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Abnormal atrial activation is common in patients with arrhythmogenic right ventricular cardiomyopathy

Short title: “Atrial abnormality in ARVC”

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Abstract

Introduction: Structural right atrial abnormalities have been described in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC). However, little is known about ECG signs of atrial involvement in ARVC as no systematic studies have been conducted.

Methods: P-wave triggered signal-averaged orthogonal ECG from 40 ARVC patients (46±15 years, 16 females) was compared with recordings from age- and gender-matched healthy control subjects for assessment of P-wave duration and morphology. P-wave morphology was classified in regard to the P-wave polarity in leads X, Y and Z.

Results: P wave duration was longer in patients (135±18 vs. 124±12 ms, p=0.003). Two typical P wave morphologies were identified in the controls: positive in X and Y and negative (45%) or biphasic (55%) in Z. In ARVC pts, typical P waves were seen in only 60% while 15 pts (37%) had atypical P waves positive in all three leads (p<0.0001). The presence of atypical P waves in ARVC group was not associated with the presence of either structural or functional right ventricular abnormality.

Conclusions: Patients with ARVC commonly demonstrate deteriorated atrial activation expressed either as prolonged P-wave duration or abnormal P wave morphology. The P wave abnormalities were not secondary to right ventricular dilatation. These findings show that atrial involvement is common in ARVC and may represent yet another manifestation of the disease to be considered for inclusion in ARVC diagnostic work-up.

Keywords: P-wave morphology, ARVC, signal-averaged ECG
INTRODUCTION

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is one of the most common causes of sudden cardiac death in young. The reported ARVC prevalence varies from 1:1000 to 1:10000 and is believed to be underdiagnosed due to subtle and variable manifestations of the disease. During early stages of the disease life-threatening cardiac arrhythmias may occur and sudden cardiac death may be the first symptom of the disease. ARVC commonly affects the heart on the ventricular level and current diagnostics is based mostly on the signs of electrical, structural or functional right and/or left ventricular dysfunction.

Despite the desmosomal proteins that are commonly involved in the pathogenesis of the disease are present both in ventricles and atria, there has not been any study that systematically evaluates possible signs of atrial involvement in ARVC. Studies in animal models of the disease consistently report the presence of fibro-fatty replacements in atrial myocardium in affected animals, while human data on this topic are limited to a handful of case reports.

The aim of the present study was to assess the presence of atrial abnormalities using signal-averaged P-wave (PSA-ECG) analysis of P-wave duration and morphology in patients with ARVC.

METHODS

Patient population

In total, 40 consecutive, unrelated patients meeting 1994 Task Force diagnostic criteria for ARVC were enrolled to the study at Rigshospitalet, Copenhagen, Denmark (n=25) and Lund University Hospital, Sweden (n=15). The diagnostic work-up of the patients was conducted in accordance with local guidelines that include initial non-invasive evaluation with resting 12-
lead ECG, 24-48 hr Holter ECG, signal-averaged ECG for assessment of ventricular late potentials, transthoracic echocardiography (n=40) and/or cardiac MRI (n=32). MRI was not routinely performed for all subjects if patients met diagnostic criteria based on other diagnostic modalities. If initial work-up was suggestive of ARVC but score did not reach diagnostic threshold, right ventricular angiography was performed (n=24). All patients included in the study had a transthoracic echocardiography performed within the last three years. Forty ethnically-, age- and gender-matched, healthy subjects were selected for a 1:1 case-control comparison from a database of healthy volunteers recruited in Southern Sweden.12
The study was approved by the local ethics committees and complied with the Declaration of Helsinki. All subjects gave informed consent to participation.

Data acquisition and analysis
Standard 12-lead ECG data, of at least 10 seconds duration were recorded using clinical equipment (a minimal sampling frequency of 500 Hz and a sampling resolution of 5 μV was required).13 To enable the analysis of orthogonal P wave morphology, orthogonal-lead ECG data were derived from the 12-lead ECG using the inverse Dower transform.14, 15 Unfiltered, signal-averaged P waves were analyzed to determine P wave morphology.13 Following high-pass (0.5 Hz) and bandstop (50 Hz) filtering the QRS complexes were automatically identified and grouped according to similarity (a cross-correlation coefficient, \( \rho > 0.9 \)). P waves were extracted using 250 ms wide signal windows preceding each QRS complex. The signal windows were then shifted in time to estimate the maximal correlation in each lead. P waves with a cross-correlation coefficient of \( \rho > 0.9 \) (analyzed separately in all leads) were grouped together and averaged. The method used is described in detail elsewhere.13, 14
wave duration was defined by manual setting of the earliest onset and latest end in any of the three orthogonal leads. All analyses were carried out in a blinded fashion.

The P wave morphology was subsequently automatically classified into one of three predefined classes described earlier\textsuperscript{13, 16, 17} (Type 1: positive Leads X and Y and negative Lead Z; Type 2: positive Leads X and Y and biphasic Lead Z (-/+); and Type 3: positive Lead X and biphasic signals in Leads Y (+/-) and Z (-/+)). Different P wave morphology types are illustrated in Figure 1.

**Statistics**

Data are expressed as the mean ± standard deviation. The Mann-Whitney U or $\chi^2$ tests were used where appropriate for statistical testing. All tests were two-sided and $P < 0.05$ was considered statistically significant. All statistical analyses were performed using PASW Statistics, version 18.0 (SPSS Inc., Chicago, IL, USA).

**RESULTS**

**Patient population**

A total of 40 ARVC patients were included in the study (age 46±15, range 15-76 years, 16 females). Of those, 13 fulfilled minor and 16 major Task Force criteria in regard to the presence of either structural or functional right ventricular abnormality on imaging (echo, cardiac MRI, or right ventricular angiography). Mean age at diagnosis or symptom onset was 37 ±19 years. Left ventricular ejection fraction (LVEF) was normal in 38 patients. None of them had any right or left atrial dilatation of clinical significance defined as right atrial short-axis diameter > 45 mm in apical four-chamber view and left atrial diameter > 45 mm in parasternal view. None of the patients had moderate or severe tricuspid regurgitation. The
remaining two patients had markedly reduced right ventricular contractility, LVEF (25% and 30% respectively) and dilatation of all cardiac chambers. In the whole ARVC group, median left atrial dimension in the parasternal view was 39 mm (range 26-44 mm) compared with 35 mm in the control group (range 32-43 mm), not showing any significant difference between the groups.

Ventricular depolarization abnormality defined as the presence of either epsilon-wave (major), isolated QRS prolongation (>110ms) in the right precordial leads (major), or positive late potentials (minor) was identified in 70% of patients. Majority of patients were not on antiarrhythmic medication at the time of ECG registration, while six were treated with beta-blockers and five were taking either sotalol or amiodarone. Characteristics of patients and control subjects are presented in Table 1.

**PSA-ECG analysis**

There was no significant difference between the groups in regard to heart rate or duration of PQ-interval (Table 2). ARVC patients had longer P-waves than control subjects (135±18 vs 124±12 ms, p=0.003). The differences remained significant after correction for the use of class III antiarrhythmic drugs. In ARVC group, the presence of major structural/functional right ventricular abnormality was associated with longer P wave duration (140 ± 15 vs 126 ± 20, p=0.049 in comparison with patients without detectable RV abnormality). None of other Task Force diagnostic criteria was associated with P wave prolongation (Table 3). There was no association between the P wave duration and the left atrial diameter.

P wave morphology was significantly different in the ARVC group when compared with healthy subjects (Table 2). In particular, 38% of ARVC patients had atypical P waves not meeting predefined morphology criteria with activation vector directed posteriorly in the
sagittal plane (Atypical or Type 4) that appeared as positive P waves in lead Z. One ARVC patient had a P wave that met criteria for advanced interatrial block with retrograde activation of the left atrium,¹⁸,¹⁹ i.e. biphasic P wave morphology in inferior leads and P wave duration >120 ms (Type 3). None of healthy subjects had either Type 3 or Type 4 P waves. Type 4 P wave morphology was not associated with ventricular depolarization or repolarization abnormalities, occurrence of ventricular arrhythmias and was not linked to the presence of structural or functional right ventricular abnormalities.

**DISCUSSION**

Our study showed that ARVC patients have not only prolonged interatrial conduction expressed as a longer P wave duration but also significant abnormalities in P-wave morphology. These findings consistently support the notion of atrial involvement in the ARVC disease process. To the best of our knowledge, our study is the first that in a systematic manner compared P wave duration and morphology in patients with ARVC and healthy subjects.

*Atrial involvement in ARVC in animal models and humans*

Atrial involvement in the ARVC disease process has been neglected until recently, when several animal models of the disease reported the loss of atrial myocardium and bilateral focal fibro-fatty atrial lesions in up to one third of affected boxer dogs⁷ and cats.⁸ Even higher number of affected animals were present with atrial enlargement due to the dilatation of the right ventricle and tricuspid regurgitation.

In humans, information on atrial involvement in ARVC is scarce. Few case reports specifically mention atrial dilatation associated with moderate/severe tricuspid regurgitation in patients
with ARVC\textsuperscript{9,20} and association of ARVC with sick sinus syndrome.\textsuperscript{9-11} In a single case report, right atrial biopsies verified the presence of fibrotic replacements in atrial myocardium in a patient with ARVC, sick sinus syndrome and atrio-ventricular conduction disturbance.\textsuperscript{10} In a more recent report, ARVC was diagnosed in a patient without ventricular arrhythmias but severe dilatation of right atrium, sick sinus syndrome and extended atrial scarring assessed using voltage mapping of the right atrium during electrophysiological study.\textsuperscript{11}

In the light of these observations, the finding of the prolonged P wave duration in ARVC patients in the present study further indicates that atrial involvement is commonly present in ARVC. Interestingly, none of ARVC patients in our study had either sick sinus syndrome or any significant right atrial dilatation by echocardiography. In agreement with earlier observations,\textsuperscript{21} left atrial diameter was not different between ARVC patients and control subjects.

We observed a borderline significant P wave prolongation in patients with advanced structural/functional right ventricular abnormality (major criterion) compared with structurally/functionally unaffected patients. This may be a consequence of the primary fibro-fatty replacement of atrial myocardium or an effect of ‘pure’ hemodynamic atrial overload due to reduced contractility of the right ventricle and/or tricuspid regurgitation. However, the lack of clinically significant atrial enlargement in the vast majority of study subjects makes the hemodynamic overload an unlikely cause of the observed P wave prolongation in ARVC group.

\textit{P wave morphology}

In our earlier studies that used morphology analysis of unfiltered signal-averaged P waves, we demonstrated that P waves with Type 1 and Type 2 morphologies, i.e. either positive or
biphasic in orthogonal lead Z and positive in leads X and Y, are the most common morphological types that are equally common in healthy population. While Type 1 is more common in adolescents and young adults, Type 2 is the predominant morphology in elderly, and commonly observed in patients with paroxysmal atrial fibrillation. Type 3 (biphasic P wave in inferior leads) corresponding to the advanced interatrial block with retrograde left atrial activation has not been observed in our cohort of healthy controls, but was present in one ARVC patient who did not have any structural right ventricular abnormality by echo or MRI.

P-waves with activation vector directed posteriorly (Type 4) were present in 15 ARVC patients (38%) and none of control subjects. While this morphology has not been specifically reported in orthogonal leads earlier, several reports indicate that P waves that are negative in lead V1 and positive in inferior and lateral leads are commonly observed in atrial rhythms originating from right atrial appendage. It is therefore tempting to suggest that shift of the origin of sinus rhythm toward anterior part or the right atrium or right atrial appendage in ARVC patients may explain the unusually high prevalence of this P wave morphology. Variability of the location of sinus rhythm origin including its extreme anterior locations has been reported earlier by Boineau et al.

**STUDY LIMITATIONS**

Our study is a cross-sectional by design and it was therefore not possible to assess whether signs of deteriorated atrial conduction occur early or late in the course of the disease. However, our findings may serve as a background for future studies aimed to answer this question. There was no correlation between P wave duration and either age at symptom onset or duration of symptomatic phase of the disease. Secondly, echocardiography has
been performed as a part of clinical routine and therefore detailed description of right atrial dimension was not available. However, apart from the two patients with bilateral atrial enlargement presented above, ARVC subjects had no signs of clinically significant atrial enlargement and were reported as having ‘normal size’ atria. Recently proposed revised Task Force ARVC diagnostic criteria\textsuperscript{27} introduced quantification of RV structural abnormalities which we have not been able to reassess retrospectively in all our patients. However, as recently shown,\textsuperscript{28} the new criteria are more likely to increase the number of possible and borderline ARVC cases rather than to revise diagnosis in patients who were diagnosed with ARVC earlier.

**CONCLUSIONS**

Patients with ARVC commonly demonstrate deteriorated atrial activation expressed either as prolonged P wave duration or abnormal P wave morphology. These findings show that atrial involvement in ARVC is common and may represent yet another manifestation of the disease to be considered for inclusion in ARVC diagnostic work-up.

**ACKNOWLEDGEMENTS**

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Rigshospitalet, and Lægernes Forsikringsforening af 1891. There are no conflicts of interest to report.

REFERENCES

Figure 1. P wave morphologies in X, Y, Z orthogonal leads and corresponding leads V₁, I and aVF observed in ARVC patients and healthy subjects. Healthy controls had only Type 1 and Type 2 morphologies while 1 ARVC patient had Type 3 and 15 patients had Type 4 P waves.
# Table 1: Subject characteristics

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td></td>
<td>n=40</td>
<td>n=40</td>
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<tr>
<td><strong>Age at symptom onset</strong></td>
<td>37 ±16</td>
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</tr>
<tr>
<td><strong>Male gender</strong>*</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td><strong>Age at ECG registration</strong>*</td>
<td>46±15</td>
<td>45±15</td>
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<tr>
<td><strong>LA dimension</strong>*</td>
<td>37±5</td>
<td>36±3</td>
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<tr>
<td><strong>Antiarrhythmic drugs</strong></td>
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<td></td>
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<tr>
<td>None</td>
<td>29</td>
<td>40</td>
</tr>
<tr>
<td>Class II</td>
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<td>0</td>
</tr>
<tr>
<td>Class III</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td><strong>ARVC Task Force Criteria (1994)</strong>(^5)</td>
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<td></td>
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<tr>
<td>Family history</td>
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<td>0</td>
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<tr>
<td>Depolarization abnormality</td>
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</tr>
<tr>
<td>Repolarization abnormality</td>
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</tr>
<tr>
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<td>RV functional/anatomical abnormality</td>
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<td>Histology</td>
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</table>

LA= left atrium; N/A= data not available; PVC=premature ventricular contractions; VT=ventricular tachycardia
*- non-significant difference between the groups
### Table 2: Results of the P-wave signal-averaged ECG analysis

<table>
<thead>
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<tr>
<td>Heart rate [bpm]</td>
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<td>69±11</td>
<td>ns</td>
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<tr>
<td>PQ interval [ms]</td>
<td>176±44</td>
<td>163±20</td>
<td>ns</td>
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<tr>
<td>P-wave duration [ms]</td>
<td>135±18</td>
<td>125±12</td>
<td><strong>0.007</strong></td>
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<tr>
<td>P-wave morphology [n]</td>
<td></td>
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<tr>
<td>Type 1</td>
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<td></td>
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<tr>
<td>Type 2</td>
<td>14</td>
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</tr>
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<td>Type 3</td>
<td>1</td>
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<tr>
<td>Type 4</td>
<td>15</td>
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</tbody>
</table>

ns= not significant

### Table 3: P wave duration in relation to the presence of ARVC Task Force diagnostic criteria, ms

<table>
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<th>Major</th>
<th>P-value</th>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Family history</td>
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<td>135±26</td>
<td>140±15</td>
<td>n.s.</td>
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<td>Depolarization abnormality</td>
<td>128±21</td>
<td>138±17</td>
<td>138±16</td>
<td>n.s.</td>
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<td>130±18</td>
<td>140±19</td>
<td>N/A</td>
<td>0.06</td>
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<tr>
<td>Arrhythmia (VT/PVC)</td>
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</tr>
<tr>
<td>RV functional/anatomical abnormality</td>
<td><strong>126±20</strong></td>
<td>136±18</td>
<td><strong>140±15</strong></td>
<td><strong>0.049</strong></td>
</tr>
</tbody>
</table>

N/A= not applicable; PVC= premature ventricular contractions; RV= right ventricular; VT= ventricular tachycardia

*- p-value concerns comparison between the patients with major structural/functional right ventricular abnormality and those without any detectable abnormality.