Progressive ECG changes over time in arrhythmogenic right ventricular cardiomyopathy precede diagnosis and continue – indices of disease substrate development?

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Funding Acknowledgement: Type of funding source: None

Background: Depolarization and repolarization abnormalities are common in arrhythmogenic right ventricular cardiomyopathy (ARVC), and are included in the diagnostic 2010 Task Force criteria (TFC2010). However, first ARVC symptoms commonly occur before ECG abnormalities reach the diagnostic thresholds and the time course of ECG abnormalities during initial phase of the disease remains obscure. Regional digital ECG archives allow computerized signal-processing and assessment of ECG phenotype during different disease phases, including the time prior to ascertainment of ARVC diagnosis.

Purpose: We aimed to assess the natural course of ECG characteristics associated with ARVC, hypothesizing that ARVC is a progressive disease and that ECG parameters progress over time due to disease substrate development.

Methods: Definite ARVC patients with at least one digital ECG recruited in three tertiary care hospitals in Sweden and Denmark were included (n=102, 66% males, 68% probands, 52% carrying a pathogenic genetic variant, 74% ICD carriers and 25% physically active >4 hours/week). Median age at diagnosis was 41 years (IQR 30–55). 12-lead digital ECGs were extracted from the regional ECG archives, containing all recordings in the hospital catchment areas since 1988. After excluding ECGs with heart rate <40 or >100/min, left bundle branch block or ventricular pacing, and those recorded prior to 14 years of age, the remaining 2067 ECGs were digitally processed and automatically analyzed using the Glasgow algorithm (median 3 [IQR 0–9] ECGs prior to diagnosis and 6 [IQR 2–14] ECGs during follow-up). Overall QRS duration as well as the right precordial lead indices exemplified by the lead V2 (terminal activation delay [TAD], area under the T-wave [T-wave area] and R-prime amplitude) were calculated and graphically represented using generalized additive model (GAM) with cubic splines (Figure 1). A median value for each measurement per patient per year was used for analysis. Blue line indicates smoothed conditional mean with 95% confidence interval (shadow). Time "0" (red line) indicates the time when TFC2010 criteria were fulfilled.

Results: Marked and consistent changes are seen in all studied depolarization and repolarization parameters over 10 years preceding ARVC diagnosis and continue afterwards. TAD demonstrates gradual increase, while T-wave area demonstrates consistent decrease over time before and after diagnosis indicating amplitude reduction and transition to T-wave inversion. The R-prime curve indicates that the terminal part of QRS complex demonstrate abnormalities first late in the course of the disease (Figure 1).

Conclusion: Electrocardiographic ARVC phenotype appears to become detectable long before the time of ARVC diagnosis indicating the progressive nature of ARVC and may explain arrhythmic events that may occur during the subclinical phase before ECG criteria are fulfilled.

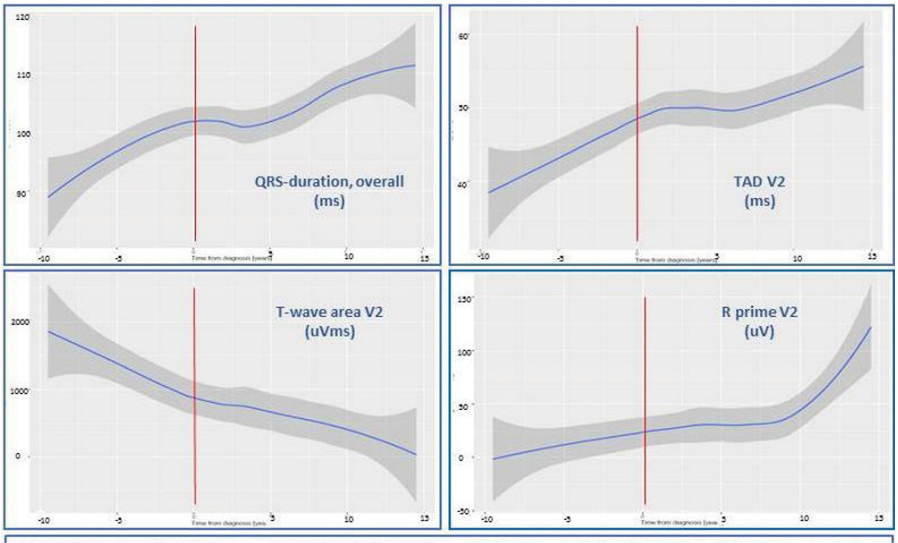

Figure 1. Progression of ECG parameters in relation to time of ARVC diagnosis (red line at time "0"). Parameter value on Y-axis and time (years) on X-axis.