Intermittent ST Depression and Mortality After Myocardial Infarction

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Background. We conducted a case-control analysis to determine the contribution made to mortality by intermittent ST depression (STD) among patients enrolled in the already completed Beta Blocker Heart Attack Trial.

Methods and Results. STD was determined by computer analysis of 24-hour ECG tapes as a change in ST level by ±0.1 mV or more from the median value of ST of all normally conducted complexes for ≥1 minute. All computer-detected ST events were verified by trained readers. To estimate risk of dying associated with STD, 261 deaths were compared with controls matched for age, sex, drug status, and time elapsed since acute myocardial infarction. In a model including relevant covariates, STD had a relative risk (RR) of 1.73 (95% confidence interval, 1.09–2.73). The RR was 2.56 (1.39–4.71) in untreated patients and 0.98 (0.48–2.00) in propranolol-treated patients. A history of angina, although not independently significant, was found to enhance these RRs. A gradient of risk was shown in the placebo group by a RR of 1.91 in those with 1–30 minutes of STD and 4.33 in those with >30 of STD (p=0.001, trend test).

Conclusions. The findings in this large study show a significant contribution to mortality among untreated early post–myocardial infarction survivors from transient STD on 24-hour monitoring. The absence or reduction of effect in the treated group also suggests an anti-ischemic mechanism by which propranolol exerts a protective effect on mortality. Trials to determine whether reduction of STD improves survival would be warranted. (Circulation 1992;85:1440–1446)

Key Words • ST segments • mortality • propranolol • angina • electrocardiography

The presence of transient ST depression (STD) on ECG monitoring of patients with clinical coronary heart disease has been shown to be reflective of ischemia.1,2 A natural concern is whether this makes a significant contribution to mortality when other prognostic variables are taken into account. To answer that question among patients who survived a myocardial infarction (MI), we conducted a large case-control study using data from the completed Beta Blocker Heart Attack Trial (BHAT).

Methods

Study Population and Study Design

The BHAT was a double-blind, randomized trial of the effects of propranolol on survival after acute MI.3 The total group numbered 3,837 patients aged 30–69.

Patients were excluded from the study if they had medical contraindications to propranolol, a history of severe congestive heart failure or asthma as an adult, or if they had or were likely to undergo cardiac surgery. Clinical and personal characteristics and ECG data, including the results of 24-hour ECG monitoring from the baseline reference examination, were completed while patients were hospitalized before randomization. Patients were followed for a minimum of one and up to three years after index MI.

There were 326 deaths during the BHAT follow-up period. We used a time-matched case–control design,4 with the case group consisting of 261 patients who died and for whom readable tapes were available. The pool of eligible controls or risk set for each case (i.e., death) consisted of individuals who eventually may have died or survived the trial but must have survived at least as long as the given case. One control was randomly selected from the eligible pool for each case. The matching criteria were age at enrollment (exact to the year), sex, drug status, and length of follow-up. Intermittent STD is defined as an STD maintained for at least 1 minute at a time.

BHAT Tapes

Five electrode sites were used to record two bipolar V₁- and V₂-like ECG leads from the right subclavicular space to V₅ position (lead CV₂) and from the left subclavicular space to V₅ position (lead CV₁) with an Avionics Model 445 two-channel reel-to-reel continu-
ous ambulatory ECG recorder. This recorder had a low-frequency response of 0.05 Hz. A calibration standard was used for each subject before the final hookup. A special ECG calibrator transmitted a series of half and full standardization pulses into the amplifiers of the Holter recorders. Approximately 1 minute of ECG calibration data was displayed on the clinic's ECG machine (all meeting AHA specifications for ECG recorders).

**Computer Analysis of 24-hour Tapes for ST Depression and ST Elevation**

Twenty-four-hour tapes were played back at 60 times real time by special-purpose hardware into the ARGUS/2H computer analysis program and digitized at a rate corresponding to a sampling rate of 250 Hz per channel. Calibration signals were measured and were manually added to the program to provide correct scaling of ST amplitudes. Identification of normally conducted complexes relied on “CYCLE” measurements produced by ARGUS. Only a complex labeled as normal followed by a second normal complex was considered for ST measurement. The ST baseline reference was the average amplitude in a 32-msec window starting 40 msec before QRS onset. Linear drift correction was performed for data points between baseline reference points of each pair of normally conducted complexes. The ST segment integral was calculated in microvolt-seconds (μV-sec) after linear drift correction in a 64-msec window centered at 60 msec past the end of the QRs (the J point). The ST integral value divided by the duration of the window gives the mean ST amplitude (in microvolts) within the window. To qualify as an intermittent ST episode, the ST integral had to be at least 6.4 μV-sec above or below the PR baseline, and the ST integral had to deviate by at least 6.4 μV-sec with respect to the median ST level for ≥60 sec. This is equivalent to ±0.1 mV deviation from the PR reference and ±0.1 mV deviation from median ST reference levels. Determination of a reference ST level was necessary for identification of intermittent ST segment change (either depression or elevation) in cases with abnormal ST findings throughout the recording. To determine the reference level, hourly median values of the ST integral were measured, and the median of these hourly ST integrals was taken as the reference. This ST median reference level can be positive or negative, i.e., above or below the PR baseline.

Figure 1 shows the definition of ST integral (shaded area) as the time integral in microvolt-seconds of the ECG voltage in a window 32 msec before and 32 msec after the J + 60 point.

The ST integral was used as the definition of ST deviation in the BHAT because by averaging over a 64-msec window, it affords substantial noise reduction over a single point for ST determination. In addition, all ST segment values were calculated as a running median of seven successive normally conducted complexes. The use of the ST integral measurement comes from its successful application in defining an ischemic response during submaximal treadmill exercise in the Multiple Risk Factor Intervention Trial; it was a strong independent predictor of 10.5-year mortality among these participants. The 0.1-mV change in ST level from reference is in line with the general wisdom regarding ischemic exercise-induced ST findings and with more recent studies of the ambulatory ECG response. The 24-hour median ST value was taken as reference so that intermittent ST shifts, whether positive or negative, could be detected. Compared with most other studies of transient ischemia, our estimates are likely to be conservative because they are adjusted for stable ST deviations.

The sampling rate was 15,000 samples per second per channel, which at playback speed 60 times real time corresponds to an effective sampling rate of 250 samples per second per channel. This rate is adequate for determining the frequency characteristics of the ST segment. It is probably marginal for QRS morphology analysis, which was not the focus of this study.

The methodology defined the reference ST level by determining the hourly median ST level and using the median ST level from all hourly periods. This procedure minimized the influence of a single hour on the median ST value for the 24 hours. The definition of ST episode required that the ST segment deviate from the PR base and from the 24-hour median by ≥6.4 μV-sec (0.1 mV) for ≥60 sec. This definition ensured that we defined an ST episode in terms of transient ST shift.

The software used for computer processing of the ambulatory ECGs (ARGUS 214) represents relatively old computer technology in terms of noise reduction and artifact rejection. Elaborate interactive quality control procedures were developed to verify all ischemic events detected and to rule out artifacts and false events.

**Visual Verification of Computer Output**

Computer-generated strips for ST episodes and a random sample of 30 plots were visually verified at the Minnesota ECG Laboratory. These computer-generated two-channel ECG strips representing 20 seconds were visually evaluated to determine the accuracy of computer measurements. Figures 2 and 3 display the visual verification procedure. Because the computer median reference level is always displayed in relation to the computer-determined PR segment, only the accuracy of PR determination was needed for visual verification. Thus, for transient ST deviation, the ST segment needed to deviate ±1 mm from the median ST value and also to deviate from the PR in the same direction. A trained coder evaluated the accuracy of the comput-
er's identification of the PR segment for each QRS displayed in the 20-second strip. If the visual assessment agreed with the computer, the ST deviation was confirmed; if not, the ST deviation was labeled false. We required that >50% beats in the sample agree with the visual determination before the ST episode was confirmed. When computer-generated STD strips equaled or exceeded 5 minutes, samples for reader verification were taken from the beginning, middle, and end. A set of 30 random plots was examined for each subject to provide a check of false-negative detection.

Limitations of Ambulatory Monitoring and Computer Methodology

The ambulatory ECG recording methodology used in BHAT was designed primarily for detection of arrhythm-
TABLE 1. Descriptive Characteristics of Deaths and Controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean for deaths</th>
<th>Mean for controls</th>
<th>Two-tailed p value for death-control difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (in.)</td>
<td>67.7</td>
<td>67.7</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (lb)</td>
<td>172.9</td>
<td>169.2</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>211.8</td>
<td>210.9</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>113.0</td>
<td>112.2</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>73.0</td>
<td>72.0</td>
<td>0.12</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>78.1</td>
<td>75.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Alcohol (days/week)</td>
<td>1.8</td>
<td>1.8</td>
<td>NS</td>
</tr>
<tr>
<td>Categorical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous MI</td>
<td>0.26</td>
<td>0.10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of angina</td>
<td>0.48</td>
<td>0.36</td>
<td>0.006</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.16</td>
<td>0.13</td>
<td>NS</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>0.60</td>
<td>0.49</td>
<td>0.009</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>0.07</td>
<td>0.02</td>
<td>0.009</td>
</tr>
</tbody>
</table>

BP, blood pressure; bpm, beats per minute; MI, myocardial infarction.

distribution of cases and controls. ST elevation was investigated similarly.

The strategy used for inclusion of variables and appropriate interactions in the logistic analyses is described in more detail under results.

Results

Prevalence

The prevalence of STD was 21% (25% in deaths, 19% in controls). This overall prevalence was identical to that found in an earlier pilot study of 100 patients randomly selected from the entire BHAT population. The prevalence of STD>30 minutes was 8% (10% in deaths, 6% in controls).

Prognosis

In the basic matched-pairs analysis, of the total of 261 pairs, 100 were discordant for STD. The RR of dying in the presence of STD was 57/43, or 1.33 (exact 95% confidence interval, 0.88–2.02). The RR of ST elevation was 60/61, or 0.98 (0.68–1.43). Variables controlled for by matching were age at enrollment, drug status, sex, and length of follow-up.

The BHAT data base contained measurements on several hundred variables in addition to propranolol status. A comparison of deaths and controls on selected variables appears in Table 1. Among these variables, six not included in our matching criteria were determined through univariate analyses and a priori considerations to be potential confounders in assessing the relation between STD and death. Table 2 presents results of logistic regression analysis examining the impact of STD on mortality when these variables were included in the model. Taking these variables into account, the RR of STD was 1.73. The increase from 1.33 in the basic analysis presumably reflects the presence of confounding variables that masked a portion of the effect of STD on mortality. Among these additional variables, history of previous MI (RR, 3.77), cigarette smoking before MI

TABLE 2. Conditional Logistic Relative Risk Estimates for Mortality Caused by STD (Basic Model)

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR</th>
<th>95% CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>STD</td>
<td>1.73</td>
<td>1.09–2.73</td>
</tr>
<tr>
<td>History of angina</td>
<td>1.27</td>
<td>0.85–1.91</td>
</tr>
<tr>
<td>Previous MI</td>
<td>3.77</td>
<td>2.08–6.82</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(per 10 mm Hg)</td>
<td>1.23</td>
<td>0.95–1.60</td>
</tr>
<tr>
<td>Heart rate (per 10 bpm)</td>
<td>1.27</td>
<td>1.05–1.55</td>
</tr>
<tr>
<td>Presence of pulmonary edema</td>
<td>2.74</td>
<td>0.96–7.85</td>
</tr>
<tr>
<td>Cigarette smoking before MI</td>
<td>2.22</td>
<td>1.42–3.50</td>
</tr>
</tbody>
</table>

STD, ST segment depression; RR, relative risk; CL, confidence limits; MI, myocardial infarction; bp, beats per minute.

Deaths matched to controls on time, age, sex, and drug status.

(RR, 2.22), and heart rate (RR, 1.27 per 10 beats per minute) were statistically significant.

The possibility that STD would influence mortality differentially in propranolol and placebo groups led us to introduce an interaction term involving STD and drug status into the model of Table 2. In Table 3 (nongradient model), it is evident that in the presence of propranolol, STD has no impact on mortality, whereas it does have a significant effect, RR, 2.56 (1.39–4.71), among those taking placebo.

We also investigated the possibility that STD might influence mortality differentially in those with and without a history of angina by introducing an interaction term to the previous regression model. Table 4 (nongradient model) shows the results for the same group of variables with the addition of an interaction term involving history of angina and STD. For untreated patients positive for both these variables, the RR was 4.50 (2.01–10.09). This interactive RR was statistically significant and substantially greater than the product of the two component RRs (1.57 and 1.05, respectively). For treated patients with STD and history of angina, the RR was reduced to 2.00 (0.75–5.27), still elevated but not statistically significant. Interaction terms involving STD and the other six variables were also investigated, but none were statistically significant.

To further refine the relation between STD and mortality, we separated patients with STD into groups with 1–30 minutes (STD1) and >30 minutes (STDa). In

TABLE 3. Conditional Logistic Relative Risk Estimates for Mortality Caused by STD (Drug Effect Model)

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR</th>
<th>95% CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nongradient model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STD (treated)</td>
<td>0.98</td>
<td>0.48–2.00</td>
</tr>
<tr>
<td>STD (placebo)</td>
<td>2.56</td>
<td>1.39–4.71</td>
</tr>
<tr>
<td>Gradient model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STD (1–30 minutes, treated)</td>
<td>0.92</td>
<td>0.40–2.09</td>
</tr>
<tr>
<td>STD (&gt;30 minutes, treated)</td>
<td>1.15</td>
<td>0.35–3.71</td>
</tr>
<tr>
<td>STD (1–30 minutes, placebo)</td>
<td>1.91</td>
<td>0.92–3.96</td>
</tr>
<tr>
<td>STD (&gt;30 minutes, placebo)</td>
<td>4.33</td>
<td>1.60–11.71</td>
</tr>
</tbody>
</table>

STD, ST segment depression; RR, relative risk; CL, confidence limits.

Deaths matched to controls on time, age, sex, and drug status. RR estimates adjusted for previous myocardial infarction (MI), history of angina, diastolic blood pressure, heart rate, cigarette smoking before MI, and presence of pulmonary edema.
a model including STD\(_1\), STD\(_{30}\), respective drug interaction terms, and covariates (Table 3, gradient model), STD, regardless of category, continued to have no impact on mortality in treated patients. In the untreated group, however, the respective RRs for STD of 1–30 minutes and >30 minutes were 1.91 (0.92–3.96) and 4.33 (1.60–11.71). A two-tailed test for trend was significant (\(p = 0.001\)), providing evidence for a gradient of risk. In this model, history of previous MI, increased heart rate, or cigarette smoking before MI continued to elevate risk significantly.

In Table 4 (gradient model), we examined the interaction between history of angina and STD in the context of the gradient model. The effect of history of angina in untreated patients was to enhance the dose–response effect of STD on mortality. The RR was 2.63 (1.00–6.91) in those with 1–30 minutes STD and 11.55 (2.97–44.88) in those with >30 minutes STD. Even in treated patients there was a suggestion, although not attaining statistical significance, of a positive trend (respective RRs of 1.27 and 4.51).

### Discussion

We found a 21% prevalence of intermittent STD in a random sample of BHAT post-MI patients. Prevalences of 28% and 45% were reported in two other smaller studies\(^{11,12}\) and 30% in a selected high-risk post-MI population.\(^{13}\) The lower prevalence of STD in the BHAT population may well reflect BHAT’s exclusion of patients with severe heart failure and those who were potential surgical candidates.

Performance of the 24-hour monitoring 7–21 days after acute MI may have contributed to the lower prevalence. About half the deaths and controls were monitored 6–9 days after MI. The distributions of deaths and controls in the 7–21-day interval were overall quite similar, and the respective median time intervals after MI were identical (8 days). Any postulated difference on the effect of monitoring interval on STD prevalence would not be likely to influence the difference in mortality observed between the two groups.

There have been few reports on the impact of STD on mortality after MI. One such study involving a small number of deaths among a subgroup of high-risk MI patients showed a positive association.\(^{13}\) In other studies, the small numbers followed did not permit a reliable assessment of mortality.\(^{14}\)

The results reported here are consistent with an independent contribution to mortality by the presence of STD of ≥1-minute duration when other relevant variables are taken into account. A gradient is evidenced by the increase in risk associated with the presence of more than 30 minutes of STD and again when an interaction occurs in the presence of history of angina. Finally, the effect is greatest when these abnormalities are present in the placebo group compared with the propranolol group.

The size of this study yielded a sufficiently large number of deaths to develop a number of statistical models from which to determine the best-fitting model. A limitation of the current study is the absence of refined measures of left ventricular function. The presence of congestive heart failure with acute MI, however, was a strong independent risk factor. It is also to be noted that intermittent STD is not synonymous with “silent ischemia,” because patient diaries were not recorded. There is abundant evidence, however, that the majority of STD episodes in a variety of settings are unaccompanied by symptoms.\(^{15}\) We found no effect on mortality from the presence of ST elevation; both similar and contradictory reports have been made by others.\(^{16,17}\) Approximately one sixth of the BHAT deaths were unavailable for analysis, mainly because of the lack of a readable 24-hour tape. To investigate possible selection bias, we compared baseline characteristics of both groups and found no appreciable differences. The limitations of the BHAT ambulatory monitoring and the computer methodology used have been noted in the “Methods” section. Any bias introduced would be random and would have the effect of underestimating the true RRs. Digitalis use and left ventricular hypertrophy can affect the ST segment, but their presence made no independent contribution to mortality. The location of MI was examined as a possible cause of bias, because STD was found to be more prevalent in inferior wall than anterior wall MI. Despite the increased number of deaths with anterior wall MI compared with controls, the location of MI did not influence the effect of STD in the multivariate model. This may be because of the 40% of deaths who had both anterior and inferior wall MI.

Chronic angina occurring among patients recovered from MI is not independently related to mortality.\(^{18}\) Therefore, it is of interest to find an interaction between history of angina before MI and intermittent STD, which is independently predictive of mortality. It would be of importance to determine whether these relations are also
characteristic of post-MI angina. If so, it would be possible to differentiate a particularly high-risk subgroup.

There have been few studies of prognosis of patients with angina in the absence of MI. In one such study, fixed STD on ECG was found to be an independent predictor of mortality, together with age and ventricular arrhythmia.\(^{19}\) Fixed STD is also a significant independent risk factor after MI with or without angina.\(^{20-22}\) The mechanism is not known, but it is likely that this ECG abnormality reflects discrete anatomical change in the heart and is thereby related to muscle dysfunction.\(^{23}\)

The work of Maseri\(^{24}\) has shown that intermittent STD in angina patients, whether accompanied by pain or not, is often caused by transient impairment of regional blood flow rather than by an excessive increase in myocardial demand. The inciting factors leading to impairment of flow are not known but are likely to be varied, including mental stress.\(^{25}\) Psychosocial factors have been shown to increase the risk of dying after MI, and an examination of their influence on intermittent STD would therefore be of interest.\(^{26}\) More recently, it has been shown that silent ischemic episodes are frequently preceded by an increase in heart rate and blood pressure, suggesting that increase in myocardial oxygen demand also plays a role.\(^{27}\) This has particular implication to mechanisms by which propranolol might exert an anti-ischemic effect.

We found that the independent contribution to mortality by STD was present primarily in the placebo group. These data suggest the possibility that propranolol blunts the effects of STD on mortality and invite speculation about additional mechanisms of propranolol effectivesness. The finding that ventricular arrhythmia was suppressed in a randomly selected group of 1,000 patients who had a repeat 6-week monitoring in the BHAT study suggested that an antiarrhythmic mechanism partially explained propranolol's effect.\(^{28}\) Metoprolol is known to have an anti-ischemic effect,\(^{29}\) but to date there has been no demonstration that this effect has significant influence on survival. The current data showing that the propranolol-treated group is less affected than the placebo group by intermittent STD are important but are only indirect evidence that the anti-ischemic effect may also be an independent contributor to survival. More information on factors responsible for transient ischemia would be useful in planning controlled trials to explore whether suppression of intermittent STD by drugs or other means might increase survival among recovered MI patients.

Acknowledgments

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