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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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Left Posterior Fascicular Block and Increased Risk of Sudden Cardiac Death in Young People

Left posterior fascicular block (LPFB) is an extremely rare electrocardiography (ECG) finding (0.06% to 0.1% in the general population) (1). Because scar patterns in nonischemic cardiomyopathy (NICM) commonly involve the inferoposterior left ventricle (2,3), we hypothesized that LPFB may be an ECG biomarker of left ventricular (LV) scarring and associated with increased risk of sudden cardiac death (SCD) in young people.

In this case-control study, we compared the frequency of LPFB in a consecutive series of young individuals who experienced SCD or aborted cardiac arrest (ACA) and a control population of apparently healthy young people. We explored the associations among LPFB and cardiac magnetic resonance (CMR) and histopathological findings.

We retrospectively compared the clinical data for 109 consecutive individuals age ≤40 years who had ACA or SCD (86 men; 32.3 ± 5.9 years [range: 17 to 40 years]) and who had at least 1 ECG in the 3 years preceding the ACA or SCD to data for 8,892 healthy individuals age ≤40 years (6,265 men; 30.5 ± 8.6 years [range: 17 to 40 years]) consecutively referred to our institution for screening. LPFB was defined by the presence of all of the following: frontal axis 100° to 180°; rS pattern in leads I and aVL; qR pattern in III and aVF; QRS duration <110 ms; and no QS pattern in I and aVL. The association of LPFB with ACA/SCD was analyzed by nominal logistic regression and was estimated with unadjusted odds ratios (ORs) and 95% confidence intervals (CIs). The study (CARITMO) was approved by our Institutional Review Board.

A total of 10 of the 109 (9.2%) individuals in the study group had LPFB (9 men; median age 27.5 years [interquartile range: 22.8 to 36.5 years]): 6 had ACA/SCD during or immediately after sport activity. In total, 8 of the 8,892 (0.09%) control subjects (5 men; median age 28.6 years [interquartile range: 22.0 to 38.7 years]) had LPFB. LPFB was significantly associated with ACA/SCD (unadjusted OR: 112.2; 95% CI: 43.3 to 290.2; $p < 0.0001$).

Overall, 4 patients and 2 control subjects had a family history of SCD, NICM, or channelopathy. A pathogenic mutation in the spectrum of NICM or arrhythmogenic cardiomyopathy (ACM) was found in 2 patients (titin, desmoglein-2) and 1 control subject (desmoplakin). Repolarization abnormalities (5 patients and 1 control subject) and low-QRS voltage in limb leads (3 patients and 1 control subject) were the main associated ECG abnormalities. In patient #2, serial ECG showed a progression from normal ECG to LPFB (**Figure 1**).

All 6 of 6 (100%) study group participants who underwent CMR showed LV late gadolinium enhancement (inferolateral/lateral in 4, inferoseptal in 1, and LV diffuse in 1).

In total, 6 of 8 control subjects with LPFB underwent CMR because of a family history of SCD (n = 2),

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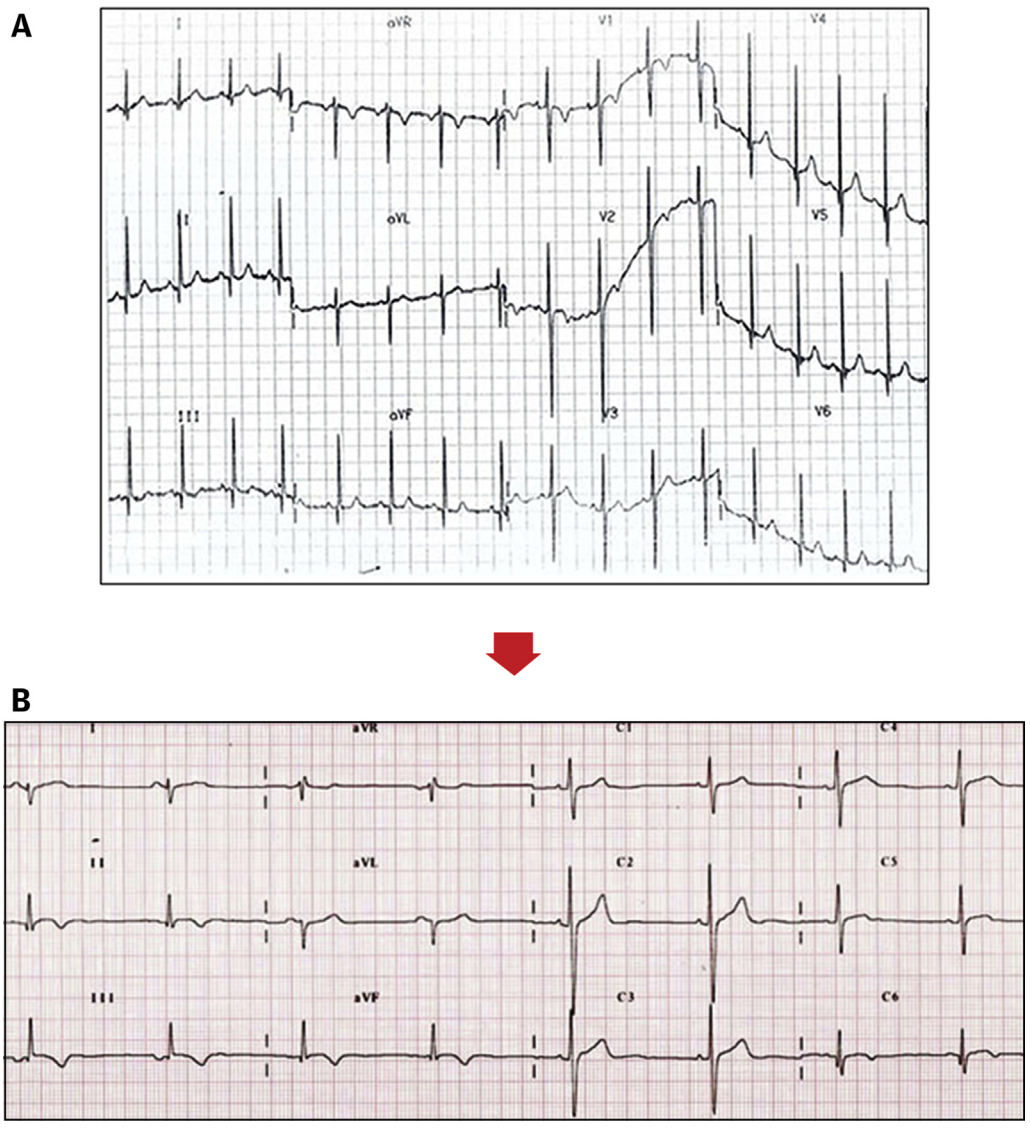
FIGURE 1 ECG Changes in Patient #2



Electrocardiogram (ECG) at age 16 years is normal **(A)**. The ECG, before sudden cardiac death at age 24 years, shows negative T waves on inferior-lateral leads, and a decrease in QRS voltages with left posterior fascicular block appearance (**B**). Cardiac magnetic resonance revealed biventricular dilation and extensive scar involving the inferolateral left ventricular wall. Autopsy confirmed biventricular dilation and fibro-fatty replacement.

hypertrophy at echocardiography (n = 1), constrictive pericarditis (n = 1), or ventricular arrhythmias (n = 2). CMR findings were abnormal for 4 of 6 (67%) control subjects; 2 showed LV late gadolinium enhancement (circumferential in 1 and inferolateral in 1 [desmoplakin mutation]).

Histopathological analysis available for 4 patients showed LV fibrosis in each, and the inferolateral LV wall was involved in 3 patients on autopsy. Of note, the 3 patients and the control participant with low-QRS voltage showed extensive LV scarring on CMR and/or autopsy.

LPFB prevalence was >100-fold higher in SCD survivors than control subjects, and LPFB was associated with structural abnormalities in all SCD patients with CMR data and 4 of 6 control subjects.

Our observations suggest that LV inferolateral, inferior, or inferoseptal fibrosis may injure posterior

radiations of the left bundle branch, leading to isolated LPFB. Fibrosis mostly occurred in the inferior and lateral LV, a hallmark site of LV ACM (3); 2 patients fulfilled task force criteria, and 2 individuals had pathogenic mutations in the ACM spectrum. Further studies are needed to assess the frequency and clinical significance of axis deviations in ACM.

The limitations of the study include the retrospective design and the long study period, which may imply selection bias despite the monocentric and consecutive inclusion. Also, we did not assess confounding factors in the association between LPFB and ACA/SCD. In fact, a causal link would make little sense mechanistically, and LPFB should be seen more as an "epiphenomenon" of underlying LV fibrosis, which in contrast is a known cause of SCD in NICM (4). Finally, complete heart block could be a possible cause of death in the 5 patients with SCD, and in patient #5, in whom only negative stress tests were performed, we cannot exclude an ischemic SCD.

Our findings suggest that isolated LPFB could be a valuable tool for arrhythmic risk stratification in young people, should be recognized as a pathological finding, and should prompt further investigation to detect underlying structural abnormalities.

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Assessment of Nonstenotic Carotid Plaques

We read with interest the work by Kopczak et al. (1) describing complicated nonstenotic carotid artery plaques (CAPs) as a possible cause for what we currently call "cryptogenic" stroke. As the investigators point out, the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria only acknowledge carotid plaques that cause >50% stenosis as a cause of stroke. Strokes with ipsilateral nonstenotic (<50% stenosis) carotid plaques are classified as "cryptogenic." However, with the advent of magnetic resonance imaging (MRI) plaque imaging, understanding of CAP architecture has improved. Various studies have shown increased risk of recurrent stroke in the presence of high-risk plaque features (2). In their meticulous study, Kopczak et al. (1) analyzed CAPs using MRI in patients with cryptogenic stroke compared with stroke patients with small-vessel disease or cardioembolic stroke. They found a significantly higher prevalence of complicated CAPs in cryptogenic stroke than in the reference group (31% vs. 15%). In their study, complicated CAPs were assessed on contrast-enhanced MRI, which is usually not part of the emergent stroke work-up. Computed tomography angiography (CTA), on the other hand, is an integral part of the initial assessment of patients presenting with suspected acute stroke. A recent study showed that nonstenotic carotid plaques on CTA in patients with cryptogenic stroke are associated with ipsilateral stroke, but no high-risk CTA plaque features could be identified (3). Evaluating plaque morphology on