to $405 \pm 22$ msec, n.s.) and on IHG $405 \pm 22$ to $415 \pm 23$ msec, n.s.). The PEP/LVET ratio showed no significant changes on metoprolol as compared with placebo treatment values, both at rest and on peak IHG.

The DBP/PEPI ratio decreased on $\beta$-blockade in respect to placebo treatment, both at rest ($p < 0.01$) and on peak IHG ($p < 0.01$); however, from rest to peak IHG the DBP/PEPI ratio increased to the same extent on metoprolol and on placebo, without significant differences between the two increases.

**Monitoring of Cardiac Function Changes**

The PEPI, LVETI, PEP/LVET ratio, and the ratio between diastolic blood pressure and PEPI did not show significant changes on placebo treatment, in comparison with placebo washout, nor between the two study periods, regardless of the treatment.

### Table 2. Blood Pressure (BP), Heart Rate, and Systolic Time Intervals (mean ± sn) in Patients at Rest and on Peak Isometric Exercise (IHG)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Placebo washout</th>
<th>Placebo</th>
<th>Slow-release metoprol</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>rest</td>
<td>66.2 ± 7</td>
<td>67.3 ± 7</td>
<td>54.4 ± 6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>IHG</td>
<td>78.3 ± 9</td>
<td>77.5 ± 7</td>
<td>59.7 ± 6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>rest</td>
<td>165.5 ± 14</td>
<td>160.8 ± 18</td>
<td>145.1 ± 16</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>IHG</td>
<td>193.2 ± 25</td>
<td>188.6 ± 24</td>
<td>169.8 ± 20</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>rest</td>
<td>108.3 ± 20</td>
<td>103.3 ± 5</td>
<td>86.0 ± 8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>IHG</td>
<td>123.5 ± 16</td>
<td>123.3 ± 10</td>
<td>108.9 ± 8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PEPI (msec)</td>
<td>rest</td>
<td>144.5 ± 15</td>
<td>145.2 ± 14</td>
<td>147.8 ± 12</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>IHG</td>
<td>140.9 ± 16</td>
<td>142.5 ± 12</td>
<td>150.9 ± 12</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVETI (msec)</td>
<td>rest</td>
<td>410.7 ± 25</td>
<td>399.7 ± 28</td>
<td>405.5 ± 22</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>IHG</td>
<td>404.8 ± 20</td>
<td>405.5 ± 22</td>
<td>415.7 ± 22</td>
<td>n.s.</td>
</tr>
<tr>
<td>PEP/LVET ratio</td>
<td>rest</td>
<td>0.37 ± 0.05</td>
<td>0.41 ± 0.05</td>
<td>0.39 ± 0.05</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>IHG</td>
<td>0.37 ± 0.06</td>
<td>0.38 ± 0.05</td>
<td>0.40 ± 0.05</td>
<td>n.s.</td>
</tr>
<tr>
<td>DBP/PEPI ratio</td>
<td>rest</td>
<td>0.72 ± 0.06</td>
<td>0.70 ± 0.07</td>
<td>0.59 ± 0.06</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>IHG</td>
<td>0.86 ± 0.09</td>
<td>0.88 ± 0.12</td>
<td>0.75 ± 0.09</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Statistical significance refers to comparisons between randomized treatments. See table 1 for explanation of abbreviations.
Figure 2. Correlation between systolic pressure reduction and the PEP/LVET ratio in patients on β-blockade and placebo treatment.

Figure 3. Correlation between diastolic pressure reduction and PEP/LVET ratio in patients on β-blockade and placebo treatment.
by the relationship with PEP/LVET ratio, PEPI, and DBP/PEPI ratio respectively, while 67%, 64%, and 31% of the total variance in diastolic pressure reduction was accounted for by the relationship with PEP/LVET ratio, PEPI, and DBP/PEPI ratio respectively.

These findings are in accordance with those reported by Plotnick et al., who observed that hypertensive patients with a pretreatment PEP/LVET ratio greater than 0.42 were significantly less likely to respond with a more than 10% diastolic pressure reduction on long-term open pindolol therapy.

The observed correlation between STI and plasma catecholamine levels, as well as the predictive value of the latter on the antihypertensive effect of atenolol, substantiate that sympathoadrenergic involvement is a key factor in the predictive value of STI on the antihypertensive response to sustained β-adrenoceptor blockade.

Since in this study we have not measured catecholamines, further investigation is needed to measure the predictive value of both STI and plasma catecholamine levels in a single trial in regard to pressure reduction under β-blockade. The possibility of a wide clinical application of STI in the prediction of blood pressure response to β-blockers should be scrutinized with caution, at least from the results of our study. In fact, approximately 50% of our hypertensive patients fell in an intermediate zone, with a resting PEP/LVET ratio of 0.43 to 0.47 and a DBP/PEPI ratio of 0.67 to 0.73 (figs. 2–4). In these patients, no apparent correlation was found between STI and blood pressure response to slow-release metoprolol. By contrast, in the remaining half of the trial population the relationship appeared suggestive at either extreme of the STI values’ distribution (figs. 2–4).

Beyond an antihypertensive effect, slow-release metoprolol did not induce significant changes of PEPI, LVETI, and of their ratio at rest, possibly because of a balance between negative inotropic effect and afterload reduction on β-blockade. A somewhat depressing effect of β-blockade on left ventricular function may be revealed by the slight reduction in the DBP/PEPI ratio both at rest and on peak IHG, although the increase of this ratio from rest to peak exercise was not dissimilar on placebo treatment and on β-blockade.

Kyle and Freis observed a significant prolongation of the prejection period in hypertensive patients treated with oral propranolol only when the total daily dose exceeded 240 mg, although the blood pressure response to treatment was not dissimilar in the patients treated with a high propranolol dose compared to those receiving a low dose. One may speculate that in human hypertensives the β-adrenergic blockers may influence the STI by way of a balance between reduced afterload due to the antihypertensive effect and cardiodepressant action due to the myocardial β-adrenoceptor blockade.
Thus, in the passage from a lower to higher daily dose the consequences of the negative inotropic effect may be expected to prevail against those of the afterload reduction in the absence of a proportional dose-related pressure effect. The concordance between our results and those of Kyle and Freis may be due to the fact that propranolol doses below 240 mg/day are not dissimilar, in terms of $\beta$-blocking activity, from our metoprolol dose of 200 mg/day.

From rest to peak IHG, systolic and diastolic blood pressure increased, respectively, by 28/20 mm Hg on placebo and 24/22 mm Hg on metoprolol. The physiological increase in afterload on peak IHG is enhanced on blockade of vascular $\beta_2$-adrenoceptors, as revealed by the significant augmentation of the effects of IHG on arterial pressure and total peripheral resistance on administration of propranolol. Consistent with this view is the lower diastolic pressure increase on metoprolol than on propranolol.

In line with other findings, no differences were detected in our study between treatment and placebo in the pressure increase from rest to peak IHG, thereby suggesting a limited influence on peripheral vascular $\beta$-adrenoceptors.

We were unable to find any correlation between changes in blood pressure as well as in STI during IHG on placebo treatment and pressure response to slow-release metoprolol at rest. It is possible that factors such as increased plasma concentration of catecholamines and mechanical obstruction to blood flow, both present during IHG, may exert an apposite increase on STI. Thus, at variance with the values at rest, the IHG-induced changes in STI would not be proper indirect gauges of sympathetic activity, thereby failing to exert any predictive role on the pressure response to $\beta$-blocking therapy.

In conclusion, provided that further evidence on a larger population confirms our data, STI, taken as an indirect measure of sympathetic nervous activity, could be reconsidered as a routine clinical guideline in selecting patients more likely to respond to $\beta$-adrenergic blocking agents, besides monitoring left ventricular function during therapy. Patients with a PEP/LVET ratio at rest of less than 0.43 or greater than 0.47 are likely to experience a major or a minor blood pressure response respectively, following sustained $\beta$-adrenoceptor blocking therapy. In patients with PEP/LVET ratio at rest of 0.43 to 0.47, however, the predictive value of STI appears limited.

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