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SUPPLEMENT PAPER

Evolution of P-wave indices during long-term follow-up as markers of atrial substrate progression in arrhythmogenic right ventricular cardiomyopathy

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Aims Patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) have increased prevalence of atrial arrhythmias indicating atrial involvement in the disease. We aimed to assess the long-term evolution of P-wave indices as electrocardiographic (ECG) markers of atrial substrate during ARVC progression.

Methods and results We included 100 patients with a definite ARVC diagnosis according to 2010 Task Force criteria [34% females, median age 41 (inter-quartile range 30–55) years]. All available sinus rhythm ECGs ($n = 1504$) were extracted from the regional electronic ECG databases and automatically processed using Glasgow algorithm. P-wave duration, P-wave area, P-wave frontal axis, and prevalence of abnormal P terminal force in lead V_1 (aPTF-V_1) were assessed and compared at ARVC diagnosis, 10 years before and up to 15 years after diagnosis.
Prior to ARVC diagnosis, none of the P-wave indices differed significantly from the data at ARVC diagnosis. After ascertainment of ARVC diagnosis, P-wave area in lead V_1 decreased from −1 to −30 μV ms at 5 years ($P = 0.002$). P-wave area in lead V_2 decreased from 82 μV ms at ARVC diagnosis to 42 μV ms 10 years after ARVC diagnosis ($P = 0.006$). The prevalence of aPTF-V_1 increased from 5% at ARVC diagnosis to 18% by the 15th year of follow-up ($P = 0.004$). P-wave duration and frontal axis did not change during disease progression.

Conclusion Initial ARVC progression was associated with P-wave flattening in right precordial leads and in later disease stages an increased prevalence of aPTF-V1 was seen.

Keywords Arrhythmogenic cardiomyopathy • P-wave area in lead V1 • P-wave area in lead V2 • P-terminal force in lead V1 • Atrial fibrillation

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What's new?

- Our study is the first to address the evolution of P-wave indices in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) during long-term observation using the large clinical electrocardiogram (ECG) database.
- We demonstrated long-term evolution of ECG markers of atrial involvement in ARVC.
- Flattening and inversion of P waves in the right precordial leads likely reflecting right atrial involvement in ARVC progression was observed starting when the patients were clinically diagnosed with ARVC and continued during the years of follow-up.
- The measure of electrocardiographic left atrial (LA) abnormality, i.e. abnormal P-terminal force in lead V_1, appeared to increase late after ARVC diagnosis indicating LA involvement later during the disease course.

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy characterized by fibrotic replacement of myocardium and is associated with increased risk of cardiac arrhythmias.[1] Recent publications have drawn attention to atrial fibrillation (AF) as an indicator of atrial involvement in the disease and that AF appears to have high prevalence among patients with ARVC.[2,3] According to the current pathophysiological paradigm, ARVC is considered to be a desmosomal disease.[4] Desmosomes are found throughout the myocardium, including the atrial myocardium, and involvement of atrial myocardium may be driven by the same desmosomal abnormalities leading to cell loss and fibrotic replacement as in the right ventricle.[5,6] On the other hand, atrial dilatation associated with disease progression may result from atrial overload caused by right ventricular (RV) dysfunction.[7] In earlier studies that addressed atrial remodelling un-related to ARVC, it has been shown that P-wave duration, P terminal negative force in lead V_1 (PTF-V_1), P-wave morphology, and P-wave area in lead V_1 reflect electrophysiological and structural abnormalities in the atria.[8,9] However, little attention has been paid to P-wave indices in patients with ARVC. In one previous study of patients with ARVC, we have shown that prolonged P-wave duration and abnormal P-wave morphology are common in ARVC.[10]

In this study, we assessed the long-term evolution of electrocardiogram (ECG) markers of atrial involvement in ARVC and evaluated AF as a clinical indicator of atrial abnormalities in patients from the Nordic ARVC Registry.

Methods

Patient population

The Nordic ARVC Registry was launched in June 2010 and has been recruiting patients with ARVC previously diagnosed using 1994 TFC and followed at eight tertiary care centres in Denmark, Norway, or Sweden, covering a population of approximately 14 million.[11,12] All patients diagnosed with ARVC prior to 2010 were reclassified by using 2010 Task Force Criteria (TFC2010). The Registry has also been prospectively including newly diagnosed patients with definite ARVC according to TFC2010[13] and their mutation-positive family members.

The present study is an analysis on a subgroup of 100 definite ARVC patients recruited at three sites participating in the Nordic ARVC Registry (www.arvc.dk) and included in the study of AF in ARVC published recently.[3] In order to assess longitudinal dynamics of P-wave indices in relation to the clinical diagnosis of ARVC, we included only patients (both probands and family members) who fulfilled definite ARVC diagnosis by TFC2010 and were enrolled at selected clinical centres participating in the Nordic ARVC Registry, which met technical requirements of having access to electronic archive of ECGs recorded in the hospitals and primary care facilities in the hospital catchment area: Rigshospitalet (Copenhagen, Denmark), Linköping University Hospital (Linköping, Sweden), and Skane University Hospital (Lund, Sweden)

Electrocardiogram extraction and processing

All ECG recordings in the hospital catchment areas were extracted from the regional electronic ECG archives, digitally processed, and analysed automatically using the Glasgow algorithm.[14]

In order to be included in the study, patients had to have at least one sinus rhythm ECG recording with heart rate <100 b.p.m. in digital format allowing export of raw digital signals. Recordings representing atrial arrhythmias, non-sinus rhythm origin, tachycardia >100 b.p.m., or atrial pacing were excluded, as well as ECGs recorded in childhood before age 14 years old. Availability of digital ECG recordings varied over time and in relation to the time point when ARVC diagnosis was ascertained. The observation period was defined as from 10 years prior to ARVC diagnosis to 15 years after ARVC diagnosis. So, the earliest ECG included in the study was recorded 10 years prior to ARVC diagnosis, and the latest ECG included in the study 15 years after. The number of ECGs available for analysis at each time point is indicated in *Table 1*.

Assessment of P-wave indices was performed automatically by the Glasgow algorithm.[14] P-wave duration was measured in milliseconds (ms). Total P-wave area in leads V_1, V_2, and V_6 was quantified based on geometric area between the electrical waveform and the isoelectric line and expressed as μV ms. Corresponding indices of amplitude (μV) and duration (ms) were measured within the P-wave complex, including its positive and negative components. P terminal force in lead V_1 (PTF-V_1) was defined as duration in ms of the terminal negative component of the P wave multiplied by its depth in millimeters (mm ms) (*Figure 1*). The PTF-V_1 > 0.04 mm s was considered abnormal using the original definition of abnormal PTF-V_1[15] included in the contemporary definition of electrocardiographic left atrial (LA) abnormality.[16] Advanced interatrial block (aIAB) was defined as a P-wave duration ≥120 ms with biphasic morphology (±) in the inferior ECG leads.

Clinical characteristics

We extracted pertinent clinical Registry data as previously described.[12] AF was a prespecified reportable clinical event in the registry.[3] In addition, we obtained information about AF from the electronic ECGs recorded at any time either before or after ARVC diagnosis. The date of first AF episode documented clinically, ECG-verified, or recorded by implantable cardioverter-defibrillator (ICD) monitoring were considered as the date of AF debut.

Sustained or non-sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) were verified on ECG or captured by ICD device diagnostics and cumulatively defined as VT/VF. Historical information regarding VT/VF was retrieved from patients' medical records.

Table 1 Evolution of P-wave indices during the course of ARVC progression

Years	−10	−5	ARVC diagnosis	5	10	15
Number of patients which had available ECGs	20	33	68	57	39	25
Number of ECGs	199	371	455	239	165	75
Overall P-wave duration (ms)	102 ± 19*	109 ± 17	107 ± 16	108 ± 17	106 ± 19	105 ± 19
P positive amplitude in lead II (μV)	118 ± 38	119 ± 45	111 ± 36	120 ± 48	106 ± 46	102 ± 52
P area in lead V_1 (μV ms)	−3 ± 73	−9 ± 74	−1 ± 79	−30 ± 100#	−33 ± 98	−44 ± 94
P area in lead V_2 (μV ms)	84 ± 102	81 ± 85	82 ± 62	61 ± 113	42 ± 103#	28 ± 105
P area in lead V_6 (μV ms)	129 ± 59	128 ± 58	118 ± 52	120 ± 61	101 ± 111	103 ± 72
P frontal axis (°)	43 ± 24	42 ± 21	44 ± 21	43 ± 24	42 ± 25	36 ± 47

The data are presented as mean ± standard deviation, variable mean value at each time point is compared with variable mean value at ARVC diagnosis.
*P value < 0.05 in comparison with value at ARVC diagnosis (paired samples t-test).
#P value < 0.01 in comparison with value at ARVC diagnosis (paired samples t-test).
ARVC, arrhythmogenic right ventricular cardiomyopathy; ECG, electrocardiogram.

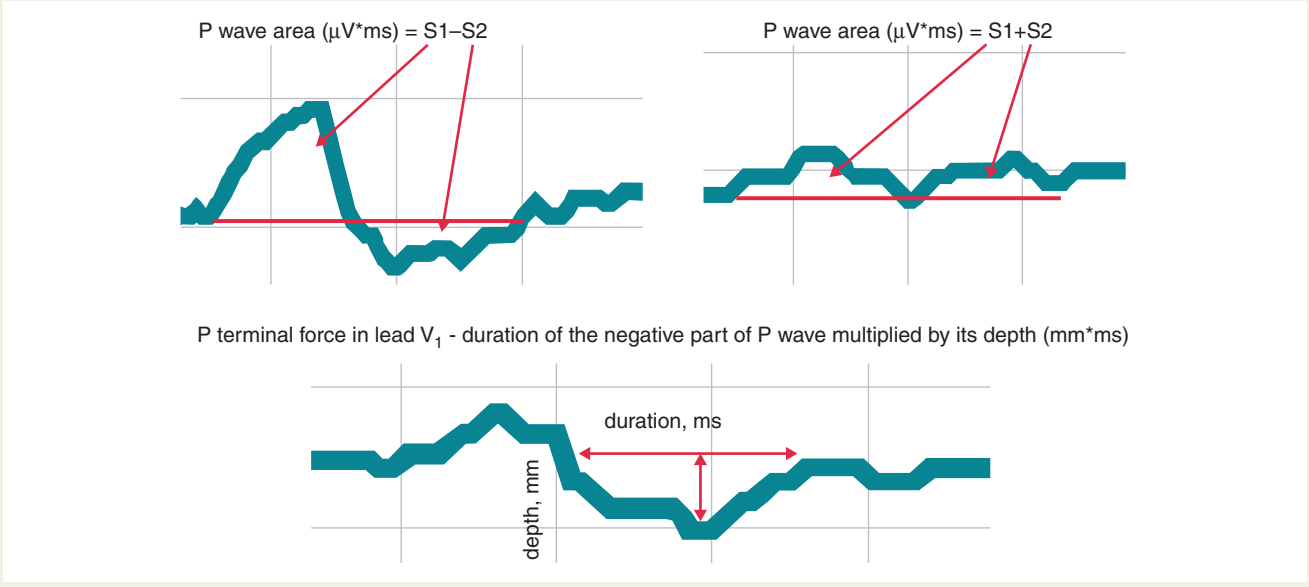

Figure 1 ECG example of measurements of P-wave area in lead V_1 (the upper panel) and P terminal force in lead V_1 (the bottom panel).

All subjects underwent transthoracic echocardiography. Left atrial and right atrial (RA) dimensions were assessed by revisiting cardiac ultrasound examinations performed at the time of ARVC diagnosis. Cardiac magnetic resonance imaging (MRI) was performed in 62 patients (62%) as a part of diagnostic work-up. Right ventricular ejection fraction (RVEF) assessed by MRI was used as an estimate of RV systolic function in those 62 patients.

Prospective follow-up information was available until May 2019 when data for the current study were retrieved. The median follow-up time after ARVC diagnosis was 9 years [inter-quartile range (IQR) 5–14 years].

Regional ethics committees approved the study. In Denmark, registry studies do not require approval from an ethics committee, but approval was obtained from the Danish Data Protection Agency. The study complies with the Declaration of Helsinki.

Statistical methods

We studied the progression of several P-wave indices in ARVC patients over time. For the graphical representation of the ARVC progression, we fitted Generalized Additive Model (GAM) with cubic splines for all the variables of interest. Generalized Additive Model allows to model non-linear relationship between P-wave indices and time by utilizing splines. To account for patient-to-patient variability, and balance the data within 1 year, we took a median for each P-wave measurement per patient per year, and then fitted GAM. Plots and the analyses were performed in statistical environment R version 3.3.3.

To create summary tables, we binned variable 'time' into several categories: −12.5 to −7.5, −7.5 to −2.5, −2.5 to 2.5, 2.5 to 7.5, 7.5 to 12.5, and 12.5 to 17.5 years. For each of the P-wave indices, we calculated mean and standard deviation. The mean values of each P-wave variable at the time 10 and 5 years prior to ARVC diagnosis and at the time 5, 10, and 15 years after ARVC diagnosis were compared to the mean values at the time of ARVC diagnosis using paired samples t-test. The prevalence of abnormal PTF-V1 at each time point was compared with the prevalence of abnormal PTF-V1 at the time of ARVC diagnosis using χ^2 test.

Clinical and imaging characteristics available at the time of ARVC diagnosis were used in a cross-sectional analysis of association between P-wave indices, disease phenotype and AF prevalence. Univariate binary logistic regression analysis was performed to evaluate odds ratios (ORs) and 95% confidence interval (CI). Significantly associated with AF variables were included in the multivariate analysis with adjustment for age at ARVC diagnosis and gender.

A two-sided *P*-value of <0.05 was considered statistically significant. Descriptive statistics and logistic regression analyses were performed using SPSS Statistics 25 (SPSS Inc., Chicago, IL, USA).

Results

Data availability

A total of 2478 ECG recordings were extracted from regional electronic ECG databases. Electrocardiograms recorded earlier than 10 years before ARVC diagnosis and later than 15 years after were not included in the study ($n = 151$). Electrocardiograms with heart rate >100 b.p.m. and atrial pacing were automatically excluded; after visual inspection, ECGs with atrial arrhythmias and non-sinus rhythm origin were excluded additionally ($n = 746$). Furthermore, 77 ECGs were excluded due to patient's age younger than 14 years old at the time of ECG recording, which left 1504 ECGs available for analysis in 100 definite ARVC patients with a median of 9 ECGs per patient (IQR 3–22). The median observation time (from the date of first ECG recording to the date of the latest ECG) was 8 years (IQR 1–15 years). There were 43 patients with observation period >10 years, 16 patients—between 5 and 10 years, and 41 patients—<5 years.

Clinical characteristics, genetic evaluation, and P-wave indices at the time of arrhythmogenic right ventricular cardiomyopathy diagnosis

Baseline characteristics of patients at the time of ARVC diagnosis are presented in *Table 2*. The majority of patients were males, had pronounced RV structural abnormalities and family history of the disease. Half of them had ventricular arrhythmias prior to ARVC diagnosis. Left atrial enlargement [LA volume index (LAVI) > 40 mL/m^2] and RA enlargement [RA volume index (RAVI) > 40 mL/m^2] were found in 12% and 11% of patients respectively. Few patients had aIAB and abnormal PTF-V_1, however the prevalence of P-wave duration > 120 ms was relatively common (13%). Among patients with LA enlargement ($n = 12$), two patients had P-wave duration > 120 ms, none had advanced IAB, and one patient had abnormal PTF-V_1. Among patients with RA enlargement ($n = 11$) none patient had P-wave duration > 120 ms, advanced IAB or abnormal PTF-V_1. None of P-wave indices at the time of ARVC diagnosis was correlated with RAVI, LAVI, RV, and left ventricular (LV) ejection fractions (Supplementary material online, *Table S1*).

Class III antiarrhythmic drug was reported at baseline in 39 patients, however, P-wave indices did not differ between patients treated with antiarrhythmic drugs and those who were not.

Genetic evaluation was performed in 81 patients (81%). The most common affected gene in mutation-positive patients was plakophillin-2 (PKP2) gen ($n = 34$, 38%), followed by desmoglein-2 (DSG2, $n = 11$, 14%), desmoplakin (DSP, $n = 8$, 10%), desmocolin-2 (DSC2, $n = 7$, 8%), plakoglobin (JUP, $n = 1$, 1%), and transmembrane protein 43 (TMEM 43, $n = 1$, 1%). Two mutations were found in four patients (5%): PKP2 and DSG2—in two patients, PKP2 and DSP—in one, and DSC2 and DSG2—in one. We did not observe statistically significant genotype–phenotype associations with P-wave indices in our cohort. Descriptive characteristics of electrocardiographic and echocardiographic arrhythmic data are presented in Supplementary material online, *Table S2*.

Table 2 Characteristics of definite ARVC (TFC2010) patients ($n = 100$) at the time of ARVC diagnosis

Variable	Value
Male gender, *n* (%)	66 (66)
Age at ARVC diagnosis (years), median (IQR 25–75%)	41 (30–55)
VT/VF before ARVC diagnosis, *n* (%)	50 (50)
AF at any time, *n* (%)	28 (28)
AF prior to ARVC diagnosis, *n* (%)	15 (15)
Hypertension, *n* (%)	9 (9)
Stroke, *n* (%)	2 (2)
Diabetes, *n* (%)	6 (6)
Ischaemic heart disease, *n* (%)	5 (5)
Heart failure ≥NYHA Class II, *n* (%)	9 (9)
Treatment with implantable cardioverter-defibrillator, *n* (%)	73 (73)
Treatment with β-blockers, *n* (%)	23 (23)
Treatment with antiarrhythmic drugs, *n* (%)	39 (39)
Major criterion imaging, *n* (%)	68 (68)
Minor criterion imaging, *n* (%)	8 (8)
Left ventricular ejection fraction, mean±SD	55 ± 8
Left ventricular ejection fraction < 45%, *n* (%)	5 (5)
Right ventricular ejection fraction, mean±SD	45 ± 12
Right ventricular end diastolic volume (mL), mean±SD	215 ± 62
Left atrial volume index (mL/m^2), mean±SD	31 ± 11
Left atrial volume index > 40 mL/m^2, *n* (%)	12 (12)
Right atrial volume index (mL/m^2), mean±SD	30 ± 11
Right atrial volume index > 40 mL/m^2, *n* (%)	11 (11)
Both (left and right) atrial volume index > 40 mL/m^2, *n* (%)	3 (3)
Major criterion repolarization, *n* (%)	42 (42)
Minor criterion repolarization, *n* (%)	16 (16)
Major criterion depolarization, *n* (%)	7 (7)
Minor criterion depolarization, *n* (%)	54 (54)
Major criterion arrhythmias, *n* (%)	19 (19)
Minor criterion arrhythmias, *n* (%)	68 (68)
Major criterion family, *n* (%)	69 (69)
Minor criterion family, *n* (%)	2 (2)
P-wave duration >120 ms, *n* (%)	13 (13)
Advanced interatrial block, *n* (%)	4 (4)
P terminal force in lead V_1 >40 mm ms, *n* (%)	6 (6)

ARVC, arrhythmogenic right ventricular cardiomyopathy; IQR, inter-quartile range; TFC2010, 2010 Task Force Criteria; VT, ventricular tachycardia; VF, ventricular fibrillation.

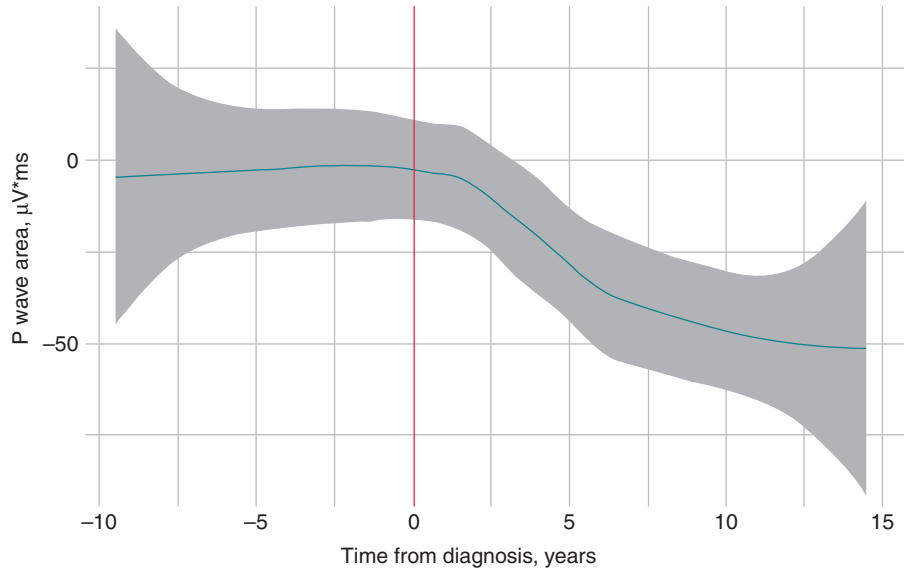

Figure 2 P area in lead V_1 10 years prior to arrhythmogenic right ventricular cardiomyopathy (ARVC) diagnosis, at $t = 0$ and 15 years after. Green line represents the mean and grey shadow—95% confidence interval.

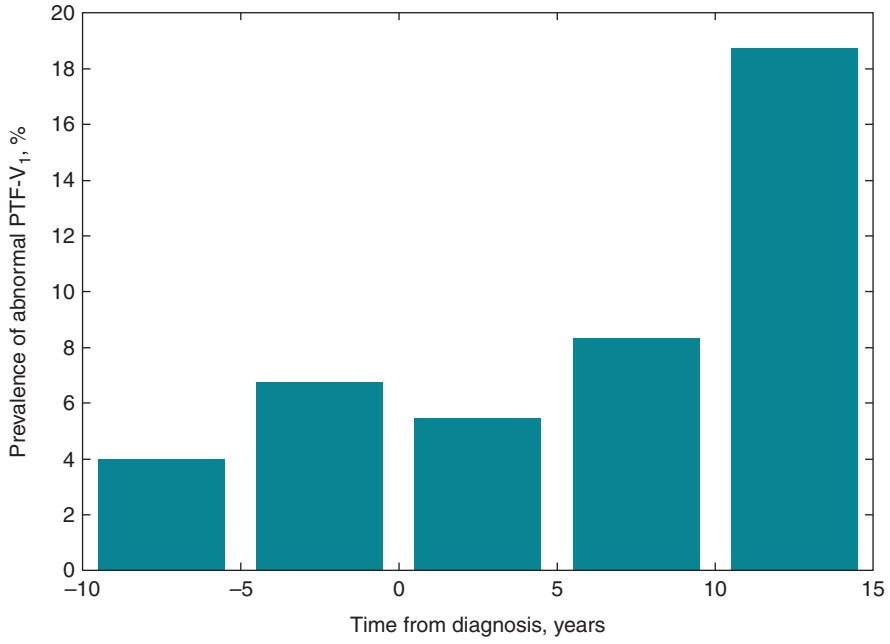

Figure 3 Prevalence of P terminal force in lead V_1 >40 mm ms 10 years prior to arrhythmogenic right ventricular cardiomyopathy (ARVC) diagnosis, at $t = 0$ and 15 years after.

P-waves indices: evolution during disease progression

The mean values of P-wave characteristics 10 years prior to and up to 15 years after ARVC diagnosis are presented in *Table 1*. Prior to ARVC diagnosis, none of the P-wave indices differed significantly from the values obtained at ARVC diagnosis. P-wave area in lead V_1 decreased from −1 μV ms at ARVC diagnosis to - 30 μV ms 5 years after ARVC diagnosis ($P = 0.002$) and further to −44 μV ms by the 15th year of follow-up ($P = 0.193$) (*Figure 2*). P-wave area in lead V_2

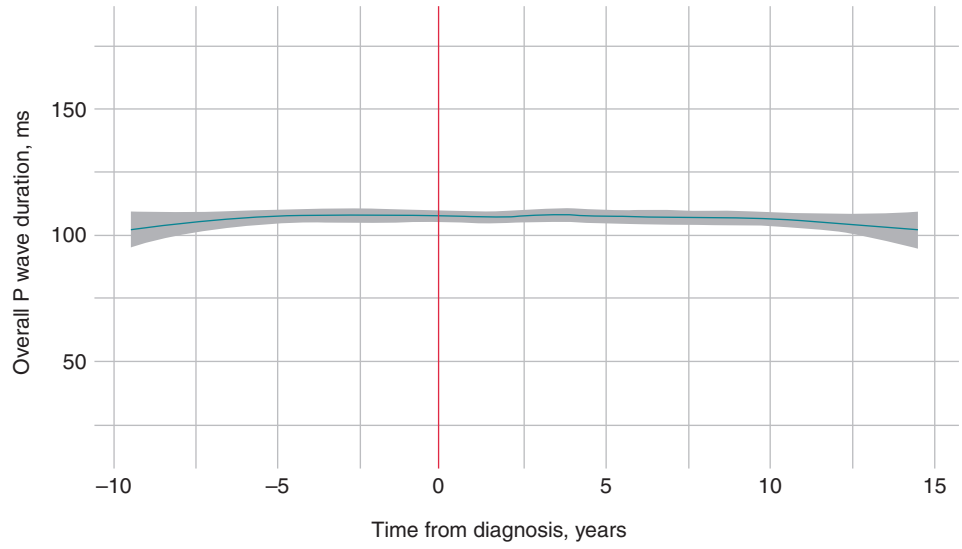

Figure 4 P-wave duration 10 years prior to arrhythmogenic right ventricular cardiomyopathy (ARVC) diagnosis, at $t = 0$ and 15 years after. Green line represents the mean and grey shadow—95% confidence interval.

decreased from 82 μV ms at ARVC diagnosis to 42 μV ms 10 years after ARVC diagnosis ($P = 0.006$). The prevalence of aPTF-V_1 increased from 5% at ARVC diagnosis to 18% by the 15th year of follow-up, $P = 0.004$ (*Figure 3*). P-wave duration (*Figure 4*), P-wave frontal axis or P-wave area in left precordial leads (exemplified by lead V_6) were not affected during the course of disease progression.

Atrial fibrillation in arrhythmogenic right ventricular cardiomyopathy patients

In total, 28 patients had AF diagnosed (28%): 15 prior to ARVC diagnosis (15%) and 13 developed AF during follow-up (13%). Median age at AF onset was 54 (IQR 36–64) years. Atrial fibrillation was paroxysmal in all patients as ECGs with sinus rhythm were required to be included in the study.

None of the assessed P-wave indices demonstrated significant association with the prevalent AF at the time of ARVC diagnosis (*Table 3*), however, the prevalent AF was associated with LAVI and documented VT of left bundle branch morphology with superior axis.

Discussion

Main findings

To the best of our knowledge, our study is the first to address the evolution of P-wave indices in patients with ARVC during long-term observation using the large clinical ECG database. We found a significant reduction in P-wave areas in leads V_1 and V_2, i.e. reduction of the positive P-wave component and deepening of the terminal P-wave inversion, which was observed starting when the patients were clinically diagnosed with ARVC and continued during the years of follow-up. Additionally, the measure of electrocardiographic LA abnormality, i.e. PTF-V_1, appeared to increase late after ARVC diagnosis indicating LA involvement later during the disease course. We have also documented high prevalence of AF among ARVC patients that reached 28% by the end of follow-up being remarkably higher than observed in the general population of the same age.[17]

P-wave indices as indicators of atrial involvement in arrhythmogenic right ventricular cardiomyopathy

P-wave indices are known ECG markers of atrial abnormalities.[8,18] It has been shown that P-wave duration is correlated to the extent of atrial fibrosis.[18] Abnormal PTF-V_1 has been shown to be associated with an increase in LA volume, and a decrease in LA contractile—and reservoir function which represents the filling of left atrium during ventricular systole.[8] However, in the context of ARVC, data regarding P-wave indices are scarce. Previously our group has shown that deteriorated atrial activation expressed either as prolonged P-wave duration or as abnormal P-wave morphology was common in ARVC patients.[10] In the current study, we observed P-wave changes that were predominantly related to the evolution of P-wave morphology, but not to changes in P-wave duration during the disease progression.

We observed a decline in P-wave area in the right precordial leads that started after ARVC was diagnosed. Recently it has been shown that the right atrium undergoes structural changes similar to those of the right ventricle known in ARVC such as a reduction of cardiomyocytes, the presence of adipocytes, interstitial fibrosis,[19,20] and an increase in size.[21] The gradual reduction of P-wave amplitude in right precordial leads in our study might reflect RA involvement progressing in parallel with RV structural abnormalities with gradual development of atrial fibrosis leading to RA dilatation. On the other hand, RA involvement in the disease progression might be a consequence of RV dysfunction.

Table 3 Results of logistic regression analysis showing the association of patient's clinical characteristics and P-wave indices with atrial fibrillation at the time of ARVC diagnosis

Variable	Odds ratio	95% confidence interval	*P* value
Univariate logistic regression			
Age at ARVC diagnosis	1.01	0.98–1.05	0.423
Male gender	2.30	0.60–8.77	0.224
Any pathogenic mutation	1.54	0.49–4.90	0.463
Hypertension	1.17	0.27–5.17	0.833
Diabetes	2.92	0.49–17.62	0.242
Ischaemic heart disease	3.95	0.60–25.96	0.153
Heart failure NYHA Class ≥II	3.29	0.73–14.75	0.123
Major criterion imaging	2.07	0.54–7.93	0.288
Minor criterion imagine	NA	NA	NA
LVEF	1.00	0.93–1.08	0.936
RVEF (MRI)	0.95	0.90–1.01	0.115
LA volume index	**1.09**	**1.03–1.16**	**0.005**
LA volume index > 40	**12.60**	**3.03–52.35**	**<0.001**
RA volume index	0.99	0.93–1.05	0.621
Major criterion repolarization	0.65	0.20–2.06	0.463
Minor criterion repolarization	0.78	0.16–3.85	0.760
Major criterion depolarization	NA	NA	NA
Minor criterion depolarization	0.71	0.24–2.13	0.538
Major criterion arrhythmias	**5.32**	**1.63–17.39**	**0.006**
Minor criterion arrhythmias	0.48	0.17–1.45	0.193
Major criterion family	0.63	0.20–1.94	0.416
Minor criterion family, *n* (%)	NA	NA	NA
P-wave duration	1.03	0.99–1.06	0.155
P area in lead V_1	1.00	0.99–1.01	0.962
P area in lead V_2	1.00	1.00–1.00	0.121
P terminal force in lead V_1	1.00	1.00–1.00	0.121
P-wave duration >120 ms	2.78	0.73–10.51	0.132
Advanced interatrial block	1.15	0.11–12.05	0.905
Final model			
Age	0.99	0.94–1.04	0.700
Male gender	0.71	0.10–5.03	0.732
Major criterion arrhythmias	**7.33**	**1.41–38.15**	**0.018**
LA volume index > 40	**12.82**	**2.23–73.71**	**0.004**

ARVC, arrhythmogenic right ventricular cardiomyopathy; LA, left atrial; LV, left ventricular; RA, right atrial; RV, right ventricular; RVEF, right ventricular ejection fraction. The boldface values reflect the statistical significance of the data.

An increase in the prevalence of abnormal PTF-V_1, being an electrocardiographical indicator for LA abnormality 10 years after diagnosis found in our study, suggests LA involvement at late stages of the disease. Previously it has been shown that LV involvement was found in 76% of ARVC patients with symptomatic heart failure.[22] Left ventricular contractile dysfunction may contribute to LA overload, increased stretch, and development of fibrosis in the atrial walls resulting in LA remodelling, which may explain the observed late development of electrocardiographic LA abnormality in patients with ARVC.[23]

The lack of apparent longitudinal changes in P-wave duration can be explained by primary involvement of the RA myocardium in the disease process. One can speculate that deterioration of conduction in RA, while affecting P-wave morphology, will likely increase the overlap between initial RA component of the P wave and less affected LA activation, thus posing minimal impact on the overall P-wave duration.

Notably, none of the P-wave indices was associated with AF at the time of ARVC diagnosis in our study. P-wave duration, PTF-V_1 and P-wave morphology are very-well known ECG indicators of atrial abnormalities resulting in the development of atrial arrhythmias.[24,25] Though we observed gradual changes in P-wave indices indicating atrial substrate changes during the disease progression, the lack of an association of P-wave indices with prevalent AF at the time of ARVC diagnosis suggests that P-wave indices may not be sufficiently sensitive for detection of LA structural abnormalities and or serve as an AF risk marker at the disease early stages in the context of ARVC.

Atrial fibrillation in arrhythmogenic right ventricular cardiomyopathy

Atrial structural abnormalities in ARVC provide a substrate for development of atrial arrhythmias, which has been reported recently,[2,7] and AF is the most common atrial arrhythmia in patients with this disease.[2] Previously we have reported AF prevalence 14% in patients with definite diagnosis from the Nordic ARVC Registry and showed the relationship of AF with the severity of the disease phenotype.[3] Our present study is a substudy, in which we included patients with definite ARVC from centres that have ECGs stored in electronic archives covering both hospital and primary care facilities in the hospital catchment areas.

In this study, in addition to the physician-reported information on clinical AF and implantable device interrogations, we also screened large-volume clinical ECG archives and included information about AF from all available ECG recordings collected from 1988. This explains that AF prevalence observed in our study is higher than previously reported for the entire Nordic ARVC Registry cohort.[3] Using this ECG-based approach for AF screening, the cumulative prevalence of AF by the end of the follow-up appeared to be 28%, i.e. twice as high as in our original study. Already at the time of ARVC diagnosis AF prevalence was as high as 15% thus greatly exceeding the AF prevalence in general population reported to be <1% for the age range 40–50 years,[17] in which most of our patients were diagnosed with ARVC.

In a cross-sectional analysis of risk factors associated with the presence of AF at the time of ARVC diagnosis, we found that AF was associated only with LAVI and the history of VT consistent with major criterion of TFC2010. The relationship between AF and LA enlargement in the context of ARVC indicates that the arrhythmia in patients with ARVC may be LA driven. None of the established clinical risk factors of AF demonstrated an association with AF thus supporting that AF is a clinical manifestation of the disease along with ventricular arrhythmias and is a part of ARVC phenotype.

Study limitation

The main limitation of our study is that not all patients had available ECG recordings at each estimated time point. Though the Nordic ARVC Registry is a prospective observational study, ECG data were collected retrospectively from electronic archives of ECGs recorded in hospitals and primary care facilities. Furthermore, due to the Nordic ARVC Registry was launched in June 2010 and has been recruiting patients with previously diagnosed ARVC and has also been prospectively including newly diagnosed patients after 2010 till nowadays, patients in our study had different periods of follow-up. However, almost half of them had the period of observation from the first ECG recording till the latest >10 years. Also this limitation might be counterbalanced by a large number of ECGs analysed in this study.

Also, we did not have serial echocardiographic measurements of atrial volumes to evaluate the atrial structural changes during the disease progression as standardized atrial measurements, until recently, have not been included in the routine examination of patients with ARVC. However, we revisited cardiac ultrasounds of all patients made at the time of ARVC diagnosis and presented the data regarding atrial volumes and their correlation with P-wave indices and atrial arrhythmias at the time of ARVC diagnosis.

Furthermore, we did not have the control group without ARVC as one would expect the effect of age on the atrial substrate and hence P-wave indices. To investigate if this holds in our data, we looked at the changes of the studied P-wave indices as a function of age, rather than diagnosis, and did not observe any significant relationship between P-wave indices and age in our material. Therefore, even though we cannot completely rule out the impact of age on the deterioration of atrial substrate we believe that observed changes in P waves are primarily related to the disease progression rather than the natural aging process in the heart.

Conclusion

Our study based on automatic processing of large volume clinical ECG archives demonstrated long-term evolution of ECG markers of atrial involvement in ARVC. Flattening and inversion of P waves in the right precordial leads become apparent during the course of the disease while electrocardiographic LA abnormality appears to be a later manifestation. Atrial fibrillation as an indicator of atrial involvement in disease progression is common in ARVC patients.

Supplementary material

Supplementary material is available at *Europace* online.

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Conflict of interest: J.H.S. reports receiving research grants from Medtronic, is a member of a Medtonic advisory board, and receives speaker fee from Medtronic. V.S. is currently employed by GlaxoSmithKline. The study was completed prior to her joining GlaxoSmithKline and was not supported by the company.

Data availability

The data underlying this article were provided by the Nordic ARVC Registry by permission. Data will be shared on a reasonable request to the corresponding author with permission of the Nordic ARVC Registry.

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