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 preejection 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 PEPI/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 PEPI/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 PEPI/LVETI ratio of 0.43 to 0.47 (50% of the trial population), STI didn’t show any correlation with the pressure response to β-blockade. A positive correlation was found between the DBP/PEPI ratio at rest on placebo treatment and systolic (r = 0.56) and 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 β-blocking therapy in mild-to-moderate essential hypertension, mostly in patients with a resting PEPI/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

T he mechanisms by which β-adrenergic blocking agents reduce blood pressure levels in essential hypertension are still incompletely defined. Factors such as renin levels,1,2 age,3 and cardiac output4 have been proposed as useful predictors of the pressure response to the β-adrenergic blockade, but too many conflicting data5-9 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 blockade.10 On the other hand, systolic time intervals (STI) have been shown to correlate with plasma catecholamine levels in essential arterial hypertension;11 moreover, the long-term antihypertensive response to β-adrenergic blockade appears predictable by pretreatment values of STI, as reported in a large open trial.12

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.13

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-
tients with clinical evidence of heart failure, second-
and third-degree heart block, bronchial asthma, or dia-
abetes mellitus requiring insulin were excluded.

At the end of a 2-week placebo washout period,
preceded by gradual discontinuation of previous anti-
hypertensive treatment, patients with resting lying dia-
stolic 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 de-
sign. 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.14

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 iso-
metric hand-grip exercise test (IHG) using a Vigori-
meter Martin cuff manometer, according to the stan-
dard protocol,13 consisting in the maintenance of 30%
maximal voluntary contraction while breathing nor-
mally. Systolic and diastolic blood pressure, heart
rate, and STI were measured in the last 15 to 20 sec-
onds 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 sys-
tolic 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 re-
gression equation reported by Weissler et al.16 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 poly-
graph 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 com-
pleted 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
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.

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 PEP/LVET ratio on placebo treatment and
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 reduction of 8 to 20 mm Hg. On the other hand, patients with a resting PEP/LVET ratio exceeding 0.47 failed to respond to slow-release metoprolol (figs. 2 and 3).

A negative correlation was also found between resting values of PEPI measured at rest on placebo treatment and systolic (r = -0.72, p < 0.01) as well as diastolic (r = -0.80, p < 0.001) pressure reduction at rest induced by /3-adrenergic blockade. Resting values of the DBP/PEPI ratio on placebo treatment correlated positively with systolic (r = 0.56, p < 0.01) as well as diastolic (r = 0.76, p < 0.01) (fig. 4) pressure reduction at rest during treatment.

The increase in systolic as well as diastolic blood pressure during IHG in placebo treatment showed no significant relationship with the antihypertensive effect of slow-release metoprolol at rest on both systolic (r = -0.11 and -0.24 respectively) and diastolic values (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.

### 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.

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

The DBP/PEPI ratio decreased on /3-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 metoprol and on placebo, without significant differences between the two increases.

### Unwanted Effects

On /3-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 metoprol 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 /3-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 /3-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

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**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 ± 12</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 ± 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 the 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.,\textsuperscript{12} 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,\textsuperscript{11} as well as the predictive value of the latter on the antihypertensive effect of atenolol,\textsuperscript{10} 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\textsuperscript{18} 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 β-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 β-adrenoceptors, as revealed by the significant augmentation of the effects of IHG on arterial pressure and total peripheral resistances in the presence 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 β-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 metoprol 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 influence 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 β-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 β-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 β-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.

Acknowledgments

The authors thank Dr. Bianca Francucci (statistical analysis), Dr. Ettore Bichisao (technical assistance), and Antonietta Paradiso (secretarial help) for their invaluable cooperation.

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Hypertension. 1983;5:140-146
doi: 10.1161/01.HYP.5.1.140

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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