Exercise-Induced Ventricular Arrhythmias and Cardiovascular Death

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Background: Exercise-induced ventricular arrhythmias (EIVA) are frequently observed during exercise testing. However, the clinical guidelines do not specify their significance and so we examined this issue in our population.

Methods: A retrospective analysis of prospectively collected data was performed on 5754 consecutive male veterans referred for exercise testing at two university-affiliated Veterans Affairs Medical Centers. Exercise test responses were recorded and cardiovascular mortality was assessed after a mean follow-up of 6 ± 4 years. EIVA were defined as frequent premature ventricular complexes (PVCs) constituting more than 10% of all ventricular depolarizations during any 30-second ECG recording, or a run of three or more consecutive PVCs during the exercise test or recovery.

Results: EIVA occurred in 426 patients (7.4%). There were 550 (10.6%) cardiovascular deaths during follow-up. Seventy-two (17%) patients with EIVA died of cardiovascular causes, whereas 478 (9.0%) of patients without EIVA died of cardiovascular causes ($P < 0.001$). Patients with EIVA had a higher prevalence of cardiovascular disease, resting PVCs, resting ST depression, and ischemia during exercise than patients without EIVA. In a Cox hazards model adjusted for age, cardiovascular disease, exercise-induced ischemia, ECG abnormalities, exercise capacity and risk factors, EIVA was significantly associated with time to cardiovascular death. The combination of both resting PVCs and EIVA was associated with the highest hazard ratio.

Conclusions: EIVA are independent predictors of cardiovascular mortality after adjusting for other clinical and exercise test variables; combination with resting PVCs carries the highest risk.

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premature ventricular contractions; mortality; exercise testing; prediction; risk

Exercise testing is an important prognostic tool, but the significance of exercise-induced ventricular arrhythmias (EIVA) remains uncertain.¹ Ventricular arrhythmias can be induced by exercise testing in healthy individuals,² but some studies suggest that EIVA confer a poor prognosis³⁻⁵ while others suggest that EIVA are benign.⁶⁻⁸ Although a recent study found that healthy volunteers with EIVA had increased mortality,⁹ earlier studies did not produce similar results.^{10,11} The purpose of this study was to determine the relationship between EIVA and cardiovascular (CV) death in a population of 5754 male veterans referred for exercise testing. We previously found an association between EIVA and all-cause mortality in a similar population.¹²

METHODS

Population

The study population consisted of 5754 consecutive male patients without atrial fibrillation or taking digoxin referred to two clinical exercise laboratories (Long Beach VA, 1987-1991, Palo Alto VA, 1992-2000). Forty-two percent were referred for testing because of angina pectoris, 35% for nonischemic chest pain, resting ECG abnormalities or elevated risk factors, 5% for exercise capacity assessment, 2% for dyspnea on exertion and the rest for miscellaneous reasons. Less than 2% were tested to evaluate arrhythmias.

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Data Collection

All exercise tests were supervised and all tests were read by two of the investigators (VF and JM). A thorough clinical history including medications and risk factors were recorded prospectively at the time of the exercise tests using computerized forms.¹³

Exercise Testing

Patients underwent symptom-limited treadmill testing using progressive protocols with small but frequent incremental steps^{14,15} followed by being placed supine immediately.¹⁶ The recorders that were utilized (Mortara X-scribe, Milwaukee, WI and Burdick Quest, Madison, WI) had arrhythmia sensing that provided tracings automatically and manually as well as freeze/playback capabilities. EIVA was considered to be present if frequent premature ventricular complexes (PVCs) (constituting more than 10% of all ventricular depolarizations during any 30-second ECG recording) or ventricular tachycardia (three or more consecutive PVCs) were visually detected during the exercise test or recovery. Resting PVCs were considered to be present if a PVC was detected in the 10-second ECG prior to exercise.

Cardiovascular disease was defined as a history of documented coronary artery disease, myocardial infarction, coronary bypass surgery, coronary angioplasty, congestive heart failure, or peripheral vascular disease.

Follow-Up

The California Death registry was used to match all of the patients using name and social security number. Data on subsequent interventions or non-fatal CV events were not available. Death status was determined as of July 2000.

Statistical Methods

Demographics, medical history, clinical and exercise test findings were compared between individuals with and without EIVA. *t*-Test, chi-square, and ANOVA were used to compare variables. CV mortality was used as the endpoint for survival analysis.

A Cox proportional hazards model was used to determine which variables were independently and significantly associated with time to CV death. Fac-

tors that were entered into the Cox model to predict CV mortality included age, presence of CV and pulmonary disease, history of hypertension, diabetes, current tobacco use, resting PVCs, resting ST segment depression, other ECG abnormalities, METs achieved, maximum exercise heart rate, exercise-induced ST depression, angina, and EIVA.

RESULTS

Prevalence

Patient demographics and exercise test findings are described in Table 1 (by the presence or absence of EIVA). EIVA were present in 426 patients (7.4%). Patients with EIVA were older and were more likely to have CV disease, abnormal ECGs, resting PVCs, and exercise-induced ischemia compared to those without EIVA. Of the 211 patients with resting PVCs, 85 (41%) developed EIVA.

Survival

There were 550 (10.6%) CV deaths during follow-up, as well as 566 deaths from other causes (Table 2). Seventy-two patients with EIVA (17%) died of CV causes, whereas 478 of patients without EIVA (9.0%) died of CV causes ($P < 0.001$). Of the patients who died of CV causes, 36 (6.5%) had resting PVCs, nearly twice the frequency in survivors ($P < 0.0001$). The total average annual CV mortality was 1.1% with a mean follow-up 6 ± 4 years. The average annual mortality in those with EIVA was 1.8% whereas it was only 1% in patients without EIVA ($P < 0.001$).

In the Cox Hazard multivariate analysis shown in Table 3, both EIVA and the combination of resting PVCs with EIVA were independent predictors of mortality after considering age, clinical, resting, and exercise test variables. PVCs occurring only at rest were significantly associated with CV death when considered univariately with age but were not when the other arrhythmia groups were considered. Whereas the hazard ratio was 1.6 for patients with EIVA ($P < 0.003$), the hazard ratio for both EIVA and resting PVCs was 2.7 ($P < 0.0001$). Because of this result, the patients were classified as without PVCs, with PVCs only at rest, with EIVA only, and with both EIVA and rest PVCs (Table 4).

Patients with both EIVA and rest PVCs had an increased CV mortality of 3.2%, which was significantly higher than in patients with EIVA only ($P < 0.001$). Of the 126 patients with rest PVCs only,

Table 1. Population Demographics with Statistical Comparison between Those with and without Exercise-Induced Arrhythmias

Variable	Total	Without EIVA	With EIVA	P Value
Number	5754	5328	426 (7.4%)	
Age	63.6 ± 10.2	58.3 ± 11.2	63.6 ± 10.2	0.01
Race caucasian	4164 (72%)	3845 (72%)	319 (75%)	NS
African American	717 (12%)	671 (12.6%)	46 (11%)	NS
BMI	28 ± 5	28 ± 5	28 ± 5	NS
Cardiovascular deaths	550 (9.6%)	478 (9.0%)	72 (17%)	<0.001
Clinical findings				
Q wave	1006 (17%)	920 (17%)	86 (20%)	NS
Resting ST-depression	477 (8.3%)	414 (7.8%)	63 (15%)	<0.001
ECG LVH with ST depression	271 (4.7%)	240 (4.5%)	31 (7.3%)	0.01
Right BBB	247 (4.3%)	222 (4.2%)	25 (5.9%)	NS
Resting PVCs	211 (3.7%)	126 (2.4%)	85 (20%)	<0.001
Abnormal ECG	1825 (32%)	1614 (31%)	211 (50%)	<0.001
Resting heart rate	77 ± 15	77 ± 15	77 ± 15	NS
Resting SBP	134 ± 21	133 ± 21	138 ± 21	0.005
Resting DBP	82 ± 12	82 ± 12	82 ± 12	NS
Medical history				
Cardiovascular disease	1918 (33%)	1741 (32.7%)	177 (42%)	<0.001
CHF	154 (2.7%)	127 (2.4%)	27 (6.3%)	<0.001
MI	1219 (21.2%)	1114 (20.9%)	105 (25%)	NS
Pulmonary disease	385 (6.7%)	357 (6.7%)	28 (6.6%)	NS
Hypertension	2750 (48%)	2534 (47%)	216 (51%)	NS
Current smoking	1797 (31%)	1694 (32%)	103 (24%)	0.001
Diabetes	596 (10.4%)	560 (10.5%)	36 (8.5%)	NS
Percutaneous coronary Intervention	354 (6.2%)	325 (6.1%)	29 (6.8%)	NS
Bypass surgery	495 (8.6%)	439 (8.2%)	56 (13%)	<0.001
Medications				
Calcium channel blocker	1551 (27%)	1416 (26.6%)	135 (32%)	0.02
Beta-blocker	1100 (19%)	1016 (19%)	84 (20%)	NS
Nitrates	1313 (23%)	1210 (23%)	103 (24%)	NS
Antihypertensive	1321 (23%)	1203 (23%)	118 (28%)	0.02
Anti-arrhythmic	75 (1.3%)	61 (1.1%)	14 (3.3%)	<0.001
Exercise test findings				
Angina occurred	974 (17%)	883 (17%)	91 (21%)	0.01
Angina reason for stopping	346 (6.0%)	308 (5.8%)	38 (8.9%)	0.01
Exercise-induced ST depression	1339 (23%)	1203 (22.6%)	136 (32%)	<0.001
Exercise-induced ischemia (angina and/or ST depression)	1836 (32%)	1660 (31%)	176 (41%)	<0.001
METs	8.3 ± 3.7	8.3 ± 3.7	7.6 ± 3.3	NS
Borg perceived exertion scale (6–20)	17 ± 3	17 ± 2	17 ± 2	NS
Max heart rate	137 ± 25	137 ± 25	136 ± 23	NS
Max SBP	179 ± 29	179 ± 29	180 ± 27	NS
Annual CV mortality	1.1%	1.0%	2.0%	<0.001

there were 18 CV deaths during the follow-up period, which represented an annualized mortality of 2.3% (Fig. 1).

DISCUSSION

Previous studies suggest that the prevalence of EIVA increases in older populations^{2,5,6} and in those with CV disease,^{2,4,17} and our findings are consistent with these. Some studies suggest that

EIVA may result from exercise-induced ischemia since the prevalence of EIVA increases in those with ischemia;^{5,18} however, other studies refute these results.^{6,8,10,19,20} In our population, ischemia was more prevalent in patients with EIVA.

The significance of resting PVCs in apparently healthy patients is somewhat controversial; while many studies have found a favorable prognosis,^{21–23} others have found increased risk of CV events.^{24,25} Resting PVCs only in our population

Table 2. Demographics of Study Population According to Outcomes

Variable	Survivors	CV Death	P	All Other Deaths	P
Total	4638	550		566	
Age	58 ± 11	64 ± 9	<0.001	63 ± 10	<0.001
Race caucasian	3298 (71%)	423 (77%)	0.003	443 (78%)	<0.001
African American	604 (13%)	54 (9.8%)	0.035	59 (10%)	NSD
BMI	28 ± 5	27 ± 5	<0.001	27 ± 5	<0.001
In patients	1039 (22%)	195 (35%)	<0.001	194 (34%)	<0.001
Clinical findings					
Q wave	711 (15%)	173 (31%)	<0.001	122 (22%)	<0.001
Resting ST-depression	305 (6.5%)	112 (20%)	<0.001	60 (11%)	<0.001
ECG LVH with ST depression	189 (4.1%)	56 (10%)	<0.001	26 (4.6%)	NS
Right BBB	171 (3.7%)	33 (6%)	0.011	43 (7.6%)	<0.001
Resting PVCs	153 (3.3%)	36 (6.5%)	<0.001	22 (3.9%)	NS
Abnormal ECG	1292 (28%)	301 (55%)	<0.001	232 (41%)	<0.001
Resting heart rate	76.9 ± 14.8	76.7 ± 15.0	NSD	80.7 ± 16.6	<0.001
Resting SBP	133.7 ± 22.8	134.6 ± 22.6	NSD	132.4 ± 22.9	NS
Medical history					
Cardiovascular disease	1369 (30%)	330 (60%)	<0.001	219 (39%)	<0.001
CHF	95 (2.0%)	39 (7.1%)	<0.001	20 (3.5%)	0.03
MI	883 (19%)	236 (43%)	<0.001	150 (27%)	<0.001
Pulmonary Disease	270 (5.9%)	50 (9.1%)	0.003	65 (11%)	<0.001
Hypertension	2176 (47%)	324 (59%)	<0.001	250 (44%)	NSD
Current smoking	1435 (30.9%)	164 (29.8%)	NSD	198 (35%)	0.05
Diabetes	466 (10%)	73 (13%)	0.022	57 (10%)	NSD
Percutaneous coronary intervention	286 (6.2%)	38 (6.9%)	NSD	30 (5.3%)	NSD
Bypass surgery	339 (7.3%)	118 (21%)	<0.001	38 (6.7%)	NSD
Medications					
Calcium channel blocker	1146 (25%)	242 (44%)	<0.001	163 (29%)	0.04
Beta-blocker	857 (18%)	135 (25%)	<0.001	108 (19%)	NSD
Nitrates	896 (19%)	238 (43%)	<0.001	179 (32%)	<0.001
Antihypertensive	965 (21%)	207 (38%)	<0.001	149 (26%)	0.002
Anti-arrhythmic	50 (1.1%)	14 (2.5%)	0.006	11 (1.9%)	NSD
Exercise test findings					
Angina occurred	749 (16%)	132 (24%)	<0.001	93 (16%)	NSD
Angina reason for stopping	263 (5.7%)	51 (9.3%)	0.001	32 (5.7%)	NSD
Exercise induced ST depression	761 (16%)	73 (13%)	<0.001	73 (13%)	0.02
Exercise-induced ischemia	1394 (30%)	262 (46%)	<0.001	180 (32%)	NSD
Maximal heart rate	139.3 ± 24.3	124.1 ± 23.6	<0.001	130.6 ± 13.2	<0.001
Borg score	17.2 ± 2.5	17.0 ± 2.4	NSD	17.3 ± 2.6	NSD
METs	8.6 ± 3.5	6.4 ± 3.4	<0.001	6.9 ± 3.7	<0.001
Max SBP	180.3 ± 28.6	171.0 ± 31.5	<0.001	174.0 ± 30.2	<0.001
EIVA only	255 (5.5%)	54 (10%)	<0.001	32 (5.7%)	NSD
EIVA and rest PVCs	57 (1.2%)	18 (3%)	<0.001	10 (1.8%)	NSD

Statistical comparisons between survivors and those with CV death and then between survivors and all other deaths; Exercise-induced ischemia = angina and/or ST depression.

have been associated with CV death even when age adjusted and we assume that PVCs at any time are associated with increased risk whether during rest or exercise.

Some studies have shown that EIVA are not strong predictors of mortality following recovery from myocardial infarction^{8,20} and in patients with coronary artery disease.^{6,7,18,26} However, other studies of patients with known or suspected heart disease demonstrate that PVCs during exercise are

associated with increased mortality.³⁻⁵ In a very large sample of CAD patients, EIVA during recovery were the strongest predictor of death.²⁷

Inconsistency in study design is largely responsible for the discrepancies in these previous studies and perhaps gender differences.²⁸ Our data were coded in terms of whether EIVA were occasional or frequent in nature, but we did not precisely quantify the PVC rate at rest or during exercise or recovery and therefore we could not determine

Table 3. Multivariate Analysis of Predictors of Cardiovascular Death

Variable	Hazard Ratio	P Value
Age (years)	1.03 (1.02–1.04)	<0.001
Exercise capacity (Mets)	0.90 (0.87–0.93)	<0.001
Cardiovascular disease	1.9 (1.6–2.3)	<0.001
Maximum heart rate	0.99 (0.98–1.0)	0.002
Resting ST-segment depression	1.4 (1.2–1.7)	<0.001
ECG LVH with ST depression	2.0 (1.5–2.7)	<0.001
Diabetes	1.3 (1.03–1.7)	0.03
History of hypertension	1.4 (1.2–1.7)	<0.001
EIVA only (n = 341)	1.6 (1.1–2.1)	0.002
EIVA w/ rest (n = 85)	2.7 (1.7–4.3)	<0.001

Pulmonary disease, resting heart rate, currently smoking, and exercise-induced ischemia were entered into the model but not chosen.

the rate of increase with exercise. Future investigators should examine how the morphology and exact quantification of EIVA affects prognosis.

CONCLUSION

Exercise-induced ventricular arrhythmias are associated with an increased risk of cardiovascular death. While other patterns could not be evaluated, patients with both rest PVCs and EIVA are at highest risk. These findings support the need for additional research to direct the clinician by further stratifying the risk.

For the clinician, our study demonstrates that EIVA carry an increased risk independent of disease and other test responses. Until future studies help in stratification and treatment, all the physician can do is tell patients the truth. EIVA are

Table 4. Demographics of Patients According to Arrhythmia Classification

Variable	EIVA Only	Rest Only	EIVA w/rest PVCs	P Value
Total	341	126	85	
Age	63 ± 10	63 ± 10	64 ± 10	NSD
BMI	28 ± 4	29 ± 5	27 ± 6	0.04
Medical history				
Cardiovascular disease	147 (43%)	53 (42%)	30 (35%)	<0.001
CHF	21 (6.2%)	5 (3.9%)	6 (7.1%)	<0.005
MI	84 (24.3%)	33 (26%)	21 (25%)	NSD
HBP	174 (51%)	69 (55%)	42 (49%)	NSD
Smoking	75 (22%)	37 (29%)	28 (33%)	<0.001
Diabetes	29 (8.5%)	14 (11%)	7 (8.2%)	<0.001
Medications				
Calcium channel blocker	107 (31%)	42 (33%)	28 (33%)	NSD
Beta-blocker	66 (19%)	19 (15%)	18 (1.2%)	<0.001
Nitrates	84 (25%)	32 (25%)	19 (22%)	NSD
Antihypertensives	94 (28%)	29 (23%)	24 (28%)	NSD
Anti-arrhythmic	9 (2.6%)	4 (3.2%)	5 (5.9%)	NSD
Clinical Findings				
Q wave	75 (22%)	30 (24%)	11 (13%)	<0.001
Resting ST-segment	49 (14%)	19 (15%)	14 (16%)	NSD
ST-inclusive LVH	23 (6.7%)	6 (4.8%)	8 (9.4%)	<0.001
Resting HR	75 ± 15	81 ± 14	84 ± 15	<0.001
Resting SBP	138 ± 21	134 ± 20	137 ± 21	NSD
Resting DBP	82 ± 13	81 ± 12	82 ± 11	NSD
Exercise Test Findings				
Angina occurred	77 (23%)	19 (15%)	14 (16.5%)	<0.001
Abnormal ST depression	113 (33%)	31 (25%)	23 (27%)	<0.001
Exercise-induced ischemia	146 (43%)	40 (32%)	30 (35%)	<0.001
METs	7.7 ± 3.3	7.5 ± 3.0	7.0 ± 3.3	NSD
Maximum heart rate	136 ± 23	138 ± 20	136 ± 22	NSD
Maximum SBP	181 ± 27	178 ± 27	176 ± 27	NSD
Maximum DBP	86 ± 16	86 ± 16	89 ± 13	NSD
Annual CV mortality	1.8%	2.3%	3.2%	-

Statistical comparisons among all three groups; exercise-induced ischemia = angina and/or ST depression.

Figure 1. Kaplan-Meier survival curves for the patient groups: 1—no PVCs, 2—rest PVCs only, 3—exercise PVCs only, and 4—both rest and exercise PVCs. The numbers in the parentheses are the annual mortalities.

not to be ignored and should lead to additional testing, risk factor modification, and/or closer follow-up. Our study has resolved any controversy of the risk of EIVA in patients seen in a typical medical center exercise lab.

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