Nagoya J. Med. Sci. 47. 67 ~ 75, 1984

SEX DIFFERENCES IN SUBMAXIMAL EXERCISE TESTS CORRELATION WITH CORONARY CINE-ANGIOGRAPHY IN 133 PATIENTS

KAZUNOBU YAMAUCHI, M.D.*, ERNST SIMONSON, M.D.**
JAMES C. DAHL, M.D.***
and RICHARD S. CROW, M.D.****

**First Department of Internal Medicine, Nagoya University School of Medicine, **Mount Sinai Hospital, Minneapolis, Minnesota, ***St. Louis Park Medical Center, Minneapolis, Minnesota ****The Laboratory of Physiological Hygiene, University of Minnesota, Minneapolis, Minnesota*

ABSTRACT

Submaximal treadmill exercise testing up to 80 percent of the maximal heart rate predicted for age was performed on 138 normal men and 142 normal women. Sex difference was analyzed in terms of 3 ST-T items: J, midpoint between J and the peak of T (mid-ST), and the peak of T in leads II, V_4 and V_6 at rest and after exercise. A greater mid-ST point depression at rest, during and after exercise was found in normal women than in men ($p < 0.001$). Sex-adjusted 95% confidence limits were estimated. Using these norms, similar evaluations were carried out on 133 patients who were being evaluated for possible coronary insufficiency, eighty-four (64 men and 20 women) of whom had significant angiographic disease ($\geq$ 75% narrowing) and forty-nine (26 men and 23 women) of whom had not. The most sensitive and specific correlate with anatomic coronary disease was the absolute change in mid-ST point. Using criteria developed in the normal group, sensitivity for angiographic positives was 70.3% (45 of 64) in men and 70.0% (14 of 20) in women (P = not statistically significant); specificity was 92.3% (24 of 26) in men and 87.0% (20 of 23) in women (P = not statistically significant). When these male standards were used in female patients, there was a decrease in specificity from 87.0% to 43.5% ($P < 0.001$). Sex-adjusted standards render the ECG exercise test as effective a diagnostic tool in women as in men.

Keywords: Sex difference, Submaximal treadmill exercise testing, Mid-ST amplitude, Ischemic heart disease.

INTRODUCTION

Electrocardiographic stress testing has been established as a sensitive marker of ischemic heart disease. Its usefulness is well accepted in screening asymptomatic subjects as well as in evaluating patients for possible clinical ischemic heart disease.[1] However, a number of reports indicate that "false positive responses" are frequent in women,[2-8] and raise questions regarding the use of graded exercise tests for clinical evaluations in women.

Significant constitutional correlates have been found with resting ECG findings in women[9,10] and a greater frequency of positive ischemic responses has been reported. This study investigates the sex difference of ST-T items and determines the 95 percentile confidence limits of normal men and women using a standardized submaximal exercise protocol.[11] Use of these standards is then made in patients being evaluated for probable ischemic heart disease and subsequently given coronary angiograms.

山内一信, Ernst Simonson · James C. Dahl · Richard S. Crow
Received for Publication October 15, 1984

MATERIALS AND METHODS

1. *Normal Subjects*

The normal population sample was made up of 138 men and 142 women evaluated at the St. Louis Park Medical Center. They were screened as to the absence of detectable disease which may affect the electrocardiogram following the guidelines described by Simonson.[9] The average age and standard deviation of the men was 48.8 ± 8.8 (age range 27–70 years) and for the women 48.9 ± 10.3 (age range 29–71 years).

The Exercise Test

The electrocardiographic exercise test performed was a progressive submaximal test to 80% of maximum age-corrected heart rate.[11] This was carried out on a treadmill at a fixed elevation of 10% grade using progressive incremental increases in speed. Prior to exercise a conventional 12-lead supine ECG was recorded. During exercise, bipolar ECG strips were recorded from lead CM5 at one-minute intervals, and the tracing was continuously monitored on a standard ECG oscilloscope. Immediately following the exercise period, conventional leads I, II, III, V_2, V_4, and V_6 were recorded in the supine position. The precordial leads were obtained first followed by recordings of the limb leads. The procedure was repeated after 2 and 4 min., respectively. All normal subjects reached the estimated target heart rate.

The following items of leads II, V_4, and V_6 were manually measured: 1) amplitude of J point; 2) amplitude of mid-ST point being midway between the J point and the peak of the T wave; 3) amplitude of the peak T wave; 4) slope of the ST segment, defined as the slope between the J and the mid-ST point. When T wave showed biphasic patterns, the peak of the positive part was chosen as the peak T, and when the T wave was completely negative, the nadir of the T was used as the peak T. These amplitudes were measured from the baseline which was defined as the line connecting 2 consecutive PQ junctions when the beat to be measured and the next beat were considered to be on a straight line. Noisy tracings recognized by inspection were omitted. When there was a distinct respiratory beat-to-beat variation, the beat which seemed to show an intermediate pattern was selected. The 95 percent range limit, mean and standard deviation of each item were determined. Statistical tests of significance of mean sex differences were performed on each item.

2. *Subjects Having Coronary Cineangiography*

One hundred and thirty-three patients were evaluated for chest pain with clinical diagnosis of possible coronary heart disease at Methodist Hospital, Minneapolis, Minneasota. Ninety subjects were men with an average age of 48.0 yr and 43 were women with an average age of 50.2 yr. Patients with valvular heart disease, primary myocardial disease, myocarditis, pericarditis, anemia, electrolyte abnormality or other forms of cardiovascular disease were excluded. None of the subjects were taking digitalis, quinidine or other drugs known to influence the ST segment response to exercise. Patients who showed ST-T abnormality in the resting ECG, i.e., measured items which were out of the 95 percentile limits of the normals obtained in this project, were left in the study if the resting items did not exceed normal limits of the post-exercise ECG. All patients performed the submaximal exercise test according to the previously mentioned protocol. The ECG items measured were the same as those in the normal control subject group.

Selective coronary arteriography was performed by Judkins' or Sones' techniques and was reviewed by at least two doctors who had no knowledge of the results of the exercise stress test. The degree of coronary obstruction was characterized by 3 groups: Group I (GI) – normal coronary arteriogram (18 men, 20 women, average age 43.6 yr, 45.6 yr, respectively); Group II (GII) – slightly abnormal coronary arteriograms with descriptions such as tortuosity, minor or minimal changes or obstructions less than 75% (8 men, 3 women, average age 47.1 yr and 53.2 yr, respectively), and Group III (GIII) – abnormal coronary arteriogram defined as showing obstruction of 75% or greater in one or more vessels (64 men, 20 women, average age 49.6 yr and 50.0 yr, respectively). Correlations between the anatomic grouping as noted and the submaximal treadmill exercise test were made using the normal range of ST-T items obtained in the normal control group.

RESULTS

1. *Sex Differences and Normal Values of Submaximal Exercise Test*

The mean and standard deviation of the submaximal heart rate attained in the exercise test were 138.5 ± 14.6 beats/min in the men and 139.2 ± 17.2 beats/min in the women (no statistically significant difference of the means).

Table I summarizes the means, standard deviations and normal 95 percentile ranges of all measurements in this study except for the slope of ST segment. Figure 1 shows means and 95 percentile range limits of the mid-ST point amplitude in leads II, V_4 and V_6. Three ST-T items, i.e., amplitude of J, mid-ST, and T at rest in leads II, V_4 and V_6, showed a highly significant sex difference between means, except for J amplitude in lead V_6. Mean amplitudes of 3 ST-T variables in the 3 leads were smaller in women than in men.

Through the three recovery stages, the mid-ST point in leads II, V_4 and V_6 showed highly significant sex differences with mean differences of 0.03 mv in lead II, 0.07 mv in V_4 and 0.03 mv in V_6, the women always having more negative amplitude than the men. There was no essential sex difference in the J point of the 3 leads immediately and 2 min after exercise, but a highly significant sex difference in the J point in leads II and V_4 was noted 4 min after exercise, with the women more negative than the men. Moreover, there was a significant sex difference in the T wave amplitude during all phases of recovery. Also, the average amplitude of T wave and J point was smaller in women than in men.

2. *Correlation of Exercise Electrocardiogram with Coronary Arteriogram in Men and Women*

Table II summarizes the prevalence of electrocardiographically abnormal findings after exercise in three groups of each sex classified by coronary arteriogram using the derived normal 95 percentile ranges in Table I. GIII group ($\geq$ 75% narrowing of affected coronary artery) was subdivided into three groups: GIII-I, one vessel disease; GIII-2, double vessel disease; and GIII-3, triple vessel disease.

It is notable that the prevalence of electrocardiographically abnormal cases in mid-ST point was high in GIII and low in GI + GII. The frequency rate in GIII was 70.3% in men and 70.0% in women and that in GI + GII was 7.7% in men and 13.0% in women. Higher mid-ST abnormality rate was noted in GIII-2 (double vessel disease) and GIII-3 (triple vessel disease) than in single vessel disease. The prevalence of J and T abnormalities was high in GI + GII compared to that of mid-ST abnormalities in GI + GII. Therefore, an abnormal finding of the mid-ST amplitude is more sensitive and more specific than other items of the exercise response for patients with ischemic heart disease.

If abnormal ECG response of mid-ST point is used as a single indicator of ischemia, and if a significant lesion of 75% or greater stenosis in a major coronary artery or branch is considered "abnormal", the results in Table III are encountered. In men, there were 45 true positive cases out of 64 abnormal patients and 24 true negative cases out of 26 normal patients resulting in a sensitivity of 70.3% and a specificity of 92.3%. In women, sensitivity was 70.0% and specificity was 87.0%. The number in parentheses demonstrates the cases which exceeded only upper normal limits, i.e., those that showed an abnormal mid-ST point elevation. There were no false positive cases shown by abnormal mid-ST elevation. A large majority of true positive cases showed mid-ST point depression. Chi-square test demonstrated no sex differences in either

Table I

Means (M), standard deviations (S.D.) and 95 percentile ranges (95% range) of ST-T items in absolute measurement at rest and after exercise in 138 normal men and 142 normal women (values expressed in 0.01 mv units)

		Men						Women					
		II		V4		V6		II		V4		V6	
		M (95% range)	S.D.	M (95% range)	S.D.	M (95% range)	S.D.	M (95% range)	S.D.	M (95% range)	S.D.	M (95% range)	S.D.
Rest	J	0.8***	4.2	0.6***	4.2	−0.3	4.2	−1.1	3.8	−1.4	4.0	−1.0	4.2
		(−8.0	10.1)	(−8.9	11.7)	(−9.9	7.4)	(−9.5	6.4)	(−10.0	6.5)	(−10.4	7.2)
	mid-ST	4.3***	4.1	13.9***	9.3	5.7***	5.8	1.6	3.4	4.1	6.5	1.3	3.9
		(−2.6	15.9)	(0.0	42.2)	(−2.8	19.6)	(−4.4	8.4)	(−7.9	21.6)	(−7.3	10.5)
	T	24.5***	9.2	52.7***	24.4	32.0***	17.0	19.8	10.4	35.3	20.6	24.6	13.6
		(6.5	45.7)	(15.8	119.5)	(6.9	82.3)	(4.2	45.6)	(5.7	87.2)	(5.4	64.2)
Immediately after exercise	J	−5.3	5.5	−6.2	4.9	−6.5*	4.6	−6.2	4.7	−7.1	4.8	−5.2	4.6
		(−20.1	2.1)	(−17.4	2.4)	(−14.9	1.8)	(−16.3	3.1)	(−16.9	0.3)	(−14.2	3.2)
	mid-ST	3.9***	6.5	10.4***	9.2	2.3***	5.4	1.0	4.6	4.0	6.8	−0.1	5.1
		(−7.3	19.8)	(−3.3	31.4)	(−6.5	15.8)	(−8.6	10.8)	(−6.5	22.2)	(−9.8	13.1)
	T	25.4	11.1	55.7**	21.9	27.6**	14.9	22.8	11.4	47.1	25.2	23.0	10.6
		(7.4	49.0)	(14.2	102.6)	(3.3	69.5)	(4.5	52.2)	(11.8	116.9)	(5.6	46.6)
2 minutes after exercise	J	−4.0*	4.2	−5.0	3.9	−5.2	4.4	−5.1	4.1	−5.5	4.0	−4.3	3.6
		(−13.2	2.7)	(−14.0	2.7)	(−15.0	3.2)	(−14.3	2.2)	(−15.7	2.1)	(−12.7	3.8)
	mid-ST	2.4***	4.9	7.9***	7.9	1.3***	4.8	0.5	4.3	1.5	6.4	−1.4	3.8
		(−6.0	12.4)	(−5.6	27.7)	(−7.9	14.1)	(−9.2	9.3)	(−9.6	19.1)	(−9.5	5.9)
	T	28.0***	11.2	49.2**	20.2	24.7*	12.7	23.5	10.7	39.8	24.6	21.5	10.4
		(7.2	49.0)	(10.4	93.3)	(3.6	50.8)	(4.5	47.0)	(5.9	112.5)	(5.3	48.1)
4 minutes after exercise	J	−1.9**	4.0	−2.6***	3.9	−2.8	4.1	−3.3	4.0	−4.5	3.8	−2.9	3.9
		(−10.8	5.0)	(−9.9	4.3)	(−10.5	5.8)	(−11.9	3.1)	(−15.1	2.1)	(−10.6	4.7)
	mid-ST	2.1***	3.8	7.4***	7.4	1.8***	4.6	0.0	3.7	0.3	4.8	−1.2	3.4
		(−5.5	10.8)	(−3.8	23.3)	(−6.2	11.9)	(−8.9	8.1)	(−8.8	12.8)	(−8.6	5.9)
	T	23.9***	9.4	40.4***	9.8	22.4*	13.3	19.4	9.2	31.5	21.1	19.1	10.8
		(5.7	43.2)	(7.3	84.8)	(3.1	46.7)	(3.2	41.5)	(0.1	93.1)	(2.8	48.9)

Note: The symbols (*$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$) indicate the level of significance of sex differences.

Table II

Correlation between coronary arteriography and ST-T items in submaximal exercise testing

Group	Men				Women			
	No. of cases	J	mid-ST	T	No. of cases	J	mid-ST	T
Normal								
GI	18	6	1	5	20	4	2	7
GII	8	3	1	3	3	1	1	0
Total (GI+GII)	26	9	2	8	23	5	3	7
(%)		(35)	(8)	(31)		(22)	(13)	(30)
Abnormal								
GIII-1	25	10	13	15	8	3	3	4
GIII-2	21	13	15	14	6	5	6	6
GIII-3	18	17	17	13	6	3	5	6
Total (GIII)	64	40	45	42	20	11	14	16
(%)		(63)	(70)	(66)		(55)	(70)	(80)

The figures are the numbers of cases which showed ECG abnormalities of ST-T items,
GI = normal coronary artery; GII = < 75% narrowing of coronary vessel; GIII-1 = one vessel disease;
GIII-2 = double vessel disease; GIII-3 = triple vessel disease.

Table III

Sensitivity and specificity of sex-adjusted 95 percentile limits for mid-ST point as applied to the same sex group

	CAD (GIII)				Non-CAD (GI + GII)			
	Total	True positive	False negative	Sensitivity	Total	True negative	False positive	Specificity
Men	64	45 (2)	19	70%	26	24	2	92%
Women	20	14 (1)	6	70%	23	20	3	87%

CAD = patients with coronary artery disease; ( ) = the number of cases who showed only abnormal mid-ST elevation; sensitivity (%) is the ratio of the true positives ($\geq$ 75% narrowing of one or more coronary vessels with an abnormal exercise test) to the sum of true positives + false negatives ($\geq$ 75% narrowing of any coronary vessel and normal exercise test); specificity (%) is the ratio of true negatives (< 75% narrowing of coronary vessel with normal exercise test) to the sum of true negatives + false positives (< 75% narrowing of coronary vessel with abnormal exercise test).

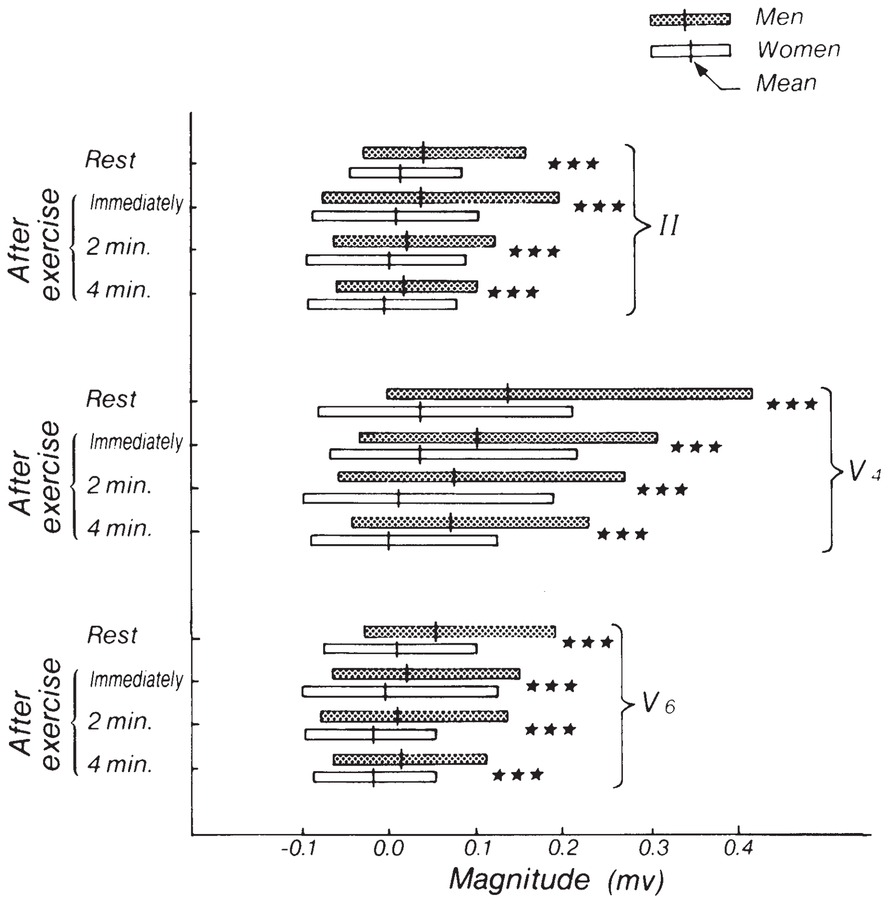

Figure 1 The 95 percentile ranges and means of mid-ST point in leads II, V_4 and V_6 in the absolute measurement in 138 men and 142 women (★★★P< 0.001).

sensitivity or specificity. However, when normal male 95 percentile ranges were applied to female subjects, specificity was reduced significantly (P< 0.01) to 43.5%, i.e., false positive cases increased to 13 from 3 and sensitivity did not increase as much as expected. The same was confirmed in male patients as well. This revealed the necessity of applying different criteria in each sex group.

The prevalence of positive exercise tests in three leads and the frequency of false negative cases were checked according to the number and location of the involved coronary artery. In both sexes, the precordial leads V_4 and V_6 showed a high rate of abnormal ECG response (approximately 50% in men and 60% in women) compared to lead II. However, any single lead among these three leads is not sufficient for diagnosis. It seems there is also no definite relationship between the location of the involved coronary artery and the three ECG leads. False negative responses were frequently observed in patients with single-vessel coronary artery disease (63 percent, 12 of 19, false negative male patients; and 83 percent, 5 of 6, false negative female patients). Not only right coronary artery disease alone, but also left anterior descending artery disease showed a false negative response of ECG.

DISCUSSION

There have been numerous reports regarding sex differences in electrocardiographic response to the exercise stress test.[2-8] The most important questions to be answered are whether the different criteria for each sex group should be established for the electrocardiographic interpretation of the exercise test. Our study revealed there were significant sex differences in 29 items of 48 ST-T items (60.4%). The magnitude in the measurements of those items was smaller in women. There were always distinct sex differences seen in mid-ST and T at all stages from rest to recovery. The mean difference of those items was most marked in V_4 with lesser differences in V_6 and II. The presence of the sex difference of means with 95 percentile ranges at mid-ST point is one of the explanations of the high incidence of women's false positive responses which are shown as "minor" ST segment abnormalities.[8] In addition, the mean difference in measurements from 0.03 mv to 0.07 mv at the mid-ST point should be considered in the evaluation of the stress test according to the independent correlation study between ECG and coronary angiogram. These results show the necessity of sex-adjusted criteria for the exercise stress test.

It is interesting to note that the lower limits of normal at mid-ST point are approximately constant in each sex group through the three recovery stages in leads II, V_4 and V_6. Hence, to facilitate an application of the normal values, it will be possible to choose a standard value of lower limits at mid-ST point at –0.05 mv for men and –0.09 mv for women. The application of the suggested criteria showed a sensitivity of 76.6% (49 of 64) and specificity of 84.6% (22 to 26) in men, and a sensitivity of 70.0% (14 of 20) and specificity of 87.0% (20 of 23) in women. If the male criterion is used to evaluate the female group, i.e., if mid-ST depression of 0.05 mv or greater is considered abnormal in women, specificity in the female group is reduced to 34.8%. The lower limit of normal at mid-ST point amplitude suggested here, –0.05 mv for men and –0.09 mv for women, should be a useful criterion, as should be the sex-adjusted normal 95 percentile ranges.

It is notable that the difference of 95 percentile ranges between both sexes, especially in T wave amplitude were, in general, not as large as the mean difference, probably due to the women's tendency to have small variance in the distribution. The extent of the mean amplitude change with 95 percentile ranges was small in women. There was no significant sex difference in J point at the early post-exercise stage (with the exception of lead V_6). This finding suggests that if a point close to the J point is chosen as a critical point and sufficient stress is given, it may be possible to reduce the sex difference of the electrocardiographic response.

Various points in the ST segment have been proposed for discrimination between positive and negative tests. Most investigators measured the amplitude at a point in the ST segment having a fixed interval (usually 60 msec or 80 msec) from a point in QRS or J.[12] In this study, the mid-ST point was chosen accoding to Blackburn and Rautaharju's suggestion that the third and fourth of eight equal ST-T amplitude samples taken from the spatial magnitude curve between J point and T peak are more powerful discriminants than J or T peak or any other intermediate ST-T values.[13] The measurement of mid-ST amplitude, which differs from prior reports, has the following advantages: 1) it is usually easy to detect the point; 2) that point is corrected or "normalized" for difference in QT interval except for particular cases; and 3) abnormality of J-junctional type depression but with slowly ascending ST-depression[13-16] could be expressed or included as abnormality of mid-ST amplitude by application of the standards.

Obviously the stress applied and the end point for stopping the treadmill stress test must be taken into consideration in ECG standards. A "maximal" stress test may be considered the ideal way to detect coronary artery disease, in that the diagnostic sensitivity of the exercise test increases with the exercise load and the heart rate. However, for many real and expedient reasons, the submaximal test has been proposed.[17] Simonson found the determining factor for the

ECG response was the heart rate when $\dot{V}o_2$ and heart rate during exercise were compared; consequently, the type of progressive exercise test appears to be of secondary importance, provided that a sufficiently high heart rate is attained in the large majority of patients with coronary insufficiency.[18] Consequently, the normal ranges obtained in this study should be applicable regardless of the type of submaximal exercise stress test, if the target heart rate (80 percent of the predicted maximal) is attained.

The prevalence of false positive responses, particularly in women, is a troublesome clinical problem. With criteria obtained from the distribution in each normal group, a considerably higher specificity was obtained than without sex adjustment. A further attempt to reduce the false positive rate was made using a combination of 95 percentile limits for the mid-ST point and the ST segment slope. This reduced the false positive response to one individual of each sex. However, the sensitivity correspondingly decreased to 43.8% in men and 50.0% in women, respectively.

ACKNOWLEDGEMENT

We thank Dr. Henry Blackburn of the Laboratory of Physiological Hygiene, University of Minnesota for his valuable guidance and recommendations. We also wish to express thanks to Prof. Otto H. Schmitt for his helpful suggestions. The other authors would like to express their appreciation of Dr. Ernst Simonson's contribution in formulating the project and initiating the work. We regret that he did not live to see it completed and we pay our respects to our friend and colleague for his guidance and wisdom.

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