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# Ventricular Premature Beats During Exercise Testing: From Autonomic Imbalance to Risk Stratification

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ABSTRACT

This analytical review integrates contemporary publications addressing the assessment of premature ventricular contractions (PVCs) recorded during treadmill testing. The main focus is on distinguishing the prognostic value of arrhythmias occurring during exercise itself from those appearing during the post-exercise recovery phase. Quantitative syntheses published in 2020–2025, based on cohorts totaling more than 30,000 participants, as well as the largest population-based UK Biobank study using machine-learning algorithms for ectopic-beat detection, are reviewed. The evidence indicates that each additional unit of arrhythmic burden is associated with a monotonic increase in the probability of adverse outcomes, with complex rhythms (couplets, triplets, and bigeminy) during the first minutes after cessation of physical activity showing the greatest predictive capacity. The pathophysiological basis of this phenomenon is insufficient reactivation of the parasympathetic nervous system in the setting of persistent adrenergic stimulation. Detection of such abnormalities requires detailed minute-by-minute analysis of the recovery interval and expanded instrumental assessment, including myocardial imaging methods.

**Keywords:** - Premature ventricular contractions, exercise ECG (treadmill test), recovery period, prognosis, autonomic nervous system, sudden cardiac death, meta-analysis.

## 1. INTRODUCTION

### From a “Benign Phenomenon” to an Independent Predictor of Mortality

For several decades, the treadmill test was regarded primarily as a tool for detecting ischemia, and interpretation focused on assessment of the ST segment. Premature ventricular contractions, recorded in approximately every fourth to fifth participant, were often ignored or interpreted as a physiological response to a catecholamine surge. The paradigm began to change following the publication by Frolkis and colleagues (2003) in the New England Journal of Medicine, which showed that frequent ventricular ectopic complexes occurring after treadmill cessation predicted death

substantially more accurately than similar events occurring at peak exercise [1]. This finding identified the recovery phase as a critically important diagnostic interval and initiated discussion of the role of autonomic dysregulation in arrhythmogenesis. In subsequent years, accumulating evidence established a new concept: ventricular ectopy during exercise ECG is an independent marker of increased cardiovascular risk and cannot be reduced simply to concomitant coronary insufficiency [2].

## 2. Autonomic Mechanisms: Why the Post-Exercise Interval Is Particularly Hazardous

### 2.1. Sympathovagal Conflict

Physical activity is accompanied by activation of the hypothalamic–pituitary–adrenal axis and the adrenal glands, resulting in massive release of norepinephrine and epinephrine. At peak exercise, sympathetic dominance is absolute. However, after movement stops, a unique and highly unfavorable state develops in the myocardium: plasma catecholamine concentrations continue to rise for 60–180 seconds, while parasympathetic innervation is only beginning to increase in activity. Zhabina and colleagues (2025) substantiated the clinical rationale for dividing the recovery period into two subintervals: an early period (from the end of exercise to the third minute) and a late period (beginning at the fourth minute) [2]. During the first interval, a "sympathetic-dependent" arrhythmogenic background persists because the vagus nerve is unable to suppress adrenergic excitation effectively. During the second interval, vagal activity predominates, and ectopy acquires a different, more favorable prognostic profile.

### 2.2. The Anti-Fibrillatory Barrier of the Vagus Nerve

Experimental studies dating back to the mid-nineteenth century have demonstrated that vagal stimulation increases the ventricular fibrillation threshold and stabilizes the electrophysiological properties of the conduction system. When vagal reactivation is impaired during the post-exercise phase, this protective mechanism is weakened, creating favorable conditions for both isolated premature beats and polymorphic ventricular tachycardia. A meta-analytic synthesis by Qiu and colleagues (2017) confirmed that delayed recovery of heart rate after exercise testing is associated with increased mortality independently of the presence of arrhythmias, indirectly supporting a predominant role of parasympathetic insufficiency [3].

### 2.3. Non-Ischemic Substrate

Contemporary population data indicate that the association between exercise-induced ectopy and adverse events is mediated to a substantial extent not by obstructive ischemia but by diffuse myocardial injury. Individuals with a high PVC frequency show increased left-ventricular end-diastolic and end-systolic volumes, reduced ejection fraction, and elevated NT-proBNP levels, suggesting subclinical structural remodeling that may not be detectable by standard echocardiography [4].

## 3. Quantitative Synthesis of the Evidence: What Do the Meta-Analyses Show?

### 3.1. Early Cohort Studies

Understanding of the role of PVCs was built on several landmark cohorts. The study by Jouven and colleagues (2000) demonstrated that men with frequent exercise-induced PVCs had an increased risk of cardiovascular mortality during 23 years of follow-up [5]. Morshedi-Meibodi and colleagues (2004), within the Framingham Offspring Study, showed that both rare (<0.22/min) and frequent PVCs during submaximal exercise were associated with increased mortality (adjusted HR 1.9 and 1.7, respectively) [6]. However, the greatest contribution to understanding the role of the recovery period came from Frolkis and colleagues (2003): in a cohort of 29,244 patients, frequent PVCs (≥7/min) during the post-exercise phase were a stronger predictor of mortality (five-year mortality 11% vs. 5%, HR 2.4) than PVCs during exercise (HR 1.8) [1]. Earlier quantitative syntheses published in 2016 also indicated an adverse role of ventricular ectopy, although they included mixed populations [7].

### 3.2. Contemporary Meta-Analytic Synthesis

#### 3.2.1. Meta-analysis by Iqbal and Colleagues (2022)

The most extensive systematic review and meta-analysis available at the time of publication,

published in Frontiers in Cardiovascular Medicine, included 13 observational studies with a combined population of more than 82,000 individuals (mean age 49 years, approximately 70% men, median follow-up 11 years) [8]. All included studies used multivariable models adjusted for classical risk determinants. The pooled statistical analysis demonstrated a significant association between exercise-induced ectopy and all-cause mortality (relative risk 1.30; 95% confidence interval 1.18–1.42) and cardiovascular mortality (1.67; 1.40–1.99) [8]. Subgroup analysis stratified by the time of arrhythmia recording showed that ectopy during the recovery phase carried greater weight (1.46 vs. 1.23 for all-cause mortality), although both coefficients remained statistically significant [8].

An important clarification is that a statistically robust association with mortality was observed exclusively for frequent PVCs (criteria varied from >5 per minute to >10% of the total number of ventricular depolarizations). For rare events, the confidence interval crossed unity, probably reflecting insufficient statistical power in the subgroup. Meta-regression found no modifying effect of age, sex, arterial hypertension, diabetes mellitus, dyslipidemia, or smoking, emphasizing the independent nature of this predictor [8]. In terms of diagnostic accuracy, post-exercise PVCs showed low sensitivity (16–19%) but high specificity (85–90%) [8]. Thus, they can be interpreted as a tool for confirming high risk, but they are not suitable for ruling out pathology.

### 3.2.2. Meta-analysis by Gupta and Colleagues (2023)

Researchers from the Indian Heart Journal applied stricter selection criteria, including only studies in which analyses were performed using multivariable models with mandatory adjustment for at least one confounder and known high-risk ECG features (ST depression, blood-pressure response, and heart-rate recovery) [9]. Of 66,000 potentially eligible participants, the final synthesis included 24,518 individuals from 7 cohorts [9]. The results partly overlapped with those of Iqbal, but differences were also identified. High-risk ectopy recorded directly during running significantly predicted both all-cause mortality (HR 1.27; 1.07–1.48) and cardiac mortality (1.69; 1.19–2.20) [9]. In contrast, arrhythmias occurring during recovery showed a significant association only with cardiovascular mortality (1.62; 1.25–2.00), whereas the confidence interval for all-cause mortality included the null effect [9]. The authors highlighted substantial heterogeneity in the definitions of "high-risk" ectopy used in the primary sources: from a simple frequency threshold (>0.22 complexes per minute in the Framingham Offspring Study [6]) to complex morphological criteria (polymorphism, R-on-T, and nonsustained tachycardia in Refaat et al. [10]). This finding indicates the need for terminology standardization in future research.

### 4. UK Biobank: Dose Dependence, Neural-Network Algorithms, and Subclinical Cardiomyopathy

The publication by van Duijvenboden and colleagues (2023) in Circulation represents the largest population-based study to date, involving 48,315 apparently healthy individuals (mean age 56.8 years, 51% women) [11]. Unlike previous studies that used visual or semi-automated assessment of ectopy, this study used a one-dimensional convolutional neural network trained on 41,025 ECG fragments and achieved a detection accuracy of 98.7% [11]. A key methodological innovation was the abandonment of a binary approach ("present/absent") in favor of incremental burden analysis. The investigators defined five degrees of ventricular ectopy during exercise (0; 1–5; 6–10; 11–20; >20 complexes) and three during recovery (0; 1–5; >5) [11].

The results showed a monotonic increase in the risk of the composite endpoint (myocardial infarction, heart failure, and life-threatening arrhythmias):

- Even with minimal burden (1–5 PVCs), risk increased by 20% (HR 1.2; $p < 0.001$) [11].
- With >20 PVCs, the relative risk reached 1.8 ($p < 0.001$) [11].
- For the post-exercise interval, the gradient persisted: 1–5 PVCs — HR 1.3; >5 — HR 1.6 [11].

The prognostic role of complex arrhythmias was particularly emphasized. Couplets, triplets, and episodes of bigeminy were associated with a more pronounced increase in risk than isolated PVCs with a comparable absolute number. Episodes containing three or more consecutive ventricular

complexes increased the probability of adverse events by more than sevenfold [11]. A fundamental finding was the absence of a significant association with myocardial infarction. PVCs significantly predicted the development of heart failure (HR up to 2.8), life-threatening arrhythmias (HR up to 3.6), and cardiac death, but not atherothrombotic complications [11]. This suggests a predominantly non-ischemic mechanism of injury: diffuse myocardial fibrosis, dysplasia, microvascular dysfunction, or channelopathies may create an arrhythmogenic substrate that is "unmasked" by adrenergic stimulation. In the subgroup with cardiac magnetic resonance data (n = 6,290; scans obtained on average 6.4 years after the test), a high PVC burden correlated with increases in chamber volumes of 11–14 mL, a 3-percentage-point reduction in ejection fraction, and a 10–13% increase in NT-proBNP concentration [11]. These changes indicate slowly progressive subclinical remodeling preceding clinically manifest dysfunction.

## 5. The Recovery Period as a Reflection of Autonomic Imbalance

The combined meta-analytic and cohort evidence convincingly demonstrates that ectopy occurring after cessation of exercise carries a worse prognosis than arrhythmias occurring at peak exercise. This is explained by several complementary mechanisms. First, insufficient vagal reactivation. In healthy individuals, vagal tone should rapidly increase after exercise cessation, producing an accelerated decline in heart rate. In individuals with post-exercise ectopy, this process is sluggish, reflecting chronic dysfunction of autonomic regulation [3]. Second, persistent adrenergic stimulation. As noted above, during the first 1–3 minutes after exercise, blood catecholamine levels continue to rise, creating a "sympathetic-dependent" arrhythmogenic background [2]. Third, a marker of occult organic pathology. Lindow and Ekström (2022) found that ectopy during recovery was closely associated with subsequent detection of structural abnormalities (hypertrophy, left-ventricular dilatation, and valvular disease) [4]. Mortality was increased predominantly among patients who combined arrhythmias with objective evidence of cardiomyopathy [4]. Zhabina and colleagues (2025) emphasize the methodological error of standard "stepwise" interpretation of exercise ECG, in which the recovery period is treated as a single unit without division into early and late subintervals [2]. This approach may mask sympathetic-dependent arrhythmias that require minute-by-minute analysis for detection. Early identification of individuals with such abnormalities, particularly among young athletes, may help prevent sudden cardiac death at a stage when the structural substrate has not yet produced clinical symptoms [2].

## 6. The Problem of Classification and Terminology Standardization

One of the major obstacles to synthesizing the literature is the lack of uniform criteria for "high-risk" ventricular ectopy. Comparison of definitions used in key cohorts reveals substantial variation [9]:

- In the study by Jouven and colleagues (2000), the criterion was the presence of ≥2 consecutive complexes or exceeding a threshold of 10% of all ventricular depolarizations [5].

- In the Framingham Offspring Study (Morshedi-Meibodi, 2004), a quantitative threshold of >0.22 PVCs per minute was used [6].

- In the Lipid Research Clinics study (Refaat, 2021), a composite approach was used: >10 per minute, polymorphism, R-on-T, and nonsustained tachycardia [10].

- In the Swedish cohort (Lindow, 2022), only complexes recorded during the first four minutes of recovery at a frequency of ≥1 per minute were analyzed [4].

The UK Biobank proposed a fundamentally different incremental approach, assessing not only frequency but also rhythm complexity [11]. This categorization appears particularly promising for subsequent standardization because it captures a dose-dependent effect without rigid binary classification.

## 7. Clinical Algorithm: From ECG Interpretation to Therapeutic Strategy

### 7.1. Recording and Analysis Methodology

Current recommendations require revision of the exercise ECG protocol. In addition to traditional

ST-segment assessment, the clinician should:

• Record the electrocardiogram for at least 5–6 minutes after cessation of exercise.

• Perform minute-by-minute analysis of the post-exercise interval, distinguishing the early (1–3 min) and late (≥4 min) periods [2].

• Consider not only the number of PVCs but also their morphology (monomorphic vs. polymorphic), the presence of couplets/triplets, bigeminy, and the R-on-T phenomenon.

• Integrate the findings with other prognostic markers: heart-rate recovery, functional capacity, and hemodynamic response.

### 7.2. Diagnostic Verification

Detection of high-risk ectopy in an asymptomatic patient should serve as an indication for more extensive evaluation:

• Transthoracic echocardiography — the mandatory first step for assessment of ejection fraction, cardiac geometry, and the valvular apparatus.

• Cardiac MRI — the method of choice in patients with a high daily burden (>10,000 PVCs), complex rhythms, suspected dysplasia or myocarditis, and in cases of normal echocardiography but high clinical suspicion [12,13].

• Holter monitoring — to assess total daily burden and detect “silent” ectopy at rest.

• Invasive coronary angiography or CT angiography — when clinical signs of ischemia are present, although according to UK Biobank data, the predominant risk mechanism probably lies outside obstructive coronary disease [11].

### 7.3. Differential Therapy

Treatment strategy should be determined by the predominant pathophysiological mechanism and the presence of structural myocardial disease [2]:

• Sympathetic-dependent ectopy (early post-exercise period, tachycardia-dependent complexes): β-blockers are first-line agents. In cases of intolerance, non-dihydropyridine calcium-channel blockers may be considered.

• Vagal-dependent PVCs (late recovery, bradycardia-dependent rhythms) in the absence of significant structural disease and ischemia: class IC agents (flecainide) demonstrate high efficacy (>70% reduction in burden), provided occult atrioventricular conduction abnormalities are excluded [2].

• In the presence of structural disease (ischemic or dilated cardiomyopathy), priority is given to treatment of the underlying disease (RAAS inhibitors, β-blockers, mineralocorticoid receptor antagonists, and revascularization). Class IC antiarrhythmic agents are contraindicated.

• Catheter ablation — indicated when daily burden is >10%, arrhythmia complexity progresses, ejection fraction decreases, or medical therapy is ineffective or not tolerated.

## 8. Unresolved Questions and Directions for Future Research

Despite the strength of the accumulated evidence, several issues remain unresolved. Causality versus association. All available data have been obtained from observational cohorts. Randomized studies demonstrating that targeted elimination of exercise-induced PVCs (pharmacologically or by ablation) reduces mortality are lacking. Young populations and athletes. Most meta-analytic syntheses include middle-aged and older patients (43–59 years). The prognostic significance of ectopy in young individuals who systematically engage in sports remains insufficiently studied, although prevention of sudden death is particularly important in this group [2]. The era of wearable devices. The widespread use of smartwatches and portable monitors capable of recording rhythm during physical activity is generating a new stream of consultations by asymptomatic patients. Primary filtering algorithms are needed to distinguish a benign physiological response from a marker of pathology [11]. Protocol standardization. Differences between definitions of “high risk” and between exercise protocols (maximal Bruce protocol versus submaximal bicycle ergometry) limit comparability of results. Adoption of the UK Biobank incremental model [11] could represent a first step toward harmonization.

## 9. CONCLUSION

The contemporary evidence base clearly indicates that premature ventricular contractions detected during exercise ECG represent an independent predictor of all-cause and cardiovascular mortality in individuals without clinically apparent cardiovascular disease [8,9]. Their prognostic significance cannot be explained solely by concomitant ischemia and is mediated by a combination of interrelated factors: autonomic dysregulation (primarily insufficient parasympathetic reactivation during recovery [2,3]) and subclinical structural myocardial remodeling [4,11]. Key principles of the modern approach include recognition of the dose-dependent nature of risk (even isolated PVCs may be significant [11]), prioritization of analysis of the early recovery interval (1–3 min [2]), assessment of arrhythmia complexity (couplets and triplets substantially increase risk [11]), and expanded myocardial imaging to exclude occult cardiomyopathy [12,13]. Exercise electrocardiography should be regarded not only as a tool for diagnosing ischemia but also as a method of arrhythmological risk stratification, requiring a systematic revision of interpretation protocols in everyday clinical practice.

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