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Frequent Ventricular Ectopy after Exercise as a Predictor of Death

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ABSTRACT

BACKGROUND

Exercise-induced ventricular ectopy predicts an increased risk of death in population-based cohorts. We sought to examine in a clinical cohort the prognostic importance of ventricular ectopy immediately after exercise, when reactivation of parasympathetic activity occurs. We hypothesized that ventricular ectopy after exercise (i.e., during the recovery phase) would predict an increased risk of death better than ventricular ectopy during exercise.

METHODS

We studied 29,244 patients (mean [±SD] age, 56±11 years; 70 percent men) who had been referred for symptom-limited exercise testing without a history of heart failure, valve disease, or arrhythmia. Frequent ventricular ectopy was defined by the presence of seven or more ventricular premature beats per minute, ventricular bigeminy or trigeminy, ventricular couplets or triplets, ventricular tachycardia, ventricular flutter, torsade de pointes, or ventricular fibrillation.

RESULTS

Frequent ventricular ectopy occurred only during exercise in 945 patients (3 percent), only during recovery in 589 (2 percent), and during both exercise and recovery in 491 (2 percent). There were 1862 deaths during a mean of 5.3 years of follow-up. Frequent ventricular ectopy during exercise predicted an increased risk of death (five-year death rate, 9 percent, vs. 5 percent among patients without frequent ventricular ectopy during exercise; hazard ratio, 1.8; 95 percent confidence interval, 1.5 to 2.1; $P<0.001$), but frequent ventricular ectopy during recovery was a stronger predictor (11 percent vs. 5 percent; hazard ratio, 2.4; 95 percent confidence interval, 2.0 to 2.9; $P<0.001$). After propensity matching for confounding variables, frequent ventricular ectopy during recovery predicted an increased risk of death (adjusted hazard ratio, 1.5; 95 percent confidence interval, 1.1 to 1.9; $P=0.003$), but frequent ventricular ectopy during exercise did not (adjusted hazard ratio, 1.1; 95 percent confidence interval, 0.9 to 1.3; $P=0.53$).

CONCLUSIONS

Frequent ventricular ectopy during recovery after exercise is a better predictor of an increased risk of death than ventricular ectopy occurring only during exercise.

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THE CLINICAL IMPORTANCE OF VENTRICULAR ectopy during exercise stress testing is uncertain. There is conflicting evidence about the relation of exercise-induced ventricular ectopy to coronary artery disease or to cardiovascular risk.[1-10] The prognostic implications of when ventricular ectopy occurs (i.e., during or after exercise) have not been well characterized.

Recent work has established that vagal reactivation normally occurs in the early period of recovery, immediately after exercise.[11] In the absence of normal vagal reactivation, heart-rate recovery is attenuated, with an associated increase in mortality.[12-15] Therefore, attenuated vagal reactivation during recovery might be associated with ventricular ectopy that is not suppressed. Accordingly, we prospectively studied the hypothesis that ventricular ectopy during recovery would be a stronger predictor of an increased risk of death than ectopy that occurred during exercise.

METHODS

STUDY DESIGN

Consecutive patients referred for symptom-limited treadmill exercise testing at the Cleveland Clinic Foundation in Cleveland between 1990 and 1999 were eligible. Exclusion criteria included an age of less than 30 years, absence of a U.S. Social Security number, symptomatic heart failure or use of digoxin, valvular disease, end-stage renal disease, presence of a pacemaker, concurrent evaluation for an arrhythmia, a history of cardiac transplantation, atrial fibrillation, heart block, and frequent ventricular ectopy at rest, as defined below. If a patient had undergone more than one treadmill test, only the first test was considered. The resulting study group of 29,244 patients included 2743 patients whom we previously reported on in a study that focused on ventricular ectopy during exercise only and that involved only two years of follow-up.[16] The local institutional review board approved research based on the prospectively obtained computerized clinical data sets from the stress laboratory. The requirement for obtaining informed consent was waived.

The methods by which clinical data are prospectively obtained in our laboratory have been described in detail.[12,13,15,17] Before treadmill testing, all patients undergo a structured interview and chart review. Data are prospectively collected regarding symptoms, risk factors, diagnoses, medicines, and prior cardiac procedures.

The exercise-testing protocols used in our laboratory have been described in detail.[17] The patients undergo symptom-limited exercise testing according to standard protocols. During each stage of exercise, data on heart rate, blood pressure, electrocardiographic changes, and arrhythmias are prospectively recorded.

Chronotropic incompetence was considered present if no more than 80 percent of heart-rate reserve was used by peak exercise in the absence of beta-blocker use.[18] An abnormal heart-rate recovery was defined as failure of the heart rate to fall by more than 12 beats during the first minute after exercise[12,13]; among patients undergoing stress echocardiography, the cutoff value was more than 18 beats per minute.[15] Functional capacity was considered abnormal if the estimated number of metabolic equivalents was fair or poor for age and sex according to a validated scheme.[17] The persons responsible for acquiring data were unaware of the hypothesis of this study or the outcome of the patients.

Information regarding ventricular ectopy was systematically recorded on the resting electrocardiogram as well as during each stage of exercise and recovery according to prespecified definitions. We prospectively defined frequent ventricular ectopy as the presence of seven or more ventricular premature beats per minute during any given stage, ventricular bigeminy, ventricular trigeminy, ventricular couplets, ventricular triplets, sustained or nonsustained ventricular tachycardia, ventricular flutter, torsade de pointes, or ventricular fibrillation. If the patient had more than one of these findings during any given stage of the exercise test, each was recorded individually. This definition of frequent ventricular ectopy was based on previous work by our group, which showed that during exercise it is associated with scintigraphically evident myocardial perfusion defects.[16]

We divided frequent ventricular ectopy into less severe and more severe categories based on the Lown classification.[19] Patients with ventricular triplets, sustained or nonsustained ventricular tachycardia, ventricular flutter, torsade de pointes, or ventricular fibrillation were considered to have more severe ventricular ectopy.

The primary end point was death from all causes, which is an objective, clinically relevant, and unbiased end point.[20,21] The end point of death from all causes was determined with use of the Social Security Death Index.[22-24] The high degree of specificity of the Social Security Death Index has been docu-

mented.[23] We have shown that application of this data base to patients in the Cleveland Clinic stress laboratory results in a sensitivity of 97 percent.[13]

STATISTICAL ANALYSIS

The cohort was divided into four groups, according to the presence or absence of frequent ventricular ectopy during exercise or during the first three minutes of recovery. Differences between groups were tested by the Kruskal–Wallis or the chi-square test. The association of frequent ventricular ectopy with time to death was tested by the construction of Kaplan–Meier curves[25] and by Cox proportional-hazards modeling.[26] The proportional-hazards assumption was confirmed by means of a time-dependent interaction covariate and by examination of weighted Schoenfeld residuals.

Although multivariable regression modeling is used to account for base-line differences, it may lead to invalid conclusions when those base-line differences are marked or numerous.[27,28] We therefore constructed nonparsimonious logistic-regression models[29] in which ventricular ectopy during exercise or during recovery was a dependent variable and the variables listed in Table 1 were independent variables. For the model in which ventricular ectopy during recovery was the dependent variable, ventricular ectopy during exercise was included as an additional independent variable. Similarly, for the model in which ventricular ectopy during exercise was the dependent variable, ventricular ectopy during recovery was included as an additional independent variable. These models made possible the calculation of a propensity score,[27] indicating the likelihood that any individual patient would have ventricular ectopy, given all other known variables except outcome. Patients with and without ventricular ectopy were then matched on the basis of their propensity score.[30]

All analyses were performed with SAS software (version 8.2, SAS).

RESULTS

Among 29,244 patients, 945 (3 percent) had frequent ventricular ectopy only during exercise, 589 (2 percent) had frequent ventricular ectopy only during recovery, and 491 (2 percent) had frequent ventricular ectopy during both exercise and recovery. The clinical and exercise-related characteristics of the patients according to the timing of frequent ventricular ectopy are shown in Table 1. Patients who had frequent ventricular ectopy during exercise or recovery were older and more likely to have coronary artery disease than patients who did not have frequent ventricular ectopy during exercise or recovery; there were multiple other differences as well.

Specific arrhythmias noted during exercise included frequent ventricular premature beats in 933 (3 percent), ventricular bigeminy in 386 (1 percent), ventricular trigeminy in 150 (0.5 percent), ventricular couplets in 92 (0.3 percent), ventricular triplets in 330 (1 percent), nonsustained ventricular tachycardia in 164 (0.6 percent), and sustained ventricular tachycardia in 4 (0.01 percent). Specific arrhythmias noted during recovery included frequent ventricular premature beats in 742 (3 percent), ventricular bigeminy in 315 (1 percent), ventricular trigeminy in 133 (0.5 percent), ventricular couplets in 45 (0.2 percent), ventricular triplets in 154 (0.5 percent), nonsustained ventricular tachycardia in 91 (0.3 percent), sustained ventricular tachycardia in 4 (0.01 percent), ventricular fibrillation in 2 (0.01 percent), and torsade de pointes in 1 (<0.01 percent). More severe ventricular ectopy was noted in 22 percent of patients who had ventricular ectopy only during exercise, 15 percent of those who had ventricular ectopy only during recovery, and 12 percent of those who had ventricular ectopy during both exercise and recovery ($P<0.001$).

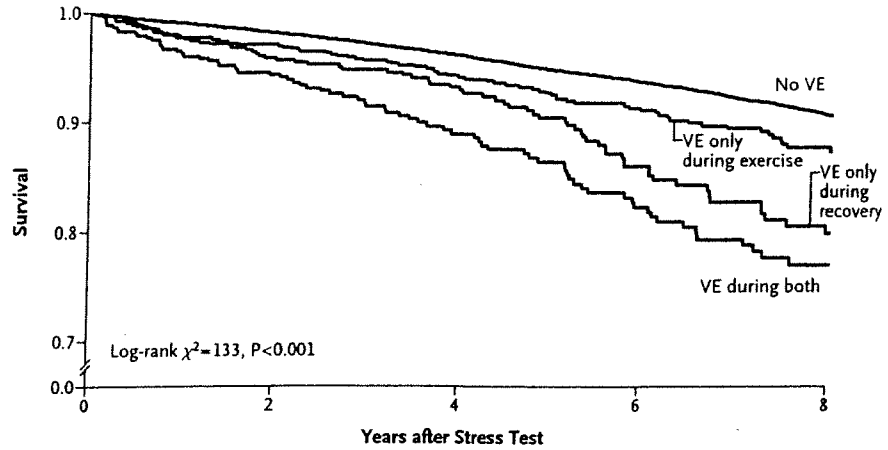
During a mean follow-up of 5.3 years, there were 1862 deaths. Among patients with frequent ventricular ectopy only during exercise, there were 81 deaths; among those with frequent ectopy only during recovery, there were 68 deaths; and among those with frequent ectopy during both exercise and recovery, there were 79 deaths. Frequent ventricular ectopy during exercise predicted a higher likelihood of death (five-year death rate, 9 percent, vs. 5 percent in patients without frequent ventricular ectopy during exercise; hazard ratio, 1.8; 95 percent confidence interval, 1.5 to 2.1; $P<0.001$), and frequent ventricular ectopy during recovery was associated with an even higher estimated likelihood of death (five-year death rate, 11 percent vs. 5 percent; hazard ratio, 2.4; 95 percent confidence interval, 2.0 to 2.9; $P<0.001$). Patients with frequent ventricular ectopy during recovery had the lowest survival rates, whereas those who had frequent ventricular ectopy only during exercise had a slightly lower survival rate than those who had no ventricular ectopy (Fig. 1).

After adjustment for the variables listed in Table 1 and for frequent ventricular ectopy during exercise, frequent ventricular ectopy during recovery

Table 1. Base-Line and Exercise-Related Characteristics of the Study Patients According to the Timing of Frequent Ventricular Ectopy.*

Variable	None (N=27,219)	Only during Exercise (N=945)	Only during Recovery (N=589)	During Both Exercise and Recovery (N=491)	P Value†
Demographic characteristics					
Age — yr	56±11	60±11	61±11	62±11	<0.001
Male sex — no. (%)	18,987 (70)	763 (81)	464 (79)	397 (81)	<0.001
Clinical history — no. (%)					
Diabetes, insulin-treated	851 (3)	18 (2)	23 (4)	17 (3)	0.11
Diabetes, not insulin-treated	2,032 (7)	85 (9)	55 (9)	38 (8)	0.12
Hypertension	10,023 (37)	393 (42)	263 (45)	246 (50)	<0.001
Tobacco use	4,844 (18)	142 (15)	95 (16)	98 (20)	0.06
Known coronary artery disease	8,372 (31)	387 (41)	290 (49)	259 (53)	<0.001
Prior coronary-artery bypass grafting	3,289 (12)	177 (19)	130 (22)	127 (26)	<0.001
Prior percutaneous coronary intervention	2,813 (10)	116 (12)	107 (18)	73 (15)	<0.001
Prior Q-wave myocardial infarction	2,264 (8)	106 (11)	90 (15)	77 (16)	<0.001
Prior myocardial infarction	4,231 (16)	195 (21)	173 (29)	167 (34)	<0.001
Medication use — no. (%)					
Beta-blocker	4,670 (17)	158 (17)	144 (24)	124 (25)	<0.001
Diltiazem or verapamil	3,326 (12)	128 (14)	84 (14)	69 (14)	0.17
Nifedipine	2,069 (8)	96 (10)	62 (11)	57 (12)	<0.001
ACE inhibitor	2,718 (10)	92 (10)	78 (13)	67 (14)	0.003
Lipid-lowering agent	3,503 (13)	124 (13)	109 (19)	89 (18)	<0.001
Aspirin	8,538 (31)	355 (38)	264 (45)	217 (44)	<0.001
Cardiovascular assessment and exercise capacity					
Body-mass index‡	28±5	29±6	28±5	29±5	0.16
Resting heart rate — beats/min	75±14	73±14	73±14	73±15	<0.001
Resting blood pressure — mm Hg					
Systolic	133±20	138±21	137±21	141±23	<0.001
Diastolic	86±11	87±11	86±11	87±11	<0.001
Peak exercise capacity — MET					
Men	9.5±2.5	9.1±2.3	8.5±2.6	8.3±2.4	<0.001
Women	7.3±2.1	7.0±2.0	6.9±2.1	6.2±2.0	<0.001
Abnormal heart-rate recovery — no. (%)	5,915 (22)	239 (25)	177 (30)	156 (32)	<0.001
Chronotropic incompetence — no. (%)	4,674 (17)	170 (18)	102 (17)	112 (23)	0.01
Ischemic electrocardiographic changes during or after stress — no. (%)					
ST-segment depression of 1–2 mm	3,137 (12)	157 (17)	81 (14)	76 (15)	<0.001
ST-segment depression of >2 mm	640 (2)	36 (4)	24 (4)	12 (2)	0.002
Physical fitness for age and sex — no. (%)					
Fair	5,579 (20)	173 (18)	123 (21)	112 (23)	0.22
Poor	1,846 (7)	47 (5)	47 (8)	51 (10)	<0.001

* Plus–minus values are means ±SD. ACE denotes angiotensin-converting enzyme, and MET metabolic equivalent.
† P values are for the comparison among all four groups.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.



No. at Risk									
No VE	27,219	26,295	22,900	19,576	16,708	13,971	11,283	9292	6480
VE only during exercise	945	900	840	687	598	504	418	352	255
VE only during recovery	589	564	474	425	331	276	226	162	121
VE during both	491	459	403	329	265	231	190	148	122

Figure 1. Kaplan–Meier Analysis of the Association of Frequent Ventricular Ectopy (VE) Only during Exercise, Only during Recovery from Exercise, or during Both Exercise and Recovery, with Survival.

was a predictor of an increased risk of death (adjusted hazard ratio, 1.6; 95 percent confidence interval, 1.3 to 1.9; P<0.001). Other predictors included older age, male sex, insulin-treated diabetes mellitus, smoking, impaired functional capacity, and attenuated heart-rate recovery (P<0.001 for all comparisons). Frequent ventricular ectopy during exercise did not predict an increased risk of death in this analysis (adjusted hazard ratio, 1.2; 95 percent confidence interval, 1.0 to 1.4; P=0.09).

Propensity matching was performed to match patients with frequent ventricular ectopy during recovery to those who did not have frequent ventricular ectopy during recovery. The C statistic of the logistic-regression model used to generate the propensity score was 0.80. The base-line characteristics of the propensity-matched cohort are shown in Table 2. The two populations were well matched.

The prognostic importance of frequent ventricular ectopy during recovery in this propensity-matched cohort is shown in Figure 2. Patients with frequent ventricular ectopy during recovery had decreased survival, particularly after three to four years of follow-up. After adjustment for the propensity score, frequent ventricular ectopy during exercise, and the other variables listed in Table 2, frequent ventricular ectopy during recovery predicted an increased risk of death (adjusted hazard ratio, 1.5; 95 percent confidence interval, 1.1 to 1.9; P=0.003).

A similar analysis was performed regarding frequent ventricular ectopy during exercise. Frequent ventricular ectopy during exercise was not associated with decreased survival in this propensity-matched cohort (adjusted hazard ratio, 1.1; 95 percent confidence interval, 0.9 to 1.3; P=0.53).

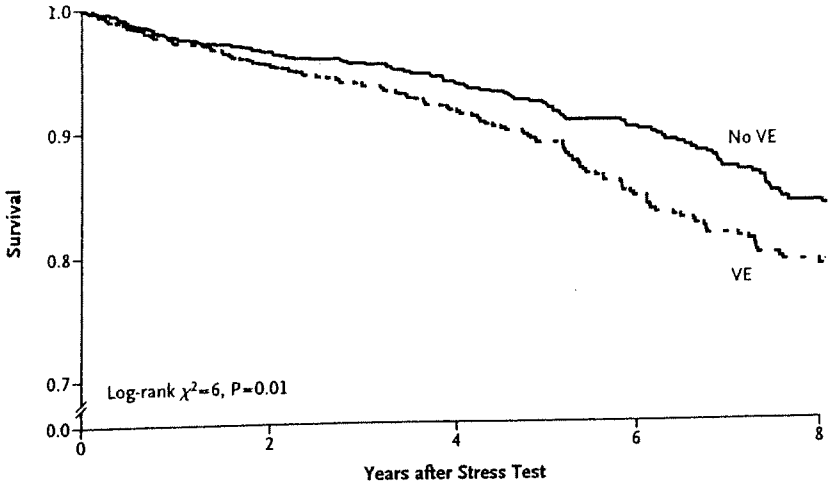
The results of prespecified subgroup analyses are shown in Table 3. Frequent ventricular ectopy during recovery was predictive of an increased risk of death in all subgroups tested. No clinically significant interactions were noted.

More severe ventricular ectopy during recovery from exercise, defined as ventricular triplets or worse, was noted in 128 patients (0.4 percent), whereas 952 (3 percent) had less severe ventricular ectopy. There was a gradient of mortality, in which death rates were lowest among patients without frequent ventricular ectopy (5 percent), higher among those with less severe frequent ventricular ectopy (12 percent), and highest among those with more severe frequent ventricular ectopy (15 percent). In a multivariable Cox regression model that adjusted for the variables listed in Table 1, less severe frequent ventricular ectopy during recovery was predictive of death (adjusted hazard ratio, 1.5; 95 percent confidence interval, 1.3 to 1.8; P<0.001), and more severe frequent ventricular ectopy was associated with a greater risk (adjusted hazard ratio, 2.1; 95 percent confidence interval, 1.4 to 3.3; P<0.001).

Table 2. Base-Line and Exercise-Related Characteristics According to the Presence or Absence of Frequent Ventricular Ectopy during Recovery in Propensity-Matched Groups.*

Variable	No Frequent Ventricular Ectopy during Recovery (N=1072)	Frequent Ventricular Ectopy during Recovery (N=1072)	P Value
Demographic characteristics			
Age — yr	61±11	62±11	0.54
Male sex — no. (%)	858 (80)	853 (80)	0.79
Clinical history — no. (%)			
Diabetes, insulin-treated	32 (3)	39 (4)	0.40
Diabetes, not insulin-treated	101 (9)	93 (9)	0.55
Hypertension	475 (44)	503 (47)	0.22
Tobacco use	193 (18)	192 (18)	0.96
Known coronary artery disease	538 (50)	541 (50)	0.90
Prior coronary-artery bypass grafting	249 (23)	251 (23)	0.92
Prior percutaneous coronary intervention	161 (15)	178 (17)	0.31
Prior Q-wave myocardial infarction	169 (16)	164 (15)	0.77
Prior myocardial infarction	292 (27)	334 (31)	0.05
Medication use — no. (%)			
Beta-blocker	269 (25)	263 (25)	0.76
Diltiazem or verapamil	150 (14)	152 (14)	0.90
Nifedipine	116 (11)	118 (11)	0.89
ACE inhibitor	140 (13)	141 (13)	0.95
Lipid-lowering agent	202 (19)	194 (18)	0.66
Aspirin	485 (45)	473 (44)	0.60
Cardiovascular assessment and exercise capacity			
Body-mass index	28±6	28±5	0.29
Resting heart rate — beats/min	73±14	73±14	0.72
Resting blood pressure — mm Hg			
Systolic	138±21	139±22	0.91
Diastolic	86±11	87±11	0.97
Peak exercise capacity — MET			
Men	8.5±2.5	8.5±2.5	0.64
Women	6.7±2.2	6.6±2.1	0.65
Abnormal heart-rate recovery — no. (%)	331 (31)	326 (30)	0.81
Chronotropic incompetence — no. (%)	214 (20)	212 (20)	0.91
Ischemic electrocardiographic changes during or after stress			
ST-segment depression of 1–2 mm — no. (%)	163 (15)	156 (15)	0.67
ST-segment depression of >2 mm — no. (%)	37 (3)	36 (3)	0.91
Physical fitness for age and sex — no. (%)			
Fair	247 (23)	233 (22)	0.47
Poor	101 (9)	94 (9)	0.60
Frequent ventricular ectopy during exercise — no. (%)	482 (45)	483 (45)	0.97

* Plus–minus values are means ±SD. ACE denotes angiotensin-converting enzyme, and MET metabolic equivalent.



No. at Risk									
No VE	1072	1020	898	769	661	561	442	378	267
VE	1072	1015	868	735	594	505	406	309	219

Figure 2. Kaplan–Meier Analysis of the Association of Frequent Ventricular Ectopy (VE) during Recovery from Exercise with Survival in the Propensity-Matched Cohort.

The cohort was derived by using propensity scores to match patients with ventricular ectopy during recovery to patients who did not have ventricular ectopy during recovery. Of 1080 patients who had ventricular ectopy during recovery, 1072 were matched. The characteristics of the cohort are shown in Table 2.

Data on left ventricular systolic function were available for 6421 patients. The ejection fraction was assessed by simultaneous echocardiography in 4007 patients (mean value, 53±6 percent) and by contrast ventriculography within three months of stress testing in 2414 patients (mean value, 53±6 percent). Impaired left ventricular systolic function, defined as an ejection fraction of 40 percent or less, was present in 751 of 5953 patients without frequent ventricular ectopy (13 percent), 39 of 212 with frequent ventricular ectopy only during exercise (18 percent), 35 of 129 with frequent ventricular ectopy only during recovery (27 percent), and 35 of 127 with frequent ventricular ectopy during both exercise and recovery (28 percent, P<0.001).

There were 485 deaths during follow-up among the patients for whom data on left ventricular systolic function were available. Frequent ventricular ectopy during recovery predicted an increased risk of death among patients with preserved left ventricular systolic function (death rate, 11 percent, vs. 6 percent among those without frequent ventricular ectopy during recovery; hazard ratio, 2.0; 95 percent confidence interval, 1.3 to 3.1; P=0.001) and among patients with depressed left ventricular systolic function (25 percent vs. 14 percent; hazard ratio, 1.8; 95 percent confidence interval, 1.1 to 3.0; P=0.02). No interaction was noted between frequent ventricular ectopy during recovery and left ventricular systolic function in the prediction of an increased risk of death (P=0.78).

In a multivariable Cox regression model that included the variables listed in Table 1 as well as frequent ventricular ectopy during recovery, frequent ventricular ectopy during exercise, and left ventricular ejection fraction, frequent ventricular ectopy during recovery was predictive of an increased risk of death (adjusted hazard ratio, 1.6; 95 percent confidence interval, 1.2 to 2.2; P=0.005), whereas frequent ventricular ectopy during exercise was not (adjusted hazard ratio, 1.1; 95 percent confidence interval, 0.7 to 1.5; P=0.73). Impaired left ventricular systolic function was an independent predictor of an increased risk of death (adjusted hazard ratio, 1.4; 95 percent confidence interval, 1.1 to 1.7; P=0.002).

Among the 4007 patients who underwent exercise echocardiography, evidence of myocardial ischemia was present in 461 (12 percent). Frequent ventricular ectopy during recovery was associated with a higher rate of echocardiographic evidence of ischemia (22 percent, vs. 11 percent in those with-

Table 3. Association between Ventricular Ectopy during Recovery and Mortality in Prespecified Subgroups.

Stratifying Variable	No Frequent Ventricular Ectopy during Recovery	Frequent Ventricular Ectopy during Recovery	Relative Risk (95% CI)*	P Value	P Value for Interaction
	no. of deaths/no. of patients (%)				
Age					
<65 Yr	659/20,798 (3)	42/575 (7)	2.4 (1.8–3.3)	<0.001	0.05
≥65 Yr	1056/7366 (14)	105/505 (21)	1.7 (1.4–2.0)	<0.001	
Sex					
Male	1310/19,750 (7)	127/861 (15)	2.5 (2.1–3.0)	<0.001	0.38
Female	405/8414 (5)	20/219 (9)	2.0 (1.3–3.1)	0.002	
History of coronary artery disease					
No	765/19,405 (4)	43/531 (8)	2.2 (1.6–3.0)	<0.001	0.64
Yes	950/8759 (11)	104/549 (19)	2.1 (1.7–2.5)	<0.001	
Hypertension					
No	833/17,748 (5)	69/571 (12)	2.7 (2.1–3.5)	<0.001	0.07
Yes	882/10,416 (8)	78/509 (15)	2.0 (1.6–2.5)	<0.001	
Diabetes					
No	1326/25,178 (5)	121/947 (13)	2.7 (2.2–3.2)	<0.001	0.03
Yes	389/2986 (13)	26/133 (20)	1.7 (1.1–2.5)	0.014	
Smoking					
No	1341/23,178 (6)	116/887 (13)	2.5 (2.1–3.0)	<0.001	0.52
Yes	374/4986 (8)	31/193 (16)	2.2 (1.5–3.2)	<0.001	
Use of beta-blockers					
No	1353/23,336 (6)	111/812 (14)	2.5 (2.1–3.1)	<0.001	0.23
Yes	362/4828 (7)	36/268 (13)	2.0 (1.4–2.8)	<0.001	
Use of aspirin					
No	1059/19,271 (5)	78/599 (13)	2.6 (2.0–3.2)	<0.001	0.28
Yes	656/8893 (7)	69/481 (14)	2.2 (1.7–2.8)	<0.001	
Use of nondihydropyridine calcium-channel blockers					
No	1330/24,710 (5)	113/927 (12)	2.5 (2.1–3.0)	<0.001	0.48
Yes	385/3454 (11)	34/153 (22)	2.2 (1.5–3.1)	<0.001	
Left bundle-branch block					
No	1655/27,836 (6)	139/1055 (13)	2.4 (2.0–2.9)	<0.001	0.73
Yes	60/328 (18)	8/25 (32)	2.1 (1.0–4.3)	0.05	
Abnormal heart-rate recovery					
No	903/22,010 (4)	67/747 (9)	2.3 (1.8–3.0)	<0.001	0.66
Yes	812/6154 (13)	80/333 (24)	2.1 (1.7–2.7)	<0.001	
Chronotropic response					
Normal	1109/23,320 (5)	103/866 (12)	2.7 (2.2–3.3)	<0.001	0.03
Impaired	606/4844 (13)	44/214 (21)	1.8 (1.3–2.4)	<0.001	
Functional capacity					
Normal	858/20,519 (4)	77/747 (10)	2.7 (2.1–3.4)	<0.001	0.10
Impaired	857/7645 (11)	70/333 (21)	2.0 (1.6–2.6)	<0.001	

* CI denotes confidence interval.

out frequent ventricular ectopy during recovery; P<0.001). There were only 6 deaths among the 34 patients who had both echocardiographic ischemia and frequent ventricular ectopy during recovery, precluding further analyses.

DISCUSSION

In a large cohort of patients referred for exercise stress testing, the occurrence of frequent ventricular ectopy during recovery was strongly predictive of an increased risk of death from all causes over a five-year follow-up period, whereas the occurrence of frequent ventricular ectopy only during exercise was not. This association persisted even after propensity-based adjustment for clinical and exercise characteristics known to predict an increased risk of death.

Until recently, it was thought that exercise-induced ventricular ectopy was not independently related to an increased risk of coronary heart disease, the extent of coronary artery disease, mortality from all causes, or the risk of major cardiac events.[4,8,16,31] However, one recent report showed that among over 6000 asymptomatic men ventricular ectopy during exercise was associated with a relative risk of death from cardiovascular disease of approximately 3 when the cohort was followed for 23 years.[6]

The current study clarifies these previous findings and extends them to a large cohort likely to be representative of patients seen in clinical practice. Because of the size of the study sample, we were able to examine carefully the prognostic importance of frequent ventricular ectopy during and after exercise in large numbers of subjects (more than 1000 patients in each group). The large cohort also made it possible for us to perform propensity matching,[27] thus allowing a more valid comparison of patients with and without frequent ventricular ectopy than would have been possible by standard regression techniques.[28] Finally, our observations were consistent with our a priori hypothesis that frequent ventricular ectopy during recovery would be a stronger predictor of risk than ectopy during exercise, which had been based on the recognition of recovery as a period of rapid vagal reactivation.[11]

Because the cohort was a heterogeneous one, including patients who underwent stress testing with electrocardiography only, with echocardiography, or with nuclear perfusion scintigraphy, we did not have systematic data on left ventricular systolic function and myocardial ischemia in all patients. Nonetheless, it is noteworthy that in the subgroup of 6421 patients for whom ejection-fraction data were available, a low ejection fraction (40 percent or less) was associated with frequent ventricular ectopy during recovery. Furthermore, both ventricular ectopy during recovery and a low ejection fraction were independent predictors of death. We focused on death from all causes and could not differentiate among deaths due to arrhythmias, those due to other cardiac causes, and those due to noncardiac causes. We and others have commented on this issue before, pointing out that only death from all causes can be considered a truly unbiased and objective end point that is also clinically relevant when arrhythmia-related outcomes are studied.[20,21]

How should the finding of an association between frequent ventricular ectopy during recovery from exercise and mortality from all causes be incorporated into clinical practice? Because this was a prospective, observational study, making treatment recommendations on the basis of our results is problematic. Nonetheless, it is clear that frequent ventricular ectopy during recovery is a marker of an increased risk of death. Accordingly, comprehensive risk-factor assessment and aggressive management of the risk factors identified may well be justified in patients with this finding. In addition, the association of asymptomatic left ventricular dysfunction with frequent ventricular ectopy during recovery suggests that echocardiography may be indicated, since treatment of asymptomatic left ventricular dysfunction is of clinical benefit.[32]

Frequent ventricular ectopy during recovery from exercise was found to be an important, independent predictor of an increased risk of death in a large clinical cohort. Frequent ventricular ectopy that occurred only during exercise did not independently predict an increased risk. In accordance with previous findings of a strong relation between attenuated recovery of the heart rate after exercise and an elevated risk of death, these results support the central importance of vagal mediation in cardiac function. They also underscore the value of the exercise stress test as a tool for prognosis and risk stratification.

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REFERENCES

1. Califf RM, McKinnis RA, McNeer JF, et al. Prognostic value of ventricular arrhythmias associated with treadmill exercise testing in patients studied with cardiac catheterization for suspected ischemic heart disease. J Am Coll Cardiol 1983;2:1060-7.
2. Calkins H. Premature ventricular depolarizations during exercise. N Engl J Med 2000;343:879-80.
3. DeMaria AN, Vera Z, Amsterdam EA, Mason DT, Massumi RA. Disturbances of cardiac rhythm and conduction induced by exercise: diagnostic, prognostic and therapeutic implications. Am J Cardiol 1974;33: 732-6.
4. Fleg JL, Lakatta EG. Prevalence and prognosis of exercise-induced nonsustained ventricular tachycardia in apparently healthy volunteers. Am J Cardiol 1984;54:762-4.
5. Goldschlager N, Cake D, Cohn K. Exercise-induced ventricular arrhythmias in patients with coronary artery disease: their relation to angiographic findings. Am J Cardiol 1973;31:434-40.
6. Jouven X, Zureik M, Desnos M, Courbon D, Ducimetière P. Long-term outcome in asymptomatic men with exercise-induced premature ventricular depolarizations. N Engl J Med 2000;343:826-33.
7. Nair CK, Aronow WS, Sketch MH, et al. Diagnostic and prognostic significance of exercise-induced premature ventricular complexes in men and women: a four year follow-up. J Am Coll Cardiol 1983;1:1201-6.
8. Udall JA, Ellestad MH. Predictive implications of ventricular premature contractions associated with treadmill stress testing. Circulation 1977;56:985-9.
9. Weiner DA, Levine SR, Klein MD, Ryan TJ. Ventricular arrhythmias during exercise testing: mechanism, response to coronary bypass surgery and prognostic significance. Am J Cardiol 1984;53:1553-7.
10. Elhendy A, Chandrasekaran K, Gersh BJ, Mahoney D, Burger KN, Pellikka PA. Functional and prognostic significance of exercise-induced ventricular arrhythmias in patients with suspected coronary artery disease. Am J Cardiol 2002;90:95-100.
11. Imai K, Sato H, Hori M, et al. Vagally mediated heart rate recovery after exercise is accelerated in athletes but blunted in patients with chronic heart failure. J Am Coll Cardiol 1994;24:1529-35.
12. Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS. Heart-rate recovery immediately after exercise as a predictor of mortality. N Engl J Med 1999;341:1351-7.
13. Nishime EO, Cole CR, Blackstone EH, Pashkow FJ, Lauer MS. Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. JAMA 2000;284:1392-8.
14. Shetler K, Marcus R, Froelicher VF, et al. Heart rate recovery: validation and methodologic issues. J Am Coll Cardiol 2001;38: 1980-7.
15. Watanabe J, Thamilarasan M, Blackstone EH, Thomas JD, Lauer MS. Heart rate recovery immediately after treadmill exercise and left ventricular systolic dysfunction as predictors of mortality: the case of stress echocardiography. Circulation 2001;104:1911-6.
16. Schweikert RA, Pashkow FJ, Snader CE, Marwick TH, Lauer MS. 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.
17. Snader CE, Marwick TH, Pashkow FJ, Harvey SA, Thomas JD, Lauer MS. Importance of estimated functional capacity as a predictor of all-cause mortality among patients referred for exercise thallium single-photon emission computed tomography: report of 3,400 patients from a single center. J Am Coll Cardiol 1997;30:641-8.
18. Lauer MS, Francis GS, Okin PM, Pashkow FJ, Snader CE, Marwick TH. Impaired chronotropic response to exercise stress testing as a predictor of mortality. JAMA 1999; 281:524-9.
19. Lown B, Graboys TB. Management of patients with malignant ventricular arrhythmias. Am J Cardiol 1977;39:910-8.
20. Lauer MS, Blackstone EH, Young JB, Topol EJ. Cause of death in clinical research: time for a reassessment? J Am Coll Cardiol 1999;34:618-20.
21. Gottlieb SS. Dead is dead — artificial definitions are no substitute. Lancet 1997; 349:662-3.
22. Boyle CA, Decoufle P. National sources of vital status information: extent of coverage and possible selectivity in reporting. Am J Epidemiol 1990;131:160-8.
23. Newman TB, Brown AN. Use of commercial record linkage software and vital statistics to identify patient deaths. J Am Med Inform Assoc 1997;4:233-7.
24. Curb JD, Ford CE, Pressel S, Palmer M, Babcock C, Hawkins CM. Ascertainment of vital status through the National Death Index and the Social Security Administration. Am J Epidemiol 1985;121:754-66.
25. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.
26. Cox DR. Regression models and life-tables. J R Stat Soc [B] 1972;34:187-220.
27. Rubin DB. Estimating causal effects from large data sets using propensity scores. Ann Intern Med 1997;127:757-63.
28. Blackstone EH. Comparing apples and oranges. J Thorac Cardiovasc Surg 2002; 123:8-15.
29. Hosmer DW Jr, Lemeshow S. Applied logistic regression. New York: John Wiley, 1989.
30. Gum PA, Thamilarasan M, Watanabe J, Blackstone EH, Lauer MS. Aspirin use and all-cause mortality among patients being evaluated for known or suspected coronary artery disease: a propensity analysis. JAMA 2001;286:1187-94.
31. Faris JV, McHenry PL, Jordan JW, Morris SN. Prevalence and reproducibility of exercise-induced ventricular arrhythmias during maximal exercise testing in normal men. Am J Cardiol 1976;37:617-22.
32. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992;327:685-91. [Erratum, N Engl J Med 1992;327:1768.]