The Actual Prevalence of False Positive ST-Segment Responses to Exercise in Clinically Normal Subjects Remains Undefined

IN A RECENT EDITORIAL REVIEW IN Circulation, Redwood and associates\(^1\) expressed their opinion that exercise testing for ST-segment abnormalities is of little value in detecting asymptomatic subjects with ischemic heart disease. Their reasoning, based on a review of the currently available literature, was that the prevalence of false positive ST-segment responses to exercise in asymptomatic subjects is unacceptably high. The authors also conclude that the high predictive accuracy\(^1\) of the exercise ST-segment response in symptomatic patients is biased by the patient populations studied and that equal diagnostic accuracy can be obtained by the clinical history alone. However, they failed to critically analyze the very few reported studies in asymptomatic subjects to determine if patient selection, faulty methods, or techniques and other variables might be instrumental in creating biased results in this group. Instead, they present existing data as though they were conclusive and further investigative studies would be unrewarding.

Redwood et al.\(^3\) based their conclusions concerning the accuracy of the ST-segment response to exercise in asymptomatic subjects on four reported epidemiologic studies\(^4\) and two studies in which coronary cineangiographic correlations were reported.\(^7\) They cited a combined predictive accuracy\(^1\) of 25% from the four epidemiologic studies based on three to six year follow-ups of the study subjects. The authors apparently assume that the absence of a new coronary event in 75% of these subjects during relatively short follow-up periods is conclusive evidence that the majority of the subjects will not manifest clinical coronary artery disease in the future.

The truth is that there are no long term follow-up data to define the natural history of new coronary events in subjects with coronary artery disease manifested solely by an abnormal maximal or near-maximal exercise ST-segment response. In our studies of clinically normal Indiana state policemen the mean time between the finding of an abnormal ST response to exercise and a new coronary event has been 4.5 years.\(^9\)

Redwood and associates referred to the coronary cineangiographic correlation studies of Borer et al.\(^8\) and Froelicher et al.\(^3\) to support their conclusion that the predictive accuracy of an abnormal ST-segment response to exercise is unacceptable in asymptomatic subjects. A critical review of these reports reveals that the majority of the subjects studied could not be considered clinically normal. In Froelicher’s study of 76 male Air Force personnel, only 43% of the subjects with an abnormal ST response to exercise had coronary artery disease. However, 58 of these subjects were chosen for study because of repolarization abnormalities on their 12-lead ECG. Their ST-segment responses to exercise were interpreted as abnormal if they demonstrated 1.0 mm or more of horizontal or downsloping ST depression during or after exercise “regardless of the degree of baseline ST segment depression.” The poor diagnostic reliability of the exercise ECG in the face of baseline repolarization abnormalities is generally accepted.\(^9\)\(^10\)

The remaining 18 subjects in Froelicher’s study group were asymptomatic and had a normal 12-lead ECG at rest. At first glance the results did not appear to be significantly different in this subgroup in that 11 of the 18 subjects or 61% had normal coronary cineangiograms. However, of the 11 subjects with a false positive ST response to exercise, the ST-segment abnormalities appeared only in a bipolar Y axis lead system in seven. Therefore, the coronary cineangiograms were abnormal in seven of the 11 subjects with an abnormal ST response on a more conventional, bipolar V\(_6\) lead system. The probability of an increased incidence of false positive ST-segment responses to

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exercise in vertically oriented lead systems has been previously pointed out.*

The study by Borer et al.* involved 30 subjects with hypercholesterolemia and an abnormal ST-segment response during exercise. No information was given as to how this highly selective group came under medical attention. As with Froelicher's study, bipolar X and Y lead systems were used to record the exercise ECG, but the percentage of abnormal ST-segment responses observed in each of the two lead systems was not given; neither was the number of subjects exhibiting an abnormal resting ECG.

The potential importance of patient selection in the study of the exercise ST-segment response in asymptomatic subjects was emphasized in a very recent report by Erickssen and associates.† They carried out thorough medical evaluations and near-maximal exercise tests on 2014 men from five firms and state agencies in Oslo, Norway. They found 75 men with an abnormal ST-segment response to exercise who were otherwise free of clinical evidence of heart disease. Every subject had a normal resting 12-lead ECG. Coronary cineangiographic studies revealed significant coronary artery disease in 48 or 64% of these subjects. Multiple CH-lead placements were used in this study to record the ECG during exercise and standard 12-lead ECG recordings were made at selected intervals post-exercise. No breakdown was given relative to the number of true and false positive responses observed in each of the recorded leads. This study also reported a significant number of false positive ST-segment responses but the predictive accuracy was much higher than that reported in the studies by Borer and Froelicher. One of the potentially important reasons for the different results observed by Erickssen and associates may have been their decision to "disregard ST-segment abnormalities of the vasoregulatory type during exercise." They do not elaborate on this statement but presumably subjects who demonstrated labile repolarization changes prior to exercise were not considered to have abnormal ST responses during exercise irrespective of the type of ST-segment changes observed.

Erickssen et al. did not state whether attempts were made to "unmask" a tendency to labile repolarization changes in their subjects prior to exercise by methods such as the Valsalva maneuver and hyperventilation. The identification of asymptomatic subjects who are prone to labile repolarization changes prior to exercise may prove to be a very important step toward identifying those subjects who are also prone to false positive ST responses during exercise. We recently reported a mean, six year follow-up of 723 clinically normal Indiana state policemen after maximal exercise ECG studies.‡ Of the 26 subjects who demonstrated an abnormal ST response on a modified bipolar V\textsubscript{6} lead, a new coronary event had occurred in nine, or 35%, during the follow-up period. From this same study group there were 19 additional subjects who were considered to have false positive ST-segment responses during exercise because labile ST depression (0.5 mm or greater) or T wave inversion was demonstrated before exercise with standing or hyperventilation. During the six year follow-up, none of these 19 subjects demonstrated a new coronary event.

A majority of the state police subjects who demonstrated labile repolarization changes before exercise and ST abnormalities with exercise were under 40 years of age. The mean age of the entire study group of 723 subjects was 37 years (range 27-57) at the time of their entry into the study. The mean age of the 19 subjects who demonstrated labile repolarization changes prior to exercise was 39 years (range 31-48), while that of the 26 subjects with an abnormal ST-segment response to exercise who were free of repolarization changes prior to exercise was 44 years (range 29-55). Redwood failed to comment on the potential importance of age in evaluating the clinical significance of an abnormal ST response to exercise in asymptomatic subjects. Of Froelicher's 76 study subjects, 46 were less than 45 years of age. Of the 30 subjects who were 45 years or older, 70% had abnormal coronary cineangiograms. Borer et al. did not list the mean age of their study subjects but the range, 21 to 55 years, was wide. The mean age of the 75 subjects with an abnormal ST response to exercise in Erickssen's study was 50 years. Of the nine subjects under 45 years of age, only three had abnormal coronary cineangiograms.

There have been very few investigative studies of the clinical significance of abnormal ST-segment responses with exercise in women. Sketch and associates obtained near-maximal treadmill exercise tests and coronary cineangiographic studies on 56 women who presented with chest pain.† The incidence of abnormal ST-segment responses with exercise was 27% (15 of 56); only 33% (5 of 15) of the women with an abnormal ST-segment response demonstrated a 75% or greater narrowing of one or more coronary arteries. Cumming et al. obtained near-maximal exercise tests on 357 asymptomatic women between 20 and 83 years of age.† They found the age adjusted incidence rates of abnormal ST-segment responses to exercise to be nearly three times greater than those reported for males of comparable age. The results of these studies certainly suggest that the incidence of false positive ST-segment responses to exercise are considerably higher in women than in men. However, the epidemiologic and coronary cineangiographic studies referred to by Redwood et al. dealt almost exclusively with male subjects and the higher incidence of false positive ST-segment responses to exercise in women cannot be implicated as a factor in the results cited.‡†

Redwood et al. discussed the use of criteria calling for greater degrees of ST depression with exercise to reduce the number of false positive responses observed in asymptomatic subjects. Based on a limited number of reported studies, they concluded that both the sensitivity and predictive accuracy of the exercise test would be reduced. The heart rates at which ST-segment abnormalities appeared during exercise in asymptomatic subjects was not considered in the three studies which provided coronary cineangiographic correlations.‡‡,†1† Based on existing knowledge of the pathophysiology of myocardial oxygen supply and demand, individuals with more advanced coronary artery disease should demonstrate abnormal ST depression at lower exercise heart rates. The appearance of 2.0 mm or greater of ST depression at exercise heart rates of 70% or less of predicted maximal should be more meaningful than similar degrees of ST depression occurring at near-maximal heart rates in terms of identifying those subjects at greatest risk of symptomatic coronary disease. The percentage of asymptomatic subjects who demonstrate false positive ST-segment
responses only with near-maximal or maximal exercise heart rates has not been reported. In those subjects who demonstrate an abnormal ST-segment response only during the post-exercise period this determination must be made by repeating the exercise test and using a submaximal heart rate as the end-point. The identification of asymptomatic subjects who are truly at near term risk may be improved by further investigative studies in this area. Serial exercise testing for the detection of earlier appearing ST-segment depression or ST depression of increasing magnitude may also prove to be of value.

Only two of the 75 subjects studied by Eriksen and associates demonstrated isolated post-exercise ST-segment abnormalities. These investigators' criteria for an abnormal ST-segment response included slow upsloping ST-segment depression which they defined as 1.5 mm or greater of ST depression at 0.08 seconds from the J point. They found the slow upsloping ST criteria just as reliable in identifying subjects with coronary artery disease as the more conventional horizontal or downsloping criteria when each criteria was applied to the ECG recorded during exercise. In the post-exercise period horizontal or downsloping ST depression was related significantly more often to coronary artery disease than slow upsloping depression. These findings are in keeping with our experience in symptomatic patients with coronary artery disease. We rarely see horizontal or downsloping ST-segment depression post-exercise which is not preceded by horizontal or slowly upsloping ST-segment abnormalities during exercise. Thus, the appearance of horizontal or downsloping ST-segment depression post-exercise without accompanying horizontal or slowly upsloping ST depression during exercise may prove to be a clue that the asymptomatic subject does not have significant coronary artery disease.

The number, the torso placements, and the type (unipolar, bipolar, orthogonal) of ECG leads which will yield the most reliable results in exercise electrocardiography remain to be defined. A recent study by Froelicher and associates clearly illustrates the need for further investigative studies in this area. He found that the magnitude of ST depression and the slope or rate of rise of the ST segment varied significantly with different V4 type lead placements even when a common exploring electrode was used. Froelicher's studies have also demonstrated that at least some vertically-oriented leads can result in a high incidence of false positive ST-segment responses with exercise. The use of multiple, orthogonally oriented leads may ultimately prove of value in identifying which asymptomatic subjects with an abnormal ST-segment response to exercise have underlying coronary disease or, at least, those who are at greatest short term risk. However, this concept has not yet been proven by sound investigative studies.

Redwood et al. concluded that "only when the strengths and weaknesses of a test are fully appreciated can it be properly employed or rejected in the assessment and management of the individual patient." I recognize that their conclusions concerning the clinical value of the ST-segment response to exercise in asymptomatic subjects may prove to be sound, but at this time, their negative conclusions do not appear to be justified based on currently available scientific data. I hope investigators will keep an open mind about this important clinical dilemma, and further, more conclusive studies will be forthcoming.

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References

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