Diagnostic and Prognostic Significance of Exercise-Induced Premature Ventricular Complexes in Men and Women: A Four Year Follow-Up

CHANDRA K. NAIR, MD, FACC, WILBERT S. ARONOW, MD, FACC, MICHAEL H. SKETCH, MD, FACC, TOM PAGANO, MD, JOSEPH D. LYNCH, MD, FACC, ARYAN N. MOOSS, MD, FACC, DENNIS ESTERBROOKS, MD, VINCENT RUNCO, MD, FACC, KAY RYSCHON, MS

Omaha, Nebraska

Two hundred eighty patients (197 men and 83 women) with normal rest electrocardiograms and no history of prior myocardial infarction were referred for evaluation of chest pain. It was found that exercise-induced premature ventricular complexes had a lower sensitivity, specificity, positive predictive value and negative predictive value in predicting significant coronary artery disease than exercise-induced ST segment depression greater than or equal to 1 mm. The incidence of exercise-induced premature ventricular complexes was not significantly different in patients with no significant coronary artery disease, single vessel disease or multivessel disease. The site of origin of exercise-induced premature ventricular complexes was not helpful in predicting the presence or severity of coronary artery disease. At a mean follow-up period of 47.1 months, exercise-induced premature ventricular complexes did not predict coronary events (cardiac death or nonfatal myocardial infarction) in men or women.

Exercise-induced ST segment depression and limited exercise duration correlate with the development of subsequent coronary events (1–10). The diagnostic and prognostic significance of exercise-induced premature ventricular complexes is controversial in men (4,11–15) and, to the best of our knowledge, unreported in women.

We studied the diagnostic value of exercise-induced premature ventricular complexes compared with exercise-induced ST segment depression greater than or equal to 1 mm in 280 patients (197 men and 83 women). All of the patients had a normal rest electrocardiogram, no history of myocardial infarction and coronary arteriography performed because of chest pain. We also studied the prognostic value of exercise-induced premature ventricular complexes for predicting subsequent coronary events (cardiac death or nonfatal myocardial infarction) in these 280 subjects after a mean follow-up period of 47.1 months.

From the Division of Cardiology, Creighton University School of Medicine, Omaha, Nebraska. Manuscript received October 12, 1982; revised manuscript received December 9, 1982, accepted December 23, 1982.

Address for reprints: Chandra K. Nair, MD, Cardiology Division, Creighton University School of Medicine, 601 North 30th Street, Omaha, Nebraska 68131.

Methods

Study patients. Two hundred ninety subjects with a normal electrocardiogram at rest and no premature ventricular complexes at rest referred for evaluation of chest pain were studied. This population consisted of 206 men (mean age 55.6 ± 9.2 years) and 84 women (mean age 53.0 ± 9.0 years). Patients suffering from prior myocardial infarction, cardiomyopathy, valvular heart disease, anemia, thyroid disease or electrolyte imbalance were excluded. No patient received digitalis, beta-adrenergic blocking agents or other antiarrhythmic agents during the 2 weeks before exercise testing. The development of coronary events was followed up in 280 (96.6%) of 290 subjects. The mean follow-up period was 47.1 ± 19.6 months (range 17 to 83) and included documentation of development of coronary events.

Exercise protocol. All patients performed a continuous multistage treadmill exercise test using the Bruce protocol (16). Standard 12 lead electrocardiograms were recorded in both the supine and standing positions before exercise. Twelve lead electrocardiograms were recorded at the end of each 3 minute stage and at the end of exercise. After exercise, electrocardiograms were recorded with the patients in the supine position at 30 seconds and 1, 2, 3, 4, 5 and 6 minutes. The patients were monitored continuously during and for at least 6 minutes after exercise. Of the 280 patients, 212

0735-1097/83/0501201-6$03.00

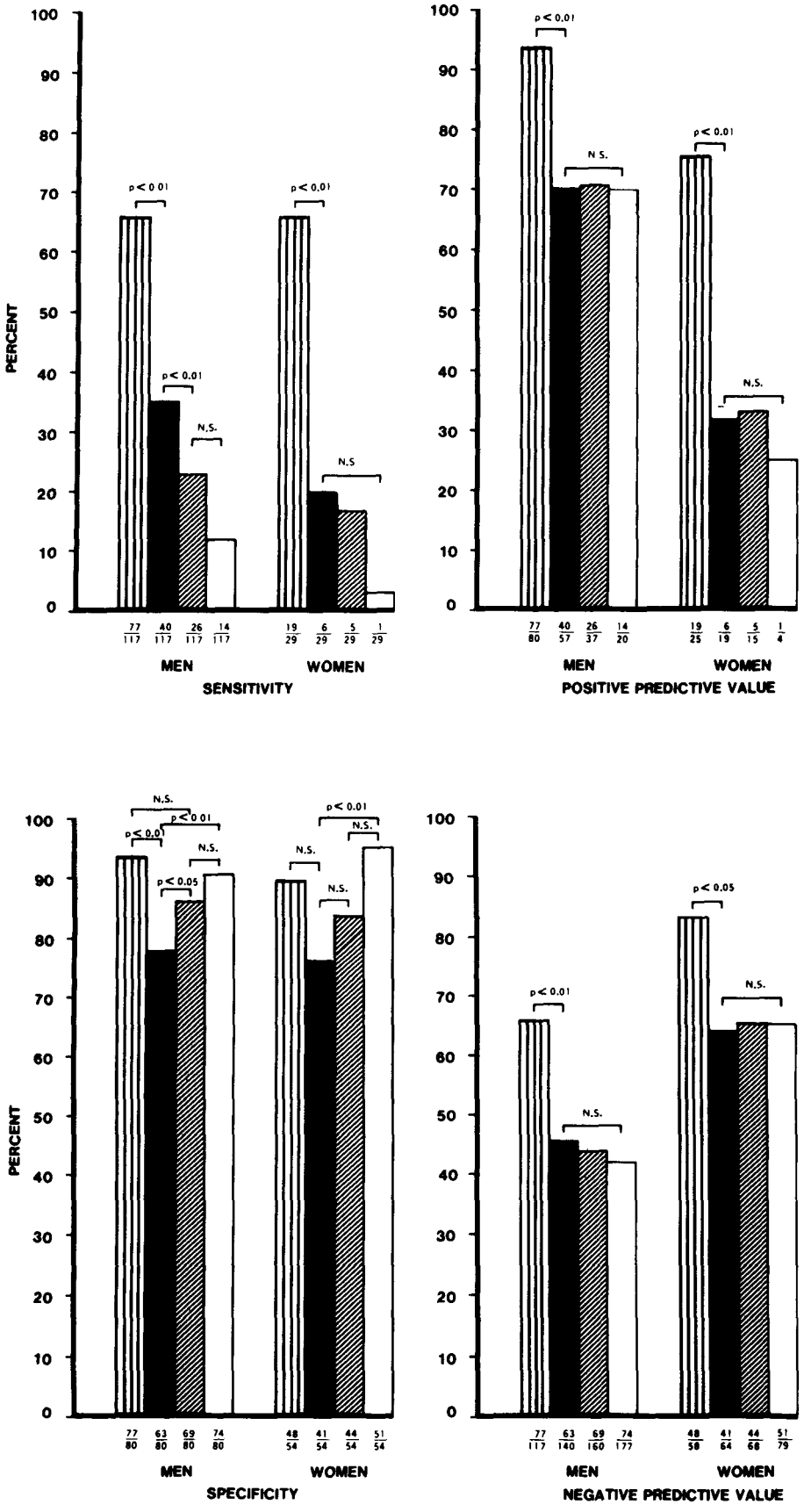

Figure 1. Sensitivity, specificity, positive predictive value and negative predictive value in men and women for significant coronary artery disease comparing exercise-induced ST segment depression greater than or equal to 1 mm (**vertically striped bars**) and exercise-induced premature ventricular complexes during and after exercise (**solid bars**), during exercise (**diagonally striped bars**) and after exercise (**clear bars**). Levels of significance are also shown. N.S. = not significant; p = probability.

J AM COLL CARDIOL
1983;1(5):1201–6

Table 1. Correlation of Exercise-Induced Premature Ventricular Complexes Occurring Before and After 70% of the Maximal Predicted Heart Rate Was Reached in Patients With Angiographically Significant Coronary Artery Disease

	Cases	Significant Coronary Artery Disease Present	
		no.	%
Exercise-induced premature ventricular complexes before 70% of maximal predicted heart rate	38	22	58
Exercise-induced premature ventricular complexes after 70% of maximal predicted heart rate	38	24	63

(75.7%) exercised until they developed chest pain, marked dyspnea or marked fatigue, 23 (8.2%) exercised until they exhibited marked ST segment depression or complex ventricular arrhythmias and 45 (16.1%) exercised until they reached 100% of their predicted maximal heart rate.

All exercise-induced premature ventricular complexes were recorded and counted. They were considered complex if they occurred in pairs or runs, if they were multiform or if they occurred at a frequency greater than 10/min. An exercise test was considered positive if one of the electrocardiographic leads manifested 1 mm or more flat or downsloping ST segment depression of 0.08 second duration.

Catheterization data. Selective coronary arteriograms were performed in all patients using either the Sones or Judkins technique within 14 days of exercise testing. The ejection fraction was calculated from the left ventriculogram in the right anterior oblique view using a simplified modification of the area-length method (17). Significant coronary artery disease was defined as a decrease in luminal diameter greater than 50% as judged by two or more of the authors without knowledge of the results of exercise testing.

Sixteen (21%) of the 76 patients with exercise-induced premature ventricular complexes and 49 (24%) of the 204 patients without exercise-induced premature ventricular complexes had coronary artery bypass graft surgery during the follow-up period.

Table 2. Correlation of Exercise-Induced Premature Ventricular Complexes With Severity of Coronary Artery Disease

	Cases	Exercise-Induced Premature Ventricular Complexes	
		no.	%
Multivessel disease	119	38	32
Single vessel disease	27	8	30
No significant disease	134	30	22

Table 3. Correlation of Site of Exercise-Induced Premature Ventricular Complexes With Angiographic Evidence of Significant Coronary Artery Disease

	Cases	Significant Coronary Artery Disease Present	
		no.	%
Left ventricular	26	15	58
Right ventricular	37	22	59
Indeterminate site of origin	13	9	69

Data analysis. All data were analyzed using an IBM System 4341 computer and programs from the statistical package for social sciences (SPSS) (18). Chi-square analyses were performed on the following data:

$$\text{Sensitivity (\%)} = \frac{\text{True positives}}{\text{True positives} + \text{False negatives}} \times 100$$

$$\text{Specificity (\%)} = \frac{\text{True negatives}}{\text{True negatives} + \text{False positives}} \times 100$$

$$\text{Positive predictive value (\%)} = \frac{\text{True positives}}{\text{True positives} + \text{False positives}} \times 100$$

$$\text{Negative predictive value (\%)} = \frac{\text{True negatives}}{\text{True negatives} + \text{False negatives}} \times 100.$$

True positives refer to patients with an abnormal test who had angiographically significant coronary artery disease. False negatives refer to patients with a normal test who had angiographically significant coronary artery disease. True negatives refer to patients with a normal test who did not have angiographically significant coronary artery disease. False positives refer to patients with an abnormal test who did not have angiographically significant coronary artery disease. Ethical guidelines were utilized throughout this retrospective study by the investigators.

Table 4. Correlation of Complex Exercise-Induced Premature Ventricular Complexes With Angiographic Evidence of Significant Coronary Artery Disease

	Cases	Significant Coronary Artery Disease Present	
		no.	%
Men	7	6	86
Women	3	1	33

Table 5. Correlation of Exercise-Induced Premature Ventricular Complexes With Coronary Events at Follow-up in Men and Women

	Men			Women			Men Plus Women		
		Coronary Events			Coronary Events			Coronary Events	
	Cases	no.	%	Cases	no.	%	Cases	no.	%
Exercise-induced premature ventricular complexes	57	6	11	19	1	5	76	7	9
No exercise-induced premature ventricular complexes	140	12	9	64	5	8	204	17	8

Results

Significant coronary artery disease was found by angiography in 117 (59%) of 197 men and in 29 (35%) of 83 women (probability [p] < 0.001). Eighty (41%) of 197 men and 25 (30%) of 83 women had a positive exercise-induced ST segment response. Fifty-seven (29%) of 197 men and 19 (23%) of 83 women had exercise-induced premature ventricular complexes.

Exercise-induced ST depression versus premature ventricular complexes. Figure 1 illustrates for both men and women the sensitivity, specificity, positive predictive value and negative predictive value for significant coronary artery disease comparing exercise-induced ST segment depression greater than or equal to 1 mm with exercise-induced premature ventricular complexes during or after exercise, during exercise only and after exercise only.

For exercise-induced ST segment depression, the sensitivity and specificity were not significantly different between men and women. The positive predictive value was higher in men (95%) than in women (75%) ($p < 0.01$). The negative predictive value was higher in women (83%) than in men (66%) ($p < 0.02$).

For exercise-induced premature ventricular complexes, the sensitivity and specificity were not significantly different between men and women. The positive predictive value was higher in men (70%) than in women (32%) ($p < 0.01$); however, the negative predictive value was higher in women (64%) than in men (45%) ($p < 0.02$).

The sensitivity, specificity, positive predictive value and negative predictive value for significant coronary artery disease in men and women when comparing exercise-induced ST segment depression and exercise-induced premature ventricular complexes with exercise-induced ST segment depression were not significantly different.

Exercise-induced premature ventricular complexes occurred in 5 (63%) of 8 patients with a left ventricular ejection fraction less than 50% and in 68 (26%) of 262 patients with an ejection fraction greater than or equal to 50% ($p < 0.025$).

Correlation with coronary angiographic findings. Table 1 shows the incidence of significant coronary artery artery disease found by angiography in patients with exercise-induced premature ventricular complexes occurring before and after 70% of the maximal predicted heart rate was reached. Table 2 indicates the incidence of exercise-induced premature ventricular complexes in patients with multivessel coronary artery disease, single vessel disease or no significant coronary artery disease. Table 3 reveals the incidence of significant coronary artery disease in patients with exercise-induced premature ventricular complexes arising from the left ventricle, right ventricle or an indeterminate site of origin. Table 4 shows the incidence of significant coronary artery disease in men and women with complex exercise-induced premature ventricular complexes. Table 5 indicates the incidence of coronary events at follow-up in men, in women and in men and women considered together with and without exercise-induced premature ventricular com-

Table 6. Correlation of Coronary Artery Bypass Graft Surgery and of No Surgery in Patients With and Without Exercise-Induced Premature Ventricular Complexes With Coronary Events in Men Plus Women

		Coronary Events	
	Cases	no.	%
Coronary surgery in patients with exercise-induced premature ventricular complexes	16	1	6
No coronary surgery in patients with exercise-induced premature ventricular complexes	60	6	10
Coronary surgery in patients without exercise-induced premature ventricular complexes	49	5	10
No coronary surgery in patients without exercise-induced premature ventricular complexes	155	12	8

Table 7. Correlation of Exercise-Induced ST Segment Depression Greater Than or Equal to 1.0 mm With Coronary Events at Follow-up in Men and Women

	Men			Women			Men Plus Women		
		Coronary Events			Coronary Events			Coronary Events	
	Cases	no.	%	Cases	no.	%	Cases	no.	%
ST segment depression present	80	11	14	25	3	12	105	14	13*
ST segment depression absent	117	7	6	58	3	5	175	10	6

*$p < 0.05$

plexes. No significant difference in coronary events occurred in men or women with or without exercise-induced premature ventricular complexes.

Role of coronary surgery. Table 6 shows the incidence of coronary events at follow-up in men plus women with 1) exercise-induced premature ventricular complexes and coronary artery bypass surgery, 2) exercise-induced premature ventricular complexes without coronary artery bypass surgery, 3) no exercise-induced premature ventricular complexes and with coronary bypass surgery, and 4) no exercise-induced premature ventricular complexes and without coronary bypass surgery. No significant differences were found.

Ventricular arrhythmias with and without significant ST depression. Table 7 shows the incidence of coronary events at follow-up in men, in women and in men plus women with and without exercise-induced ST segment depression greater than or equal to 1.0 mm. Coronary events occurred in 11 (14%) of 80 men with and in 7 (6%) of 117 men without exercise-induced ST segment depression ($p = 0.0632$), in 3 (12%) of 25 women with and in 3 (5%) of 58 women without exercise-induced ST segment depression (p = not significant) and in 14 (13%) of 105 men plus women with and 10 (6%) of 175 men plus women without exercise-induced ST segment depression ($p < 0.05$).

Discussion

The clinical significance of exercise-induced premature ventricular complexes is controversial (4,11–15). Our data show that in men or women with normal rest electrocardiograms and no history of myocardial infarction referred for evaluation of chest pain, exercise-induced premature ventricular complexes have a lower sensitivity, specificity, positive predictive value and negative predictive value than exercise-induced ST segment depression greater than or equal to 1 mm for predicting the presence or absence of significant coronary artery disease. The incidence of coronary artery disease was not significantly different if exercise-induced premature ventricular complexes occurred before or after 70% of the predicted maximal heart rate was reached. The incidence of exercise-induced premature ventricular complexes was not significantly different in patients with no significant coronary artery disease, single vessel disease or multivessel disease. Moreover, the site of origin of the exercise-induced premature ventricular complexes was not helpful in predicting the presence or severity of coronary artery disease.

In addition, our data indicate that exercise-induced premature ventricular complexes did not predict subsequent coronary events in men or women at 4 year follow-up. However, the small number of patients with complex exercise-induced premature ventricular complexes and abnormal left ventricular ejection fraction in our study does not allow us to draw any conclusions about this subgroup.

We express our appreciation to Mary Lou Butler for technical assistance and Ann Hensleigh for secretarial assistance.

References

1. Bruce RA, McDonough JR. Stress testing in screening for cardiovascular disease. Bull NY Acad Med 1969;45:1288–305.
2. Kattus AA, Jorgensen CR, Worden RE, Alvaro AB. ST segment depression with near maximal exercise in detection of preclinical coronary heart disease. Circulation 1971;44:585–95.
3. Froelicher VF Jr, Yanowitz FG, Thompson AJ, Lancaster MC. The correlation of coronary angiography and the electrocardiographic response to maximal treadmill testing in 76 asymptomatic men. Circulation 1973;48:597–604.
4. Froelicher VF, Thomas MM, Pillow C, Lancaster MC. Epidemiologic study of asymptomatic men screened by maximal treadmill testing for latent coronary artery disease. Am J Cardiol 1974;34:770–6.
5. Ellestad MH, Wan MKC. Predictive implications of stress testing. Follow-up of 2700 subjects after maximum treadmill stress testing. Circulation 1975;51:363–9.
6. Aronow WS, Cassidy J. Five-year follow-up of double Master's test, maximal treadmill stress test and resting and postexercise apexcardiogram in asymptomatic persons. Circulation 1975;52:616–8.
7. McNeer JF, Margolis JR, Lee KL, et al. The role of the exercise test in the evaluation of patients for ischemic heart disease. Circulation 1978;57:64–70.
8. Allen WH, Aronow WS, Goodman P, Stinson P. Five-year follow-up of maximal treadmill stress test in asymptomatic men and women. Circulation 1980;62:522–7
9. Bruce RA, DeRouen T, Peterson DR, et al. Noninvasive predictors of sudden cardiac death in men with coronary disease. Predictive value of maximal stress testing. Am J Cardiol 1977;39:833–40.
10. Weiner DA, McCabe CH, Ryan TJ, et al,. Combining treadmill time and ST segment response during exercise testing to predict survival

of coronary patients (CASS) (abstr). Circulation 1982;66(suppl II):II-342.

11. Udall JA, Ellestad MH. Predictive implications of ventricular premature contractions associated with treadmill stress testing. Circulation 1977;56:985–9.
12. McHenry PL, Morris SN, Kavalier M, Jordan JW. Comparative study of exercise-induced ventricular arrhythmias in normal subjects and patients with documented coronary artery disease. Am J Cardiol 1976;37:609–16.
13. Cohn K, Kamm B, Fetech N, Brand R, Goldschlager N. Use of a treadmill score to predict presence and severity of coronary artery disease. Circulation 1979;59:286–96.
14. Robb GP, Marks HH. Postexercise electrocardiogram in arteriosclerotic heart disease: its value in diagnosis and prognosis. JAMA 1967;200:918–28.
15. Helfant RH, Pine R, Kabde V, Banka VS. Exercise-related ventricular premature complexes in coronary heart disease. Correlations with ischemia and angiographic severity. Ann Intern Med 1974;80.589–92
16. Doan AE, Peterson DR, Blackmon JR, Bruce RA. Myocardial ischemia after maximal exercise in healthy men. A method for detecting potential coronary heart disease Am Heart J 1965,69:11–21.
17. Yang SS, Bentivoglio LG, Maranho V, Goldberg H. From Cardiac Catheterization to Hemodynamic Parameters 2nd ed. Philadelphia. FA Davis,1978:119–26.
18. Nie NH, Hull CH, Jenkins JK, Steinbrunner K, Bent DH. Statistical Package for Social Sciences. 2nd ed. New York: McGraw-Hill, 1975:218–48