Computer Quantitation of the ST-Segment Response during Maximal Treadmill Exercise

Clinical Correlation


SUMMARY

The ST-segment response during maximal treadmill exercise was quantitated by digital computer after excessive noise in the electrocardiographic data was reduced by computer averaging. Both the slope and the depression were quantitated.

Two groups of subjects were studied. Group A consisted of 35 subjects between 33 and 57 years of age with confirmed or suspected coronary artery disease. Group N consisted of 73 clinically normal subjects between 24 and 52 years of age. The responses of the group A subjects and the 26 subjects over age 35 in group N were compared by graphically plotting their ST slope and depression values from the last minute of exercise. A linear discriminant analysis computed from these values resulted in a line of separation between the majority of subjects in each of these two groups. This separation was accomplished even though the majority of subjects in group A did not demonstrate segmental ST depression.

Additional Indexing Words:
Coronary artery disease
Quantitation of ST slope and depression
ST-segment abnormalities during exercise

Quantitation of the ST-segment response to maximal treadmill exercise (MTE) has shown considerable promise as a method for detecting individuals with latent or preclinical coronary artery disease (CAD).1–5 Most studies dealing with this form of stress testing have emphasized the ST-segment changes appearing after completion of exercise. Distortion of the electrocardiographic signal during maximal exercise by excessive noise and artifact frequently prevents accurate quantitation of the ST-segment response. This inability to measure consistently the ST-segment changes during strenuous exercise may represent a significant diagnostic handicap. Several investigators have reported that the information gained from stress testing is greater if one also studies the ST-segment response during exercise or within a few seconds after termination of exercise.1–4,6–8 Recently, computer averaging techniques have been utilized to reduce the random noise in electrocardiographic data recorded during maximal exercise.2,9–11 A considerable increase in the signal-to-noise ratio can be accomplished without distorting the electrocardiographic complex, and the desired measurements on the final averaged data can be readily computed with the digital computer.

Most investigators studying the ST-segment response to maximal exercise have considered 1.0 mm or more of horizontal or declining (segmental) ST depression to be
the only unequivocally positive response, both
during and after exercise. Although segmental
ST depression is now generally accepted to be
the only positive ST-segment change in
response to more conventional, submaximal
stress tests,12-14 there have been no stud-
ies to establish what constitutes an abnormal
response to maximal exercise, especially
during exercise when the metabolic and physi-
ologic conditions are so different. Maxi-
mal exercise as a test for the detection of
individuals with early or potential CAD may
be made less sensitive by restricting the
criterion for a positive response to one shown
to be associated with advanced CAD.12

With the present-day computer capabil-
ities, it has become feasible to study the total
ST-segment response (slope and depression)
during strenuous exercise to define better
the ranges of response characteristic of in-
dividuals with and without CAD. The early
results of such a study being carried out at
the School of Aerospace Medicine have re-
cently been reported.15 The ST-segment res-
ponses during MTE were quantitated for a
group of subjects suspected of having CAD
because of nonspecific electrocardiographic
abnormalities and for a group of clinically
normal subjects of similar age. When the last
minute slope and depression values for each
subject were graphically plotted for com-
parison, a distinct separation of the two
groups was apparent. This separation was
possible even though the majority of subjects
with suspected CAD did not demonstrate
segmental ST depression. Considerable over-
lap existed between the two groups when a
similar comparison was made with either
the slope or the depression values alone.
This study has been continued to verify
further this observation and, as more subjects
have been studied, an attempt has been made
to define the normal range of response. The
present report deals with the combined re-
sults of 108 subjects studied during and
after MTE.

Minor modifications of the original method
for computer quantitation of the ST segment
are also described.

Methods

Our methods for collecting the electrocardi-
ographic data have been described in detail
previously.15 Although considerable reduction in
noise is accomplished by computer averaging,
it is still imperative that the raw data be col-
clected as free of noise and artifact as possible.
Relatively minor degrees of residual noise in the
averaged complex can lead to significant errors
in the computed ST-segment values, especially
in the ST slope. We have been able to obtain
optimal noise reduction by using a right and left
chest V5 electrode placement and a constant
speed treadmill program. The treadmill is run
at 3.3 mph while the grade is increased at a
rate of 1% per minute.

The subjects are instructed to walk on the
treadmill until they can no longer continue, and
they are strongly encouraged prior to testing to
give a maximal effort.

The electrocardiographic data are collected on
analog tape, and computer processing is initiated
by passing the data in parallel into an analog
computer and an analog-to-digital (A/D) con-
verter. Accurate averaging by the digital com-
puter is dependent upon the generation of time
reference pulses for aligning the individual QRS
complexes prior to the averaging operation. The
analog computer scheme illustrated in figure 1
provides these reference pulses, and the pulses then
undergo A/D conversion simultaneously with the
electrocardiographic data. The generation of the
reference pulses is triggered by the maximal
rate of change of the R wave. A more complete
description of the analog trigger circuit is pre-
sented in Appendix A. This approach has other
advantages in addition to providing an accurate
fiducial point. These advantages include the
capability to discriminate against most aberrant
premature complexes due to differences in the
maximal rate of change in the R wave, and an
adjustable refractory period that inhibits the
generation of reference pulses by noise spikes
and premature complexes occurring in the T-P
interval.

The parallel inputs into the A/D converter are
digitized at a rate of 500 samples per channel
per second. For each subject, 100 QRS com-
plexes with the corresponding reference pulses
are digitized from the recumbent and standing
baseline data, from the third minute of exercise,
and from every fifth minute of exercise beyond
this time up to and including the last minute of
exercise. In the postexercise period the im-
mediate, the 2, 5, and 8 minute periods are
handled similarly. One hundred 1 mv stan-
dardization pulses are also digitized.

The digitized electrocardiographic data are
stored in the memory bank of the digital com-
ST-SEGMENT RESPONSE DURING EXERCISE

Figure 1

Block diagram of analog computer circuit used to generate time reference pulses for subsequent alignment of the QRS complexes prior to averaging. A complete description of the circuit is given in Appendix A.

Computer along with the reference pulses, each of which is aligned with an R wave. Proper alignment of the ECG complexes for averaging is accomplished by locating the leading edge of the reference pulse, identifying the corresponding point in time on the negative slope of the R wave, and then extracting the values from a fixed time interval about this point. The extracted data are shifted to another memory bank, where the reference point is aligned with the reference point(s) of the previous QRS complex(es). This process is continued until four groups of 25 complexes have been aligned and averaged using every fourth QRS complex from a series of 100. ST-segment slope and depression values are computed for each of the four averaged groups, and standard errors are computed for the means of the four group values.

Once the averaging procedure is completed, the point representing the first positive slope of each averaged QRS complex is located. Starting at 30 msec before this point the mean voltage over a 10 msec interval (5 points) is computed as the PQ or baseline segment. The point representing the peak of the R wave is then located, and the mean voltages for two consecutive 10-msec intervals starting at 50 msec beyond this point are computed. These two intervals are designated ST1 and ST2. Their mean voltages are used to compute two ST-segment-depression values relative to the mean voltage of the PQ segment by:

$$\text{ST (mv)} = \frac{\text{Mean ST} - \text{mean PQ}}{\text{Mean millivolt calibration}}$$

In our early studies the ST-segment slope was computed from a 20-msec interval starting with the first point in the ST2 interval and ending with the last point from a third consecutive 10-msec interval (ST3). This slope value and the ST1-depression values were used in making the individual comparisons of the ST-segment responses. As a result of these studies, certain disadvantages to this approach became apparent. A number of subjects were found to have delays in terminal intraventricular conduction sufficient to cause the ST1 interval to fall within the terminal portion of the S wave. This problem could be partially avoided by using the nadir of the S wave as a point from which to locate the desired area in the ST segment, but a minority of subjects had no S wave with our lead system. Therefore, we are now using the ST2 interval as our primary source of ST-depression data. As more data were collected on
The subjects were selected from male flying personnel referred to the School of Aerospace Medicine for complete outpatient medical evaluation. A total of 108 subjects between the ages of 24 and 57 years were studied. They were placed into one of two groups depending on the reason for their medical evaluation. Group N consisted of 73 subjects who were evaluated for reasons other than suspected cardiovascular disease. The majority (49 subjects) of these men were undergoing medical evaluation prior to participation in some special United States Air Force project. The remaining 24 subjects were referred for medical problems unrelated to the cardiovascular system, most often of an ophthalmological or ear, nose, and throat nature. Medical evaluation of these 73 subjects revealed no evidence of cardiovascular disease. For presentation, group N has been further subdivided into two subgroups based on the ages of the subjects. Subgroup NY consists of the 47 subjects between 24 and 35 years of age and subgroup NO the 26 subjects between 36 and 52 years of age.

The subjects in the second group, group A, were chosen for study because of a referral diagnosis indicating the presence of cardiac disease. No subjects were subsequently eliminated from group A because we were unable to confirm a diagnosis of cardiac disease. Since the purpose of this paper is to present a comparative study of subjects with and without confirmed or suspected CAD, those subjects with a final diagnosis of valvular or hypertensive heart disease have been eliminated. Group A consisted of 35 men between the ages of 33 and 57 years. The diagnoses leading to their referral to the School of Aerospace Medicine are listed in table I. The majority of the electrocardiographic abnormalities were detected on routine recordings, and the subjects were asymptomatic by history. The subjects in group A have been further classified into two subgroups, depending on the final clinical impression after a thorough medical evaluation. Subgroup AD consisted of 14 subjects in whom a definitive diagnosis of CAD was made based on the presence of one or more of the following clinical findings: (1) the appearance of significant Q waves on the ECG as a serial change; (2) a history of precordial chest pain characteristic of myocardial ischemia or myocardial infarction; (3) the appearance of ST-T depression on a routine ECG as a serial change after the age of 35 years and in the

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Table 1

Reasons for the Medical Evaluations of the Subjects in Group A

<table>
<thead>
<tr>
<th>Referral diagnosis</th>
<th>Number of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonspecific electrocardiographic abnormality</td>
<td>26</td>
</tr>
<tr>
<td>Nonspecific T-wave changes*</td>
<td>10</td>
</tr>
<tr>
<td>Nonspecific ST-segment changes†</td>
<td>3</td>
</tr>
<tr>
<td>Borderline abnormal double Master‡</td>
<td>7</td>
</tr>
<tr>
<td>Frequent premature ventricular contractions</td>
<td>4</td>
</tr>
<tr>
<td>Abnormal left axis deviation§</td>
<td>2</td>
</tr>
<tr>
<td>History of nonspecific chest pain</td>
<td>3</td>
</tr>
<tr>
<td>Arteriosclerotic heart disease</td>
<td>6</td>
</tr>
<tr>
<td>With angina pectoris</td>
<td>2</td>
</tr>
<tr>
<td>With serial development of abnormal Q waves on ECG</td>
<td>2</td>
</tr>
<tr>
<td>With history of acute myocardial infarction</td>
<td>2</td>
</tr>
</tbody>
</table>

*T-wave changes were labile in eight subjects.
†ST depression present on only one routine ECG in each subject.
‡±0.5 to 0.9 mm of segmental ST depression.
§Not demonstrated to be a serial change.

absence of other demonstrable causes; (4) a positive double Master two-step test (1.0 mm or more of segmental depression). Only three of these 14 subjects had a positive double Master two-step test; in no instance was this the sole abnormality leading to the diagnosis of CAD. A definitive clinical diagnosis of CAD could not be made on the remaining 21 subjects by these rather rigid criteria, but this diagnosis remained highly suspect in the majority. These 21 subjects have been classified as subgroup AS. In no instance was the ST-segment response to MTE used to arrive at the final diagnosis.

Results
Less than 5% of the subjects tested were eliminated from the study because of excessive residual noise or artifact after averaging. Although artifactual distortions of the averaged data were uncommon, significant smoothing errors resulting from variations in the reference point on individual QRS complexes prior to averaging6,11 were occasionally noted. This type of artifact could sometimes be eliminated by re-digitizing the data after adjusting the analog computer to trigger on the positive slope of the R wave. The most frequent cause of excessive residual noise was 60-cycle interference, which appeared in our recording apparatus intermittently during the early phases of the study. Since 60-cycle interference is a nonrandom event, it is not reduced in amplitude by averaging proportional to random noise. The amount of residual random noise in the electrocardiographic data after computer averaging was reflected by the standard error or the measure of deviation for the mean of the four averaged groups of 25 QRS complexes. The standard error for ST2 during the last minute of exercise averaged ±0.069 mm or 6% for the 108 subjects tested. The last minute standard error for slope II averaged ±0.420 mv/sec or 13%.

The mean ages and exercise durations and the maximal heart rates for the two groups of subjects and their respective subgroups are listed in table 2. The peak heart rates for each age group are comparable to those reported in other maximal exercise studies.1,3–5,11 It was not necessary to terminate exercise in any of these subjects because of ventricular tachycardia or chest pain, and no significant complications were encountered.

Table 2
Maximal Treadmill Exercise Data

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Mean age</th>
<th>Max HR mean</th>
<th>Exercise duration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>35</td>
<td>44</td>
<td>173</td>
<td>13.5</td>
</tr>
<tr>
<td>Subgroup AS</td>
<td>21</td>
<td>44</td>
<td>175</td>
<td>14.4</td>
</tr>
<tr>
<td>Subgroup AD</td>
<td>14</td>
<td>44</td>
<td>169</td>
<td>12.2</td>
</tr>
<tr>
<td>Group N</td>
<td>73</td>
<td>34</td>
<td>188</td>
<td>17.7</td>
</tr>
<tr>
<td>Subgroup NO</td>
<td>26</td>
<td>42</td>
<td>182</td>
<td>16.9</td>
</tr>
<tr>
<td>Subgroup NY</td>
<td>47</td>
<td>30</td>
<td>192</td>
<td>18.5</td>
</tr>
</tbody>
</table>
Both groups of subjects demonstrated progressive ST-segment depression accompanied by progressive increments in the slope of the ST segment as the workloads and the heart rates increased. In group N, the older age subjects (subgroup NO) demonstrated more ST depression than the younger subjects (subgroup NY) at higher workloads, especially in the ST2 segment (table 3). In subgroup NY there was a distinct leveling off of the ST2-segment depression after the eighth minute of exercise without an equivalent effect in the ST1 segment. This plateau in ST2 depression was the result of the greater increments in the slope of the ST segment after the eighth minute in the younger subjects. With the smaller increments in the ST-segment slope with increasing workloads subgroup NO continued to have progressive depression in both the ST1 and ST2 segments.

The computed ST-segment values for the subjects in group A and its subgroups are listed in table 4. The increments in ST depression with increasing workloads are striking and are nearly equivalent for the ST1 and ST2 segments as reflected in the small increments in the ST-segment slope. The mean slope and depression values for subgroups AD and AS were compared by the Students’ t-test for significant differences. At lower workloads the differences are not significant ($P > 0.05$). At maximal workload the difference between the ST-depression values becomes significant ($P < 0.05$) but, because of the larger standard errors, the two slope values are still not statistically different.

The differences between the mean ST-segment values of the group A subjects and the subjects of similar age in subgroup NO (tables 3 and 4) are highly significant for each period of exercise ($P < 0.001$). The differences between the mean ST-segment values for subgroups NO and AS are also significant for each exercise period ($P < 0.01$). The individual ST-segment values from the last minute of exercise for the subjects in group A and subgroup NO are best illustrated by a graph with the ST2 depression plotted on the ordinate and the ST slope on the abscissa (fig. 3). When the ST-segment responses are plotted in this manner, a distinct difference is seen between the young and old subjects.

### Table 3

<table>
<thead>
<tr>
<th>Exercise period</th>
<th>$ST_1 \pm SE^*$</th>
<th>$ST_2 \pm SE^*$</th>
<th>Slope II $\pm SE^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group N</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>+ 0.031 ± 0.027</td>
<td>+ 0.130 ± 0.027</td>
<td>+ 1.138 ± 0.098</td>
</tr>
<tr>
<td>2-3 minutes</td>
<td>- 0.556 ± 0.060</td>
<td>- 0.429 ± 0.053</td>
<td>+ 1.518 ± 0.109</td>
</tr>
<tr>
<td>7-8 minutes</td>
<td>- 0.796 ± 0.064</td>
<td>- 0.636 ± 0.057</td>
<td>+ 2.074 ± 0.141</td>
</tr>
<tr>
<td>12-13 minutes</td>
<td>- 0.947 ± 0.070</td>
<td>- 0.698 ± 0.065</td>
<td>+ 3.228 ± 0.175</td>
</tr>
<tr>
<td>Last minute</td>
<td>- 1.054 ± 0.081</td>
<td>- 0.758 ± 0.076</td>
<td>+ 4.125 ± 0.226</td>
</tr>
<tr>
<td><strong>Subgroup NO</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>+ 0.051 ± 0.049</td>
<td>+ 0.183 ± 0.052</td>
<td>+ 1.044 ± 0.139</td>
</tr>
<tr>
<td>2-3 minutes</td>
<td>- 0.514 ± 0.074</td>
<td>- 0.385 ± 0.071</td>
<td>+ 1.300 ± 0.173</td>
</tr>
<tr>
<td>7-8 minutes</td>
<td>- 0.770 ± 0.083</td>
<td>- 0.619 ± 0.085</td>
<td>+ 1.850 ± 0.216</td>
</tr>
<tr>
<td>12-13 minutes</td>
<td>- 0.981 ± 0.088</td>
<td>- 0.762 ± 0.110</td>
<td>+ 2.715 ± 0.278</td>
</tr>
<tr>
<td>Last minute</td>
<td>- 1.203 ± 0.140</td>
<td>- 0.930 ± 0.141</td>
<td>+ 3.348 ± 0.317</td>
</tr>
<tr>
<td><strong>Subgroup NY</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>+ 0.021 ± 0.030</td>
<td>+ 0.101 ± 0.031</td>
<td>+ 1.191 ± 0.101</td>
</tr>
<tr>
<td>2-3 minutes</td>
<td>- 0.580 ± 0.075</td>
<td>- 0.453 ± 0.072</td>
<td>+ 1.639 ± 0.138</td>
</tr>
<tr>
<td>7-8 minutes</td>
<td>- 0.811 ± 0.090</td>
<td>- 0.646 ± 0.074</td>
<td>+ 2.198 ± 0.183</td>
</tr>
<tr>
<td>12-13 minutes</td>
<td>- 0.928 ± 0.115</td>
<td>- 0.663 ± 0.081</td>
<td>+ 3.513 ± 0.216</td>
</tr>
<tr>
<td>Last minute</td>
<td>- 0.971 ± 0.090</td>
<td>- 0.663 ± 0.087</td>
<td>+ 4.555 ± 0.288</td>
</tr>
</tbody>
</table>

*The standard errors are for the mean ST depression and ST-slope values for the entire group or subgroup and are not related to the SE computed for each subject.

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Table 4

Mean ST Depression (mm) and ST-Slope (mv/sec) Values for Each Period of Exercise Studied. Group A and Its Subgroups AD and AS

<table>
<thead>
<tr>
<th>Exercise period</th>
<th>ST1 ± SE*</th>
<th>STs ± SE*</th>
<th>Slope II ± SE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>-0.102 ± 0.018</td>
<td>-0.092 ± 0.018</td>
<td>+0.370 ± 0.065</td>
</tr>
<tr>
<td>2-3 minutes</td>
<td>-0.872 ± 0.102</td>
<td>-0.819 ± 0.091</td>
<td>+0.640 ± 0.111</td>
</tr>
<tr>
<td>7-8 minutes</td>
<td>-1.420 ± 0.121</td>
<td>-1.354 ± 0.114</td>
<td>+0.837 ± 0.135</td>
</tr>
<tr>
<td>Last minute</td>
<td>-2.033 ± 0.132</td>
<td>-1.698 ± 0.122</td>
<td>+1.385 ± 0.207</td>
</tr>
</tbody>
</table>

Subgroup AD

<table>
<thead>
<tr>
<th>Exercise period</th>
<th>ST1 ± SE*</th>
<th>STs ± SE*</th>
<th>Slope II ± SE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>-0.140 ± 0.023</td>
<td>-0.131 ± 0.021</td>
<td>+0.352 ± 0.098</td>
</tr>
<tr>
<td>2-3 minutes</td>
<td>-1.070 ± 0.168</td>
<td>-1.016 ± 0.163</td>
<td>+0.695 ± 0.254</td>
</tr>
<tr>
<td>7-8 minutes</td>
<td>-1.741 ± 0.202</td>
<td>-1.704 ± 0.218</td>
<td>+0.769 ± 0.297</td>
</tr>
<tr>
<td>Last minute</td>
<td>-2.324 ± 0.150</td>
<td>-2.212 ± 0.145</td>
<td>+0.975 ± 0.427</td>
</tr>
</tbody>
</table>

Subgroup AS

<table>
<thead>
<tr>
<th>Exercise period</th>
<th>ST1 ± SE*</th>
<th>STs ± SE*</th>
<th>Slope II ± SE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>-0.084 ± 0.014</td>
<td>-0.073 ± 0.013</td>
<td>+0.388 ± 0.031</td>
</tr>
<tr>
<td>2-3 minutes</td>
<td>-0.742 ± 0.095</td>
<td>-0.688 ± 0.098</td>
<td>+0.603 ± 0.082</td>
</tr>
<tr>
<td>7-8 minutes</td>
<td>-1.200 ± 0.096</td>
<td>-1.121 ± 0.096</td>
<td>+0.882 ± 0.115</td>
</tr>
<tr>
<td>Last minute</td>
<td>-1.832 ± 0.175</td>
<td>-1.689 ± 0.166</td>
<td>+1.686 ± 0.177</td>
</tr>
</tbody>
</table>

*The standard errors are for the mean ST depression and ST-slope values for the entire group or subgroup and are not related to the SE computed for each subject.

Figure 3

The ST2 depression and ST slope (II) values from the last minute of exercise are plotted for each subject in subgroup NO and group A (subgroups AS and AD). Line X represents the best line of separation between subgroups NO and group A, and line Y the best line of separation between subgroups AS and AD.
grouping of the subjects in subgroup NO becomes apparent, with a clear separation from the group A subjects. To find the best line of separation a linear discriminant analysis was computed using the ST2 depression and ST-slope values for these two groups. Line X in figure 3 defines the best linear combination of these values. The same type of analysis was computed for subgroups AS and AD, and a line of separation between the majority of subjects in each of these two subgroups was also defined (line Y). Statistical analysis confirms the visual impression of a grouping of the ST-segment responses of these subjects during maximal exercise which conforms closely to the grouping of the subjects based on clinical impressions. A separation of comparable accuracy could not be accomplished by the computed ST-segment values from any of the postexercise periods.

Discussion

Maximal exercise has become increasingly popular as a method for cardiac stress testing, but what constitutes an abnormal ST-segment response to maximal stress has not been established. Investigators studying the ST-segment response to maximal exercise have reported that the most significant changes occur during or immediately following maximal exercise.1-4 The physiologic and metabolic conditions existing during maximal exercise are much different from those following less strenuous exertion, such as with the Master two-step test, and the criteria for significant ST-segment changes may also differ. The results of the present study demonstrate that there is an abnormal range of ST-segment response during MTE that is considerably broader than strict segmental ST depression. Of the 14 subjects with a definitive diagnosis of CAD (subgroup AD), 13 had ST-segment responses which clearly separated them from the majority of normal subjects (line X, fig. 3). Only five of these 14 demonstrated segmental ST depression of 1.0 mm or more during maximal exercise, while three others had similar ST-segment changes restricted to the periods after exercise (table 5).

Only two of the subjects classified as suspect for CAD (subgroup AS) demonstrated segmental ST depression, both after exercise.

Table 5

| Subjects Demonstrating Segmental ST Depression of 1.0 mm or More during or after Maximal Treadmill Exercise (MTE) |
|---|---|---|---|---|---|
| | Age | During MTE | Immediately After exercise | 2 minutes After exercise | 5 minutes After exercise | 8 minutes After exercise |
| Subgroup AD | | | | | | |
| S.J. | 33 | + | + | + | 0 | 0 |
| J.B. | 36 | + | + | + | + | 0 |
| D.F. | 48 | + | + | + | + | + |
| W.C. | 42 | + | + | 0 | 0 | 0 |
| D.L. | 45 | + | + | 0 | 0 | 0 |
| E.W. | 39 | 0 | 0 | + | 0 | 0 |
| C.W. | 50 | 0 | 0 | + | + | 0 |
| G.G. | 36 | 0 | 0 | 0 | 0 | + |
| Subgroup AS | | | | | | |
| R.J. | 48 | 0 | 0 | 0 | + | + |
| J.L. | 40 | 0 | 0 | 0 | + | + |
| Subgroup NO | | | | | | |
| D.W. | 37 | 0 | 0 | 0 | + | + |
| Subgroup NY | | | | | | |
| W.L. | 28 | + | 0 | + | + | 0 |

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(table 5), but as a group their ST-segment responses during maximal exercise were also distinctly different from the majority of normal subjects (line X, fig. 3).

Figure 4

Striking ST segment and T-wave abnormalities occurring in a clinically healthy 28-year-old man after a brief period of hyperventilation.
Before any conclusions can be drawn concerning the findings in this study, a considerably larger group of clinically normal subjects over a broader age range will have to be studied. Long-term clinical follow-up will be necessary on those subjects demonstrating an "abnormal" ST-segment response before the clinical significance of such a response can be determined. We anticipate that eventually a graph with a statistically derived line separating the normal and abnormal ranges of response, as illustrated in figure 3, can be utilized to evaluate the responses of subjects studied during MTE. For such a graph to be of clinical value, the range of ST-segment response defined as abnormal must be relatively free from false-positive responders. Other investigators have found that healthy males under the age of 35 years do not develop ST-segment changes in response to exercise comparable to individuals with CAD, regardless of the workload.\textsuperscript{1, 11, 16} Only one of the 47 subjects between the ages of 24 and 35 years (subgroup NY) had ST-segment values during maximal exercise of a magnitude sufficient to place him above line Y in figure 3 with most of the subjects with clinical CAD. This 28-year-old man was thought to have a false-positive response since similar ST-segment changes could be produced repeatedly by short periods of hyperventilation (fig. 4). One additional 32-year-old man had an ST-segment response that placed him between lines X and Y of the graph in figure 3. If one assumes that this man represents a false-positive responder, this gives a 4\% incidence of false-positive responses in this age group. However, the 28-year-old subject would have been positive if the criterion of segmental ST depression were used (table 5).

Four of the 26 clinically normal subjects between 36 and 52 years of age had ST-segment responses placing them above line X (subgroup NO, fig. 3). Only one of the four demonstrated segmental ST depression of 1.0 mm (table 5), but two others had 0.7 mm of segmental depression after exercise. These three subjects with segmental depression after exercise also had ST-segment responses during maximal exercise, placing them above line Y in figure 3. Whether these men represent false-positive responders or individuals with a high risk of developing overt CAD in the future remains to be determined. If they do have early or potential CAD, it is not readily apparent why they have ST-segment responses more like the subjects with definitive CAD rather than the suspect subjects. The small number of normal subjects 36 years of age and older used in this comparable analysis prevents firm conclusions regarding what type of "abnormal" response distribution may be found in a larger sampling.

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\section*{Appendix A}

The analog trigger circuit illustrated in figure 1 operates on the principle that the rate of change of the R wave is unique when compared with other parts of the electrocardiographic signal. The circuit is designed to pass selectively those frequency components characteristic of the R wave and reject all others. The synchronizing reference pulse is then generated when an empirically adjusted threshold value is exceeded by the point of maximum rate of change of the R wave. Our studies have shown this point to be stable, even in the presence of severe noise and respiratory modulation.

Analog electrocardiographic signals are reproduced from magnetic tape and fed simultaneously to the A/D converter and synchronizing pulse circuit. Potentiometer P1 controls the amplitude of the signal to be subsequently fed to the bandpass filter composed of amplifiers 3 and 4 and the associated capacitors. Switch FS permits the selection of either an upright or inverted complex, allowing the operator to choose the leading or trailing profile of the R wave as the signal from which the reference pulse will be generated. For the X lead used in our studies, the majority of subjects display greater R-wave slope on the trailing edge. The filtered signal shown at the output of amplifier 4 is proportional to the rate of change of all negative sloping components of the input signal into amplifiers 3-4, the positive components having been clipped off by

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the diodes on these amplifiers. The largest component displayed is a result of the high rate of change seen on the trailing edge of the R wave. Inversion and biasing are accomplished in amplifier 5, resulting in the input shown at amplifier 6. Potentiometer P2 is empirically adjusted to a level that allows only the peak values of the signal to exceed the threshold of the trigger circuit, amplifier 6-E/CO. The reference pulse from E/CO activates the circuit composed of amplifiers 7 and 8 and E/C 1 via potentiometer P3. Adjustment of P3 determines the rate at which the trigger circuit may be triggered, thus allowing for an adjustable refractory period. This period is set to the minimum expected R-R interval. All signals of shorter interval will be rejected. Potentiometer P4 controls the duration of the pulses sent to the A/D converter via amplifier 9. Amplifier 9 merely inverts the reference pulses to the upright position. The insignificant delay in the analog circuit maintains the alignment of the derived reference pulses with the electrocardiographic complexes from which they were formed. The electrocardiographic data and associated synchronizing pulses are thus digitized for subsequent digital processing.

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