Electrophysiology

Prevalence and prognostic value of exercise-induced ventricular arrhythmias

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Objective The purpose of this study was to determine the prevalence and prognostic significance of exercise-induced ventricular arrhythmias (EIVAs) in patients referred for exercise testing, considering the arrhythmic substrate and exercise-induced ischemia.

Background EIVAs are frequently observed during exercise testing, but their prognostic significance is uncertain. The design of this study was a retrospective analysis of prospectively collected data, and it took place in 2 university-affiliated Veterans Affairs Medical Centers. Patients comprised 6213 consecutive males referred for exercise tests. We measured clinical exercise test responses and all-cause mortality after a mean follow-up of 6 ± 4 years. EIVAs were defined as frequent premature ventricular contractions (PVCs) constituting >10% of all ventricular depolarizations during any 30 second electrocardiogram recording, or a run of ≥3 consecutive PVCs during exercise or recovery.

Results A total of 1256 patients (20%) died during follow-up. EIVAs occurred in 503 patients (8%); the prevalence of EIVAs increased in older patients and in those with cardiopulmonary disease, resting PVCs, and ischemia during exercise. EIVAs were associated with mortality irrespective of the presence of cardiopulmonary disease or exercise-induced ischemia. In those without cardiopulmonary disease, mortality differed more so later in follow up than earlier. In those without resting PVCs, EIVAs were also predictive of mortality, but in those with resting PVCs, poorer prognosis was not worsened by the presence of EIVAs.

Conclusions Exercise induced ischemia does not affect the prognostic value of EIVAs, whereas the arrhythmic substrate does. EIVAs and resting PVCs are both independent predictors of mortality after consideration of other clinical and exercise-test variables. These findings are of limited clinical significance because of the modest change in risk and the lack of any established intervention. However, they explain some of the previous controversy and highlight the need to consider resting PVCs and follow-up duration in assessing the clinical implications of EIVAs. (Am Heart J 2003;145: 139-46.)

Recent exercise testing consensus documents confirm that exercise testing is an important prognostic tool. Low exercise capacity and exercise-induced cardiac ischemia were reported to be the strongest predictors of mortality.[1] Ventricular arrhythmias can be induced by exercise testing[2]; however, at present, the prognostic significance of exercise-induced ventricular arrhythmias (EIVAs) remains unclear. Previous research studying the prognostic significance of EIVAs in those investigated for cardiac disease offers conflicting results. Some studies suggest that EIVAs confer a poor prognosis[3-5] while others demonstrate that EIVAs are benign.[6-8] The clinical significance of EIVAs in those without documented cardiovascular disease presents another prognostic dilemma. Although a recent study found that healthy volunteers with EIVAs had increased mortality,[9] earlier studies did not produce similar results.[10,11] It is unclear whether the prognosis associated with EIVAs differs based on the presence of cardiovascular disease, ischemic changes during exercise, and presence of premature ventricular contractions at rest (ie, an indicator of the arrhythmic substrate).

In order to further elucidate the prognostic significance of EIVAs, we analyzed the association of EIVAs with mortality in our database of >6000 male veterans referred for exercise tests. We assessed the risk associated with EIVAs on the basis of patient demographics, medical history, resting electrocardiogram (ECG) find-

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ings, and exercise test results after a mean period of follow up of 6 years.

Methods

Population

The population consisted of 6213 consecutive male patients referred to 2 clinical exercise laboratories (Long Beach VA 1987-1991, Palo Alto VA 1992-2000) directed in a consistent fashion by 2 of the authors (VF and JM). Patients who were subjects in research protocols were not considered in the analyses.

Data collection

Both labs had affiliations with Universities and had academic medical staffs with rotating house officers and fellows. All tests were supervised directly by these individuals or by nurse practitioners; all tests were over-read by 2 of the investigators (VF and JM). A thorough clinical history, listing of medications, and risk factors were recorded prospectively at the time of the exercise tests by use of computerized forms beginning in 1987.[12,13] The forms included standard definitions of clinical conditions and exercise responses. No imaging modality was performed in conjunction with the tests.

Exercise testing

Patients underwent treadmill testing that used progressive protocols with small but frequent incremental steps.[14-16] Tests were symptom-limited except for those stopped according to the criteria listed in the guidelines.[1] Medications were not changed or stopped before testing. Patients were encouraged to use the handrails only if necessary for balance. Heart rate targets were not used as an end point or to judge the adequacy of the test. Patients did not perform a cool down walk but were placed supine as soon as possible postexercise.[17]

After careful skin preparation, a standard 12 lead ECG was obtained before and continuously during exercise and for at least 5 minutes into recovery. ST-segment depression was measured visually at the J junction; ST slope was measured over the following 60 ms and classified as upsloping, horizontal, or downsloping. The ST-segment response considered was the most horizontal or downsloping ST-segment depression in any lead except aVR during exercise or recovery. An abnormal response was defined as $\geq$1 mm of horizontal or downsloping ST-segment depression. Exercise ischemia was coded when angina and/or abnormal ST depression occurred. The commercially available recorders used, Mortara X-scribe (Milwaukee, Wis) and Burdick Quest (Madison, Wis), had arrhythmia sensing that provided tracings automatically and manually, as well as freeze/playback capabilities. EIVAs were considered to be present if frequent premature ventricular contractions (PVCs), constituting >10% of all ventricular depolarizations during any 30-second ECG recording, or ventricular tachycardia, a run of $\geq$3 consecutive PVCs, were visually detected by test supervisors during the exercise test or recovery. Resting PVCs were considered present if any PVC was detected in the 10-second supine ECG before exercise. When PVCs appeared at rest, in order for EIVAs to be considered present, PVCs had to become frequent with exercise.

Blood pressure was taken manually and METs (metabolic equivalents) were estimated from treadmill speed and grade.[18] No test was classified as indeterminate.[19] Normal standards for age-predicted exercise capacity were derived from regression equations published previously among veterans referred for exercise testing[20]: we defined patients with cardiovascular and/or pulmonary disease as those with a history of angiographically-documented coronary artery disease, myocardial infarction, coronary bypass surgery, coronary angioplasty, congestive heart failure, peripheral vascular disease, or an abnormal exercise test response suggesting coronary artery disease ($\geq$1.0 mm ST-segment depression, exercise-induced angina, or both). Seven percent of the population also had a history of mild pulmonary disease defined as diagnosed obstructive disease not requiring medications or obviously limiting exercise; these subjects were included in the diseased group (n = 3679). All others were classified as normal (n = 2534).

Follow-up

The Social Security Death Index was used to match all of the patients by use of name and social security number. The index is updated weekly and current information was used. Death status was determined as of July 2000 and was complete. Unfortunately, we do not have cause of death or other follow-up information on our patients.

Statistical analysis

Number Crunching System Software (Salt Lake City, Utah) was used for all statistical analyses after transferring the data from an ACCESS (Microsoft, Redmond, Wash) database. Demographics, medical history, and clinical and exercise test findings were compared between those with and without EIVAs. The t test and χ^2 analysis were used to compare variables univariately. Survival analysis was performed by use of Kaplan Meier curves to compare variables and cut-points, and log rank tests were used to assess whether statistically significant differences in survival were present. Total (all-cause) mortality was used as the end point for survival analysis. Censoring was not performed because data regarding subsequent interventions were not available for all patients. The age-adjusted hazard ratios for EIVAs along with the 95% CIs were calculated from a Cox proportional hazards model adjusted for age.

A Cox proportional hazards model was used to determine which variables were independently and significantly associated with time to death. Hazard ratios were calculated along with their 95% CIs. Risk factors that were entered into the Cox model to predict mortality included age, presence of cardiovascular and pulmonary disease (with the exception of exercise-induced ischemia), history of hypertension, diabetes, current smoking habit, resting tachycardia, resting PVCs, resting ST-segment depression, ECG left ventricular hypertrophy with ST depression (strain), poor exercise capacity (<5 METs), maximum heart rate <85% of age-predicted value (chronotropic incompetence), exercise-induced ST depression and/or angina and EIVAs.

Table I. Prevalence of EIVAs based on patient demographics, medical history, ECG findings, and exercise test findings

Variable	Total	EIVA−	EIVA+	*P*
Total	6213	5710 (92%)	503 (8%)	<.001
Age (y)	59 ± 11	59 ± 11	64 ± 11	<.001
Race (%)				
White	74	73	77	NS
African American	12	12	10	NS
Height (in)	69.3 ± 3.6	69.3 ± 3.5	69.3 ± 4.4	NS
Weight (lbs)	190.8 ± 36.8	191.2 ± 36.7	186.9 ± 37.2	.013
BMI	28.0 ± 5.0	28.1 ± 5.0	27.4 ± 4.7	.007
In-patients (%)	25	25	27	NS
Deaths (%)	20	19	29	<.001
Clinical findings				
Q wave (%)	18	18	21	NS
Resting ST-depression (%)	11	10	19	<.001
ECG LVH with ST depression (%)	2	2	4	0.003
RBBB (%)	4	4	5	NS
LBBB (%)	1	1	2	.012
Atrial fibrillation (%)	2	2	7	<.001
Resting PVCs (%)	4	3	20	<.001
Resting heart rate (beats/min)	78 ± 23	78 ± 23	78 ± 16	NS
Resting SBP (mm Hg)	134 ± 22	133 ± 21	138 ± 26	<.001
Resting DBP (mm Hg)	82 ± 16	82 ± 16	82 ± 12	NS
Medical history (%)				
Cardiovascular disease	59	58	72	<.001
CHF	8	8	18	<.001
MI	29	29	36	<.001
Pulmonary disease	7	7	8	NS
Hypertension	48	48	50	NS
Current smoking	31	31	24	<.001
Diabetes	11	11	9	NS
PTCA and/or stent	6	6	7	NS
Bypass surgery	9	9	13	<.001
Medications (%)				
Digoxin	5	5	12	<.001
Calcium-channel blocker	27	27	32	.008
β-Blocker	19	19	19	NS
Nitrates	23	23	25	NS
Antihypertensives	24	24	29	.003
Antiarrhythmics	2	2	4	<.001
Exercise test findings				
Angina occurred (%)	18	17	22	.005
Angina reason for stopping (%)	6	6	9	.009
Exercise-induced ST depression (%)	25	24	35	<.001
Exercise-induced ischemia (angina and/or ST depression) (%)	34	33	45	<.001
METs	8.2 ± 3.7	8.2 ± 3.7	7.3 ± 3.3	<.001
Perceived exertion rate	17 ± 3	17 ± 3	17 ± 2	NS
Maximum heart rate (beats/min)	137 ± 28	137 ± 28	136 ± 25	NS
Maximum SBP (mm Hg)	178 ± 30	178 ± 30	178 ± 31	NS
Maximum DBP (mm Hg)	86 ± 20	86 ± 19	88 ± 32	.016

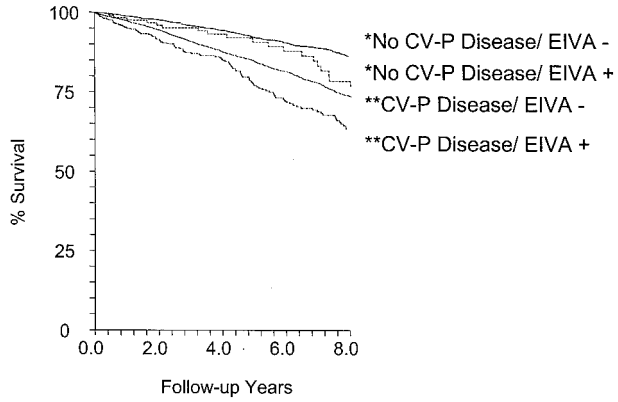
BMI, Body mass index; *RBBB*, right bundle branch block; *LBBB*, left bundle branch block; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *CHF*, congestive heart failure; *MI*, myocardial infarction; *NS*, not significant.

Results

Prevalence

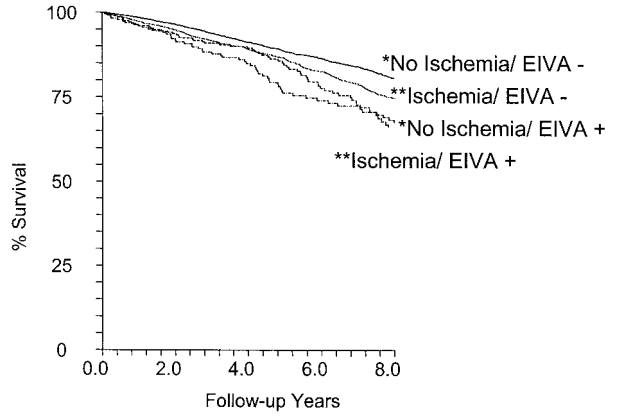
Of the 6213 male veterans included in the study, none had frequent PVCs at rest. Patient demographics and the prevalence of cardiovascular comorbidities, and clinical and exercise test findings are described in Table I. EIVAs were present in 503 patients (8%). Patients with EIVAs were older and were more likely to have cardiovascular and/or pulmonary disease, resting PVCs, and exercise-induced ischemia (exercise test induced abnormal ST depression and/or angina) compared with those without EIVAs. Among patients with

Figure 1



Kaplan-Meier curve demonstrating survival in those with or without EIVAs (*EIVA*) in association with the presence or absence of cardiovascular or pulmonary disease (*CV-P*). EIVAs predict mortality in those with and those without cardiovascular or pulmonary disease. *Asterisk*, $P = .025$; *double asterisks*, $P < .001$.

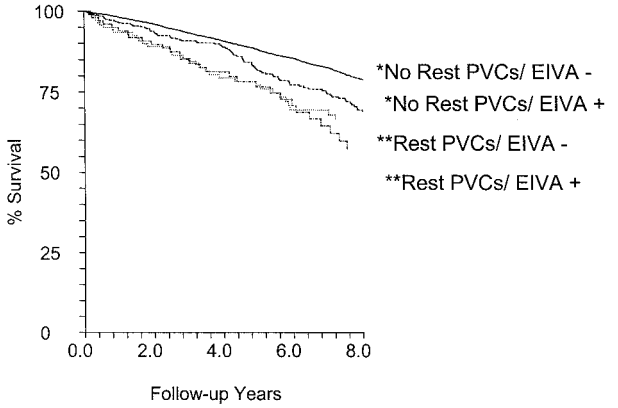
Figure 2



Kaplan-Meier curve demonstrating survival in those with or without EIVAs (*EIVA*) in association with the presence or absence of myocardial ischemia during exercise. EIVAs predict mortality in those with or without exercise-induced myocardial ischemia. *Asterisk*, $P = .002$; *double asterisks*, $P < .001$.

resting PVCs, 101 (41%) developed frequent PVCs or ventricular tachycardia, 88 (36%) had occasional PVCs, and 56 (23%) had suppression of resting PVCs with exercise. Among those with EIVAs during exercise testing, 76 (15%) of the tests were stopped because of arrhythmia, which partially explains the lower MET level.

Figure 3



Kaplan-Meier curve demonstrating survival in those with or without EIVAs (*EIVA*) in association with the presence or absence of *PVCs* at rest. EIVAs predict mortality in those without PVCs at rest, but were not predictive of mortality in those with PVCs at rest.

Survival

The average annual all-cause mortality was 3.2% (mean follow-up 6 ± 4 years). The average annual mortality in those with EIVAs (4.6%) was significantly greater than for those without EIVAs (3.0%) ($P < .001$). The log rank test for determining statistically significant differences in survival demonstrated that, in those with PVCs at rest, survival was similar between those with and without suppression of PVCs with exercise ($P = .665$). A Kaplan Meier survival curve was constructed for those with and without EIVAs according to the presence or absence of cardiovascular and/or pulmonary disease (Figure 1). The Log rank test found that EIVAs predicted mortality in those with ($P < .001$) and without disease ($P = .025$). In the group without disease, the univariate hazard ratio indicated that there was no increased mortality associated with EIVAs at 4-years follow up (1.13 [95% CI 0.66-1.95]); however, at 8-years follow up, EIVAs were a significant predictor of mortality (1.97 [95% CI 1.27-3.04]).

In order to assess the prognostic utility of EIVAs in relation to other clinical findings, Kaplan Meier curves were constructed for those with and without EIVAs in association with the presence or absence of ischemia during exercise (exercise induced angina and/or ST-segment depression) (Figure 2). Log rank tests demonstrated that EIVAs predicted mortality in those with ($P < .001$) and without ($P = .002$) ischemia during exercise testing. Figure 3 presents the Kaplan Meier curves for those with and without EIVAs in association with the presence or absence of resting PVCs. The log

rank tests demonstrated that although EIVAs were predictive in those without resting PVCs ($P < .001$), EIVAs did not predict mortality in those with resting PVCs ($P = .495$).

After adjusting for age, hazard ratios associated with EIVAs demonstrated that EIVAs did not predict mortality in those without cardiovascular and/or pulmonary disease ($P = .241$) and with resting PVCs ($P = .766$) (Table II).

Because prognosis was similar for patients with resting PVCs and those with resting PVCs that became frequent with exercise, these 2 groups were combined into 1 resting PVC group. Demographics, medical history, clinical findings, and exercise test findings were then compared among 3 groups: those with no ventricular ectopy at rest or during exercise, those with EIVAs only, and those with resting PVCs with or without EIVAs. As shown in Table III, those without any ventricular ectopy were younger and had a lower prevalence of cardiovascular or pulmonary disease and exercise-induced ischemia than the other 2 groups. Resting heart rate was greater in those with resting PVCs compared with those with EIVAs only ($P < .001$), and the prevalence of exercise-induced ischemia ($P = .027$) was greatest in those with EIVAs only.

In the Cox hazard multivariate analysis shown in Table IV, both EIVAs and resting PVCs were independent predictors of mortality after considering age, clinical, resting, and exercise test variables. Aside from age, poor exercise capacity (<5 METs) and cardiovascular and pulmonary disease were the strongest predictors of mortality. Exercise-induced ischemia was not found to be an independent predictor of mortality when clinical and other exercise test variables were considered.

Table II. Age-adjusted hazard ratios associated with EIVAs in specific clinical populations

Variable	Hazard ratio (95% CI)	P
Total population	1.33 (1.12-1.59)	.001
Cardiovascular/pulmonary disease −	1.29 (0.84-1.96)	NS
Cardiovascular/pulmonary disease +	1.29 (1.07-1.56)	.009
Exercise-induced ischemia −	1.33 (1.04-1.68)	.023
Exercise-induced ischemia+	1.33 (1.03-1.70)	.027
Rest PVCs −	1.26 (1.03-1.53)	.021
Rest PVCs+	1.07 (0.68-1.69)	NS

Discussion

Previous studies

EIVAs are common during exercise testing, and although researched extensively, their clinical significance remains poorly defined. Previous studies consistently suggest that the prevalence of EIVAs increases in older populations[2,5,6] and in those with cardiovascular disease.[2,4,21] Some studies suggest that EIVAs may result from exercise-induced ischemia, because the prevalence of EIVAs increases in those with ischemia[5,22]; however, other studies refute these results.[6,8,10,23,24]

The prognostic significance of EIVAs has also generated controversy. Some studies have shown that EIVAs are not strong predictors of mortality after recovery from myocardial infarction[8,24] and in patients with coronary artery disease (CAD). In a small study by Nair et al,[25] frequent or complex exercise-induced PVCs did not predict 4-year mortality in patients with CAD. Sami et al[7] and Weiner et al[22] also reported that patients who experienced at least 1 PVC during exercise were not at increased risk of mortality during a 5-year follow-up period. More recently, Schweikert et al[6] found that in patients with CAD with no history of severe ventricular ectopy at rest, exercise-induced frequent or complex PVCs were not predictive of 2-year mortality. Other studies of patients with known or suspected heart disease demonstrate that PVCs during exercise are associated with increased mortality.[3-5] In asymptomatic individuals, studies of those without known heart disease found no association between EIVAs and mortality[10,11]; however, Jouven et al[9] recently reported that asymptomatic males with frequent exercise-induced PVCs had a 2.5-times greater risk of long-term mortality than males without EIVAs.

Inconsistency in study design is largely responsible for the discrepancies in these previous studies. Many earlier studies used small sample sizes and short follow-up periods. Sex of the study population most likely also affected the results. The Framingham study reported that while asymptomatic males with frequent or complex PVCs on ambulatory ECG were at increased risk of mortality, asymptomatic females were not.[26] This study and findings by Jouven et al[9] found EIVAs to be predictive of mortality when male populations were considered. Previous studies have used varying criteria to define EIVAs, with some studies considering EIVAs to be present if any PVC was recorded during exercise. The prevalence of EIVAs will be more reproducible on future exercise tests if frequent or complex PVCs are used as markers for EIVAs instead of occasional PVCs.[24] In addition, others have documented an increased risk of mortality in those with frequent or complex PVCs during exercise compared with those with only occasional PVCs.[3,9] Finally, there is inconsistency in previous reports regarding the inclusion or exclusion of those with resting PVCs.

This study tried to address these limitations. A large sample size was used with a relatively long follow-up. The prognostic significance of EIVAs was compared between those with and without cardiovascular disease by use of the same methodology. Unlike many

Table III. Demographics, medical history, clinical and exercise test findings in those with no ventricular ectopic beats, EIVAs only, and resting PVCs or resting PVCs with EIVAs

Variable	No ventricular ectopy (rest or exercise)	EIVAs only*	Resting PVCs (with or without EIVA)*	*P* (all 3)	*P*
Total	5558 (90%)	402 (7%)	244 (4%)		
Age	59 ± 0.1	64 ± 0.6	64 ± 0.7	<.001	NS
BMI	28.0 ± 0.1	27.5 ± 0.3	28.1 ± 0.3	NS	NS
In-patients	1403 (25%)	112 (28%)	52 (21%)	NS	NS
Medical history (%)					
Cardiovascular/pulmonary disease	58	73	66	<.001	NS
CHF	7	18	16	<.001	NS
MI	29	37	35	<.001	NS
Hypertension	48	51	54	NS	NS
Smoking	31	22	28	<.001	NS
Diabetes	11	9	12	NS	NS
Medications (%)					
Digoxin	5	12	10	<.001	NS
Calcium-channel blocker	27	32	32	.014	NS
β-Blocker	19	19	16	NS	NS
Nitrates	23	25	26	NS	NS
Antihypertensives	24	29	28	.019	NS
Antiarrhythmic	2	4	5	<.001	NS
Clinical findings					
Q wave (%)	18	23	21	.030	NS
Resting ST-segment (%)	10	18	21	<.001	NS
ST-inclusive LVH (%)	2	4	5	<.001	NS
Resting heart rate (beats/min)	78 ± 0.3	76 ± 1	82 ± 1	.009	<.001
Resting SBP (mm Hg)	133 ± 0.3	138 ± 1.1	135 ± 1.4	<.001	NS
Resting DBP (mm Hg)	82 ± 0.2	82 ± 0.8	81 ± 1.0	NS	NS
Exercise test findings					
Angina (%)	17	23	17	.008	NS
Abnormal ST depression (%)	24	37	28	<.001	.016
Exercise-induced ischemia (%)	33	46	37	<.001	.027
METs	8.2 ± 0.05	7.5 ± 0.2	7.1 ± 0.2	<.001	NS
Age-adjust exercise capacity	89 ± 0.5	88 ± 2	85 ± 2	NS	NS
Maximum heart rate (beats/min)	137 ± 0.4	136 ± 1.4	138 ± 1.8	NS	NS
Maximum SBP (mm Hg)	178 ± 0.4	179 ± 1.5	175 ± 1.9	NS	NS
Maximum DBP (mm Hg)	86 ± 0.3	88 ± 1.0	87 ± 1.3	NS	NS

**P* value for EIVAs only and resting PVC with or without EIVAs groups.

previous studies, ours took into consideration the presence of exercise-induced ischemia and resting PVCs when determining the prognostic utility of EIVAs.

Cardiovascular disease

We confirmed that the prevalence of EIVAs increased in those who have cardiovascular and/or pulmonary disease. By use of the log rank statistic, EIVAs were found to be predictive of mortality in those with and without disease. Although EIVAs were not a marker of mortality in those without disease after adjusting for age, in a univariate analysis, we found that the risk associated with EIVAs was nonsignificant early in follow up but became significant near the end of follow up. In the study by Jouven et al,[9] EIVAs were long-term predictors of mortality in a healthy population. From these findings we hypothesize that the arrhythmic substrate responsible for EIVAs may pose no immediate risk for mortality, but individuals could become more susceptible to its effects with age. Aging is associated with loss of vagal tone[27] and other processes that can result in myocardial fibrosis and ischemia, potentially lowering the threshold to arrhythmias later in life in those who are initially free of cardiovascular disease.

Exercise-induced ischemia

We found that ischemia (ST depression and/or angina) was associated with EIVAs because ischemia was more prevalent in the "EIVAs only" subgroup compared with those with resting PVCs with or without EIVAs and those with neither rest nor exercise ventricular ectopy. The presence of EIVAs added greater pre-

Table IV. Cox hazard analysis of Predictors of all-cause mortality

Variable	Hazard ratio (95% CI)	*P*
Age (y)	1.05 (1.04-1.06)	<.001
Poor exercise capacity (<5 METs)	1.63 (1.44-1.86)	<.001
Cardiovascular or pulmonary disease (excluding those with only exercise-induced ischemia)	1.57 (1.39-1.78)	<.001
Maximum heart rate <85% age-predicted	1.32 (1.16-1.49)	<.001
Current smoking	1.24 (1.10-1.41)	<.001
Resting ST-segment depression	1.33 (1.13-1.56)	<.001
Rest PVCs	1.46 (1.14-1.87)	.003
Resting tachycardia (>100 beats/min)	1.35 (1.11-1.65)	.003
EIVAs	1.24 (1.03-1.49)	.02
ECG LVH with ST depression (strain)	1.30 (0.96-1.77)	.095
Diabetes	1.12 (0.93-1.34)	.241
Exercise-induced ischemia	0.96 (0.85-1.08)	.518
History of hypertension	0.99 (0.89-1.11)	.924

*Age was entered as a continuous variable and the other variables are dichotomous.

dictive power to the finding of exercise-induced ischemia alone.

Resting PVCs

Our findings indicate that resting PVCs were associated with the development of EIVAs. Although resting PVCs are associated with EIVAs, they do not seem to contribute additional prognostic information to the finding of resting PVCs alone. Further studies investigating EIVAs should differentiate those with resting PVCs from those without resting PVCs because this marker of the arrhythmic substrate impacts on the prevalence and prognostic significance of EIVAs.

Limitations

Our findings are limited in that they are applicable only to men, which could be important due to possible sex differences in the prognostic significance of PVCs. In addition, we only had all-cause mortality data; we did not have specific cause of death nor were we able to censor on cardiovascular interventions. In the study by Jouven et al,[9] EIVAs predicted mortality when both all-cause mortality and cardiovascular mortality were used as end points. Our "apparently healthy" group had no history of cardiovascular or pulmonary disease and had a normal exercise test response, but all of the patients in this group were referred for exercise testing within the Veterans Affairs health care system.[28] However, echocardiograms might have detected cardiac disease in a portion of them either initially or during follow up.

Further limitations relate to our a priori determined coding of PVCs. Although this is a strength for hypothesis testing, we were unable to go back and recode our data. In fact, this strengthens our findings and supports further work in this area by now most assuredly considering resting PVCs. Our data were coded in terms of whether EIVAs were occasional or frequent in nature, but we did not precisely quantify the PVC rate at rest or during exercise, and therefore we could not determine the rate of increase with exercise. We did not code exercise PVCs as appearing solely during recovery and we did not code PVC morphology. Further investigations should examine how the morphology of EIVAs affects prognosis and, for those with PVCs at rest, whether the rate of increase of PVCs with exercise further influences mortality.

Finally, the increase in mortality associated with PVCs that we found was modest (slightly >1% annually) and there is no established therapy, making our findings of limited clinical significance.

Conclusion

Because EIVAs are associated with an increased risk for death, health professionals should encourage men with EIVAs, particularly those with known cardiopulmonary disease, to receive regular health maintenance, comply with established therapies, and to aggressively modify risk factors. Patients without cardiopulmonary disease should be reassured that EIVAs present no immediate risk but be reevaluated after 5 years.

References

1. Gibbons RJ, Balady GJ, Beasley JW, et al. ACC/AHA guidelines for exercise testing: a report of the American College of Cardiology/American Heart Association Task force on Practice Guidelines. J Am Coll Cardiol 1997;30:260-311.
2. McHenry PL, Fisch C, Jordan JW, et al. Cardiac arrhythmias observed during maximal treadmill exercise testing in clinically normal men. Am J Cardiol 1972;29:331-6.
3. Udall JA, Ellestad MH. Predictive implications of ventricular premature contractions associated with treadmill stress testing. Circulation 1977;56:985-9.
4. Califf RM, McKinnes RA, McNeer R, et al. Prognostic value of ventricular arrhythmias associated with treadmill testing in patients studied with cardiac catheterization for suspected ischemic heart disease. J Am Coll Cardiol 1983;2:1060-7.
5. Marieb MA, Beller GA, Gibson RS, et al. Clinical relevance of exercise-induced ventricular arrhythmias in suspected coronary artery disease. Am J Cardiol 1990;66:172-8.
6. Schweikert RA, Pashkow FJ, Snader CE, et al. Association of exercise-induced ventricular ectopic activity with thallium myocardial perfusion and angiographic coronary artery disease in stable, low-risk populations. Am J Cardiol 1999;83:530-4.
7. Sami M, Chaitman B, Fisher L, et al. Significance of exercise-induced ventricular arrhythmia in stable coronary artery disease: a coronary artery surgery study project. Am J Cardiol 1984;54:1182-8.
8. Casella G, Pavesi PC, Sangiorgio P, et al. Exercise-induced ventricular arrhythmias in patients with healed myocardial infarction. Int J Cardiol 1993;40:229-5.

9. Jouven X, Zureik M, Desnos M, et al. Long-term outcome in asymptomatic men with exercise-induced premature ventricular depolarizations. N Engl J Med 2000;343:826-33.
10. Busby MJ, Shefrin EA, Fleg JL. Prevalence and long-term significance of exercise-induced frequent or repetitive ventricular ectopic beats in apparently healthy volunteers. J Am Coll Cardiol 1989; 14:1659-65.
11. Froelicher VF, Thomas MM, Pillow C, et al. Epidemiologic study of asymptomatic men screened by maximal treadmill testing for latent coronary artery disease. Am J Cardiol 1974;34:770-6.
12. Froelicher VF, Myers, J. Research as part of clinical practice: use of Windows-based relational data bases. Veterans Health System Journal March 1998;3:10-5.
13. Froelicher VF, Shiu P. Exercise test interpretation system. Physicians and Computers 1996;14:40-4.
14. Wolthuis R, Froelicher VF, Fischer J, et al. New practical treadmill protocol for clinical use. Am J Cardiol 1977;39:697-700.
15. Myers J, Buchanan N, Walsh D, et al. A comparison of the ramp versus standard exercise protocols. J Am Coll Cardiol 1991;17: 1334-42.
16. Myers J, Do D, Herbert W, et al. A nomogram to predict exercise capacity from a specific activity questionnaire and clinical data. Am J Cardiol 1994;73:591-6.
17. Lachterman B, Lehmann KG, Abrahamson D, et al. Recovery only ST-segment depression and the predictive accuracy of the exercise test. Ann Intern Med 1990;112:11-6.
18. American College of Sports Medicine. Guidelines for exercise testing and prescription. 6th ed. Baltimore: Lippincott, Williams, and Wilkins; 2000.
19. Reid M, Lachs M, Freistein A. Use of methodological standards in diagnostic test research. JAMA 1995;274:645-51.
20. Morris CK, Myers J, Froelicher VF, et al. Nomogram based on metabolic equivalents and age for assessing aerobic exercise capacity in men. J Am Coll Cardiol 1993;22:175-82.
21. Faris JV, McHenry PL, Jordan JW, et al. Prevalence and reproducibility of exercise-induced ventricular arrthymias during maximal exercise testing in normal men. Am J Cardiol 1976;37:617-22.
22. Weiner DA, Levine SR, Klein MD, et al. Ventricular arrhythmias during exercise testing: mechanism, response to coronary bypass surgery, and prognostic significance. Am J Cardiol 1984;53:1553-7.
23. McHenry PL, Morris SN, Kavalier M, et al. Comparative study of exercise-induced ventricular arrhythmias in normal subjects and patients with documented coronary artery disease. Am J Cardiol 1976;37:609-16.
24. DeBusk RF, Davidson DM, Houston N, et al. Serial ambulatory electrocardiography and treadmill exercise testing after uncomplicated myocardial infarction. Am J Cardiol 1980;45:547-54.
25. Nair CK, Thomson W, Aronow WS, et al. Prognostic significance of exercise-induced complex ventricular arrhythmias in coronary artery disease with normal and abnormal left ventricular ejection fraction. Am J Cardiol 1984;54:1136-8.
26. Bikkina M, Larson M, Levy D. Prognostic implications of asymptomatic ventricular arrhythmias: the Framingham heart study. Ann Inter Med 1992;117:990-6.
27. Levy WC, Cerqueira MD, Harp GD, et al. Effect of endurance training on heart rate variability at rest in healthy young and older men. Am J Cardiol 1998;82:1236-41.
28. Ashton CM, Petersen NJ, Wray NP, et al. The Veterans Affairs medical care system: hospital and clinic utilization statistics for 1994. Medical Care 1998;36:793-803.