tients in this subset is very small in each series, and there may well be differences in the extent of the CAD in the patient groups (13 of 20 such patients in our study had only single-vessel CAD). The other studies parallel our own in showing a low incidence of false positive tests (14–33%) but an excessive incidence of false negative tests (55–73%). It is apparent that treadmill stress testing provides an imperfect means of evaluating the success of myocardial revascularization and that the high incidence of false negative exercise tests limits the usefulness of such a normal test in the individual postoperative patient.

Acknowledgment

The authors gratefully acknowledge the secretarial assistance of Mrs. Joyce Neumann.

References


Estimation of the Probability of Exercise-induced Ischemia by Quantitative ECG Analysis

MAARTEN L. SIMOONS, M.D., AND PAUL G. HUGENHOLTZ, M.D.

SUMMARY In order to improve the value of exercise tests for the detection of coronary artery disease (CAD) a system for on-line computer processing of the Frank lead exercise ECG was developed. Data were analyzed from 95 patients with CAD and 129 ostensibly healthy men. All subjects had a normal ECG at rest.

Visual ECG interpretation during exercise yielded a sensitivity of 50% and a specificity of 95%. A large number of QRS and ST measurements were compared by discriminant function analysis in a group of 86 normal subjects and 52 patients (designated training group). Best results were obtained with a combination of two ST amplitudes from lead X: sensitivity, 85%, specificity, 90%. This was confirmed in a test group of 43 patients and 43 normal subjects.

The results of the discriminant function were expressed as the likelihood ratio for an abnormal or normal ST segment at a given heart rate, a figure which provides a quantitative assessment of the degree of exercise-induced ischemia. This is a more realistic approach than classification into normal or abnormal since persons with and without CAD fall along the same continuous spectrum.

GRADED EXERCISE TESTS on a bicycle ergometer or on a treadmill have been advocated as reliable methods for the early detection of subjects with coronary artery disease (CAD). In recent studies a correlation has been shown between the presence of ST depressions in the electrocardiogram during exercise (XECG) and the findings on selective cine-coronary arteriography in male patients with chest pain. Furthermore it has been shown that asymptomatic subjects with ST depressions during exercise have a considerably higher probability of developing manifest CAD than those without such ECG changes. However, the exercise tests which are currently in use have four important shortcomings.

1) The interpretation of the tracings is often difficult when excessive muscle noise, baseline drift or artifacts occur, despite careful skin preparation and electrode fixation.
2) Part of the test cannot be interpreted when the patient terminates the test before sufficient stress of the cardiovascular system is provoked.
3) As a result of these and other factors, the fraction "false negative" tests reported in all studies is considerable. The sensitivity of the ECG during symptom-limited exercise tests for prediction of obstructive CAD ranges from 52% to 85% at a specificity level between 83% and 100% (fig. 1).
4) According to current criteria, exercise ECGs are inter-

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TABLE 1. Selection Criteria of the Subjects in the Training Set and in the Test Group

<table>
<thead>
<tr>
<th>Selection Criteria</th>
<th>Training group</th>
<th>Test group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essentially healthy men, no complaints of chest pain</td>
<td>86</td>
<td>43</td>
</tr>
<tr>
<td>blood pressure &lt;160/95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>serum cholesterol &lt;6.7 mM/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient with chest pain and</td>
<td>32</td>
<td>9</td>
</tr>
<tr>
<td>79% or greater obstructions in one or more coronary arteries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with typical angina pectoris during the exercise test, which disappeared within 5 min after exercise</td>
<td>11</td>
<td>30</td>
</tr>
<tr>
<td>Patients with a nontransmural myocardial infarction: typical history, serial enzyme changes and serial ECG changes</td>
<td>9</td>
<td>4</td>
</tr>
</tbody>
</table>

Details of the selection procedure of the normal subjects have been published in a previous report. All subjects had a normal ECG at rest. 6.7 mM/L = 260 mg % cholesterol.

The selection criteria for development of criteria for computer assisted interpretation of XECGs, those from the remaining 43 normals and

interpreted either as "normal" or as "abnormal." This seems a rather arbitrary separation since in reality a whole spectrum exists between subjects with normal coronary arteries and patients with completely occluded vessels. It is also likely that ischemia develops gradually when the oxygen demand of the myocardium increases during exercise.

Computer processing of the ECG signal during and after exercise may help to overcome each of these four shortcomings. The signal quality can be improved by averaging of a number of selected beats. Different types of ST measurements can be taken and can be compared with values obtained in normal subjects at the same heart rate during or after exercise.

The results of the present investigation indicate that in this manner the fraction of false negative tests can be reduced. Finally, a procedure is presented which permits assessment of the degree of abnormality of the ECG at all stages of the test.

Selection of Subjects and Methods

Exercise electrocardiograms were analyzed from 129 normal men and 95 male patients with coronary artery disease. The selection criteria are presented in Table 1. The records from 86 normals and 52 patients were used as a training set for development of criteria for computer assisted interpretation of XECGs, those from the remaining 43 normals and

43 patients were employed as a test set for verification of the results from the training set.

All subjects had a normal QRS complex and ST segment at rest according to the Minnesota code (21): Q waves indicative of myocardial infarction were absent and the ST-T segment was within normal limits. Patients with P wave abnormalities and first degree atrioventricular (A-V) block were disregarded. None of the subjects had Wolff-Parkinson-White syndrome (WPW). Patients receiving digitalis or β-blocking drugs within two weeks prior to the exercise test were not included. The subjects were selected without prior knowledge of the XECG. The age distributions of the subjects are shown in Table 2.

All subjects underwent a symptom limited exercise test on a bicycle ergometer with stepwise workload increments of 10 W/min or 30 W/3 min. Details on the procedure have been published elsewhere. ST depressions were the reason to terminate the test in only nine patients. After the highest level of exercise, cycling was continued during 6 min in order to prevent discomfort caused by pooling of blood in the legs. All tests at the Thoraxcenter were performed in the same air-conditioned room. Temperature was kept between 16° and 20°C. A physician and a technician were always present.

TABLE 2. Age Distribution of the Patients and Normal Subjects in the Two Sets of Data

<table>
<thead>
<tr>
<th>Age Group (years)</th>
<th>Control set</th>
<th>Test set</th>
</tr>
</thead>
<tbody>
<tr>
<td>21-25</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>26-30</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>31-35</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>36-40</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>41-45</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>46-50</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>51-55</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>56-60</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>61-65</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

T = total number of subjects in each group.
A defibrillator, oxygen, anti-arrhythmic drugs and nitrates were immediately available. Blood pressure was measured with a cuff around the upper arm at rest and every second minute during and after exercise.

The Frank lead ECG was recorded with chest electrodes at the level of the fifth intercostal space in sitting position. The F electrode was placed on the sacrum, the H electrode on the neck. Much attention was paid to proper preparation of the skin (rubbing with gauze soaked in alcohol) and fixation of the electrodes and wires. The ECG was continuously monitored on a nonfading oscilloscope, and recorded on paper with alternating low (10 mm/sec), normal (25 mm/sec) and high (50 mm/sec) paper speeds. The calibration was 1 mV/cm. In addition the ECG was continuously recorded on a FM tape recorder.

Data Processing

The ECGs were processed with a PDP-8E computer system. The three orthogonal leads were sampled during 20 seconds at rest, in supine and sitting position, every second or third minute during exercise and the first four minutes of the recovery period. The sample rate was 500 per second. Single representative beats were computed by selective averaging as reported earlier. Waveform analysis was done by the program and checked visually. A large number of measurements were taken from the averaged ECGs including:

1) amplitudes and slopes at 10 msec intervals from 0 until 90 msec after the end of the QRS complex,17, 18, 20
2) Time normalized amplitudes and slopes of the PQ, QRS and ST segment,16
3) Time-integrals of the positive and negative parts of the ST segment.16

An attempt was made to improve the separation of patients and normal subjects by combinations of ECG measurements instead of a single measurement. Such a combination is called a discriminant function. A discussion of the mathematical aspects of these discriminant functions is beyond the scope of this paper, but can be found in statistical handbooks.23

Linear discriminant function analysis was performed with a program developed at the University Computer Center in Utrecht, utilizing a CDC 7600 system. This program generated discriminant functions with all possible combinations of at most four parameters. This limitation waschosen because the series were relatively small. The results of different algorithms of separation of normals and patients with CAD were expressed in terms of the sensitivity (fraction of abnormal findings in the patients) and the specificity (fraction of normal findings in the control group).

Table 3. Discriminant Function Analysis of ST Amplitudes at Fixed Intervals after the End of QRS

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Spec.</th>
<th>Sens.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST50&lt;sub&gt;x&lt;/sub&gt;</td>
<td>0.78</td>
<td>0.90</td>
</tr>
<tr>
<td>ST50&lt;sub&gt;x&lt;/sub&gt;, ST70&lt;sub&gt;x&lt;/sub&gt;</td>
<td>0.83</td>
<td>0.87</td>
</tr>
<tr>
<td>ST50&lt;sub&gt;x&lt;/sub&gt;, ST70&lt;sub&gt;y&lt;/sub&gt;, ST90&lt;sub&gt;x&lt;/sub&gt;</td>
<td>0.84</td>
<td>0.88</td>
</tr>
<tr>
<td>ST30&lt;sub&gt;x&lt;/sub&gt;, ST50&lt;sub&gt;x&lt;/sub&gt;, ST70&lt;sub&gt;y&lt;/sub&gt;, ST90&lt;sub&gt;x&lt;/sub&gt;</td>
<td>0.84</td>
<td>0.90</td>
</tr>
</tbody>
</table>

Based on maximum exercise records. ST50 = 50 msec after QRS etc; Spec. = specificity (fraction of normal ECGs in the normal subjects); Sens. = sensitivity (fraction of abnormal ECGs in the patients).

Results

Since only subjects were selected who had a normal QRS complex and ST segment at rest, it is not surprising that even with multivariate analysis of the ECG measurements at rest, a poor separation of the patients and normal subjects in the training set was achieved. With a linear discriminant function of four ST measurements the sensitivity and the specificity were each 67%. This indicated that the ECGs at rest in the patients were very similar to those in the normals.

The best separation of patients and normals at the highest workload was obtained with ST amplitudes at a fixed interval after the end of the QRS complex. Representative results are presented in table 3. Time-normalized ST amplitudes, ST slopes, ST areas and ST Chebyshev coefficients did not improve the separation of the two groups, nor did transformation to polar coordinates or measurements of the differences between the rest and exercise ECG. Extensive data on these different measurements will be published elsewhere.24

In a previous study it was demonstrated that many ST measurements in normal subjects change gradually during exercise.25 An example of this pattern is shown in figure 2. Two straight lines could be computed which enclose the measurements in the normal subjects. A considerable improvement of the separation of patients and normals could be obtained when the distances of the ST amplitudes toward line II were employed instead of the actual amplitudes. Representative results are presented in table 4.

The results of application of the derived criteria for interpretation of exercise ECGs to the independent test set are presented in table 5. Visual interpretation of the ECGs ac-

Table 4. Discriminant Function Analysis of the Distance from the ST Measurements to the Lower Limit of Measurements in the Normal Subjects at the Same Heart Rate (fig. 2)

<table>
<thead>
<tr>
<th>Measurement(s)</th>
<th>Spec.</th>
<th>Sens.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST50&lt;sub&gt;x&lt;/sub&gt;</td>
<td>0.93</td>
<td>0.81</td>
</tr>
<tr>
<td>ST20&lt;sub&gt;q&lt;/sub&gt;, ST80&lt;sub&gt;q&lt;/sub&gt;</td>
<td>0.91</td>
<td>0.85</td>
</tr>
<tr>
<td>ST10&lt;sub&gt;q&lt;/sub&gt;, ST20&lt;sub&gt;q&lt;/sub&gt;, ST40&lt;sub&gt;q&lt;/sub&gt;, ST50&lt;sub&gt;q&lt;/sub&gt;</td>
<td>0.90</td>
<td>0.87</td>
</tr>
</tbody>
</table>

For legend see table 3.
According to the standard criterion of a 0.1 mV horizontal ST depression yielded a sensitivity of 50% and 51% in the two groups while the specificities were also similar: 94% and 95%. Furthermore, excellent reproducibility was obtained with a linear combination of two heart rate adjusted ST amplitudes from lead X: sensitivities 85% and 84%; specificities 91% and 88% in the two groups.

Further analysis of the combined data from the training group and the test group indicated that the difference between the results obtained by the three criteria in Table 5 was not due to the choice of the cut-off point for separation of the two groups since the sensitivity of the combination of ST20x and ST80x exceeded the sensitivity of ST60x at all cut-off points which yielded a specificity between 70% and 90%. This is illustrated in Figure 3. Both criteria for computer-assisted interpretation of the XECG were superior to visual ECG reading, as shown in the figure.

No significant differences were observed between the XECGs in the three groups of patients selected according to different criteria (Table 1). The combination of ST20x and ST80x at the highest workload produced an abnormal response in 34 out of 41 patients with documented coronary artery obstructions, in 35 out of 41 patients with angina pectoris during the exercise test, and in 11 out of 13 with a non-transmural infarction.

**Interpretation of the ECG at Different Levels of Exercise**

In the preceding paragraphs, only the data obtained at the highest workload reached by each individual were analyzed. However, it is convenient to perform on-line analysis of the ECG at all stages of the exercise test. This might lead to detection of ECG abnormalities at an early stage of the test before they can be distinguished by visual inspection of the ECGs. It would then also become possible to terminate these tests at a lower workload. Therefore the two best criteria for classification of the ECG at the highest workload were applied to all records at rest and during exercise from the patients and the controls from both the training group and the test group. The results in Table 6 show some reduction in specificity for ST60x at lower heart rates and a large reduction of the specificity of the combined ST20x and ST80x amplitudes. This indicates that the threshold values for separation of normal and abnormal ECGs should be different at high and low heart rates.

In Figure 4 the results of the discriminant function applied to all records obtained during exercise have been plotted. These discriminant scores of the patients and the normal subjects at low heart rates overlap almost completely. This is in accordance with the fact that only patients with a normal ECG at rest were selected for these studies. At higher heart rates the separation of the patients and the controls gradually improved. However, at heart rates over 160 beats/min the measurements from the two groups overlapped again. Thus the 15 patients who reached these high heart rates during exercise could not be distinguished from the normal subjects on basis of the XECG.

Five of these patients had documented obstructions in the coronary arteries, three had had a previous infarction, and

**Table 5. Comparison on Specificity and Sensitivity of Visual ECG Interpretation and of Computer ECG processing with ST Amplitudes Adjusted for Instantaneous Heart Rate**

<table>
<thead>
<tr>
<th>Training Group</th>
<th>Test Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual ECG interpretation</td>
<td>81/86 0.94</td>
</tr>
<tr>
<td>Heart rate dependent criteria</td>
<td>26/52 0.50</td>
</tr>
<tr>
<td>ST60x</td>
<td>80/86 0.93</td>
</tr>
<tr>
<td>ST20x, ST80x</td>
<td>78/86 0.91</td>
</tr>
</tbody>
</table>

The criteria were derived from a training group of 86 normals and 52 patients. The results were verified in an independent test group of 43 patients and 43 normals.

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**Table 6. Comparison of Specificity and Sensitivity of Two Criteria for Interpretation of Exercise ECGs at Different Workloads**

<table>
<thead>
<tr>
<th>Max. Workload only</th>
<th>All records</th>
<th>All records*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR &gt; 100</td>
<td>rest + exercise</td>
<td>rest + exercise</td>
</tr>
<tr>
<td>ST60x</td>
<td>0.93 0.74</td>
<td>0.90 0.77 0.84 0.77</td>
</tr>
<tr>
<td>ST20x, ST80x</td>
<td>0.90 0.84</td>
<td>0.57 0.85</td>
</tr>
</tbody>
</table>

*129 normal subjects and 95 patients with coronary artery disease. Note reduction of specificity when the records at early stages of the test are included, in particular, for the discriminant function of ST20x and ST80x. HR = heart rate.
seven experienced chest pain during the exercise test. It may be argued that no myocardial ischemia occurred in these patients, in spite of the strenuous exercise. However, the chest pain in seven of these suggests otherwise. Also it is possible that small ischemic areas were present, with locations such that the injury currents were cancelled. At present it is not possible to prove or disprove one of these or other mechanisms because no independent quantitative information on the degree and extent of ischemic myocardial areas was available.

Estimation of the Probability of Myocardial Ischemia During Exercise

When is assumed that the measurements have normal distributions, the ratio can be computed of the probability that a given value is found in the patients and the probability that it occurs in the controls. This quantity is called the likelihood ratio. In figure 5 the likelihood ratio has been plotted for different scores of the discriminant function of ST20\textsubscript{x} and ST80\textsubscript{x} at heart rates between 140 and 159 beats/min. For example, at a discriminant score of $-100\,\mu V$ the likelihood ratio abnormal/normal equals 25, while the ratio is 3.7 at a score of $-50\,\mu V$. In this particular example the ratio equals one at a discriminant score of zero. The likelihood ratio functions corresponding to the heart rate intervals in figure 4 have been plotted in figure 6. Those for the heart rates from 60 to 140 beats/min are more or less parallel (curves 1–4). The positions of these curves relative to the horizontal axis correspond to the positions of the histograms of the normal subjects along the same axis in figure 4. The other two curves appeared to be less steep. In particular the likelihood ratios at the highest heart rate interval are much closer to unity than the others (curve 6, 160 to 179 beats/min). This reflects the overlap of measurements in this range of heart rates.

In order to test its applicability for on-line interpretation of XECGs throughout the test, the likelihood procedure was applied to all records in this study. A ratio abnormal/normal of 2.7 or more was found in at least one record in 17 of the 129 normal subjects (13%) and in 70 of 95 patients (74%). This likelihood ratio corresponded to a specificity of 95% at the different heart rate intervals. In only three normal subjects (2%) such a likelihood ratio was found twice or more during the test, while this occurred in 57 patients (60%). Thus in clinical practice the exercise tests can be terminated after two observed likelihood ratios greater than or equal to 2.7 without increasing the fraction of false positive tests.

Discussion

In the introduction four shortcomings of visual interpretation of exercise ECGs were given. The results of the present
PROBABILITY OF EXERCISE-INDUCED ISCHEMIA/Simoons, Hugenholtz

investigation indicate that these can be avoided to a large extent by computer assisted ECG interpretation. Thus a considerable improvement of the diagnostic value of exercise ECGs can be achieved.

Part of this gain by computer processing was due to noise reduction and part to detection of small ECG changes in patients who stopped the test at a low heart rate. In addition, the results of the exercise ECG could be presented in a manner which indicated the probability of exercise induced myocardial ischemia at all stages throughout the test.

Selection of Patients and Normal Subjects

It is obvious that, in order to prevent bias, the XECG itself should not be used as a criterion for the selection of either patients or controls. In most recent studies of the correlation between CAD and the XECG,\textsuperscript{1-7} a narrowing of 70\% or more in one of the major coronary arteries was chosen as the independent selection criterion. In the present study this criterion was maintained. In order to enlarge the data base, patients with a documented myocardial infarction as well as patients who had angina pectoris during the exercise test were also accepted. It was expected that this would not influence the results significantly since in the study of Bartel et al.\textsuperscript{4} 87\% (203 out of 235) of the subjects with angina pectoris during the test had coronary artery narrowings exceeding 70\%. Furthermore grouping all patients together is by the observation that the results of visual ECG reading as well as computer assisted interpretation in the present investigation appeared to be independent of the selection criteria.

It should be emphasized that the patients were selected on clinical evidence (infarcts), on anatomical evidence (angiography) or on basis of the history (angina pectoris during the stress test). These criteria indicate the presence of CAD. However, it does not necessarily follow that all patients had coronary insufficiency during the test. Furthermore the occurrence of coronary insufficiency is often but not necessarily accompanied by detectable ST segment changes. This is explained in part by our earlier observation that the spatial orientation of the ST shift in patients with CAD and a normal ECG at rest cannot be distinguished from the orientation of the ST shift in normals.\textsuperscript{26}

In previous studies on the diagnostic power of XECGs, patients without significant abnormalities in the coronary arteriogram were used as controls.\textsuperscript{3-7} This was not done in the present study since it might have biased the results. At the Thoraxcenter coronary arteriograms are made mainly in those patients who are likely candidates for coronary bypass surgery. All these patients have a history of severe chest pain suggesting CAD. As a result of this selection procedure significant narrowings of the major coronary arteries could be demonstrated in all but 10\% of the patients who underwent an exercise test and coronary arteriography during the study period. Therefore, as a control group, subjects were selected who had no signs of manifest CAD and in whom the major risk factors for development of CAD were absent. These men had no history of chest pain, a normal ECG at rest, a normal blood pressure and normal serum cholesterol levels. Despite these precautions it still remains possible that some subjects in the control group had abnormal coronary arteries. In fact, seven of these had a 0.1 mV or greater ST depression during exercise. However, this factor is of no great influence when a specificity of 90-95\% is chosen for the diagnostic criteria. Preliminary data on comparison of the reference population in the present study with subjects without significant obstructions in the coronary arteriogram studied at another hospital indicate that the XECGs in these groups are similar.\textsuperscript{26}

Comparison with Other Studies

Visual interpretation of the exercise ECG yielded a sensitivity of 50\% and a specificity of 95\%. These results are in good agreement with those reported by Ascoop et al.\textsuperscript{5} In other investigations higher sensitivities were found. This difference is probably related to patient selection. For example in two studies\textsuperscript{1, 8} patients with slight repolarization abnormalities at rest were included while other authors\textsuperscript{4, 9} included patients with abnormal QRS complexes. In two reports\textsuperscript{4, 5} very high sensitivities were found (85\% and 83\%). These may be due to the small numbers of subjects studied by these authors (57 and 50 patients respectively). The largest series\textsuperscript{10} produced a sensitivity of 65\% and a specificity of 91\% in 367 patients with both normal and abnormal ECGs at rest. The strong influences of the patient selection are further illustrated by the results of coronary arteriography in asymptomatic subjects with an "abnormal" XECG since in about half of these the coronary arteries were completely normal.\textsuperscript{26-28}

"Best" ECG Measurements during Exercise

The best separation between patients with CAD and normal subjects was obtained by ST measurements from lead X. Addition of measurements from the other two leads did not separate the two groups any further. These results are in agreement with other reports.\textsuperscript{29, 30} Therefore a single bipolar lead like CM\textsubscript{4} or CB\textsubscript{B} may be sufficient for detection of myocardial ischemia during exercise in patients with a normal ECG at rest.\textsuperscript{26} However, in patients with abnormal ECGs at rest, multiple leads remain necessary since the ST changes during exercise in these patients occur in all possible directions\textsuperscript{26} and may therefore be missed by a single lead. The best parameter for prediction of CAD appeared to be a linear combination of two ST amplitudes. Addition of other parameters like ST slopes or ST time integrals did not improve the results. This may seem contradictory to the results obtained by McHenry et al.\textsuperscript{17} and Ascoop at al.\textsuperscript{20, 21} However, when one realizes that a combination of the ST amplitude and ST slope as proposed by these authors is mathematically the same as a linear combination of two amplitudes from the same lead, these findings are not surprising.

In the present investigation the corrected orthogonal Frank lead system was used. The same type of criteria may be applied to conventional leads when the changes of the measurements from these leads during exercise have been established.

The Probability of an Abnormal ECG Response during Exercise

Exercise tests are frequently performed in order to find objective evidence of CAD in patients who present with atypical chest pain. The results of the test are usually
reported as “positive” when ST depressions are found, or “negative” when the ECG stays within normal limits. In reality, however, a considerable number of tracings are neither clearly “normal” nor “abnormal.” Therefore a procedure was developed to estimate the probability of exercise-induced myocardial ischemia for one individual patient. The likelihood ratio was chosen since it can readily be understood by clinicians. This ratio is the quotient of the probabilities that a given measurement is found in the patients or in the normal reference population. Thus the likelihood ratio is a measure of the degree of abnormality of a given set of measurements. This ratio has been computed with the assumption that the measurements have normal distributions. This is certainly not true for all data (see fig. 4). However, such a finding does not necessarily mean that the results obtained for data not normally distributed are incorrect, as pointed out by Cornfield. In the present series, for example, a likelihood ratio of 2.7 corresponded to a specificity close to 95% at all stages of the test even though the ST parameters at different heart rates were not always normally distributed (fig. 4).

The fraction of false positive results increased when criteria for classification of the ECG which had been developed from maximum exercise records were applied to earlier stages of the test (table 6). This could be corrected by computation of likelihood ratio functions at different heart rate intervals. Therefore the developed criteria may be applied to all records throughout a symptom limited exercise test, as well as to records obtained during a submaximal test, provided that similar workload increments are used.

Conclusions

Detailed computer analysis of the ECG during exercise in the present series resulted in an increased sensitivity relative to standard visual interpretation for detection of CAD, especially when heart rate was taken into account, while the specificity could be kept at the same level. These results in a training population of 86 normal men and 52 patients with CAD could be reproduced in a test population of 43 patients and 43 normals. While these results are highly encouraging, verification of the developed criteria in larger series is mandatory before they can be used routinely. In particular further studies are needed of the ECG changes during exercise in male patients with abnormal ECGs at rest and also in women, since these were not included in the present investigation.

The results of the ECG analysis could be expressed on a continuous scale with a likelihood ratio procedure. With this method the probability of myocardial ischemia during the exercise test can be estimated instantaneously. Tests which are performed for diagnostic reasons may now be terminated as soon as a certain confidence level is reached. This should reduce the risks of the test, as well as the discomfort of the patient and the time involved in exercise testing. Furthermore this approach may help to circumvent the contradictions discussed in recent editorials since the likelihood ratio can easily be combined with the prevalence of coronary artery disease in different settings in order to obtain the true probability of obstructive coronary artery disease in a given subject. It is concluded that quantitative analysis of exercise ECGs with a computer system will enhance the value of exercise tests as a noninvasive method for the detection of coronary artery disease and for the assessment of the effect of treatment in patients with this illness.

Acknowledgment

The authors thank Els Leufuin, Thérèse Kriebbers, Ed Smallungen, Joop de Wit, Annélies van de Velde, Muriël Wildschut, Astrid Melker and Maud van Nierop for technical and secretarial assistance.

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Mechanisms of Ischemic ST-Segment Displacement
Evaluation by Direct Current Recordings

G. Michael Vincent, M.D., J. A. Abildskov, M.D.,
and Mary Jo Burgess, M.D.

SUMMARY The electrophysiologic basis of ischemic ST-segment displacement was investigated in 40 open chest dogs. Epicardial and subendocardial electrograms were recorded with direct current coupled amplifiers during partial and complete coronary artery occlusion. The time course and magnitude of DC potential changes, and the effects on the DC potentials of heart rate and subendocardial ischemia were investigated.

TQ segment depression, representing loss of resting membrane potential, was found to be the consistent and most specific mechanism of "ST displacement" due to ischemia. True ST-segment displacement, due to alterations of phase 2 of the transmembrane action potential, occurred less frequently, and was not specific for ischemia. The DC potential changes were similar in both subendocardial and epicardial tissue. Increased heart rate by atrial pacing increased the magnitude of TQ segment depression and produced subendocardial ischemia during partial coronary flow reduction.

The findings have importance in the clinical interpretation of ST-segment displacement. Potential limitations in the use of precordial ST-segment mapping to estimate infarct size or severity are described. The results help explain the variable and conflicting findings of previous studies investigating the mechanisms of ST displacement, and may help explain the poor correlation between rapid atrial pacing-induced ST displacement and coronary artery disease defined by angiography. Electrocardiographic interpretation based on physiologic data such as those presented in this study should improve the usefulness and accuracy of the electrocardiographic examination.

ST-SEGMENT DISPLACEMENT, one of the most useful signs of acute ischemic heart disease, has at least two major possible physiologic mechanisms: localized loss of resting membrane potential and alteration of the transmembrane action potential waveform or time of onset of the action potentials. Action potential waveform changes resulting in ST displacement include alterations in the duration, amplitude, and slope of phase 2. The time of onset of the action potential may be altered by conduction abnormalities which result in delayed activation and therefore delayed repolarization. Previous studies investigating the relative frequency and magnitude of these two mechanisms have produced conflicting results. These variable results, plus the increased interest in the use of ST-segment displacement brought about by precordial ST-segment mapping, and body surface isopotential mapping, indicate that further elucidation of the underlying physiologic mechanisms is needed.

In the standard electrocardiogram, using capacitor coupled (A-C) amplifiers, both TQ segment and true ST-segment displacement appear as "ST-segment displacement," and the two cannot be differentiated. The technique of recording cardiac potentials using direct current coupled amplifiers does, however, allow the identification of these two mechanisms individually. Using this technique, loss of resting membrane potential is manifest by a depression of the TQ segment (baseline), while action potential waveform or timing changes are manifest by a shift of the true ST segment. These two separate mechanisms are illustrated in figure 1. Previous studies using this technique have reported variable results, some indicating only TQ segment depression, and others reporting both mechanisms to be present, but with variable relative importance. This study describes the time course and magnitude of changes in direct current recorded epicardial and endocardial electrograms from ischemic cardiac tissue in the experimental animal. Additional new information is reported on the effect of heart rate on the DC recorded electrogram. Through the use of coronary artery flow probes to document the magnitude of coronary artery flow reduction, the effects of partial flow reduction and subendocardial ischemia are described.

Methods

The mechanism of ST displacement produced by com-
Estimation of the probability of exercise-induced ischemia by quantitative ECG analysis.

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