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Beyond counting ectopy: exercise as a dynamic phenotyping tool in cardiomyopathies

Más allá de contar extrasístoles: el ejercicio como herramienta de fenotipado dinámico en las miocardiopatías

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Clinical guidelines for the recognition and diagnosis of inherited cardiomyopathies are well established, but individualized arrhythmic risk stratification remains a significant challenge. Contemporary phenotyping integrates genetic information with electrocardiography, ambulatory monitoring, and cardiac magnetic resonance (CMR).[1,2] Late gadolinium enhancement (LGE) on CMR, reflecting myocardial replacement fibrosis and scar, has emerged as an important marker of arrhythmic risk among cardiomyopathies.[3] Viable myocardial channels within the border zones of fibrofatty or fibrotic scar tissue provide a substrate for slow conduction and re-entry that can trigger and sustain ventricular arrhythmia.[4] In addition,

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sympathetic activation can further promote ventricular electrical instability.[5] Clinical evaluation during exercise provides an opportunity to interrogate this substrate under chronotropic, adrenergic and hemodynamic stress, potentially revealing abnormalities that are concealed at rest. This dynamic information may be clinically meaningful: in asymptomatic UK Biobank participants, ventricular ectopy during both exercise and recovery was associated with long-term cardiovascular outcomes and markers of subclinical cardiomyopathy.[6] While contemporary European Task Force criteria include frequent or exercise-induced ventricular ectopy as an arrhythmic criterion of arrhythmogenic cardiomyopathy,[2] whether exercise-induced electrical phenotypes can further inform substrate characterization and arrhythmic risk remains an important clinical question.

Against this background, Sola-García et al.,[7] in a recent article published in *Revista Española de Cardiología*, examined 77 patients with different cardiomyopathies that had predominantly left ventricular involvement and who underwent CMR and treadmill exercise testing (table 1). Exercise-induced right bundle branch block-pattern ventricular ectopy (EI-RBBB-VE) was common, occurring in 48.1% of patients, and was more frequent among those without LGE (67.6% vs 40.0%; *P* = .015). EI-RBBB-VE remained associated with LGE after multivariable adjustment (odds ratio [OR], 3.92; 95% confidence interval [95%CI], 1.28-12.00). The authors also observed that patients with LGE developed ectopy earlier in the exercise protocol and at a lower percentage of age-predicted maximal heart rate.

While previous studies have observed an association between resting ventricular ectopy burden and LGE, in this cohort, ectopy counts on exercise or prior Holter monitoring, did not differ significantly by LGE status. The lack of significance may be due to the heterogeneous mix of cardiomyopathies within the cohort and the relatively small sample size compared with other studies. Each cardiomyopathy has different underlying disease biology and should therefore be considered individually. The observation of an association between time to first ectopic beat

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during exercise and LGE, suggests that there may be value in dynamic phenotyping that considers not only how ectopy burden, but also its timing and physiological context.

The RBBB morphology observed is compatible with the primarily left ventricular disease represented in this cohort, and the superior axis is consistent with the predominantly inferolateral distribution of LGE. Approximately 67% of patients with EI-RBBB-VE also exhibited LBBB-pattern ectopy, potentially indicating patients with biventricular involvement. Multifocal ventricular ectopy has previously been reported to be more common in athletes with LV LGE,[11] but whether multiple morphologies identify a more extensive myocardial substrate or carry prognostic information in cardiomyopathies remains unknown. Future studies combining exercise testing, CMR and noninvasive electrocardiographic imaging could examine the spatial relationship between ventricular triggers and scar, with potential implications for substrate mapping and catheter ablation in selected patients.[12]

Pathogenic or likely pathogenic variants were identified in 77.9% of the cohort, spanning a heterogeneous range of cardiomyopathy genes. Genotype positivity showed similarly modest discrimination for LGE compared with EI-RBBB-VE (area under the receiver operating characteristic curve [AUC], 0.606 vs 0.638), although genotype status did not remain independently associated with LGE after adjustment. The clearest genotype-specific signal arose in the small desmosomal subgroup, in which 11 of 12 patients had LGE. Otherwise, analyses of the association between EI-RBBB-VE and LGE within genetic subgroups were directionally consistent but underpowered. Genetic testing, CMR and exercise testing interrogate different dimensions of disease: inherited predisposition, structural phenotype and electrical expression under physiological stress, respectively. The similar AUCs should not be interpreted as a head-to-head comparison of clinical utility: genetic testing informs disease etiology, diagnosis, and family screening, whereas exercise testing captures the expressed electrical phenotype under physiological stress. Larger cohorts are needed to determine whether the relationship between

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the exercise-induced electrical phenotype and structural substrate differs by cardiomyopathy and genotype subgroup.

Although statistically significant, the adjusted association between EI-RBBB-VE and LGE is imprecisely estimated (OR, 3.92; 95%CI, 1.28-12.00). The cross-sectional design also precludes assessment of the prognostic significance of EI-RBBB-VE. The multivariable model provides only moderate discrimination and has not been externally validated. Eleven patients with implantable cardioverter-defibrillators were excluded from the primary multivariable analysis because of inadequate CMR image quality; these patients had substantially lower left ventricular ejection fraction, and sensitivity analyses cannot fully eliminate potential selection bias. LGE was assessed qualitatively, without quantification of scar burden or characterization of diffuse interstitial fibrosis. The 24-hour Holter used for comparison had also been obtained a median of 6 months before exercise testing, limiting inference about incremental information over contemporaneous ambulatory premature ventricular complex burden. Moreover, interpretation of the lower heart-rate threshold warrants caution: beta-blocker dose and treatment management on the day of testing were not reported, nor was beta-blocker exposure compared according to LGE status. The lower percentage of age-predicted maximal heart rate should therefore be viewed as a descriptive feature of the exercise-induced electrical phenotype rather than a validated individual arrhythmic threshold. More broadly, independent association with LGE should not be equated with incremental diagnostic utility.

These limitations also frame the current clinical interpretation of exercise-induced ectopy. CMR remains the reference imaging modality for myocardial tissue characterization and accurate assessment of ventricular structure and function in cardiomyopathy,[1] while LGE is an established imaging marker with prognostic relevance.[3,13] There is insufficient evidence to use EI-RBBB-VE as a substitute for CMR or as a standalone risk marker. The absence of EI-RBBB-VE is also insufficient to exclude structural disease: LGE was still present in 40% of patients without EI-

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RBBB-VE in the present study. Conversely, the appearance of RBBB-pattern ectopy during exercise, particularly when it occurs early, may reasonably heighten suspicion and support comprehensive phenotypic assessment in the appropriate clinical context. Established arrhythmogenic right ventricular cardiomyopathy risk models already incorporate 24-hour premature ventricular complex burden, illustrating that ventricular ectopy can contribute to multivariable risk assessment.[14] Whether exercise-derived morphology and timing provide incremental prognostic information beyond existing clinical, imaging, genetic and electrical variables remains to be demonstrated.

The next step is to establish whether this exercise-induced electrical phenotype is reproducible and whether morphology, timing and exercise-test phase add prognostic information beyond established genetic, imaging, and electrical markers. Recent data in desmosomal arrhythmogenic cardiomyopathy suggest that both genotype and the exercise-test phase may modify prognostic information,[9] while exercise-induced ventricular arrhythmias were independently associated with subsequent major arrhythmic events in a broader arrhythmogenic cardiomyopathy cohort.[10] Sola-García et al.[7] extend this evolving dynamic phenotyping framework, identifying ectopic morphology and timing as candidate features for prospective validation. The broader message is that exercise testing may be most informative not by counting ectopy alone, but by characterizing its morphology, timing, and behaviour under physiological stress.

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STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

Artificial intelligence (ChatGPT) was used as a tool to perform an initial literature review. The authors take full responsibility for the accuracy and originality of the work.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest.

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Table 1

Selected studies evaluating exercise-induced ventricular arrhythmias in arrhythmogenic and inherited cardiomyopathies

Study	Population	Exercise phenotype	Key findings and contribution
Finocchiaro et al.[8] (2022)	30 patients. Definite ARVC	Complex or repetitive ventricular arrhythmias after stage 2 of ETT	Exercise-induced arrhythmias occurred in 40% and were associated with larger LV and RV volumes and more frequent LV LGE (67% vs 22%). Structural correlates were evaluated; no clinical outcome model
Castrichini et al.[9] (2025)	147 patients. Desmosomal ACM. 326 exercise tests	PVC burden and complexity evaluated at baseline, peak exercise, and recovery	*PKP2*-ACM showed a distinct recovery-phase arrhythmic phenotype. Recovery arrhythmias predicted major ventricular arrhythmic events in *PKP2*-ACM (adjusted hazard ratio, 3.85), but not in other genotypes
Mengozzi et al.[10] (2026)	157 patients with definite ACM or a P/LP variant in an ACM-associated gene and a negative/borderline phenotype	Exercise-induced ventricular arrhythmias during ETT or CPET	EIVA occurred in 39%, was associated with lower peak VO_2 and numerically more frequent myocardial fibrosis (52% vs 37%; *P* = .071), and independently predicted the arrhythmic endpoint (hazard ratio, 2.8)
Sola-García et al.[7] (2026)	77 patients with cardiomyopathies with predominantly left ventricular involvement	EI-RBBB-VE morphology, burden, and timing during ETT	EI-RBBB-VE occurred in 48.1% and was associated with LGE (67.6% vs 40.0%; adjusted OR, 3.92). LGE-positive patients developed ectopy earlier and at a lower percentage of predicted maximal heart rate. Cross-sectional study; no longitudinal outcomes

ACM, arrhythmogenic cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy; CPET, cardiopulmonary exercise testing; ETT, exercise tolerance testing; EI-RBBB-VE, exercise-induced right bundle branch block-pattern ventricular ectopy; EIVA, exercise-induced ventricular arrhythmias; LGE, late gadolinium enhancement; LV, left ventricle; P/LP, pathogenic/likely pathogenic; PVC, premature ventricular complex; RV, right ventricle.