Ventricular Arrhythmias During Clinical Treadmill Testing and Prognosis

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Background: Although exercise-associated ventricular arrhythmias are frequently observed during exercise testing, their prognostic significance remains uncertain. Therefore, we aimed to evaluate the clinical correlates and prognostic significance of exercise-associated premature ventricular complexes (PVCs) during and after exercise testing.

Methods: We studied 1847 heart failure–free patients who underwent clinical treadmill testing between March 13, 1997, and January 15, 2004, in the Veterans Affairs Palo Alto Health Care System. Logistic regression was used to evaluate the clinical and exercise test associations of exercise and recovery PVCs. Propensity score–adjusted Cox survival analyses were used to evaluate the prognostic significance of exercise-associated PVCs.

Results: Of the 1847 subjects, 850 (46.0%) developed exercise PVCs (median rate, 0.43 per minute) and 620 (33.6%) had recovery PVCs (median rate, 0.60 per minute). Resting PVCs, age, and systolic blood pressure were key predictors of both exercise and recovery PVCs. Whereas exercise PVCs were related to the heart rate increase with exercise, recovery PVCs were related to coronary disease (previous myocardial infarction, coronary revascularization procedure, or pathological Q waves on resting electrocardiogram) and ST-segment depression. During a 5.4-year mean follow-up, 161 subjects (8.7%) died, and 53 of these deaths (32.9%) were due to cardiovascular causes. Recovery PVCs, but not exercise PVCs, were associated with 71% to 96% greater propensity-adjusted mortality rates (hazard ratio, 1.96 [95% confidence interval, 1.31-2.91] for infrequent PVCs; hazard ratio, 1.71 [95% confidence interval, 1.07-2.73] for frequent PVCs compared with subjects without PVCs), and occurrence of recovery PVCs reclassified 33.2% of subjects with intermediate-risk Duke Treadmill Scores into higher-risk subgroups.

Conclusion: In our heart failure–free population, recovery PVCs were associated with increased mortality and augmented established risk markers.

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EXERCISE TESTING IS AN IMPORTANT prognostic tool, but the prognostic significance of exercise-associated ventricular arrhythmias remains uncertain.[1,2] Frequent ventricular ectopy during and after exercise has been independently associated with adverse prognosis in some populations,[3-6] but not in others.[7-9] In these series, frequent ectopy, which was variously defined as ectopy composing greater than 10% of all complexes or greater than 7 premature ventricular complexes (PVCs) per minute, was present in only 2% to 8% of studied subjects. In the Framingham community cohort, however, PVCs during exercise were associated with increased mortality at lower and more prevalent PVC rates than had been previously reported.[10] Thus, while some authors have proposed that ectopy be used as a new criterion for exercise test positivity,[11] the optimal definition of significant arrhythmia and utility for risk stratification of individual patients are yet unresolved. Furthermore, the relative prognostic significance of exercise and recovery-period ectopy also remains unclear. While some have found that recovery ectopy is more robustly associated with adverse prognosis than exercise ectopy,[3] other results suggest otherwise.[10]

These apparent disparities may result from inconsistent methods, varied definitions of significant arrhythmia, and differences in sample size (which has varied from fewer than 1000 to greater than 30 000 subjects) and length of follow-up (which has ranged between 3 and ≥20 years). They may also be due to etiologic differences in PVCs in the various subject populations that have been studied. While the clinical correlates of exercise PVCs have been investigated in a community population,[10] the clinical associations of exercise PVCs in patients referred for exercise testing for clinical reasons have not been investigated. We aimed in this study to evaluate the clinical correlates and relative prognostic significance of exercise and recovery PVCs in subjects referred for clinical exercise treadmill testing.

Table 1. Characteristics of Study Population According to Occurrence of PVCs[a]

Variable	No PVCs (n=831)	PVCs During Exercise Only (n=396)	PVCs During Recovery Only (n=166)	PVCs During Exercise and Recovery (n=454)
Demographics				
Age, y[b]	53 (47-61)	56 (50-65)	57 (51-66)	63 (54-71)
Female sex	48 (5.8)	12 (3.0)	7 (4.2)	21 (4.6)
Height, cm[b]	175 (170-180)	175 (170-183)	175 (173-183)	178 (170-183)
BMI	28 (25-31)	27 (25-31)	28 (25-31)	28 (25-31)
Medical history				
Previous MI	101 (12.2)	46 (11.6)	25 (15.1)	62 (13.7)
Typical chest pain	96 (11.6)	32 (8.1)	23 (13.9)	53 (11.7)
Atypical chest pain	226 (27.2)	114 (28.8)	44 (26.5)	108 (23.8)
Previous coronary intervention	96 (11.6)	44 (11.1)	25 (15.1)	65 (14.3)
COPD	32 (3.9)	14 (3.5)	5 (3.0)	23 (5.1)
Claudication	34 (4.1)	18 (4.6)	5 (3.0)	22 (4.8)
Smoking history				
Ever	558 (67.1)	261 (65.9)	113 (68.1)	273 (60.1)
Currently[b]	260 (31.3)	85 (21.5)	49 (29.5)	80 (17.6)
Diabetes mellitus[c]	134 (16.4)	59 (15.2)	22 (13.3)	66 (15.1)
Cardiovascular medications				
Calcium channel blocker	101 (12.2)	65 (16.4)	26 (15.7)	67 (14.8)
β-Blocker	192 (23.1)	75 (19.0)	41 (24.7)	93 (20.5)
ACE inhibitor	195 (23.5)	90 (22.7)	41 (24.7)	121 (26.7)
Clinical findings				
Resting heart rate, beats/min[b]	82 (73-90)	81 (71-91)	78 (71-88)	82 (72-92)
Resting SBP, mm Hg[b]	128 (115-140)	130 (120-142)	132 (120-149)	138 (121-150)
QRS duration, ms[b]	88 (80-98)	86 (79-96)	90 (80-100)	90 (82-98)
QTc, ms[b]	408 (399-418)	408 (401-417)	408 (400-418)	412 (403-426)
Abnormal ECG				
Q wave[b]	63 (7.6)	23 (5.8)	32 (19.3)	58 (12.8)
Resting ST-segment depression[b]	21 (2.6)	10 (2.5)	7 (4.2)	24 (5.3)
LVH with ST-segment depression	3 (0.4)	2 (0.5)	0 (0)	4 (0.9)
Right BBB	39 (4.7)	11 (2.8)	5 (3.0)	15 (3.3)
Resting ectopy[b]	10 (1.2)	6 (1.5)	4 (2.4)	67 (14.8)

Abbreviations: ACE, angiotensin-converting enzyme; BBB, bundle-branch block; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; LVH, left ventricular hypertrophy; MI, myocardial infarction; PVCs, premature ventricular complexes; QTc, corrected QT interval; SBP, systolic blood pressure.

[a] Continuous variables are presented as median (interquartile range) and categorical variables are presented as number (percentage).

[b] $P<.05$ for Kruskal-Wallis and χ^2 tests between groups for continuous and categorical variables, respectively.

[c] Denominators are 818, 389, 165, and 438, respectively. Missing data resulted from incorrect coding at the time of data collection. All missing covariate data were replaced by imputation prior to subsequent analysis.

METHODS

STUDY POPULATION

We studied 2075 subjects referred in the Palo Alto Veterans Affairs Health Care System between March 13, 1997, and January 15, 2004, for clinical treadmill testing who were tested by means of a device (QUEST; Burdick Corp, Deerfield, Wisconsin) that enabled continuous digital electrocardiogram (ECG) recording. This represented approximately one-half of all patients referred for exercise testing during this period; selection was determined solely by equipment availability. Subjects did not undergo concurrent imaging studies at the time of exercise testing. Serum creatinine was measured within 30 days of exercise testing, and glomerular filtration rate was estimated according to the method of Levey et al.[12] All other clinical data were obtained at the time of exercise testing. We excluded subjects with atrial fibrillation (n=62), paced rhythm (n=26), supraventricular tachycardia (n=13), insufficient digital ECG data recording durations (n=15), and a clinical history of heart failure (n=112), leaving 1847 patients for analysis. All subjects gave written informed consent, and the study was approved by the Stanford University Institutional Review Board.

EXERCISE TESTING

Subjects underwent symptom-limited treadmill testing with the use of an individualized ramp protocol, exercised to maximum exertion,[13] and assumed a supine position after exercise without a cool-down walk.[14] Exercise capacity was estimated in metabolic equivalents from treadmill speed and grade, and 12-lead ECG data were recorded at 500 samples per second. An abnormal ST-segment response was defined as 1 mm or more of horizontal or down-sloping ST-segment depression measured visually at the J junction. The Duke Treadmill Score was calculated as previously described.[15]

PVC CHARACTERIZATION

PVC Detection

Digitally recorded complexes were classified as either normal or abnormal on the basis of QRS morphologic features. Abnormal beats were typified by morphologic deviation in 2 or more leads relative to the dominant beat. These beat classifications were used to compute PVC rates in beats per minute for exer-

cise and the first 5 minutes of recovery. The PVCs were confirmed by visual ECG analysis, and resting PVCs were considered to be present if any PVC was detected in the 10-second ECG recorded before exercise.

Classification of PVCs

Application of previously used definitions of frequent ectopy (PVCs composing 10% of all ventricular depolarizations during any 30-second ECG recording or ventricular tachycardia)[4-7] yielded a low prevalence of frequent ectopy (3.0% during exercise only, 0.5% during recovery only, and 1.0% during both exercise and recovery). Therefore, we used alternative definitions for PVC frequency: subjects with PVC rates less than and greater than the median value for all subjects with PVCs were classified as having infrequent and frequent PVCs, respectively.[10] These classifications were used for both exercise and recovery periods such that subjects were classified as having no PVCs, infrequent PVCs, and frequent PVCs during both periods. Severe ectopy was classified according to the Lown et al criteria[16] and as previously described[3,10] as the presence of 1 or more of the following: couplets or ventricular tachycardia, multiform PVCs, or ventricular fibrillation.

FOLLOW-UP

We considered all-cause and cardiovascular mortality outcomes. Mortality data were gathered through March 1, 2006, from the Social Security Death Index and California Death Registry. Cause of death was determined from the registry classification and confirmed by means of the Veterans Affairs medical record. Cardiovascular mortality was defined as death from a clearly identifiable cardiovascular cause or death of subjects with a history of cardiovascular disease and with no identifiable noncardiovascular cause. Classification was made by consensus of 2 observers blinded to the exercise test results, with conflicts being resolved by the senior author (V.F.F.).

STATISTICAL ANALYSIS

Clinical and exercise test variables in subjects with PVCs during exercise, recovery, or both were compared by means of χ^2 tests (categorical variables) and the Kruskal-Wallis test (continuous variables). The associations between clinical and exercise test variables and infrequent and frequent PVCs during and after exercise were analyzed by means of multiple logistic regression analysis.

Associations between PVCs during and after exercise and outcomes were analyzed by means of Kaplan-Meier and propensity-adjusted Cox proportional hazards analyses. The propensities to have infrequent or frequent PVCs during and after exercise were calculated by nonparsimonious multiple logistic regression including all variables in **Table 1**. Exercise and recovery PVC occurrences were also included for the propensity to have recovery and exercise PVCs, respectively. Separate propensity scores were calculated for PVCs occurring before and after exercise, and separate Cox survival analyses were used to evaluate the prognostic significance of exercise and recovery PVCs. Covariate data were complete in 97.5% of subjects; missing values were imputed before analysis by using the "transcan" function developed by Harrell et al.[17] Subjects were matched by propensity score differences less than 0.015, and baseline and exercise test characteristics were again compared to assess the adequacy of propensity score balancing of potential confounders. Given 161 total deaths, 53 cardiovascular deaths, and a 2-sided error rate of 5%, we estimated that the study had a statistical power of 80% to detect changes of 31% and 33% in the hazards of all-cause mortality for subjects with exercise and recovery PVCs, respectively, and changes of 59% and 66% in the hazards of cardiovascular mortality for subjects with exercise and recovery PVCs, respectively.

Effect modifications by other clinical and exercise test variables were evaluated by including interaction terms in propensity score–adjusted Cox survival models. For analysis of exercise PVCs, we evaluated interactions with severity of ectopy, age, known coronary disease (defined as previous myocardial infarction, Q waves, or revascularization procedure), heart rate increase with exercise, abnormal ST-segment depression, resting PVCs, and recovery PVCs. For analysis of recovery PVCs, we evaluated additional interactions with heart rate recovery and exercise PVCs.

Five hierarchical multivariate Cox regression analyses were used to further evaluate the prognostic utility of exercise-induced PVCs: (1) a model including known clinical cardiovascular risk factors (age, coronary disease, smoking history, history of diabetes mellitus, resting heart rate, and resting systolic blood pressure); (2) a model adding PVCs at rest; (3) a model adding the Duke Treadmill Score,[18] heart rate increase with exercise,[19] and heart rate recovery[20]; and models adding either (4) exercise PVCs or (5) recovery PVCs. The discriminative accuracy of each model was assessed by means of the right-censored concordance index (C index) validated with 200 bootstrap samples. The conditional probability that each model represented the best fit of all candidate models was assessed by Akaike weights.[21] The proportional hazards assumption was evaluated by the scaled Schoenfeld residual.

Statistical analyses were performed with NCSS (NCSS Inc, Salt Lake City, Utah) and the Design and Hmisc libraries in S-Plus 7.0 (Insightful Corp, Seattle, Washington). A 2-sided $P < .05$ was considered statistically significant.

RESULTS

PREVALENCE OF PVCs AND SUBJECT DEMOGRAPHICS

Premature ventricular complexes during or after exercise were observed in 55.0% of subjects in digital analysis and 59.0% of subjects in visual analysis; visual and computer detection of PVCs was 96.3% concordant. Digital analysis demonstrated that 850 subjects developed PVCs during exercise (46.0%; median rate, 0.43 per minute) and 620 subjects had recovery PVCs (33.6%; median rate, 0.60 per minute). Patient demographics and exercise test findings according to the occurrence of PVCs are described in Table 1 and **Table 2**, respectively.

CLINICAL ASSOCIATIONS OF PVCs DURING EXERCISE

Associations between clinical characteristics, exercise testing results, and exercise-associated PVCs are presented in **Table 3**. Greater age and mean QRS duration at rest, PVCs at rest, and greater exercise capacity and heart rate increase with exercise were associated with greater odds of infrequent exercise PVCs ($P < .05$). Greater age, greater height, higher systolic blood pressure, higher resting heart rate, greater corrected QT interval, PVCs at rest, and greater heart rate increase with exercise were associated

Table 2. Exercise Test Results According to Occurrence of PVCs[a]

Variable	No PVCs (n=831)	PVCs During Exercise Only (n=396)	PVCs During Recovery Only (n=166)	PVCs During Exercise and Recovery (n=454)
Angina during exercise				
Occurred	76 (9.1)	33 (8.3)	23 (13.9)	33 (7.3)
Stopped the test[b]	31 (3.7)	10 (2.5)	12 (7.2)	9 (2.0)
Exercise-induced ST-segment depression[b]	52 (6.3)	27 (6.8)	27 (16.3)	52 (11.5)
Maximal heart rate, beats/min[b]	144 (125-161)	151 (133-164)	142 (123-157)	145 (127-161)
Heart rate increase, beats/min[b]	74 (56-92)	82 (68-96)	74 (58-90)	76 (59-91)
Heart rate recovery at 2 min, beats/min[b]	44 (34-53)	46 (36-54)	42 (33-52)	40 (31-50)
Borg Rating of Perceived Exertion[c]	17 (16-19)	17 (17-19)	18 (16-19)	17 (15-19)
Exercise capacity, METs[b]	9 (6-11)	9 (7-11)	8 (5-10)	8 (6-10)
Duke Treadmill Score[b]	8 (5-11)	9 (6-11)	6 (2-10)	7 (4-10)

Abbreviations: METs, metabolic equivalents; PVCs, premature ventricular complexes.
[a] Continuous variables are presented as median (interquartile range) and categorical variables are presented as number (percentage).
[b] $P<.05$ for Kruskal-Wallis and χ^2 tests between groups for continuous and categorical variables, respectively.
[c] Quantified as described.[22]

Table 3. Associations Between Clinical and Exercise Test Variables and PVCs According to Multiple Logistic Regression Analysis[a]

	Odds Ratio (95% CI)			
	Exercise		Recovery	
Variable	Infrequent PVCs (n=419)	Frequent PVCs (n=431)	Infrequent PVCs (n=336)	Frequent PVCs (n=284)
Significant associations				
Age (SD, 12 y)	1.5 (1.3-1.8)	2.4 (2.0-2.8)	1.4 (1.2-1.6)	1.4 (1.2-1.6)
Height (SD, 9 cm)	1.1 (1.0-1.3)	1.3 (1.1-1.5)	1.2 (1.1-1.4)	1.3 (1.1-1.5)
Previous coronary disease	1.1 (0.8-1.5)	1.1 (0.8-1.5)	1.4 (1.0-1.9)	1.9 (1.3-2.9)
Resting heart rate (SD, 14 beats/min)	1.1 (1.0-1.3)	1.2 (1.1-1.4)	1.1 (0.9-1.2)	1.1 (1.0-1.4)
Resting SBP (SD, 19 mm Hg)	1.0 (0.9-1.2)	1.2 (1.0-1.4)	1.2 (1.1-1.4)	1.2 (1.0-1.4)
QTc (SD, 20 ms)	1.0 (0.9-1.2)	1.2 (1.0-1.3)	1.0 (0.8-1.1)	1.0 (0.9-1.2)
QRS duration (SD, 16 ms)	0.8 (0.7-1.0)	0.8 (0.7-0.9)	1.0 (0.9-1.2)	1.1 (1.0-1.4)
PVCs at rest	3.1 (1.6-6.6)	8.1 (4.4-15.5)	3.1 (1.6-6.4)	8.3 (4.2-16.3)
Exercise capacity (SD, 3 METs)	1.2 (1.1-1.5)	0.9 (0.7-1.0)	0.9 (0.8-1.1)	0.9 (0.7-1.1)
Abnormal ST-segment depression	1.1 (0.7-1.8)	0.8 (0.5-1.3)	1.5 (1.0-2.4)	2.4 (1.4-4.1)
Heart rate increase (SD, 23 beats/min)	1.3 (1.1-1.5)	1.7 (1.4-2.0)	1.1 (0.9-1.4)	1.1 (0.8-1.5)
Ectopy during exercise				
Infrequent	NA	NA	2.2 (1.6-2.9)	3.8 (2.4-6.1)
Frequent	NA	NA	4.4 (3.1-6.2)	25.2 (16.4-39.2)
Nonsignificant associations				
Female sex	0.9 (0.5-1.7)	1.0 (0.5-1.9)	1.8 (0.9-3.6)	2.1 (0.9-5.1)
GFR (SD, 21 mL/h)	1.1 (0.9-1.2)	1.1 (1.0-1.2)	0.9 (0.8-1.1)	0.9 (0.8-1.1)
Smoking history				
Ever	1.2 (0.9-1.5)	0.9 (0.7-1.2)	0.8 (0.6-1.1)	0.9 (0.6-1.3)
Currently	0.8 (0.6-1.1)	0.8 (0.6-1.2)	1.0 (0.7-1.4)	1.2 (0.8-2.0)
COPD	1.5 (0.9-2.8)	1.3 (0.7-2.5)	1.3 (0.7-2.5)	1.1 (0.5-2.5)
β-Blocker use	1.1 (0.8-1.5)	1.1 (0.8-1.5)	1.0 (0.7-1.4)	1.3 (0.9-2.0)
Calcium channel blocker use	1.3 (0.9-1.9)	1.1 (0.8-1.6)	0.7 (0.5-1.0)	1.0 (0.6-1.5)
ACE inhibitor use	1.0 (0.8-1.4)	1.0 (0.8-1.4)	0.9 (0.7-1.3)	1.1 (0.7-1.6)
Angina during exercise				
Occurred	0.7 (0.5-1.1)	0.9 (0.6-1.4)	1.1 (0.7-1.7)	0.8 (0.4-1.4)
Stopped the test	0.5 (0.2-1.1)	0.6 (0.3-1.3)	1.2 (0.6-2.5)	1.6 (0.6-3.8)
Heart rate recovery	NA	NA	1.0 (0.9-1.3)	0.8 (0.7-1.1)

Abbreviations: ACE, angiotensin-converting enzyme; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; METs, metabolic equivalents; NA, not applicable; PVCs, premature ventricular complexes; QTc, corrected QT interval; SBP, systolic blood pressure.
[a] Infrequent and frequent exercise PVCs refer to PVC rates less than and greater than the median value, respectively, for all subjects with PVCs (median values, 0.43 PVC per minute for exercise and 0.60 PVC per minute for the recovery period). Multiple logistic regression analysis included all variables in table. Odds ratios for continuous variables are presented for an increase of 1 SD in each variable. The reference group in each case comprised subjects without PVCs during the respective period.

with greater odds of frequent exercise PVCs ($P<.05$). The presence of resting PVCs had the strongest association with the development of exercise PVCs (adjusted odds ratio [OR], 3.1; 95% confidence interval [CI], 1.6-6.6; and adjusted OR, 8.1; 95% CI, 4.4-15.5, for infrequent and frequent exercise PVCs, respectively).

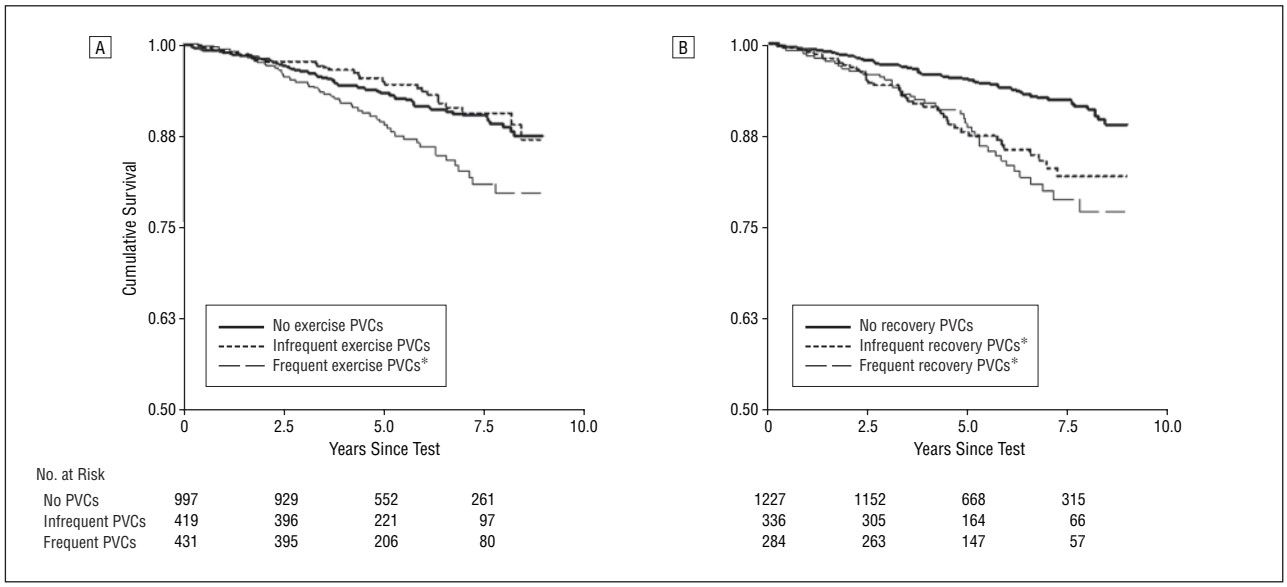

Figure 1. Kaplan-Meier analysis of the associations between exercise premature ventricular complex (PVC) frequency and all-cause mortality (A) and recovery PVC frequency and all-cause mortality (B). *$P<.05$ vs subjects without PVCs during each exercise period by log-rank test.

CLINICAL ASSOCIATIONS OF PVCs DURING RECOVERY

Subjects who were older and taller and who had greater resting systolic blood pressure, previous coronary disease, PVCs at rest, abnormal ST-segment depression, and exercise PVCs had greater odds of both infrequent and frequent recovery PVCs (Table 3; $P<.05$). Greater resting heart rate was also associated with greater odds of frequent recovery PVCs ($P=.01$). Frequent exercise PVCs had the strongest association with recovery PVCs (adjusted OR, 4.4; 95% CI, 3.1-6.2; and adjusted OR, 25.2; 95% CI, 16.4-39.2, for infrequent and frequent recovery PVCs, respectively).

PVCs DURING EXERCISE AND PROGNOSIS

There were 161 (8.7%) deaths during the 5.4-year mean follow-up, of which 53 (32.9%) were due to cardiovascular causes. Whereas subjects without PVCs during exercise had a 5-year mortality rate estimated via Kaplan-Meier analysis of 6.7% (95% CI, 5.0%-8.4%), subjects with infrequent and frequent exercise PVCs had 5-year mortality rates of 5.1% (95% CI, 3.7%-7.4%) and 10.1% (95% CI, 7.4%-13.9%), respectively (**Figure 1**A). However, subjects with PVCs during exercise only (no associated recovery PVCs) did not have survival rates that were significantly different from those of subjects without any PVCs (**Figure 2**). Results of Cox survival analysis for all-cause and cardiovascular mortality outcomes are presented in **Table 4**. The C statistics for the calculated propensities to have infrequent and frequent exercise PVCs were 0.65 and 0.84, respectively. Propensity score matching demonstrated no significant differences in baseline and exercise testing characteristics between groups (**Table 5**). Neither infrequent nor frequent exercise PVCs were significantly associated with all-cause mortality in propensity score–adjusted Cox survival analyses. Frequent exercise PVCs were, however, associated with increased cardiovascular mortality rates (hazard ratio [HR], 2.26; 95% CI, 1.03-4.62) (Table 4). None of the prespecified variables considered were found to be effect modifiers ($P>.05$ for interaction terms).

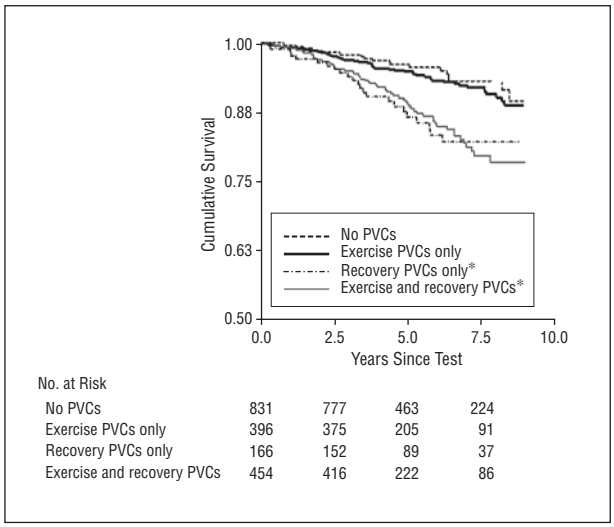

Figure 2. Kaplan-Meier analysis of the associations between exercise and recovery premature ventricular complex (PVC) occurrence and all-cause mortality. *$P<.05$ vs subjects without PVCs by log-rank test.

PVCs DURING RECOVERY AND PROGNOSIS

In Kaplan-Meier survival analysis, the 5-year mortality rate was 4.9% (95% CI, 3.6%-6.2%) for subjects without PVCs during recovery, while 5-year mortality rates were 12.2% (95% CI, 8.2%-16.1%) for subjects with infrequent recovery PVCs and 11.6% (95% CI, 7.4%-15.6%) for subjects with frequent recovery PVCs (Figure 1B). Subjects with PVCs after exercise and subjects with PVCs both during and after exercise had similar 5-year mortality rates, which were significantly greater than mortality rates for subjects without any PVCs and

Table 4. Associations Between Exercise Test–Induced PVCs and All-Cause and Cardiovascular Mortality According to Cox Survival Analysis[a]

Variable	Analysis	All-Cause Death		Cardiovascular Death	
		No. of Events/ No. at Risk (%)	HR (95% CI)	No. of Events/ No. at Risk (%)	HR (95% CI)
Exercise PVCs[b]					
None	Reference	79/997 (7.9)	1 [Reference]	20/997 (2.0)	1 [Reference]
Infrequent	Univariate	28/419 (6.7)	0.85 (0.55-1.31)	8/419 (1.9)	0.96 (0.42-2.17)
	Propensity adjusted	NA	0.83 (0.54-1.30)	NA	0.90 (0.39-2.08)
Frequent	Univariate	54/431 (12.5)	1.69 (1.20-2.40)	25/431 (5.8)	3.12 (1.73-5.63)
	Propensity adjusted	NA	1.34 (0.88-2.04)	NA	2.26 (1.03-4.62)
Recovery PVCs[c]					
None	Reference	77/1227 (6.3)	1 [Reference]	20/1227 (1.6)	1 [Reference]
Infrequent	Univariate	42/336 (12.5)	2.14 (1.47-3.12)	15/336 (4.5)	2.95 (1.51-5.77)
	Propensity adjusted	NA	1.96 (1.31-2.91)	NA	2.08 (1.02-4.25)
Frequent	Univariate	42/284 (14.8)	2.44 (1.67-3.56)	18/284 (6.3)	4.04 (2.13-7.63)
	Propensity adjusted	NA	1.71 (1.07-2.73)	NA	1.66 (0.74-3.72)

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not applicable; PVCs, premature ventricular complexes.

[a] Infrequent and frequent exercise PVCs are defined as in Table 3. The reference group in each case comprised subjects without PVCs during the respective period.

[b] Predictive accuracy (bootstrap-validated right-censored concordance index calculated from univariate models), 0.56 and 0.62 for all-cause death and cardiovascular death, respectively.

[c] Predictive accuracy (bootstrap-validated right-censored concordance index calculated from univariate models), 0.60 and 0.63 for all-cause death and cardiovascular death, respectively.

subjects with PVCs during exercise only (Figure 2). The C statistics for the calculated propensities to have infrequent and frequent recovery PVCs were 0.67 and 0.87, respectively, and baseline characteristics were similar in all recovery PVC groups to those of propensity-matched subjects without recovery PVCs (**Table 6**). In propensity score–adjusted Cox survival analysis, findings of infrequent and frequent recovery PVCs were associated with 96% and 71% higher hazards of death compared with subjects without PVCs, respectively (HR, 1.96; 95% CI, 1.31-2.91; and HR, 1.71; 95% CI, 1.07-2.73, respectively) (Table 4). No significant effect modification was observed among any of the prespecified interaction terms ($P > .05$).

PREDICTIVE ACCURACY AND RISK STRATIFICATION

Recovery PVCs were more accurate predictors of both all-cause and cardiovascular mortality than were exercise PVCs in univariate Cox survival analysis (Table 4). Similarly, in hierarchical Cox survival modeling, the addition of recovery PVCs to clinical and exercise test risk factors yielded a model with the highest conditional probability of best fit (83%), while the model that included exercise PVCs had a best fit probability of less than 10% (**Table 7**). The associations between recovery PVCs and all-cause mortality were similar in this full hierarchical model (HR, 1.85; 95% CI, 1.25-2.73; and HR, 1.53; 95% CI, 1.01-2.32 for infrequent and frequent recovery PVC rates, respectively) to those observed in propensity score–adjusted analysis. Recovery PVCs had the greatest utility for risk stratification in subjects with intermediate Duke Treadmill Scores (**Table 8**). Of these subjects, 33.2% had recovery PVCs (infrequent or frequent) and associated age-adjusted mortality rates similar to those observed in subjects in the highest-risk tertile of the Duke Treadmill Score.

COMMENT

Premature ventricular complexes were observed during or after exercise in more than half of the individuals in our large heart failure–free clinical cohort. However, similar to findings in the Framingham community cohort,[10] few met previously described criteria for frequent ectopy (>10% of all complexes or ventricular tachycardia[4-7]). The median PVC rates for exercise and recovery periods in our cohort were higher than those previously described in the Framingham community cohort,[10] which may be explained by the higher prevalence of cardiopulmonary disease in our clinical population. In contrast to previous findings from this community cohort,[10] we found that PVCs during exercise were associated with increased mortality rates only if accompanied by PVCs after exercise. Furthermore, neither infrequent nor frequent exercise PVCs were significantly associated with increased hazards in propensity score–adjusted survival analysis.

However, similar to previous findings in clinical cohorts,[3] we found that recovery PVCs were robustly associated with adverse prognosis regardless of the presence of PVCs during exercise. Of note, the hazards for infrequent and frequent PVCs after exercise were similar, suggesting that the absolute presence of recovery PVCs has more prognostic significance than does the recovery PVC frequency, at least as it was defined in this investigation. This observation is further supported by the similar estimated mortality rates for subjects with infrequent and frequent recovery PVCs in Kaplan-Meier analysis. Furthermore, recovery PVCs stratified more than 30%

Table 5. Characteristics of Study Subjects With Exercise PVCs and Propensity-Matched Control Subjects[a]

Variable	Infrequent PVCs		Frequent PVCs	
	Propensity-Matched Controls (n=366)	Subjects (n=366)	Propensity-Matched Controls (n=245)	Subjects (n=245)
Demographics				
Age, y	56 (50-64)	56 (50-65)	60 (53-70)	63 (53-68)
Female sex	10 (2.7)	15 (4.1)	7 (2.9)	7 (2.9)
Height, cm	175 (170-180)	175 (170-180)	175 (172-183)	175 (170-180)
BMI	28 (25-31)	28 (24-31)	28 (25-31)	27 (25-31)
Clinical findings				
Estimated GFR, mL/h	80 (65-93)	81 (67-93)	77 (64-91)	80 (67-93)
Resting heart rate, beats/min	79 (70-88)	82 (71-91)	79 (70-89)	80 (71-92)
Resting SBP, mm Hg	130 (120-145)	130 (120-142)	134 (120-148)	136 (120-146)
QRS duration, ms	89 (79-97)	87 (79-97)	90 (80-98)	88 (80-98)
QTc, ms	407 (399-417)	408 (401-418)	409 (400-420)	408 (401-420)
Abnormal ECG				
Resting ST-segment depression	9 (2.5)	11 (3.0)	9 (3.7)	11 (4.5)
LVH with ST-segment depression	0	2 (0.5)	2 (0.8)	1 (0.4)
Right BBB	17 (4.6)	14 (3.8)	8 (3.3)	8 (3.3)
Resting PVCs	10 (2.7)	12 (3.3)	10 (4.1)	10 (4.1)
Medical history				
Typical chest pain	41 (11.2)	39 (10.7)	20 (8.2)	27 (11.0)
Atypical chest pain	106 (29.0)	101 (27.6)	73 (29.8)	60 (24.5)
Previous coronary disease[b]	76 (20.8)	70 (19.1)	54 (22.0)	56 (22.9)
COPD	16 (4.4)	13 (3.6)	9 (3.7)	10 (4.1)
Claudication	20 (5.5)	18 (4.9)	7 (2.9)	10 (4.1)
Smoking history				
Ever	241 (65.8)	240 (65.6)	150 (61.2)	155 (63.3)
Currently	76 (20.8)	85 (23.2)	43 (17.6)	49 (20.0)
Diabetes mellitus	56 (15.3)	51 (13.9)	36 (14.7)	41 (16.7)
Cardiovascular medications				
Calcium channel blocker	48 (13.1)	56 (15.3)	30 (12.2)	34 (13.9)
β-Blocker	91 (24.9)	80 (21.9)	49 (20.0)	49 (20.0)
ACE inhibitor	89 (24.3)	85 (23.2)	59 (24.1)	67 (27.3)
Exercise test findings				
Maximal heart rate, beats/min	146 (128-162)	149 (131-163)	144 (128-160)	146 (130-163)
Heart rate increase, beats/min	79 (61-95)	80 (63-95)	80 (62-94)	81 (61-94)
Heart rate recovery at 2 min, beats/min	45 (35-53)	45 (35-53)	43 (34-53)	44 (35-53)
Borg Rating of Perceived Exertion[c]	18 (16-19)	18 (17-19)	17 (16-19)	17 (16-19)
Duke Treadmill Score	8 (5-11)	8 (5-11)	8 (3-10)	7 (5-10)
Outcomes				
Deaths	26 (7.1)	25 (6.8)	21 (8.6)	27 (11.0)
CV deaths	11 (3.0)	8 (2.2)	9 (3.7)	15 (6.1)

Abbreviations: ACE, angiotensin-converting enzyme; BBB, bundle-branch block; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; CV, cardiovascular; ECG, electrocardiogram; GFR, glomerular filtration rate; LVH, left ventricular hypertrophy; PVCs, premature ventricular complexes; QTc, corrected QT interval; SBP, systolic blood pressure.

[a] Continuous variables are presented as median (interquartile range) and categorical variables are presented as number (percentage). $P > .10$ for Kruskal-Wallis and χ^2 tests between controls and subjects with PVCs for all continuous and categorical variables, respectively.

[b] Defined as previous myocardial infarction, revascularization procedure, or pathological ECG Q waves.

[c] Quantified as described.[22]

of subjects deemed to be at intermediate risk by the Duke Treadmill Score into subgroups with mortality rates similar to those in the highest-risk Duke Treadmill Score tertile. Although recovery PVCs added little to the discriminative accuracy of established risk factors, this augmentation of risk stratification by other established risk factors is clinically meaningful.[23]

The different associations between exercise and recovery PVCs and clinical characteristics may provide rationale for these findings. The presence of PVCs at rest, greater age and height, and elevated resting heart rate and systolic blood pressure were consistent predictors of both exercise and recovery PVCs. These associations are consistent with previous observations that age-associated fibrosis of the myocardium, ischemia, ventricular hypertrophy, and loss of vagal tone may lower the arrhythmic threshold.[11,24] However, a predisposition to or findings consistent with ischemia were associated only with recovery PVCs after adjusting for other variables in our population. Although previous reports associated coronary disease and ischemia with exercise ectopy,[24,25] our findings suggest that this association was independent of other factors only in the recovery period, during which cardiovascular vagal tone is high.[26]

Table 6. Characteristics of Study Subjects With Recovery PVCs and Propensity-Matched Control Subjects

Variable	Infrequent PVCs		Frequent PVCs	
	Propensity-Matched Controls (n=313)	Subjects (n=313)	Propensity-Matched Controls (n=179)	Subjects (n=179)
Demographics				
Age, y	58 (51-67)	58 (51-67)	60 (52-70)	62 (53-70)
Female sex	12 (3.8)	13 (4.2)	4 (2.2)	4 (2.2)
Height, cm	178 (173-183)	175 (173-183)	178 (173-183)	175 (172-180)
BMI	28 (25-31)	28 (25-31)	27 (25-30)	27 (24-32)
Clinical findings				
Estimated GFR, mL/h	79 (66-91)	78 (66-93)	79 (65-92)	75 (62-90)
Resting heart rate, beats/min	81 (72-91)	80 (71-91)	82 (72-92)	82 (72-92)
Resting SBP, mm Hg	134 (120-145)	133 (120-146)	138 (120-150)	135 (120-146)
QRS duration, ms	89 (80-99)	89 (80-98)	90 (80-100)	90 (82-99)
QTc, ms	409 (400-419)	409 (401-418)	409 (401-421)	414 (405-425)
Abnormal ECG				
Resting ST-segment depression	10 (3.2)	13 (4.2)	8 (4.5)	10 (5.6)
LVH with ST-segment depression	2 (0.6)	2 (0.6)	1 (0.6)	2 (1.1)
Right BBB	11 (3.5)	8 (2.6)	7 (3.9)	8 (4.5)
Resting PVCs	10 (3.2)	15 (4.8)	13 (7.3)	10 (5.6)
Medical history				
Typical chest pain	34 (10.9)	33 (10.5)	18 (10.1)	22 (12.3)
Atypical chest pain	80 (25.6)	77 (24.6)	51 (28.5)	44 (24.6)
Previous coronary disease[b]	74 (23.6)	70 (22.4)	42 (23.5)	48 (26.8)
COPD	9 (2.9)	15 (4.8)	9 (5.0)	8 (4.5)
Claudication	11 (3.5)	12 (3.8)	13 (7.3)	11 (6.1)
Smoking history				
Ever	195 (62.3)	194 (62.0)	123 (68.7)	128 (71.5)
Currently	70 (22.4)	69 (22.0)	40 (22.3)	42 (23.5)
Diabetes mellitus	36 (11.5)	41 (13.1)	28 (15.6)	29 (16.2)
Cardiovascular medications				
Calcium channel blocker	42 (13.4)	39 (12.5)	31 (17.3)	34 (19.0)
β-Blocker	65 (20.8)	66 (21.1)	37 (20.7)	49 (27.4)
ACE inhibitor	89 (28.4)	77 (24.6)	55 (30.7)	51 (28.5)
Exercise test findings				
Maximal heart rate, beats/min	146 (130-161)	146 (126-162)	146 (131-162)	143 (127-160)
Heart rate increase, beats/min	79 (60-92)	77 (60-94)	78 (60-92)	73 (57-90)
Heart rate recovery at 2 min, beats/min	44 (35-53)	43 (34-53)	42 (32-51)	40 (30-49)
Borg Rating of Perceived Exertion[c]	17 (16-19)	17 (15-19)	17 (17-19)	17 (16-19)
Duke Treadmill Score	8 (5-10)	8 (4-10)	7 (4-10)	5 (4-9)
Outcomes				
Deaths	18 (5.8)	37 (11.8)[d]	12 (6.7)	22 (12.3)
CV deaths	5 (1.6)	12 (3.8)	6 (3.4)	9 (5.0)

Abbreviations: ACE, angiotensin-converting enzyme; BBB, bundle-branch block; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; CV, cardiovascular; ECG, electrocardiogram; GFR, glomerular filtration rate; LVH, left ventricular hypertrophy; PVC, premature ventricular complex; QTc, corrected QT interval; SBP, systolic blood pressure.

[a] Continuous variables are presented as median (interquartile range) and categorical variables are presented as number (percentage).

[b] Defined as previous myocardial infarction, revascularization procedure, or pathological ECG Q waves.

[c] Quantified as described.[22]

[d] $P < .05$ for Kruskal-Wallis and χ^2 tests between controls and subjects with PVCs for continuous and categorical variables, respectively.

In contrast, both infrequent and frequent exercise PVCs were directly related to the heart rate increase with exercise and exercise capacity, which have been shown to have protective relationships with outcome.[8,19] Increased sympathetic activity has been implicated in the development of ventricular ectopy at rest and during exercise.[16,27] Thus, the association we observed between greater heart rate increase with exercise and increased odds of exercise PVCs may have resulted from the increased sympathetic activity in subjects who were able to attain higher peak heart rates.

Our study has several important limitations. Our study population was composed almost entirely of older men and therefore may not be generalizable to other age groups or to women. Furthermore, our exercise protocol does not include a cool-down walk; the prevalence and significance of recovery PVCs could be different in patients tested with a protocol that includes a cool-down walk. Our power analysis indicated that the study was adequately powered to detect previously reported associations between PVCs and mortality in a community cohort.[10] However, the possibility remains that this study was not adequately powered to detect associations of lesser magnitude in our clinical population. Similarly, the lack of consistent associations between exercise-associated

Table 7. Model Fit and Discriminative Accuracy for All-Cause Mortality According to Clinical and Exercise Test Variables and PVCs at Rest and During and After Exercise

Variables	Probability of Best Fit (Akaike Weight)[a]	Predictive Accuracy (C Index)[b]
Age, resting SBP, resting heart rate, previous coronary disease, history of diabetes mellitus, smoking history	< 0.01	0.72
Age, resting SBP, resting heart rate, previous coronary disease, history of diabetes, smoking history, PVCs at rest	< 0.01	0.72
Age, resting SBP, resting heart rate, previous coronary disease, history of diabetes, smoking history, PVCs at rest, Duke Treadmill Score, heart rate increase, heart rate recovery	0.10	0.74
Age, resting SBP, resting heart rate, previous coronary disease, history of diabetes, smoking history, PVCs at rest, Duke Treadmill Score, heart rate increase, heart rate recovery, exercise PVCs	0.07	0.74
Age, resting SBP, resting heart rate, previous coronary disease, history of diabetes, smoking history, PVCs at rest, Duke Treadmill Score, heart rate increase, heart rate recovery, recovery PVCs	0.83	0.75

Abbreviations: PVCs, premature ventricular complexes; SBP, systolic blood pressure.
[a] Akaike weights estimate the conditional probability of best fit for each model out of all candidate models. Greater Akaike weights indicate a greater conditional probability that a candidate model represents the best-fit model.
[b] C index refers to the bootstrap-validated right-censored concordance index for each model.

Table 8. Predicted Age-Adjusted 5-Year Mortality Rates According to Tertile of Duke Treadmill Score and Recovery PVC Occurrence

Recovery PVCs	Duke Treadmill Score		
	> 11 (n=618)	6-11 (n=635)	≤ 5 (n=594)
None			
Total, No. (%)[a]	459 (74.3)	424 (66.8)	344 (57.9)
5-y Mortality rate, %[b]	0.7	6.3	12.9
Infrequent			
Total, No. (%)	104 (16.8)	111 (17.5)	121 (20.4)
5-y Mortality rate, % (95% CI)[c]	1.2 (0.6-1.7)	14.0 (6.9-28.9)	18.2 (11.1-30.2)
Frequent			
Total, No. (%)	55 (8.9)	100 (15.7)	129 (21.7)
5-y Mortality rate, % (95% CI)[c]	NA[d]	16.9 (8.3-34.7)	17.0 (10.4-27.6)

Abbreviations: CI, confidence interval; NA, not applicable; PVCs, premature ventricular complexes.
[a] Percentage of subjects in each tertile of Duke Treadmill Score classified by recovery PVC occurrence.
[b] Centered cumulative hazard.
[c] As calculated from cumulative hazard and hazard ratio in each category.
[d] Unable to calculate hazard ratio owing to inadequate number of events.

PVCs and cardiovascular mortality may have resulted from a limited number of such events. Although we excluded subjects with a clinical history of heart failure, we did not have data on left ventricular systolic function. Finally, the clinical benefits, if any, of interventions aimed at reducing exercise PVC occurrence remain to be demonstrated.

This study demonstrates that PVCs occurring during recovery from exercise testing have prognostic significance that augments established risk factors and other exercise test findings, whereas PVCs occurring solely during exercise have limited prognostic significance. More sensitive noninvasive testing with exercise echocardiography, myocardial scintigraphy, or evaluation of left ventricular systolic function may be warranted in subjects with recovery PVCs, particularly those with intermediate findings during exercise treadmill testing.

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Author Contributions: Mr Dewey had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design*: Dewey, Kapoor, Williams, Hadley, Myers, and Froelicher. *Acquisition of data*: Williams, Lipinski, Myers, and Froelicher. *Analysis and interpretation of data*: Dewey, Kapoor, Williams, Lipinski, Ashley, Hadley, and Froelicher. *Drafting of the manuscript*: Dewey, Kapoor, Williams, Hadley, and Froelicher. *Critical revision of the manuscript for important intellectual content*: Dewey, Kapoor, Williams, Lipinski, Ashley, Hadley, Myers, and Froelicher. *Statistical analysis*: Dewey, Williams, Ashley, Hadley, Myers, and Froelicher. *Administrative, technical, or material support*: Lipinski, Hadley, Myers, and Froelicher. *Study supervision*: Williams, Myers, and Froelicher.
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