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Prevalence and Prognostic Significance of Exercise-Induced Nonsustained Ventricular Tachycardia in Asymptomatic Volunteers

BLSA (Baltimore Longitudinal Study of Aging)

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Objectives This study sought to determine the clinical predictors and prognostic significance of exercise-induced nonsustained ventricular tachycardia (NSVT) in a large population of asymptomatic volunteers.

Background Prior studies have reported variable risk associated with exercise-induced ventricular arrhythmia.

Methods Subjects in the BLSA (Baltimore Longitudinal Study of Aging) free of known cardiovascular disease who completed at least 1 symptom-limited exercise treadmill test between 1977 and 2001 were included. NSVT episodes were characterized by QRS morphology, duration, and rate. Subjects underwent follow-up clinical evaluation every 2 years.

Results The 2,099 subjects (mean age: 52 years; 52.2% male) underwent a mean of 2.7 exercise tests, in which 79 (3.7%) developed NSVT with exercise on at least 1 test. The median duration of NSVT was 3 beats (≤5 beats in 84%), and the median rate was 175 beats/min. Subjects with (vs. without) NSVT were older (67 ± 12 years vs. 51 ± 17 years, $p < 0.0001$) and more likely to be male (80% vs. 51%, $p < 0.0001$) and to have baseline electrocardiographic abnormalities (50% vs. 17%, $p < 0.0001$) or ischemic ST-segment changes with exercise (20% vs. 10%, $p = 0.004$). Over a mean follow-up of 13.5 ± 7.7 years, 518 deaths (24.6%) occurred. After multivariable adjustment for age, sex, and coronary risk factors, exercise-induced NSVT was not significantly associated with total mortality (hazard ratio: 1.30; 95% confidence interval: 0.89 to 1.90; $p = 0.17$).

Conclusions Exercise-induced NSVT occurred in nearly 4% of this asymptomatic adult cohort. This finding increased with age and was more common in men. After adjustment for clinical variables, exercise-induced NSVT did not independently increase the risk of total mortality. (J Am Coll Cardiol 2013;62:595–600) © 2013 by the American College of Cardiology Foundation

A number of studies have examined the predictors and prognostic significance of exercise-induced ventricular premature depolarizations (VPDs) and nonsustained ventricular tachycardia (NSVT) in subjects with known or suspected coronary artery disease or other cardiomyopathies (1–4). In these settings, exercise-induced ventricular arrhythmia has been shown to have an adverse effect on prognosis. However, the long-term prognostic significance of ventricular arrhythmias induced by exercise testing in apparently healthy subjects is controversial. We previously observed a benign prognosis in a small number of subjects with exercise-induced NSVT over 2 to 5 years of mean follow-up (5,6). The goal of the present study is to examine the prevalence, predictors, and prognostic significance of exercise-induced NSVT in a larger cohort of healthy subjects with long-term follow-up.

Methods

The BLSA (Baltimore Longitudinal Study of Aging) is a prospective study of the aging process that is continuously enrolling active, generally healthy, community-dwelling volunteers aged 21 years and older (7). Subjects undergo 2 to 3 days of medical, physiological, and psychological testing at the

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Abbreviations and Acronyms

BLSA = Baltimore Longitudinal Study of Aging
CI = confidence interval
ECG = electrocardiogram
HR = hazard ratio
NSVT = nonsustained ventricular tachycardia
VPD = ventricular premature depolarization
VT = ventricular tachycardia

Gerontology Research Center and the National Institute of Aging Clinical Research Unit, both in Baltimore, Maryland, approximately every 2 years. Treadmill exercise testing is offered on alternate visits to all individuals without clinical heart disease or major noncardiac diseases that would limit the ability to perform aerobic exercise.

Between September 1977 and December 2001, 2,178 subjects underwent a total of 5,854 maximal exercise treadmill tests (mean of 2.7 tests per subject). Of these 2,178 subjects, 79 (3.8%) were excluded for various reasons as shown in Figure 1, leaving 2,099 subjects in the present analysis. Exercise treadmill testing was performed using a modified Balke protocol, during which the treadmill grade was increased 3% every 2 min, starting from a horizontal position; women walked at an initial speed of 3.0 mph and men at 3.5 mph (8). In more aerobically fit subjects, speed was increased by 0.5 mph 1 to 3 times during the test. Before exercise, a standard 12-lead electrocardiogram (ECG) was recorded with the subject in the supine and seated positions, after 30 s of forced hyperventilation, and after 30 s of standing. A 12-lead ECG and brachial artery cuff blood pressure were recorded every 2 min during exercise, at maximal effort, immediately after cessation of exercise, and every 2 min for at least 6 min into recovery. Testing was terminated because of fatigue, dyspnea, or leg discomfort; NSVT was not the reason for early exercise termination unless accompanied by symptoms.

Resting and exercise ECG abnormalities were assessed by Minnesota Code criteria by a single observer (J.L.F.). Ischemic ECG changes were coded as previously described (8). NSVT was defined by the presence of 3 or more consecutive premature ventricular beats at a rate >100 beats/min with spontaneous termination within 30 s. Exercise tests showing NSVT were subsequently reviewed by an electrophysiologist (J.E.M.) and additional information, including duration, rate, and ventricular tachycardia (VT) morphology, was extracted.

Cardiovascular risk factors were assessed for all subjects at the time of the initial exercise test. Hypertension was defined by use of antihypertensive drug therapy or a current blood pressure ≥140/90 mm Hg, hypercholesterolemia was defined by a plasma total cholesterol level ≥240 mg/dl, diabetes mellitus was defined by the use of insulin or oral hypoglycemic agents or a fasting plasma glucose level ≥126 mg/dl, and current smoking was defined as ≥5 cigarettes/day. Body mass index was calculated as weight in kilograms/(height in meters)^2. Mortality information was obtained via death certificates and autopsy reports as available and supplemented by the National Death Index through December 31, 2006.

The clinical characteristics of the cohort are shown as mean ± SD or percent and compared using the unpaired *t* test or chi-square test as appropriate. Univariate predictors of mortality were obtained using Kaplan-Meier analysis, and

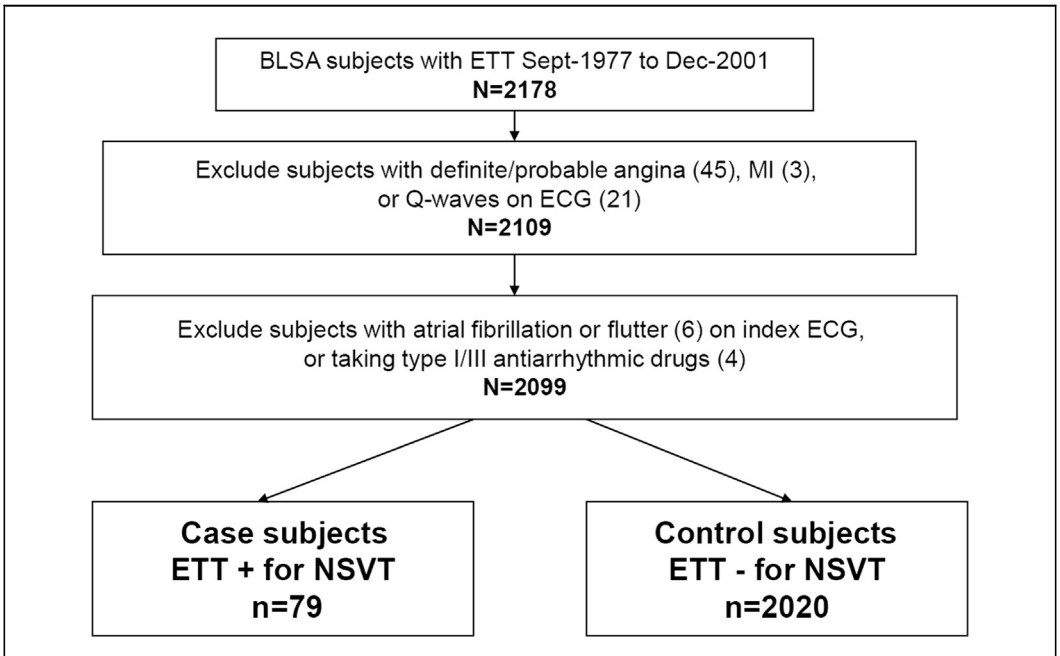

Figure 1 Study Flow Diagram

The figure shows the steps in selection of subjects for inclusion in the study analysis. BLSA = Baltimore Longitudinal Study of Aging; ECG = electrocardiogram; ETT = exercise tolerance test; MI = myocardial infarction.

multivariate analyses were performed using the Cox proportional hazards model. The multivariate model included NSVT status, age, sex, diabetes, hypertension, body mass index, smoking status, hypercholesterolemia, any baseline ECG abnormality, ischemic ST-segment depression with exercise, and exercise duration. The final model was derived using the backward elimination method. NSVT status was forced into the model because it was the variable of interest. Unadjusted and adjusted Kaplan-Meier plots were constructed to show the difference in the mortality of the 2 NSVT groups pre- and post-adjustment. The Statistical Analysis System (version 9.1, SAS Institute, Cary, North Carolina) was used for all analyses. A 2-tailed probability value <0.05 was required for statistical significance.

Results

The final cohort included 2,099 subjects (mean age: 52 years; 52.2% male) who underwent a mean of 2.7 tests, and 79 (3.7%) developed NSVT during at least 1 exercise test. Participant characteristics are shown in Table 1. Subjects with (vs. without) NSVT were substantially older (age 67 ± 12 years vs. 51 ± 17 years), were more likely to be male and hypertensive, and had a modestly higher body mass index. There were no significant differences in the prevalence of other coronary risk factors. The median duration of NSVT was 3 beats (≤5 beats in 84%), and the median rate was 175 beats/min. NSVT was polymorphic in 60% of subjects, monomorphic in 29%, and indeterminate in 11%; NSVT occurred during exercise only in 74% of subjects, recovery only in 20%, and both in 6%. Early termination of exercise testing because of NSVT was not required in any subject. Of the 42 individuals who underwent at least one subsequent exercise test after the test demonstrating NSVT, NSVT recurred in 12 subjects (29%).

The prevalence of exercise-induced NSVT was 5.7% in men (63 of 1,095 subjects) and 1.6% in women (16 of 1,004) ($p < 0.0001$). As shown in Figure 2, the prevalence of exercise-induced NSVT increased strikingly with age. Of note, the age-associated increase in NSVT was much more prominent in men than in women.

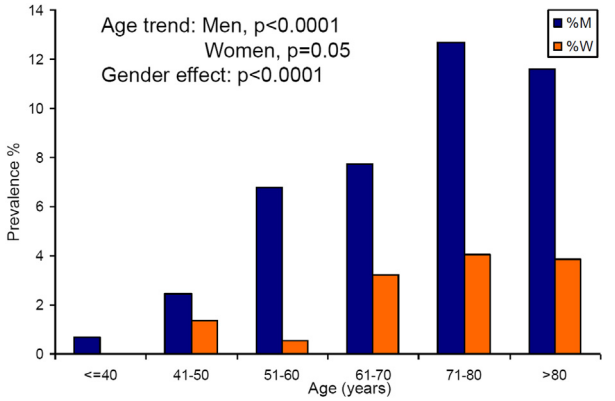

Figure 2 Prevalence of Exercise-Induced NSVT by Age and Sex

The bar graph shows the prevalence of NSVT observed on at least 1 exercise test stratified by decade of age and sex. A marked effect of age on the prevalence of exercise-induced NSVT was seen in men and to a lesser degree in women. NSVT = nonsustained ventricular tachycardia.

Table 2 compares the resting ECG of subjects with and without exercise-induced NSVT. Subjects with NSVT were significantly more likely to have ECG abnormalities than those without NSVT (49.5% vs. 17%, $p < 0.0001$). Isolated VPDs, conduction defects other than left bundle branch block, and minor ST-T changes were significantly more prevalent in subjects with exercise-induced NSVT.

Table 3 shows the exercise testing results. Subjects with NSVT had lower exercise tolerance and lower peak heart rate but achieved a similar rate-pressure product and percentage of age-predicted maximum heart rate compared with those without NSVT. Ischemic ST-segment changes induced by exercise were more prevalent in subjects with NSVT (20.2% vs. 10.2%, $p = 0.004$). Multivariable predictors of exercise-induced NSVT were older age (hazard ratio [HR]: 1.04/year; 95% confidence interval [CI]: 1.03 to 1.06; $p < 0.0001$), male (HR: 4.9; 95% CI: 2.7 to 9.0; $p < 0.0001$), VPD on resting ECG (HR: 4.6; 95% CI: 2.0 to 10.6; $p < 0.001$), and ischemic

Table 1 Clinical Characteristics of Subjects

Characteristic	NSVT (n = 79)	No NSVT (n = 2,020)	p Value
Age (yrs)	67.0 ± 12	51.4 ± 17	<0.0001
Sex (% men)	63 (79.7)	1033 (51.1)	<0.0001
Body mass index (kg/m^2)	26.3 ± 4.8	25.1 ± 4.0	0.03
Ethnicity (% white)	61 (77.2)	1558 (77.1)	0.98
Smoking status (% current)	3 (3.8)	86 (4.2)	0.84
Hypertension	26 (33)	402 (20)	0.004
Diabetes	3 (3.8)	58 (2.8)	0.63
Hypercholesterolemia	10 (12.6)	373 (18.4)	0.18

Values are mean ± SD or n (%).
NSVT = nonsustained ventricular tachycardia.

Table 2 Baseline Electrocardiographic Characteristics

Characteristic	NSVT (n = 79)	No NSVT (n = 2,020)	p Value
Atrial PDs	4 (5.1)	56 (2.7)	0.23
Ventricular PDs	10 (12.7)	51 (2.5)	<0.0001
First-degree AV block	7 (8.8)	54 (2.6)	0.0013
Left axis deviation	11 (13.9)	96 (4.7)	0.0003
Right bundle branch block	5 (6.3)	25 (1.2)	0.004
Left bundle branch block	0	3 (0.15)	1.00
Minor IVCD	5 (6.3)	62 (3.7)	0.10
Minor ST-T changes	11 (13.9)	109 (5.4)	0.0014
Any of these characteristics	40 (49.5)	368 (17.0)	<0.0001

Values are (%).
AV = atrioventricular; IVCD = intraventricular conduction delay; NSVT = nonsustained ventricular tachycardia; PD = premature depolarization; ST-T = ST-segment–T-wave.

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Table 3 Exercise Test Characteristics

Characteristic	NSVT (n = 79)	No NSVT (n = 2,020)	p Value
Exercise duration (min)	8.9 ± 2.6	10.6 ± 3	<0.0001
Peak heart rate (beats/min)	155 ± 17	168 ± 21	<0.0001
Maximum predicted heart rate (%)	101 ± 9	99 ± 8	0.24
Peak systolic blood pressure (mm Hg)	187 ± 26	171 ± 28	0.0004
Peak rate-pressure product (beats/min × mm Hg)	28,991 ± 5,260	28,918 ± 5,487	0.90
Ischemic ST-segment changes	16 (20.2)	206 (10.2)	0.0044

Values are mean ± SD or n (%).
Abbreviation as in Table 1.

ST-segment changes during exercise (HR: 1.8; 95% CI: 1.04 to 3.2; $p < 0.05$).

Over a mean follow-up of 13.5 ± 7.7 years, 518 subjects (24.6%) died. The median follow-up of the entire sample was 12.5 years, with a median follow-up of 9.5 years in subjects with exercise-induced NSVT and 12.7 years in subjects without this finding. As shown in Figure 3A, the unadjusted total mortality rate was higher in subjects with exercise-induced NSVT than in those without (39% vs. 24%, $p < 0.0001$). However, after adjustment for baseline demographic variables and coronary risk factors, the total mortality rate was not significantly different between subjects with and without exercise-induced NSVT (Fig. 3B). Unadjusted total mortality rates did not vary significantly by morphology of NSVT or by whether VT occurred on a single test or multiple tests. Mortality also did not differ significantly between the 74% of subjects with NSVT only during exercise and the 20% with NSVT only in recovery (chi-square p value = 0.53). In addition, the risk of death was similar in the 12 subjects who had NSVT on more than 1 visit compared with the 30 subjects who had NSVT on only 1 visit (chi-square p value = 0.55).

Multivariate determinants of total mortality in a Cox model that included baseline demographic variables, coronary risk factors, resting ECG, and exercise variables are shown in Table 4. Older age, male, diabetes, hypertension, and shorter exercise duration were independent predictors of total mortality in the cohort. However, the presence of exercise-induced NSVT was not independently predictive of mortality.

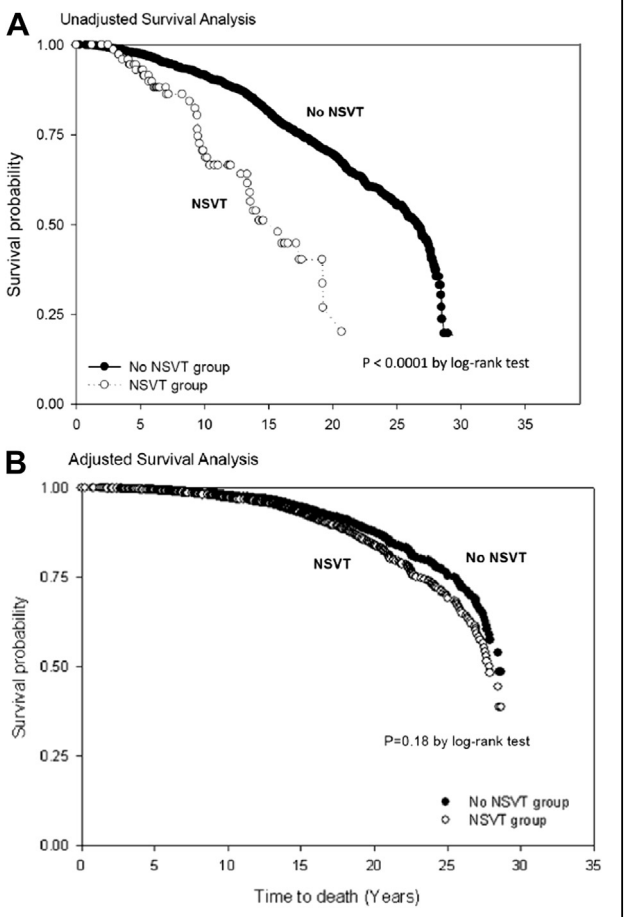

Figure 3 Kaplan-Meier Analysis of Survival Probability Stratified by the Presence or Absence of NSVT

(A) Unadjusted survival analysis of study subjects stratified by the presence or absence of exercise-induced NSVT. **(B)** Adjusted survival analysis of study subjects stratified by NSVT status, adjusted for the final Cox model, which included NSVT status, age, sex, diabetes, hypertension, body mass index, smoking status, hypercholesterolemia, any baseline electrocardiographic abnormality, exercise duration, and ischemic ST-segment depression. Abbreviations as in Figures 1 and 2.

Discussion

In the current analysis, exercise-induced NSVT occurred on 1 or more tests in 3.7% of asymptomatic community-dwelling BLSA volunteers who were free of clinical heart disease on initial testing. The finding was more prevalent in men, older subjects, and those with hypertension. Conduction and repolarization abnormalities and VPDs on resting ECG and exercise-induced ischemic ST-segment changes were more frequent in subjects with exercise-induced NSVT. Although the unadjusted total mortality rate was higher in subjects with exercise-induced NSVT, this finding did not persist after adjustment for baseline clinical characteristics and was largely explained by differences in age and sex.

In a prior BLSA study, 10 older individuals who were found to have exercise-induced NSVT had similar coronary risk factors, exercise tolerance, and ST-segment response to exercise compared with age- and sex-matched subjects without NSVT. Over 2 years of mean follow-up, all individuals remained free of cardiac events (5). In a later study, subjects with frequent exercise-induced VPDs (n = 62) or NSVT (n = 18) displayed no difference in the prevalence

Table 4 Multivariable-Adjusted Predictors of Mortality

Variable	Hazard Ratio	95% Confidence Interval for Hazard Ratio	p Value
NSVT	1.30	0.89–1.90	0.17
Age (/yr)	1.11	1.09–1.12	<0.0001
Male	1.75	1.42–2.13	<0.0001
Hypertension	1.51	1.10–2.00	<0.01
Diabetes	2.06	1.37–3.08	0.0005
Exercise duration (/min)	0.91	0.87–0.94	<0.0001

Hazard ratios are indicated after multivariable adjustment for the final Cox model, which included NSVT status, age, sex, diabetes, hypertension, body mass index, smoking status, hypercholesterolemia, any baseline electrocardiographic abnormality, exercise duration, and ischemic ST-segment depression.

Abbreviation as in Table 1.

of coronary risk factors or exercise-induced ischemia than age- and sex-matched controls. Over a mean follow-up of 5.6 years, subjects with NSVT had similar cardiovascular outcomes compared with subjects without NSVT (6). The present study confirms and extends these findings in a larger group of subjects with exercise-induced NSVT, with comparison to the entire BLSA cohort over a much longer follow-up.

Most prior studies examining the prognosis of asymptomatic persons with exercise-induced ventricular arrhythmias have focused largely on VPDs rather than NSVT. Jouven et al. (4) examined the results of exercise testing on a cohort of 6,101 asymptomatic male French civil servants aged 42 to 53 years with a mean follow-up of 23 years and found that frequent VPDs during exercise (defined at 2 or more consecutive beats or >10% of total beats) predicted increased total and cardiovascular mortality.

Frolkis et al. (1) reviewed exercise tests on 29,244 patients undergoing exercise testing for clinical indications (1). They found that frequent VPDs during exercise (defined as the presence of 7 or more ventricular premature beats/min during any given stage, ventricular bigeminy, ventricular trigeminy, ventricular couplets, ventricular triplets, sustained or nonsustained VT ventricular flutter, torsades de pointes, or ventricular fibrillation) predicted increased total mortality (HR: 1.8) over a mean follow-up of 5.3 years on univariate analysis. However, after propensity matching for confounding variables, only frequent ventricular ectopy during recovery predicted increased mortality, whereas frequent ventricular ectopy that occurred during exercise did not.

Eckart et al. examined 585 patients with exercise-induced ventricular arrhythmia (defined as ventricular couplets, triplets, or multifocal ventricular ectopy) during clinically indicated exercise testing and compared outcomes with 2,340 matched control subjects without arrhythmia over a mean follow-up of 2 years (2). They found that exercise-induced ventricular arrhythmia with right bundle branch block morphology or with multiple morphologies predicted higher mortality. However, patients with left bundle branch block morphology of ventricular arrhythmia had outcomes similar to those of matched patients without arrhythmia. Our study differs in that we examined only asymptomatic subjects who were free of known cardiac disease. It is likely that exercise-induced VPDs have greater prognostic significance in a population with a clinical suspicion and higher prevalence of coronary artery disease.

Most relevant to the current study, Yang et al. (3) found that exercise-induced NSVT developed in 50 (1.5%) of 3,351 patients (97% men; mean age: 62 years) undergoing clinically indicated exercise testing at the Long Beach Veterans Affairs Medical Center. In 30 of these patients (60%), the NSVT was 3 beats in duration; NSVT occurred with nearly equal frequency during exercise (52%) and in recovery (48%). Only 2 of 26 patients with NSVT who underwent repeat exercise testing developed NSVT on the subsequent test. Over a mean follow-up of 26 months, the unadjusted total mortality rate in the NSVT group (3.6%) was not significantly different than the mortality rate in the total group (5.1%). Both the clinical characteristics and lack of prognostic significance of the exercise-induced NSVT are concordant with our findings, although their follow-up was of relatively short duration (3).

A noteworthy finding in the present study was the striking age-related increase in exercise-induced NSVT, particularly in men. The reasons for the marked increase of exercise-induced NSVT with age are not clear but may relate to age-related cardiovascular changes. Previous work has demonstrated that myocyte hypertrophy, increased cardiac matrix connective tissue, and altered calcium handling occur with aging (9–12). Moreover, myocyte loss and reactive hypertrophy occur to a greater degree in men than in women (13). Increased cardiac beta-receptor stimulation during exercise, as demonstrated by exaggerated augmentation of plasma catecholamines in older versus younger men, may contribute to increased ventricular ectopic activity in this milieu (14).

Our findings do not negate the risk of exercise-induced NSVT in patients with coronary artery disease, cardiomyopathies, and inherited arrhythmia syndromes. When NSVT occurs in a milieu of myocardial fibrosis, hypertrophy, or ischemia, it is a prognostic indicator of adverse events. Increased risk of sudden death with spontaneous and exercise-induced NSVT has been demonstrated for patients with hypertrophic cardiomyopathy (15,16), Chagasic cardiomyopathy (17), arrhythmogenic right ventricular dysplasia (18), and catecholaminergic polymorphic VT (19). Assessing for such diseases in a patient with exercise-induced NSVT would therefore be reasonable if clinically suspected. Likewise, our results do not necessarily suggest that exercise-induced NSVT should be disregarded in patients referred for clinically indicated exercise testing. Rather, our findings suggest that in older individuals in whom significant coronary or other heart disease is unlikely, the finding of exercise-induced NSVT alone, particular brief, asymptomatic runs, does not indicate an adverse prognosis, require extensive evaluation or medical treatment, or necessitate exercise restrictions.

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Study limitations. The BLSA recruits subjects primarily from a single geographic region of the United States, and volunteers are self-selected and generally health conscious and of higher socioeconomic status. Thus, our findings require confirmation in a more general population. The use of antihypertensive medications such as beta-blockers and calcium channel blockers as well as secular changes in cardiac risk factors over the long follow-up period could have affected long-term mortality, although these factors would affect both the NSVT and control groups. Our subjects were a volunteer group of apparently healthy subjects who were exercised using a modified Balke protocol, which may limit direct comparison with other studies that used different populations, treadmill protocols (1–3), or cycle exercise (4). The modest number of subjects with exercise-induced NSVT in this study limits the ability to perform subgroup analysis. Because cause of death could not be reliably ascertained in all subjects, the current analysis was limited to total mortality. We therefore cannot exclude the possibility that the risk of death from ventricular arrhythmia is higher in subjects with exercise-induced NSVT. Finally, because the overwhelming majority of NSVT episodes in the current study were 3 to 5 beats in length, the benign prognosis may not necessarily apply to persons with longer NSVT runs.

Conclusions

We found that exercise-induced NSVT in asymptomatic volunteers free of known cardiovascular disease was more prevalent in older subjects and in men and occurred more frequently in those with resting ECG abnormalities and with exercise-induced ischemic ST-segment changes. Although total mortality was higher in subjects with exercise-induced NSVT, these findings were largely explained by differences in coronary risk factors and other baseline characteristics, particularly age. Our results suggest that brief asymptomatic runs of exercise-induced NSVT, in the absence of clinical heart disease, are not uncommon in older adults and should not require further medical evaluation, treatment, or restriction of exercise.

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Key Words: aging ■ exercise testing ■ ventricular tachycardia.