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The diagnostic value of electrocardiogram in the left variants of desmosomal arrhythmogenic cardiomyopathy

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Electrocardiogram (ECG) may play a crucial role in the diagnosis of left-sided variants of desmosomal arrhythmogenic cardiomyopathies. This article discusses the most common ECG changes, such as T-wave inversion and low QRS voltages, and new ECG signs such as Q-waves, low voltages in specific leads, posterior fascicle block, and R/S ratio ≥ 0.5 in V1. In addition, ventricular arrhythmias have peculiar features in these patients. Electrocardiogram may be an early marker of this insidious cardiomyopathy and allow to avoid sudden cardiac death often in young people. Electrocardiogram abnormalities may also be indicators of disease evolution over time.

Introduction

Arrhythmogenic cardiomyopathies (ACMs) are a heterogeneous group of pathologies characterized by fibro or fibrofatty myocardial replacement, predisposing to potentially malignant ventricular arrhythmias (VAs) and sudden cardiac death.[1]

The current classification of ACM includes the following phenotypic variants:

- the 'dominant-right' variant, characterized by the predominant or exclusive right ventricular (RV) involvement,
- the 'biventricular disease' variant, characterized by the parallel involvement of the RV and left ventricle (LV); and
- the 'dominant-left' variant characterized by the predominant LV involvement, with no or minor RV abnormalities.[1]

The genetic bases of ACM are pathogenic variants in genes encoding desmosomal proteins, and also non-desmosomal mutations were reported.[1–3] Recent technological advances in cardiovascular imaging have gained rising interest as part of the clinical evaluation of patients with ACM. Since they cannot be proposed for systematic evaluation, the electrocardiogram (ECG) plays a key role in the assessment of patients with ACM.

The ECG is a simple, reproducible, widely accessible, and low-cost tool for the first-line screening of symptomatic and asymptomatic patients. A learned and careful interpretation of ECG features can raise suspicion among the presence of ACM. The purpose of this review is to emphasize the important role of the ECG in the diagnostic work-up in left variants of

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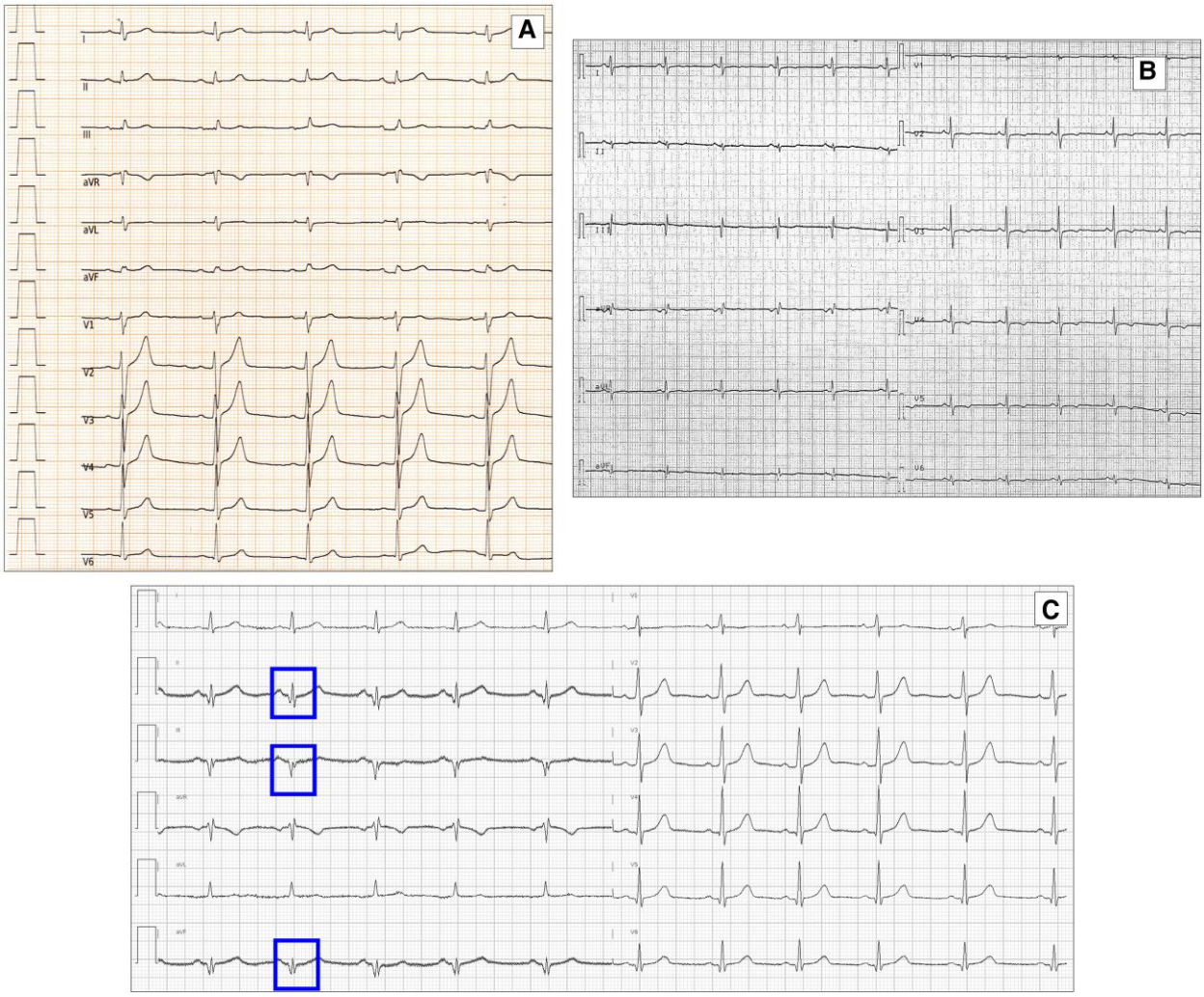

Figure 1 Depolarization abnormalities in patients with left variant of desmosmal arrhythmogenic cardiomyopathy. (*A*) The electrocardiogram performed in a 29-year-old male with a pathogenic mutation in desmoplakin gene shows low QRS voltage in limb leads. (*B*) A 38-year-old female with desmoplakin mutation displays on electrocardiogram pathological Q-waves in inferior leads (leads III-aVF) and the sum of the R-wave in leads I and II ≤ 8 mm and the sum of the S-wave in lead V1 and R-wave in lead V6 ≤ 12 mm. Repolarization abnormalities (T-wave inversion) in anterolateral leads (V3-6) are also present. (*C*) A case of a 48-year-old man affected by arrhythmogenic left ventricular cardiomyopathy with a pathogenic mutation on DSG2 gene. His electrocardiogram shows pathological Q-waves in inferior leads (boxes) and a prominent R-wave in V1 with an R/S ratio ≥ 0.5. ALVC, arrhythmogenic left ventricular cardiomyopathy; DSG2, desmoglein-2; DSP, desmoplakin; LQRSV, low QRS voltages.

desmosomal ACM (dACM), in order to guide clinicians to identify ECG features typical of this cardiomyopathy. Further larger studies should examine the prognostic value of new ECG markers in order to improve risk stratification in left variants of dACM.

Several depolarization and repolarization abnormalities have been reported in patients with dACM.

Electrocardiogram repolarization abnormalities

The most common repolarization abnormality reported in patients affected by ACM is the presence of T-wave inversion (TWI), with a prevalence of 15-45%.[3,4] T-wave inversion was defined as a T inversion of ≥0.1 mV in depth in ≥2 contiguous leads, in the absence of left bundle branch block (LBBB).[5] In our previous study,[6] 57.4% of patients showed TWI, more often in inferior, lateral, or inferolateral leads, in line with previous observations. Norman *et al.*[3] described inferior and/or lateral TWI in 70% of patients of a family with a dominant mutation in desmoplakin. Casella *et al.*[7] showed that 68% of their population had TWI in inferior, lateral, or inferolateral leads. A strict relationship between TWI in inferior and/or lateral leads and the extension of late gadolinium enhancement (LGE) in LV was observed.[8] De Lazzari *et al.*[9] revealed that the extent of TWI towards V4-6 and/or inferior leads predicted severe RV dilatation.

The presence of isolated TWI in left precordial leads (V4-6), with or without involvement of inferior leads, in the absence of LBBB was included as a minor ECG criteria for diagnosis of left variant ACM in the recent European Task Force consensus report by Corrado *et al.*[1]

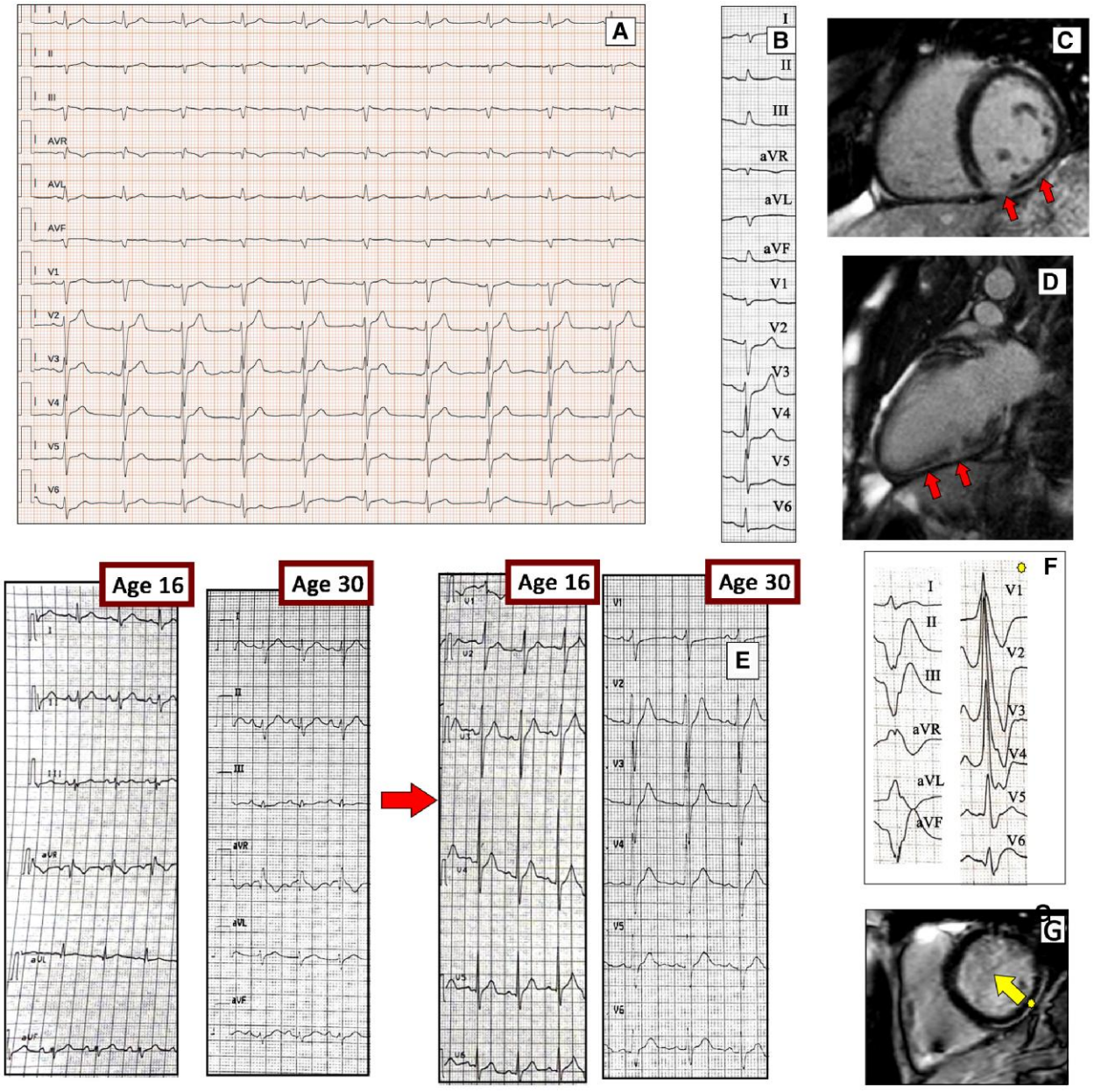

Figure 2 Conduction disturbances, electrocardiogram changes, and ventricular arrhythmias in patients with left variant of desmosmal arrhythmogenic cardiomyopathy. (*A*) The electrocardiogram performed in a 36-year-old male with arrhythmogenic left ventricular cardiomyopathy due to a desmoplakin pathogenic variant displays a left anterior fascicular block. (*B*) A 42-year-old male with desmosmal arrhythmogenic cardiomyopathy (pathogenic desmoplakin variant) shows on electrocardiogram a left posterior fascicular block (AQRS ≈ +110°). His cardiac magnetic resonance (*C*–*D*) reveals the presence of subepicardial late gadolinium enhancement involving the left ventricular inferior and inferoseptal wall (arrows). The patient experienced an aborted cardiac arrest few months after the diagnosis. (*E*–*G*) A case of a 30-year-old-male with diagnosis of dACM after an out-of hospital aborted cardiac arrest. The 12-lead surface electrocardiogram recorded during recovery showed an extreme axis deviation in the frontal plane (AQRS ≈ >120°). His electrocardiogram at the age of 16 did not show significant electrocardiogram abnormalities (*E*). Beyond the clinical onset, the scar on cardiac magnetic resonance was suspected because of the presence of ventricular arrhythmias with a right bundle branch block morphology (asterisk, *F*), suggesting an origin from the left ventricular inferolateral wall (arrow, *G*). ACA, aborted cardiac arrest; ALVC, arrhythmogenic left ventricular cardiomyopathy; CMR, cardiac magnetic resonance; DSP, desmoplakin; LV, left ventricular.

Electrocardiogram depolarization abnormalities

Depolarization abnormalities have been often reported in the literature.[1-10]

Low QRS voltage

A peculiar ECG finding described in patients affected by ACM is the presence of low QRS voltages (LQRSVs) in limb leads, defined as QRS complexes with a peak-to-peak amplitude < 0.5 mV in all peripheral leads.[4,8,11] Low QRS

voltage is an uncommon ECG pattern in the general population whereas it is frequently noticed in a sizeable proportion of patients with cardiomyopathy (15–20%) (*Figure 1A*). It is related to a LV fibrofatty myocardial replacement and it had been found in an advanced stage of left or biventricular disease variants.[1]

De Lazzari *et al.*[9] noted that LQRSV predicted the presence of LV LGE with a specificity of 100%. This characteristic was related to the amount of fibrosis in the LV. In our experience,[6] LQRSV in limb leads was noticed in 14.8% of patients, according to literature.[8] The presence of LQRSV in peripheral leads was reported as a major criterion for diagnosis of ACM in the European Task Force consensus report for diagnosis of ACM.[1]

Limited studies have been published among the presence of LQRSV in specific ECG leads. Oloriz *et al.*[12] found a strict relationship between *r* in V3 $\leq$ 0.3 mV and QRS < 0.6 mV in inferior leads and the presence of fibrosis in the LV anteroseptal and inferolateral region, respectively. A lower amplitude of R-wave in lead II was recently suggested as an independent predictor of sudden cardiac death in non-ischaemic cardiomyopathy.[13] Recently, it has been observed that LQRSV in aVF and V6 is associated to LV regional electroanatomic or cardiac magnetic resonance (CMR) abnormalities specific for ventricular tachycardia substrate in non-ischaemic cardiomyopathy.[14] Sokolow and Lyon[15] considered the sum of the S-wave amplitude in lead V1 and R-wave in V5 or V6 $\leq$ 15 mm as expression of LQRSV. We have revealed that in our experience, in patients with dACM, the R-wave voltage is very low in inferolateral leads in comparison with controls; therefore, the sum of the R-wave in leads I and II $\leq$ 8 mm and the sum of the S-wave in lead V1 and R-wave in lead V6 $\leq$ 12 mm are a specific criterion for left dominant variant with a sensitivity of ~45%[6] (*Figure 1B*).

Pathological Q-waves

In non-ischaemic cardiomyopathy, Oloriz *et al.*[12] showed inferolateral fibrosis associated with lower QRS voltage in limb leads, abnormal Q-waves, and fragmented QRS in inferior and lateral leads. Pathological Q-waves progressively appear over time in relation to the deposition of collagen tissue and have a prognostic role, probably related to the fibrotic substrate.[16] In our experience,[6] pathological Q-waves were found in one-third of patients (*Figure 1B* and *C*). This ECG pattern is highly variable in terms of the presence and distribution, considering that LV-dACM has varying degrees of fibrosis with different patterns of distribution.

Prominent R-wave in V1

De Luna *et al.*[17] described the importance to analyse the amplitude of R-wave in V1 in the presence of LV lateral LGE, the typical area of LV-dACM fibrosis, and observed that this ECG sign was specific even if with a low sensitivity. Tzou *et al.*[18] showed that V1 R $\geq$ 0.15 mV and V6 S $\geq$ 0.15 mV predicted the presence of basal-lateral LV fibrosis in non-ischaemic cardiomyopathy. We have noted a prominent R-wave in V1 with an R/S ratio $\geq$ 0.5 in 24% of patients with left variant of dACM[6] (*Figure 1C*), and this sign was very specific. The presence of an R/S ratio $\geq$ 0.5 in V1 is more frequently noted in 56% of patients with a transmural fibrosis distribution vs. 18% in those without it.

Conduction disturbances

Left anterior fascicular block and non-specific intraventricular conduction delay are often found in patients affected by ACM (*Figure 2A*), even if they are not specific ECG signs. Left posterior fascicular block (LPFB) is an extremely rare ECG finding in the general population, because of anatomical features. If present, it may be the expression of an underlying fibrotic injury and therefore a marker of inferior and inferolateral LV fibrosis in ACM (*Figure 2B-D*). It has been reported, in a case-control study, that the prevalence of LPFB was 100-fold higher in young patients with sudden cardiac death or aborted cardiac arrest than in healthy controls.[19] Interestingly, it has been observed in a large Danish registry that LPFB was associated with the highest risk of death, although they were in the youngest age group (median age 35 years).[20] In our group of patients with left variants of dACM,[6] we have revealed an LPFB in ~20% of subjects.

Other electrocardiogram features

An epsilon-like wave in the lateral leads was rarely found,[11,21] while a left deviation of the QRS axis in some patients was noted.[21]

Electrocardiogram progression

In our experience, ECG findings change over time in about half of the patients[6] (*Figure 2E*). Therefore, ECG could be a marker of disease progression and it could guide clinicians to check fibrosis evolution during follow-up. However, specific studies with CMR data during follow-up are needed to confirm this hypothesis.

Ventricular arrhythmias

A right bundle branch block (RBBB) morphology of VA is related to an origin from LV. A RBBB pattern is highly suspicious for LV variants of dACM (*Figure 2F* and *G*), and it is more often associated with underlying pathological structural diseases as reported by Muser *et al.*[22] Among patients with premature ventricular complexes with RBBB morphology, a superior axis pattern is most frequently related to a scar at CMR compared with RBBB inferior axis morphology.[23,24] A recent study[25] identified the contemporary presence of a QR pattern in lead aVR and V1 in the subgroup of patients with RBBB/superior axis and a narrow QRS in the subgroup with RBBB/inferior axis, as predictors of the absence of LV scar.

Conclusions

The 12-lead ECG remains the best non-invasive tool for identifying the peculiar findings in ACM. The knowledge of these signs is useful for an early diagnosis of LV variants of dACM.

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Data availability

No new data were generated or analysed in support of this research.

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