Clinical Correlates and Prognostic Significance of Exercise-Induced Ventricular Premature Beats in the Community

The Framingham Heart Study

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Background—Recent investigations suggest that ventricular premature beats during exercise (EVPBs) are associated with increased cardiovascular mortality in asymptomatic individuals, but mechanisms underlying the association are unclear.

Method and Results—We evaluated 2885 Framingham Offspring Study participants (1397 men; mean age, 43 years) who were free of cardiovascular disease and who underwent a routine exercise stress test; 792 participants (27%) had development of EVPBs (median, 0.22/min of exercise). Logistic regression was used to evaluate predictors of EVPBs. Cox models were used to examine the relations of infrequent (less than or equal to median) and frequent (greater than median) versus no EVPBs to incidence of hard coronary heart disease (CHD) event (recognized myocardial infarction, coronary insufficiency, or CHD death) and all-cause mortality, adjusting for vascular risk factors and exercise variables. Age and male sex were key correlates of EVPBs. During follow-up (mean, 15 years), 142 (113 men) had a first hard CHD event and 171 participants (109 men) died. EVPBs were not associated with hard CHD events but were associated with increased all-cause mortality rates (multivariable-adjusted hazards ratio, 1.86, 95% CI, 1.24 to 2.79 for infrequent, and 1.71, 95% CI, 1.18 to 2.49 for frequent EVPBs versus none). The relations of EVPBs to mortality risk were not influenced by VPB grade, presence of recovery VPBs, left ventricular dysfunction, or an ischemic ST-segment response.

Conclusions—In our large, community-based sample of asymptomatic individuals, EVPBs were associated with increased risk of death at a much lower threshold than previously reported. Additional studies are needed to confirm these findings and to clarify the underlying mechanisms. (Circulation. 2004;109:2417-2422.)

Key Words: exercise mortality ventricles cardiovascular diseases arrhythmia

Exercise stress testing has been recommended for the risk stratification of asymptomatic individuals with an intermediate pretest probability of coronary heart disease (CHD), with the expectation that people identified as high risk could be targeted for primary prevention measures. Several variables obtained during a routine exercise test are widely accepted as indicators of elevated CHD risk. These include an ischemic ST-segment response or the occurrence of angina, a hypotensive blood pressure, poor exercise capacity, and an impaired heart rate response to exercise.

More recently, attention has focused on the prognostic significance of ventricular premature beats developing during exercise (EVPBs). Several recent clinical investigations have examined the association of EVPBs with risk of death in patients referred for diagnostic exercise testing. Two of these studies reported that EVPBs were associated with increased risk of death on follow-up, but a third study reported otherwise. A fourth investigation reported that VPBs occurring during the recovery period after exercise were associated with elevated mortality risk, but EVPBs alone did not portend an adverse prognosis.

Whereas patients with suspected CHD may have EVPBs caused by the presence of an ischemic substrate, the clinical correlates of EVPBs in asymptomatic individuals without such a substrate are incompletely understood. Furthermore, the prognostic significance of EVPBs in asymptomatic people is also unclear. Several initial reports indicated that EVPBs were benign in otherwise healthy individuals on short-term (<5 years) follow-up. Recently, two large, prospective studies of asymptomatic individuals reported that...
frequent EVPBs are associated with increased risk of cardiovascular mortality over a longer period of follow-up exceeding 20 years. Both studies were limited partly by empirical and varying definitions of “frequent” EVPBs and a failure to exclude individuals with VPBs on the resting preexercise ECG. Of note, neither study elucidated the mechanisms by which EVPBs increased mortality risk. They did not assess the risk of nonfatal CHD on follow-up that could help clarify whether the elevated cardiovascular mortality rate associated with EVPBs is mediated through an increased risk of CHD on follow-up. Additionally, neither study evaluated left ventricular (LV) systolic function at baseline to provide insights into whether individuals with frequent EVPBs have myocardial dysfunction as an underlying substrate that could predispose them to both arrhythmia and cardiovascular mortality, a hypothesis proposed by some investigators.

The objectives of our investigation were to characterize the clinical correlates of EVPBs and assess their prognostic impact in a large, community-based sample of young to middle-aged men and women free of overt cardiovascular disease (CVD). We also sought to elucidate potential mechanisms by which EVPBs can elevate mortality risk.

Methods

Study Design and Sample

The Framingham Offspring Study is an epidemiological study of CVD risk factors that began in 1971 with the recruitment of the offspring of the original Framingham Heart Study participants and their spouses. Offspring Study participants are examined every 4 years. During their second examination (1978 to 1982), all participants underwent a routine treadmill exercise test in addition to a physician-obtained medical history, physical examination, 12-lead ECG, 2-dimensionally guided M-mode echocardiography, and biochemical tests (including glucose and lipid profile).

Of the 3427 attendees who underwent exercise testing, we excluded 542 participants from this investigation for the following reasons: prevalent CVD (n=84), valvular heart disease (n=13), chronic obstructive lung disease (n=69), usage of cardiac glycoside or β-blocking agents (n=81), existence of VPBs at rest (n=39), inability to exercise for at least 1 minute during the first stage of the standard Bruce protocol and the reason for the cessation of exercise was not the occurrence of EVPBs (n=3), lack of follow-up data (n=2), age <20 years at baseline (n=10), or missing covariate data (n=241). After these exclusions, 2885 participants (1397 men) were eligible.

Exercise Testing Protocol

All participants underwent submaximal exercise test according to the standard Bruce protocol while their ECGs were continually monitored and recorded (simultaneous V1 and V5, Clinical Data Inc) during exercise and for 5 minutes of recovery. The test was terminated (without a cool-down period) when participants reached their target heart rate (85% age-predicted peak heart rate). Exercise testing was terminated prematurely for the following reasons: limiting chest discomfort, dyspnea, fatigue or leg discomfort; hypotension or a severe hypertensive response; or the development of significant ECG abnormalities including ≥2-mm ST-segment depression. An ischemic ST-segment response was defined as a ≥1-mm additional horizontal or down-sloping ST-segment depression (measured 80 ms after the J-point) during exercise or recovery compared with the resting ECG. All exercise ECGs were subsequently analyzed for the presence of atrial or ventricular premature beats with the use of a high-speed digital computer system (Clinical Data Inc). All EVPBs and atrial premature beats (APBs) were identified by a technician and confirmed by a cardiologist. The numbers of EVPBs and APBs during each stage of exercise were counted for each participant from the recorded tracings.

Follow-Up and Outcome Events

All study participants were under continuous surveillance for the development of CVD events. For this investigation, we chose 2 primary end points: (1) incidence of a first “hard” CHD event—recognized myocardial infarction, coronary insufficiency, or sudden death; and (2) all-cause mortality. Criteria for the diagnosis of these end points have been described in detail. A committee of 3 experienced physicians reviewed all available medical records (including hospitalization data) for the adjudication of these end points.

Definitions of ‘Frequent’ EVPBs and Their Grade

In our sample, 792 individuals (27%, 436 men) had development of EVPBs. Some prior studies have defined frequent ectopy as an EVPBs count of >10% of all depolarizations during exercise. Only 4 of 2885 individuals met this criterion for frequent ectopy; the distribution of EVPBs expressed as a percentage of all beats during exercise that were VPBs had a mean of 0.15, median of 0, and 99th percentile of 2.7. Given the very low occurrence of frequent EVPBs by this criterion, we examined the distribution of the frequency of EVPBs expressed as VPBs per minute of exercise (calculated for each subject by dividing the total number of EVPBs by the total duration of exercise in minutes). The median value of EVPBs per minute of exercise in our sample was 0.22 in both sexes (≈1 EVPB for every 4.5 minutes of exercise), with 95th percentiles of 2.53 in women and 3.76 in men. We divided our study participants into 3 groups: (1) those without any VPBs during exercise; (2) those with VPBs at or below the median value for the sample (infrequent EVPBs); and (3) those with VPBs above the median (frequent EVPBs).

The morphology of EVPBs may also have prognostic significance. Therefore, we further categorized EVPBs as high grade if one or more of the following were present (Lown criteria), consistent with prior reports: frequency >30/h, multiform, couplets, and nonsustained (≥3 consecutive VPBs lasting <30 seconds) or sustained ventricular tachycardia. In the absence of these features, EVPBs were labeled low grade.

VPBs During Recovery After Exercise

Recent investigations have suggested that VPBs during recovery may be associated with a worse prognosis compared with EVPBs. We therefore examined the frequency of VPBs during recovery after exercise and dichotomized our study participants into those with and those without VPBs during recovery after exercise.

APBs During Exercise

Similar to EVPBs, we calculated the average number of APBs per minute of exercise for each subject and divided participants into 3 groups (frequency-based indexes): (1) those without any APBs; (2) those with APBs at or below the median value for the sample (0.25 APB/min of exercise; infrequent APBs during exercise [EAPBs]); and (3) those with APBs above the median (frequent EAPBs).

Statistical Analyses

Initially, we examined the clinical correlates of EVPBs; EVPBs refers to VPBs only during exercise (VPBs during recovery were not included in this group). Next, we evaluated the association of the following arrhythmias with the risk of outcome events: (1) EVPBs; (2) VPBs during recovery; and (3) APBs during exercise.

Clinical Correlates of EVPBs

We used logistic regression to evaluate the clinical correlates of EVPBs. EVPBs were modeled as a binary variable initially (presence versus absence of EVPBs). Covariates evaluated in these analyses included age, sex, body mass index (BMI), smoking, hypertension, ratio of serum total cholesterol to HDL cholesterol, diabetes mellitus, resting heart rate, reduced LV fractional shortening (defined as <0.29, a value that corresponds to approximately an ejection fraction of 0.50).
Exercise and Risk of Outcome Events

Relations of Arrhythmias During and After Exercise and Risk of Outcome Events

We used sex-stratified multivariable Cox proportional hazards regression to examine the association of EVPB category and the incidence of hard CHD and all-cause mortality (separate analyses for each outcome). Subjects without EVPBs served as the reference group to which those with infrequent EVPBs and frequent EVPBs were compared.

Three sets of models were constructed in hierarchical fashion: (1) models adjusting for age alone; (2) models additionally adjusting for known CVD risk factors (age, BMI, smoking, hypertension, ratio of serum total cholesterol to HDL cholesterol, diabetes mellitus, resting heart rate) and exercise variables known to be prognostically important (ischemic ST-segment response, peak heart rate achieved [a measure of chronotropic competence], and duration of exercise [a measure of fitness]); and (3) models adjusting for occurrence of a CVD event on follow-up (for analyses examining all-cause mortality). The latter model clarifies if EVPBs influence mortality risk by promoting risk of CVD on follow-up. Heart rate recovery after exercise, a measure of autonomic function, was not included in any of the models because we have previously reported that in our sample, this measure was not related to mortality risk.

A similar analytical strategy was used to evaluate the prognostic significance of grade of EVPBs (low grade and high grade EVPBs were compared with the referent group without any EVPBs); VPBs during recovery after exercise (binary variable); and EAPBs (those with infrequent and frequent APBs were compared with the group without any APBs).

Additional Analyses

Analyses examining the prognostic impact of EVPBs were repeated with additional adjustment for reduced fractional shortening in the multivariable models. Effect modification by age, sex, presence of an ischemic ST-segment response, grade of EVPBs, and presence of VPBs during recovery was assessed by evaluating interaction terms in multivariable models. Effect modification by age, sex, presence of an ischemic ST-segment response, grade of EVPBs, and presence of VPBs during recovery was assessed by evaluating interaction terms in multivariable models.
Results

The baseline characteristics of our sample are shown in Table 1 according to EVPBs category. Participants with frequent EVPBs were likely to be older, have a higher prevalence of hypertension, and a higher prevalence of VPB after exercise during recovery. Only 28 of 399 individuals (7%) with infrequent EVPBs had high grade VPBs (Table 1). During exercise, 231 participants (8%) had ischemic ST-segment changes. Twenty-one individuals had a reduced fractional shortening, and they were distributed similarly across the categories of EVPBs.

Correlates of EVPBs

In logistic models, presence of EVPBs was associated with increasing age (multivariable-adjusted OR per 10-year increment of 1.37; 95% CI, 1.24 to 1.51) and male sex (OR, 1.44; 95% CI, 1.19 to 1.74). In models evaluating predictors of frequent EVPBs, age (OR per 10-year increment of 1.46; 95% CI, 1.29 to 1.65), male sex (OR, 1.33; 95% CI, 1.04 to 1.70), and hypertension (OR, 1.34; 95% CI, 1.01 to 1.76) emerged as key correlates. None of the other variables examined (including an ischemic ST-segment response or reduced fractional shortening) was related to the presence of EVPBs.

Outcome Events on Follow-Up

On follow-up (mean, 15 years), 171 participants (109 men) died. There were 38 deaths (31 men) attributable to CVD events deaths. Ninety participants died of cancer, whereas 43 individuals died of other causes. One hundred forty-two participants (113 men) had a first hard CHD event. The unadjusted cumulative incidence of death increased progressively across the 3 categories of EVPBs (Figure 1). The age-adjusted 15-year incidences of death were 4.21% (95% CI, 3.33 to 5.09) for the group with no EVPBs, 7.03% (95% CI, 4.62 to 9.44) for participants with infrequent EVPBs, and 8.27% (95% CI, 5.67 to 10.88) for individuals with frequent EVPBs.

EVPBs and Risk of Outcome Events

Table 2 displays the results of Cox models relating EVPBs to risk of the 2 outcome events. EVPBs were not associated with risk of hard CHD events either in age-adjusted or in multivariable-adjusted models, whereas known CHD risk factors (age, total/HDL cholesterol, diabetes, smoking, exercise duration, peak heart rate, resting heart rate (all defined at baseline), and interim CVD during follow-up). EVPBs were associated with a 66% to 71% higher risk of death in the multivariable models B and C. Infrequent EVPBs were associated with 80% to 86% higher risk of death (models B and C). Age (hazards ratio [HR] per year increment,
In our large, community-based sample, EVPBs were observed in more than a quarter of individuals, but only 4 individuals met the criterion for frequent EVPBs (>10% of all beats) proposed in the literature. Differences in our study sample characteristics and exercise test protocols may account for this divergence from prior reports. We used, therefore, an alternative definition of frequent EVPBs (>0.22 bpm) based on the distribution of their frequency.

The association of infrequent and frequent EVPBs with all-cause mortality was not influenced by the grade of VPBs, the presence (or absence) of an ischemic ST-segment response, or reduced LV fractional shortening were not.

On long-term follow-up, both infrequent and frequent EVPBs were associated with a 60% to 80% increased risk of death from all causes. It is noteworthy that the mortality risk was observed at a much lower threshold of number of EVPBs than previously reported. In secondary analyses, frequent EVPBs were associated with increased cardiovascular mortality, consistent with prior reports. The association of EVPBs with all-cause mortality was not influenced by the grade of VPBs, the presence (or absence) of an ischemic ST-segment response, VPBs during the recovery period, or by presence of reduced LV fractional shortening. It is important to note that though mortality risk was elevated in participants with EVPBs, the increase was modest in terms of the absolute annual death rates.

In our sample, neither infrequent nor frequent EVPBs were related to the risk of hard CHD events. This is in contrast to another recent investigation in which an association of EVPBs with hard CHD events was observed. The latter report evaluated a sample of symptomatic patients with a higher prevalence of CHD risk factors (such as hypertension, dyslipidemia, smoking, and diabetes) and a higher CHD event rate. It is plausible that EVPBs may predict hard CHD events in patients with a higher pretest probability of CHD.

APBs during exercise and VPBs during recovery were not related to any of the outcome events. The latter finding is in contrast to a recent report that VPBs during the recovery period were of greater prognostic significance in a referral sample of patients evaluated for suspected CHD. It is conceivable that
VPBs during recovery may be more important in those with an intermediate or greater pretest probability of CHD who may have an altered parasympathetic tone.

**Potential Mechanisms for Association of EVPBs and Death**

The demonstration of a temporal sequence (EVPBs antedated outcomes), the strength of the association, and the consistency with prior reports support the possibility of a causal association between EVPBs and mortality risk. Furthermore, such an association is biologically plausible. EVPBs may promote risk of death through multiple mechanisms. They may be markers of ischemia or of an underlying arrhythmogenic substrate (even in the absence of ischemia), or they may be associated with increased risk of vascular events that in turn could lead to death. We did not find evidence in our investigation to support any of these mechanisms. As noted previously, EVPBs were not related to ischemic response or to presence of a reduced LV fractional shortening. The increased risk of mortality associated with EVPBs also was not influenced by these features. Last, EVPBs were not related to risk of hard CHD events. Additional studies are needed to elucidate the underlying mechanisms by which EVPBs may mediate their hazard.

**Strengths and Limitations**

The strengths of our investigation include the large, community-based sample with long-term follow-up of more than 15 years, the careful characterization of EVPBs, VPBs during recovery and APBs on the basis of their actual distributions, the assessment of risk of hard CHD events (in addition to death), and the evaluation of LV dysfunction at the baseline examination to provide insights into mechanisms by which EVPBs increase mortality risk. An important limitation is that our findings are generalizable only to asymptomatic, relatively young, white individuals. The generalizability of our findings to other age groups, different ethnicities, or to individuals with a higher pretest probability of CHD is unknown.

**Clinical Implications**

Given the observational nature of our study, its therapeutic implications are uncertain. It is unclear if additional diagnostic testing or treatment with β-blocking agents is warranted. Comprehensive assessment of vascular risk factors and appropriate management of risk factors according to global risk would seem to be an apt strategy.

**Conclusions**

In our large, community-based sample of asymptomatic individuals, EVPBs were associated with increased risk of death at a much lower threshold than previously reported. Additional studies are needed to confirm these findings and to clarify the underlying mechanisms.

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