The Prognostic Value of Right Ventricular Deformation Imaging in Early Arrhythmogenic Right Ventricular Cardiomyopathy

Running title: The Prognostic Value of RV Deformation Imaging in Early ARVC

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STRUCTURED ABSTRACT

**Background:** Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by variable disease expressivity among family members, which complicates family screening protocols. Previous reports have shown that echocardiographic deformation imaging detects abnormal right ventricular (RV) deformation in the absence of established disease expression in ARVC.

**Objectives:** We aimed to investigate the prognostic value of echocardiographic deformation imaging in ARVC to optimize family screening protocols.

**Methods:** First-degree relatives of ARVC patients were evaluated according to 2010 Task Force Criteria (TFC), including RV deformation imaging (n=128). Relatives fulfilling structural TFC were excluded for further analysis. At baseline, deformation patterns of the subtricuspid region were scored by Type-I: normal deformation, Type-II: delayed onset, decreased systolic peak, and post-systolic shortening, or Type-III: systolic stretching and large post-systolic shortening. The final study population comprised relatives who underwent a second evaluation during follow-up. Disease progression was defined as the development of a new 2010 TFC during follow-up that was absent at baseline.

**Results:** Sixty-five relatives underwent a second evaluation after a mean follow-up of 3.7±2.1 years. At baseline, 28 relatives (43%) had normal deformation (Type-I) and 37 relatives (57%) had abnormal deformation (Type-II/Type-III) in the subtricuspid region. Disease progression occurred in 4% of the relatives with normal deformation at baseline and in 43% of the relatives with abnormal deformation at baseline (P<.001). Positive and negative predictive values of abnormal deformation were respectively 43% (95CI:27%-61%) and 96% (95CI:82%-100%).

**Conclusion:** Normal RV deformation in the subtricuspid region is associated with absence of disease progression during a nearly 4-year follow-up in ARVC relatives. Abnormal RV deformation seems to precede the established signs of ARVC. RV deformation imaging may potentially play an important role in ARVC family screening protocols.
CONDENSED ABSTRACT

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a disease that is characterized by variable disease expressivity among family members, which complicates family screening protocols. A recent consensus statement by an international Task Force recommends repeated clinical assessment in all relatives every 2-3 years, even in relatives without any morphological or functional abnormalities. The present study was conducted to optimize family screening protocols by evaluating the value of echocardiographic deformation imaging as a predictor of disease progression. The results suggest echocardiographic deformation imaging may potentially play an important role in ARVC family screening protocols.

ABBREVIATIONS LIST

ARVC = arrhythmogenic right ventricular cardiomyopathy
RV = right ventricle/ventricular
TFC = Task Force criteria
ECG = electrocardiogram
CMR = cardiac magnetic resonance imaging
PPV = positive predictive value
NPV = negative predictive value

KEY WORDS

ARVD/C, arrhythmogenic right ventricular cardiomyopathy, deformation imaging, strain imaging, family screening, disease progression
INTRODUCTION

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy clinically characterized by ventricular arrhythmias and predominantly right ventricular (RV) dysfunction (1). Typical genetic features of ARVC are reduced penetrance and variable disease expressivity, which complicates family screening (2-4). Comprehensive cardiac screening of ARVC family members is routinely performed by electrocardiography (ECG), Holter monitoring, and cardiac imaging, and aims to detect typical ARVC related abnormalities (3,5,6). However, early ARVC is characterized by a lack of overt structural abnormalities detected by conventional imaging approaches (3,7). Novel imaging techniques could be of incremental value in optimizing ARVC family screening protocols (8).

Echocardiographic deformation imaging is a technique that enables quantification of regional ventricular deformation and provides insight in mechanical synchrony and regional contractility (9,10). Previous reports suggest that this technique is capable to detect subtle functional abnormalities in the absence of structural abnormalities by conventional imaging (11-13). We recently introduced a new approach that combines multiple deformation parameters into three distinct deformation patterns. A clear correlation between abnormal deformation patterns and disease severity among ARVC desmosomal mutation carriers was found (14). In addition, we were able to characterize the underlying electromechanical substrate of these patterns by dedicated computer simulation of deformation patterns. Abnormal deformation was typically seen in the basal area of the RV free wall (or subtricuspid region) which is recognized as one of the earliest affected areas in ARVC (12-15). Importantly, abnormal deformation in this specific area was seen during the earliest subclinical stage in which established phenotypic disease expression according to the 2010 Task Force Criteria (TFC) was absent (5). Therefore, echocardiographic deformation imaging may potentially play a pivotal role in improving ARVC family screening.

While all previously published data was obtained in a cross-sectional study design, this longitudinal study was conducted to explore the value of deformation imaging in ARVC family member screening. Our hypothesis is that distinct RV deformation abnormalities precede the conventional signs of disease during the early ARVC stages and can therefore help stratifying relatives at risk for disease progression.

METHODS

Study population
During a 10-year observational period (2006-2016), we performed echocardiographic examination according to our ARVC protocol in probands (all fulfilling definite diagnosis by 2010 TFC) and their relatives during their clinical work-up for ARVC (9,16). The study participants (n=194, age>18years) were derived from the Dutch National ARVC registry with patients from University Medical Center Utrecht (n=161), Academic Medical Center Amsterdam (n=18), and University Medical Center Groningen (n=15). Altogether, an echocardiographic exam with appropriate RV recordings for RV deformation imaging was available in 66 ARVC probands and 128 first-degree relatives. All participants were genetically tested for known ARVC related pathogenic mutations: plakophilin-2 (PKP2), desmoglein-2 (DSG2), desmocollin-2 (DSC2), desmoplakin (DSP) and plakoglobin (JUP) (5). Non-desmosomal analysis included transmembrane protein 43 (TMEM43) and phospholamban (PLN) (5,17).

The following participants were eligible for this study: 1) first-degree relatives carrying the identical pathogenic ARVC mutation as identified in the probands, or 2) first-degree relatives of mutation-negative probands. These relatives (n=128) were classified according to the presence of subsets of 2010 TFC during clinical work-up at baseline (5,14):

- **Structural stage:** Relatives fulfilling 2010 TFC for structural abnormalities detected by echocardiography or cardiac magnetic resonance imaging (CMR).
- **Electrical stage:** Relatives without structural abnormalities fulfilling 2010 TFC, but with ECG abnormalities (repolarization and/or depolarization) and/or history of ventricular arrhythmias as defined by the 2010 TFC.
- **Subclinical stage:** Relatives without any electrical or structural TFC.

To investigate the value of echocardiographic deformation imaging during the early clinical ARVC stages (i.e. subclinical and electrical stage), relatives fulfilling TFC for structural abnormalities (i.e. structural stage) were excluded for further analysis (n=19). Of the remaining 109 early-staged first-degree relatives, a subset of 65 first-degree relatives (60%) who underwent a second complete cardiac evaluation during follow-up were included in the final study population (Figure 1). The other 44 subjects (40%) did not have a second complete evaluation with all diagnostic modalities during follow-up. Supplementary Table 1 provides a baseline comparison between subjects with follow-up and without complete follow-up. The local medical ethical committees of each participating center approved this study.
Cardiac evaluation

A comprehensive description of the cardiac evaluation is found in the Supplementary Methods. In brief, all subjects underwent standard 12-lead ECG, which was scored for the presence of repolarization and depolarization abnormalities as defined by the 2010 TFC (5). Holter recordings for 24 hours were analyzed for the presence of ventricular tachycardia (VT) and premature ventricular complexes (PVC) (5). Structural abnormalities as defined by 2010 TFC were primarily assessed by echocardiography according to standard ARVC protocols (5,9,16). Additionally, left ventricular (LV) involvement was assessed by visual wall motion analysis and measurement of LV ejection fraction (LVEF) using Simpson biplane method. Additional CMR was performed at the discretion of the treating physician (typically in cases where echocardiography was of insufficient quality or to verify new abnormalities seen by echocardiography). CMR studies were analyzed for fulfillment of TFC and LV systolic function was assessed by measurement of LVEF (5,18). Contrast enhanced images after administration of gadolinium were acquired to identify myocardial fibrosis in both the RV and LV. ARVC definite diagnosis was based on the presence of subsets of 2010 TFC, which requires 2 major criteria, 1 major and 2 minor criteria, or 4 minor criteria (5).

Echocardiographic RV deformation imaging

All subjects underwent RV echocardiographic deformation imaging with GE Vivid 7 or GE Vivid E9 (General Electric, Milwaukee, MN) (9). Details on image acquisition and post-processing were extensively described elsewhere (9,16). In brief, a focused modified narrow-angled 2D image in the apical 4 chamber view was recorded to assess the RV. Frame rates between 55-110/s were accepted for RV deformation imaging. GE EchoPac 10.2 – PC software by GE Healthcare was used to perform 2D speckle tracking. After manual tracing, the RV lateral free wall was divided automatically into the basal, mid, and apical segment. Pulmonary valve timing was assessed by Doppler traces in the RV outflow tract obtained in parasternal short axis view. The following deformation parameters were measured in the basal area: time to onset of shortening (19), systolic peak strain value (10,20), and post-systolic index (12) (for definitions see Supplementary Figure 1). These deformation parameters can be combined into three distinct deformation patterns, as previously published (Figure 2) (14).

- **Type-I**: defined as normal deformation characterized by onset shortening ≤90 ms, systolic peak strain ≥|20%|, and ≤10% post-systolic shortening.
- **Type-II**: characterized by delayed onset of shortening (>90ms), reduced systolic peak strain (< -20% ; > -10% ), and minor post-systolic shortening (>10%).

- **Type-III**: characterized by predominantly systolic stretching (systolic peak strain < -10% ), and major post-systolic shortening.

**ARVC disease progression**

In the final study population of 65 first-degree relatives who underwent two separate complete cardiac assessments, disease progression was defined as the presence of a new major or minor TFC (structural, depolarization, repolarization, or arrhythmic) that was absent at baseline. RV deformation patterns in the basal area at baseline were evaluated for the predictive value for disease progression.

**Statistical analysis**

Means were expressed as mean ± standard deviation or median [inter-quartile range] if appropriate. Normal distribution was tested by the Shapiro-Wilk test. Mean group values were compared independent Student’s t-test or Mann-Whitney-U test if appropriate. Distributions of proportions were performed by Fischer Exact test. Predictive values were expressed as positive/negative predictive value (PPV/NPV) with the 95% confidence interval (95CI) calculated by the Clopper-Pearson method. For inter-observer analysis a second operator performed RV deformation analysis in 20 random subjects. For determination of intra-observer agreement, this sample was re-analyzed by the first observer 6 weeks after the first analysis. Inter- and intra-observer agreement were determined by linear weighted Kappa statistics. P-values were considered statistically significant if P<.05 All statistical analyses were performed in commercially available software: IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.

**RESULTS**

**Clinical evaluation at baseline**

The final study population comprised 65 subjects with a mean age of 31.8±16.6 years of which 24 (37%) were male. The majority carried a pathogenic mutation (n=54, 83%) which mostly considered a desmosomal mutation (n=50, 77%). Based on baseline clinical evaluation, 37 subjects were assigned to the subclinical stage and 28 subjects had electrical abnormalities according to the 2010 TFC ([Figure 1](#)). Subjects that showed electrical abnormalities at
baseline were significantly older compared to subjects in the subclinical stage (respectively 26.4±13.9 years vs. 39.0±17.4 years, P<.001). Gender and the presence of a pathogenic mutation were not significantly different between subjects in the subclinical or electrical stage (Table 1). At baseline, CMR was available in 23 (62%) subjects in the subclinical stage and 19 (68%) subjects in the electrical stage. All mean values of the structural parameters (by CMR as well as echocardiography) were comparable between subjects in the electrical and subclinical stage (Table 1). At baseline, none of the subjects had signs of LV involvement by echocardiography or CMR. None of the included subjects had a history of sustained ventricular arrhythmias and none were on anti-arrhythmic medication. Eight (12%) subjects had an implantable cardiac defibrillator (ICD) implanted at baseline for primary prevention (3 in the subclinical stage and 5 in the electrical stage). No baseline differences were seen between subjects that underwent a second evaluation (n=65) and those without (n=44) (Supplementary table 1).

RV deformation patterns in relatives at baseline

In the final study population, Type-I deformation was seen in 28 (43%) subjects, Type-II deformation was seen in 33 (51%) subjects and Type-III deformation was seen in 4 (6%) subjects. Abnormal deformation (Type-II and Type-III) was more frequently seen in older subjects (36.6±7.2 years vs. 25.5±13.7 years, P=.005) and in pathogenic mutation carriers (92% vs. 71%, P=.045). Sex was equally distributed among subjects with normal and abnormal deformation patterns (male: 36% vs. 38%, P=1.00).

The 37 subjects in the subclinical stage were mainly characterized by deformation pattern Type-I (n=23, 62%), whereas deformation pattern Type-II was seen in the remaining 14 (38%) subjects. The electrical stage was mainly characterized by deformation pattern Type-II (n=19, 68%). In the remaining subjects in the electrical stage, Type-I was seen in 5 (18%) and Type-III was seen in 4 (14%). The distribution of baseline deformation patterns specified for the presence of ECG abnormalities as defined by TFC is shown in Supplementary Table 2.

Inter- and intra-rater reproducibility for RV deformation pattern classification was high, respectively 0.94 (95CI: 0.81-1.00) and 0.93 (95CI: 0.79-1.00).

Disease Progression
The mean follow-up duration was 3.7±2.1 years and was equally distributed between subjects that showed signs of disease progression compared to subjects without signs of disease progression (respectively 4.5±2.0 vs. 3.5±2.1 years, P=0.09). Altogether, 17 (26%) relatives showed signs of ARVC disease progression.

Electrical progression occurred more frequently compared to structural progression: 11 subjects showed only electrical progression, 4 subjects showed electrical progression along with structural progression, and 2 subjects showed structural progression on top of already pre-existing electrical disease at baseline. None of the subjects suffered from a sustained arrhythmic event or appropriate ICD intervention during follow-up.

The progression rates among the carriers of different mutations are shown in Supplementary figure 2.

**Predictive value of abnormal deformation in early ARVC**

Of the 28 subjects with a normal deformation pattern (Type-I) at baseline, only one subject showed disease progression, expressed as an increased PVC count of >500/24hrs during second evaluation. In the 37 subjects with an abnormal deformation pattern (Type-II and Type-III) at baseline, disease progression was seen in 16 (43%) subjects. The NPV of normal deformation at baseline for disease progression was 96% (95CI:82%-100%). The PPV of abnormal deformation at baseline for disease progression was 43% (95CI:27%-61%). The predictive values were similar in a sub-cohort only consisting of mutation-positive relatives (n=54); NPV: 95% (95CI:75%-100%), PPV: 44% (95CI:27%-62%).

**Figure 3** shows a flowchart of the rate of disease progression specified for both deformation pattern and clinical stage at baseline. In the 23 subjects in the subclinical stage with normal deformation at baseline, only one subject showed disease progression; NPV: 96%, (95CI:78%-100%). In the 14 subjects in the subclinical stage with abnormal (Type-II) deformation, 9 (64%) showed disease progression (Figure 3). This results in a PPV of 64% (95CI: 35%-87%)

In the 5 electrical staged subjects with normal deformation at baseline, disease progression occurred in none; NPV: 100% (95CI:48%-100%). Of the 19 subjects in the electrical stage with Type-II pattern at baseline, 5 (26%) showed signs of disease progression. Two of the four (50%) subjects in the electrical stage with deformation pattern Type-III showed disease progression. The PPV of abnormal deformation (Type-II or Type-III pattern) on disease progression in the electrical stage is 30% (95CI:13%-53%).
The main findings of our study are that, in case of normal findings by conventional echocardiography and CMR, 1) first-degree relatives of ARVC patients with normal deformation in the RV basal area do not show disease progression during a mean follow-up of nearly 4 years and that 2) the presence of abnormal deformation at baseline is associated with unequivocal signs of disease progression during follow-up in early ARVC. The results of this study might have implications for our follow-up strategy of relatives in clinical practice. Relatives with normal RV deformation on top of normal results during standard cardiac screening seem to have an excellent mid-term prognosis and less frequent cardiac screening might be equally effective.

Normal RV deformation imaging in early ARVC

Our study shows that deformation imaging is able to identify relatives at low-risk for disease progression. This particularly holds true for relatives in the earliest stage without any established disease expression as defined by TFC. Normal deformation in the RV basal area in addition to the absence of abnormalities detected by ECG, Holter, and conventional cardiac imaging largely excludes disease progression for at least almost 4 years. Previously, we demonstrated with computer modeling that deformation pattern Type-I represents normal electromechanical properties of the RV myocardium such as seen in healthy individuals (14). We focused on the RV basal area (subtricuspid region) since previous studies have convincingly shown that this area is one of the first affected regions in ARVC (12,15,19). Our results suggest that relatives without any disease expression (including normal deformation in the subtricuspid region) are in a clinical stage that precedes the subclinical stage. Traditionally, a clinical stage without any disease expression in ARVC is often considered as the concealed stage (1). Our data show that deformation imaging helps to discriminate between relatives who are in a true concealed stage and relatives with subtle local RV mechanical dysfunction not detected by conventional approaches (subclinical stage) (Figure 4). A recent consensus statement by an international Task Force recommends repeated clinical assessment in all ARVC family members every 2-3 years, even in individuals without any morphological or functional abnormalities (6). In the present study we observed low progression rates in ARVC relatives in the true concealed stage, i.e. relatives with normal deformation in the subtricuspid region in addition to normal findings by conventional techniques. This allows us to speculate that the follow-up interval in this group might be extended beyond the current recommendations (6). However, further studies with longer follow-up and preferentially larger patient numbers, in which disease progression
is accurately assessed by CMR, are needed to further substantiate our findings. Moreover, individual factors (e.g. cardiac symptoms and sports activity) should always be considered when determining individual follow-up intervals.

Abnormal RV deformation imaging in early ARVC

By definition, relatives in the subclinical stage lack any established disease expression as defined by TFC. Interestingly, one third of the included subclinical staged subjects in this study were identified with an abnormal deformation pattern (Type-II). In a recent study, we showed that this abnormal deformation pattern is present in almost half of the desmosomal mutation carriers in the subclinical stage and the underlying electromechanical substrate seems to be regional hypocontractility and mildly increased passive wall stiffness (14). This finding is confirmed in the present study where abnormal deformation patterns were encountered in subclinical staged subjects without any established disease expression, including the absence of ECG abnormalities (Supplementary Table 2). One of our main findings was that the presence of abnormal deformation actually precedes ECG abnormalities since approximately half of the subjects in the subclinical stage with abnormal deformation developed unequivocal signs of disease progression during follow-up, primarily electrical disease progression. The association between the presence of abnormal deformation and the occurrence of established disease expression during follow-up supports our hypothesis that the observed deformation patterns are a functional representation of an underlying pathological electromechanical substrate.

The subjects in our cohort did not suffer from any life threatening events such as sudden cardiac death, sustained ventricular arrhythmia, or appropriate ICD intervention during follow-up. This could be explained by the fact that all relatives fulfilling structural TFC were excluded from our study, while especially this form of disease expression is seen in all relatives prior to sustained arrhythmic events (3,4,7). Another explanation could be that this cohort is too small and the lack of events is possibly a matter of chance. Although we were not able to prove any association between abnormal deformation and sustained arrhythmias, we do speculate that abnormal deformation is an early sign of structural changes. Considering the apparent low arrhythmic risk in patients with no structural expression, cardiac screening every 2 years in accordance with the current Task Force consensus statement seems to be sufficient and safe (6). (Figure 4)

Towards optimization of family screening protocols.
To our best knowledge, the present study is the first one to prospectively investigate the prognostic value of RV deformation imaging in early ARVC. A recent retrospective study by Leren et al. reported a multi-modality approach in identifying subjects at risk for ventricular arrhythmias during early ARVC and thereby aiming at the use of deformation imaging in addition to conventional techniques (21). Our study is in line with their multi-modality design during family screening, and further highlights the additional value of RV deformation imaging in ARVC.

A recent expert consensus document of the European Heart Association supports the additional use of strain echocardiography in the echocardiographic assessment in ARVC, particularly in early ARVC when the diagnosis is challenging (8). We may be entering a new era in which echocardiographic deformation imaging will participate in the field of clinical decision making in ARVC (22).

Limitations:

Based on the rates of disease progression that were observed in our cohort after almost four years, we made suggestions for follow-up intervals for ARVC family members. However, these intervals may not be suitable for all ARVC family members. Firstly, it is known that the disease behaves differently among the carriers of different mutations while our cohort mainly represented PKP2 and PLN mutation carriers (17). Additionally, in our proposed follow-up intervals we did not take into consideration factors such as age, gender, presence of cardiac symptoms and sports activity (4,23). These factors may have a significant influence on disease progression and thus should be taken into consideration in studies aiming to make recommendations for follow-up intervals. Even though the current study includes a relatively large cohort of patients with this relatively rare disease, our study population was too small to correct for genetic profile and additional clinical factors in a multivariate analysis.

Forty percent of the baseline cohort could not be included in the study because their second evaluation did not take place during our study period, or because the second evaluation did not include all diagnostic modalities that are needed to adequately assess disease progression. Based on the baseline comparison between subjects with follow-up and without available follow-up (Supplementary table 1), relevant selection bias seems unlikely.

Structural disease progression was primarily assessed by conventional echocardiography, and 25 subjects (38%) had additional CMR. However, the sensitivity of conventional echocardiography is known to be inferior to CMR, which...
could potentially lead to lower detection of structural abnormalities in subjects that did not have CMR (24). In future studies, disease progression should be accurately assessed by both CMR and echocardiography.

CONCLUSION

Echocardiographic deformation imaging is capable to identify relatives who are at low risk of disease progression during the early stages of ARVC. A normal RV deformation pattern at baseline is associated with an absence of disease progression during mid-term follow-up in relatives of ARVC patients, suggesting that a low-frequency follow-up strategy would suffice. Moreover, the presence of abnormal RV deformation in early ARVC is associated with unequivocal signs of disease progression. Therefore, our data suggest that echocardiographic deformation imaging may potentially be implemented in ARVC family screening protocols. Future studies including a larger study population are required to validate our data.

PERSPECTIVES

Competency in medical knowledge: The present study demonstrates that in the absence of structural TFC, normal echocardiographic deformation in the subtricuspid region identifies ARVC family members who are at low risk of disease progression. Abnormal echocardiographic deformation in this region is associated with unequivocal signs of disease progression.

Translational outlook: Future studies including a larger number of ARVC family members and with a longer follow-up are required to validate the predictive value of echocardiographic deformation imaging in risk stratification in early ARVC. Echocardiographic deformation imaging may become an important part of family screening protocols in ARVC. We should be heading in the direction of a predictive model in which a variety of clinical parameters are implemented, to create individual, tailor-made follow-up strategies for ARVC family members.
REFERENCES


**Figure Legends:**

*Figure 1. Study design:* Relatives with available RV deformation imaging were eligible for this study. The presence of structural abnormalities (as defined by 2010 TFC) resulted in exclusion of the study. Only relatives in the early clinical stages (electrical stage and subclinical stage, n=109) were included. Sixty-five relatives underwent a complete second cardiac evaluation.

ARVC=arrhythmogenic right ventricular cardiomyopathy; ECG=electrocardiography; RV=right ventricle; TFC=task force criteria.

*Figure 2. Right ventricular deformation patterns:* Three distinct deformation patterns are observed in ARVC. In a previous report by our group, we used a computer model to simulate Type-II (middle panel) pattern by the induction of a mechanical substrate (hypocontractility and increased passive wall stiffness) in the subtricuspid region (14).

Type-III (right panel) was simulated by aggravating this substrate. No local pathological electromechanical substrate was present in Type-I (normal deformation) (left panel).

ARVC=arrhythmogenic right ventricular cardiomyopathy; PVO/PVC=timing of pulmonary valve opening/closure.

*Figure 3. Rate of disease progression specified for deformation patterns and clinical stage at baseline:* These rates result in a NPV of 96% (95CI: 82-100%) and a PPV of 43% (95CI: 27-61%) for abnormal deformation imaging in the subtricuspid region. For relatives in the subclinical stage, the NPV and PPV are respectively 96% (95CI: 78-100%) and 64% (95CI: 35-87%). For relatives in the electrical stage, the NPV and PPV are respectively 100% (95CI: 48-100%) and 30% (95CI: 13-53%).

*Figure 4. Central illustration. Suggested follow-up strategies in relatives depends on the clinical ARVC stage:* In the concealed stage, RV deformation imaging shows normal deformation (Type-I), suggesting the absence of electromechanical substrate. In the subclinical stage, RV deformation imaging shows an abnormal pattern, but electrical and structural abnormalities (as defined by the TFC) are not detectable. The electrical stage is characterized by electrical abnormalities, deformation imaging in this stage shows a transition between Type-II and Type-III deformation patterns. In the structural stage there are both electrical and structural abnormalities as defined by the TFC, deformation imaging in this stage shows Type-III deformation, which is associated with a large RV electromechanical substrate. Normal deformation (Type-I) without any other detected abnormalities excludes the...
presence of an electromechanical substrate and follow-up intervals in this stage might be less frequent compared to the follow-up strategies recommended by current guidelines (6).

ECG=electrocardiogram; PVC=premature ventricular complexes; RV-FAC=right ventricular fractional area change; RVOT-PLAX=right ventricular outflow tract – parasternal long axis view; TAD=terminal activation duration; TFC=task force criteria; TWI=T-wave inversion.
Table 1. Baseline characteristics of 65 first-degree relatives with two complete cardiac evaluations

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<td>T-wave inversion: V1-V6</td>
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<td>1 (4)</td>
<td>.431</td>
</tr>
<tr>
<td>T-wave inversion: V1-V6 with RBBB</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Arrhythmia TFC (major/minor) (%)</td>
<td>0 (0)</td>
<td>13 (46)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>(Non-)sustained VT with superior axis</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.00</td>
</tr>
<tr>
<td>(Non-)sustained VT with inferior or unknown</td>
<td>0 (0)</td>
<td>2 (7)</td>
<td>.182</td>
</tr>
<tr>
<td>PVC&gt;500/24h</td>
<td>0 (0)</td>
<td>12 (43)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Family history TFC (major) (%)</strong></td>
<td>37 (100)</td>
<td>28 (100)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Echocardiography</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV-WMA</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>1.00</td>
</tr>
<tr>
<td>PLAX RVOT (mm/m²)</td>
<td>15.2 ± 2.5</td>
<td>15.3 ± 2.2</td>
<td>.870</td>
</tr>
<tr>
<td>PSAX RVOT (mm/m²)</td>
<td>16.3 ± 2.8</td>
<td>15.7 ± 2.4</td>
<td>.464</td>
</tr>
<tr>
<td>RV-FAC (%)</td>
<td>46.4 ± 6.2</td>
<td>45.7 ± 7.1</td>
<td>.691</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>58.7 ± 4.6</td>
<td>59.9 ± 6.2</td>
<td>.432</td>
</tr>
<tr>
<td><strong>CMR</strong></td>
<td>N=23</td>
<td>N=19</td>
<td></td>
</tr>
<tr>
<td>RV-WMA</td>
<td>2 (9)</td>
<td>2 (11)</td>
<td>1.00</td>
</tr>
<tr>
<td>RV-EDV (ml/m²)</td>
<td>95.9 ± 14.9</td>
<td>91.9 ± 8.1</td>
<td>.055</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>53.0 ± 7.2</td>
<td>53.4 ± 7.6</td>
<td>.890</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>56.9 ± 5.7</td>
<td>56.2 ± 8.4</td>
<td>.749</td>
</tr>
<tr>
<td>LGE</td>
<td>2 (9)</td>
<td>1 (5)</td>
<td>1.00</td>
</tr>
</tbody>
</table>
Values are n (%) or mean ± standard deviation. Definite ARVC diagnosis is defined as the presence of either two major, one major and two minor, or four minor TFC. Borderline diagnosis of ARVC is defined as the presence of either one major and one minor, or three minor TFC.

ARVC=arrhythmogenic right ventricular cardiomyopathy; CMR=cardiac magnetic resonance imaging;

DSG2=desmoglein-2; DSP=desmoplakin; LGE=late gadolinium enhancement; LVEF/RVEF=left/right ventricular ejection fraction; PKP2=plakophilin-2; PLAX/PSAX=parasternal long/short axis view; PLN=phospholamban;

PVC=premature ventricular complexes; RBBB=right bundle branch block; RV-EDV=right ventricular end-diastolic volume; RV-FAC=right ventricular fractional area change; RVOT=right ventricular outflow tract; TAD=terminal activation duration; TFC=task force criteria; VT=ventricular tachycardia; WMA=wall motion abnormality.
Figure 1. Study design

ARVC imaging registry with available RV deformation imaging

66 Probands
128 First-degree Relatives

Cardiac imaging
Presence of **structural** TFC

NO

ECG, Holter, History of arrhythmias
Presence of **electrical** TFC

NO

YES

Probands Exclusion
\( n = 66 \)

Structural stage Exclusion
\( n = 19 \)

Clinical work-up at baseline

Subclinical stage
\( n = 64 \)

Electrical stage
\( n = 45 \)

↓

Second evaluation

Subclinical stage
\( n = 37 \)

Electrical stage
\( n = 28 \)
Figure 2. Right ventricular deformation patterns
Figure 3. Rate of disease progression specified for deformation patterns and clinical stage at baseline.

Subjects that underwent a second evaluation

<table>
<thead>
<tr>
<th>Deformation patterns</th>
<th>Subclinical stage n = 37</th>
<th>Electrical stage n = 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>TYPE-I n = 23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TYPE-II n = 14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TYPE-III n = 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TYPE-I n = 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TYPE-II n = 19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TYPE-III n = 4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Disease progression

- Subclinical stage:
  - TYPE-I: 1 (4%)
  - TYPE-II: 9 (64%)
  - TYPE-III: 0 (0%)

- Electrical stage:
  - TYPE-I: 5 (26%)
  - TYPE-II: 2 (50%)
Figure 4. Suggested follow-up strategies in relatives depending on clinical ARVC stages