Right ventricular systolic function and mechanical dispersion identify patients with arrhythmogenic right ventricular cardiomyopathy

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Purpose To assess right ventricular (RV) regional and global systolic function using feature tracking (FT) in patients with a definite diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC) and to investigate if changes in strain amplitude and mechanical dispersion indicate a propensity for arrhythmia.

Materials and Methods Twenty-seven patients fulfilling Task Force Criteria for ARVC and 24 healthy volunteers underwent MR at 1.5 Tesla. Steady-state free precession cine of long-axis slices and a short-axis stack of the RV was acquired. Segmental longitudinal systolic strain amplitude and time-to-peak (TTP) strain were measured in the four- and two-chamber views of the RV.

Results Compared to controls, patients with ARVC had lower RV ejection fraction (RVEF), (53% vs 57%, \( P = 0.012 \)) and lower longitudinal strain amplitude in the RV free wall (-20.6 vs -26.3%, \( P = 0.014 \)) and in the basal part of the RV (-22-8 vs -31.7%, \( P < 0.001 \)). Mechanical dispersion, defined as the standard deviation (SD) of TTP of RV segments, was larger in patients with ARVC (48 ms [21-74] vs 35 ms [13-66 ms], \( P = 0.02 \)). Patients with ventricular tachycardia (VT) or non-sustained VT had lower RVEF (46% vs 55%, \( P = 0.008 \)), but did not have significantly lower RV strain amplitude (-19.5% vs 21.0%, \( P = 0.073 \)) and no signs of mechanical dispersion (49 ms vs 48 ms, \( P = 0.861 \)) compared to patients without arrhythmia.

Conclusion ARVC patients had lower longitudinal absolute strain amplitude in basal RV segments and increased mechanical dispersion compared to healthy volunteers, but the presence of mechanical dispersion was not predictive of ventricular arrhythmia.

Introduction
Arrhythmogenic right ventricular cardiomyopathy (ARVC) can cause sudden cardiac death as an initial disease manifestation in a patient without family history or exist as a developing condition in at-risk family members harbouring known mutations. Cardiac involvement is characterized by fibro-fatty replacement of the myocardium in the right ventricle (RV) and frequently in the left ventricle (LV) as well (Lindstrom et al., 2005). Myocardial cell loss and replacement fibrosis are associated with electrical instability manifested as ventricular arrhythmia, which increases the risk of sudden death. Ventricular dysfunction may develop, progressing to clinical heart failure at a later advanced stage. Magnetic resonance imaging (MRI) is considered the gold standard for measuring RV volume due to its high accuracy and repeatability enabled by the sharp definition of the endocardial border and the unique ability to cover the entire RV. However, even if MRI visualizes the entire RV, assessment of segmental RV function remains based on an observer-dependent visual scoring of wall motion.

Speckle tracking is used in echocardiography to detect and track patterns in myocardial grey scale which allow the calculation of tissue velocity, displacement and strain (deformation). Differences in time to peak of strain curves (‘mechanical dispersion’) of the left ventricle have been found to be elevated in patients with left ventricular dysfunction treated with an internal defibrillator (Haugaa et al., 2010).
Speckle tracking has been adapted to magnetic resonance imaging (MR) and promoted as ‘feature tracking’ (FT) (Maret et al., 2009; Hor et al., 2011a; Schuster et al., 2016). Feature tracking has been successfully applied to the LV, and some reports exist on its application to the RV as well (Lu et al., 2013; Heermann et al., 2014; Prati et al., 2015). However, the degenerative changes from advancing ARVC, such as thinning of the wall and a reduction in the amplitude of wall motion, challenge the ability of the software to track and quantify global and segmental changes.

The aim of this study was to compare strain amplitude and mechanical dispersion of the RV in patients with a definite diagnosis of ARVC compared to healthy volunteers. We hypothesized that feature tracking would detect changes that could indicate a propensity for arrhythmia in ARVC.

**Materials and Methods**

**Study population**

Ethical approval was obtained from the Regional Ethical Review Board, and all participants provided written informed consent. The study has been listed in the ISRCT registry (ISRCTN99714144). We included all patients that at the time of referral for cardiac MRI in retrospect fulfilled the 2010 Task Force Criteria (TFC) of definite ARVC and had not...
received an implantable cardioverter defibrillator (ICD). After review, 27 patients (16 males, 59%) were included. The average age of patients at the time of the investigation was 48 yrs (range 19–68 yrs). In addition to MRI, all patients underwent comprehensive non-invasive testing including electrocardiogram (ECG), echocardiogram, signal-averaged ECG and 24-h Holter recording, allowing for the establishment of a diagnosis according to the TFC (Marcus et al., 2010).

Twenty-four healthy volunteers (19 males, 79%) aged 22–67 yrs (mean age 39.9 yrs) served as control subjects and were recruited through advertisements posted to the university web page. All volunteers were asymptomatic, lacked a family history of premature cardiovascular disease and did not receive cardiac medication. All control subjects underwent a cardiac exercise test to confirm the absence of heart disease.

### Diagnostic criteria

The twelve-lead ECG was analysed for abnormalities of repolarization (T-wave inversion in V1 to V3 in the absence of right bundle branch block) and depolarization (time activation delay [TAD] >55 ms in precordial leads and the presence of epsilon waves defined as a distinct deflection after the QRS complex first returned to the isoelectric level). Signal-averaged ECG was obtained with a high-pass filter at 40–250 Hz as recommended, and the terminal part of the QRS was analysed (Breithardt et al., 1991a,b). Late potentials were considered pathologic if at least two of the following criteria were fulfilled: a filtered QRS duration (QRSd) >114 ms, low-amplitude signal (high-frequency low-amplitude [HFLA] <40 μV) duration >38 ms and late QRS root mean square voltage (RMS) <20 μV (Breithardt et al., 1991a,b). A transthoracic echocardiogram was performed to assess structural abnormalities as defined in the TFC (4). Holter monitoring was performed over 24 h to detect arrhythmia, defined as non-sustained or sustained ventricular tachycardia (VT) of left bundle branch morphology or ventricular premature beats in excess of 500 per 24 h.

Genomic DNA was extracted from whole blood samples and DNA sequencing performed, as the presence of a pathogenic genetic variant is a major diagnostic criterion. DNA analysis involved exons of the genes plakophilin 2 (PKP2), desmoglein 2 (DSG2), desmocollin 2 (DSC2), desmoplakin (DSP), transmembrane protein 43 (TMEM43) and plakoglobin (JUP).

### Magnetic resonance imaging protocol

All subjects underwent cardiac MRI using a 1.5 T scanner (Achieva Nova Dual, Philips Healthcare, Best, The Netherlands). Cine images were acquired with retrospective ECG-gating during repeated breath holds using a k-space segmented balanced steady-state free precession sequence (b-SSFp). Six long-axis slices were acquired by rotating the slice position in 30° increments around the right ventricular long axis, which was drawn from the middle of the tricuspid valve to the right ventricular apex (Fig. 1). The lateral, anterior and inferior RV walls were identified. Standard functional imaging included a short-axis stack of cine images perpendicular to the left ventricular long axis extending from the base to the apex. Typical parameters were slice thickness 8 mm, TR/TE 3.6/1.81, flip angle 60°, field of view 380 × 380. Cine images were acquired with retrospective ECG-gating using a field of view of 380 × 380 and a matrix size 256 × 156 (TR 20–100 ms, TE 1.9 ms). A short-axis stack of cine images was acquired perpendicularly to the left ventricular long axis extending from the base to the apex. Typical parameters were slice thickness 8 mm, TR/TE 3.6/1.81, flip angle 60°, field of view 380 × 380. Additional late gadolinium enhancement imaging was acquired using a segmented gradient echo balanced steady-state free precession (b-SSFP) sequence with an inversion delay of 20 ms, TR 6.0 ms, TE 2.4 ms, flip angle 90°, FOV 380 × 380, matrix size 256 × 156, 20 slices, thickness 8 mm. Every slice was acquired in a single breath hold.

### Table 1 Clinical characteristics of ARVC patients and controls.

| Parameter                     | ARVC (n = 27) | Controls (n = 24) | Difference | P-value* |
|-------------------------------|---------------|------------------|------------|---------|
| Age (yrs)                     | Mean (SD)     | 48.4 (15.1)      | 39.8 (16.0) | 0.042   |
|                               | Median (range)| 47 (19–72)       | 36 (22–64) | 0.042   |
| Gender (% female)             | Male          | 16 (59)          | 20 (83)    | 0.073   |
|                               | Female        | 11 (41)          | 4 (17)     | 0.073   |
| Weight (kg)                   | Mean (SD)     | 75.1 (16.2)      | 73.2 (7.4) | 0.830   |
|                               | Median (range)| 75 (52–120)     | 72 (61–88) | 0.830   |
| Height (cm)                   | Mean (SD)     | 172.4 (9.5)      | 178.7 (6.6) | 0.011   |
|                               | Median (range)| 171 (155–191)   | 180 (166–190) | 0.011   |
| BMI (kg/m²)                   | Mean (SD)     | 25.0 (4.1)       | 22.9 (2.2) | 0.063   |
|                               | Median (range)| 24.7 (17.9–35.0)| 22.5 (18.8–27.3)| 0.063   |
| BSA (M²)                      | Mean (SD)     | 1.88 (0.23)      | 1.91 (0.12) | 0.428   |
|                               | Median (range)| 1.89 (1.51–2.42)| 1.93 (1.68–2.08) | 0.428   |
| HR (beats/min)                | Mean (SD)     | 65.3 (9.9)       | 68.5 (11.1) | 0.394   |
|                               | Median (range)| 65 (40–83)      | 70 (48–98) | 0.394   |
| Systolic blood pressure       | Mean (SD)     | 121.5 (14.9)     | 123.5 (12.3) | 0.364   |
|                               | Median (range)| 115 (100–170)   | 125 (102–140) | 0.364   |
| Diastolic blood pressure      | Mean (SD)     | 73.7 (8.7)       | 70.5 (8.4)  | 0.242   |
|                               | Median (range)| 72 (60–95)      | 70 (60–90) | 0.242   |

*Fisher’s exact test for gender and Mann–Whitney U-test for the continuous variables.

ARVC, arrhythmogenic right ventricular cardiomyopathy; SD, standard deviation; BMI, body mass index; BSA, body surface area; HR, heart rate.
350 × 350 mm, matrix 288 × 288 and breath holding time 16 s. We retrospectively reconstructed the cine images into 30 cardiac phases, corresponding to a temporal resolution in the range of 24–41 milliseconds (mean 37 ms). Left and right ventricular volumes and ejection fractions were calculated from the short-axis segmentation.

Data analysis and postprocessing

FT strain analysis was applied to the RV four- and RV two-chamber views (Fig. 1) using 2D CPA MR software (v.1.2, Tomtec GmbH, Germany). The endocardial contour of each ventricle was manually outlined beginning at the septal annulus and finishing at either side (Fig. 2, 3). The software created 48 points along the boundary that were automatically tracked (Hor et al., 2011a). If the tracking was unsatisfactory, the contours were manually adjusted and the tracking repeated. We did not attempt to segment the epicardium.

Each wall was divided into three segments: base, mid and apex. Longitudinal strain was calculated in 15 segments: nine for the RV (anterior, inferior and lateral walls), three for the septum and three for the LV lateral wall. The regional longitudinal strain was averaged for each wall as well as for the three levels of the RV (RV base, RV mid and RV apex).

RV global strain (RVGLS) was calculated from the nine RV segments and the septum. Time-to-peak (TTP) strain was analysed in all segments, and the mean TTP was calculated for each wall. The degree of intra-ventricular synchronous contraction (mechanical dispersion) in the RV was analysed as the standard deviation (SD) of the TTP between all RV segments, including the septum and for each of the three RV levels (base, mid and apex). The SD of TTP was also extracted for the RV 4-chamber view only (septum and RV free wall).

Images were analysed in random order by the same investigator.

Reproducibility

To evaluate intra- and interobserver variability, two operators performed strain measurements on the same 10 randomly selected subjects (five patients and five controls) in a blinded manner. The main investigator in the study performed these measurements twice, with at least 1-month interval. Both operators have evaluated ARVC patients for >15 yrs and have used feature tracking for more than 6 yrs.

Statistics

Continuous variables are reported as mean (SD) and median (range). The Mann–Whitney U-test was used for continuous variables in descriptive statistical comparisons between groups and the Chi-square test (or Fisher’s exact test if appropriate) for frequencies. A P-value of <0.1 was required for each variable to be included in the multiple logistic regression analysis. A composite index was created using a linear combination of the regression coefficients of the significant variables [log

![Figure 3](https://example.com/figure3.png)

Figure 3 Strain amplitude curves and mechanical dispersion from the right ventricle in a patient with ARVC. Longitudinal strain curves from the right ventricle (lower viewport). Black arrow indicates increased temporal dispersion of time-to-peak amplitude.
(OR)] multiplied by the parameter in question. Receiver operator characteristics (ROC) curves were used to display the relationship between specificity and sensitivity. Inter- and intraobserver variability were calculated using the intraclass correlation coefficient (ICC) and presented with a 95% confidence interval. Statistica v. 12 (Statsoft Inc. Tulsa, OK, USA) was used for the statistical analyses and MedCalc Statistical Software version 16.8.4 (MedCalc Software, Ostend, Belgium; 2016) for creating ROC curves.

**Results**

Clinical characteristics of the patient population are summarized in Table 1. Twenty-four patients (89%) were probands. Fourteen (51.8%) had a family history of ARVC or sudden cardiac death at their first visit to the department. Symptoms suggestive of arrhythmia such as palpitations, presyncope or syncope were documented in 17 patients (62.8%). One patient survived cardiac arrest as the first manifestation of ARVC. No patients had symptoms of heart failure. Twenty-two patients had an abnormal ECG at rest, with T-wave inversion beyond precordial lead V1 in 20 patients (74.1%) and right bundle branch block in two patients (Fig. 2, 3). An epsilon wave was detected in one patient. Signal-averaged ECG was recorded in 24 of the 27 patients and pathological late potentials in 13 (54.2%). Genetic analysis was available for 22 patients (81.8%), and a mutation known to be associated with ARVC was found in 18 (81.8%) patients (13 PkP2, 3 DSP and 2 DSG2). None of the patients had concomitant disease such as diabetes or hypertension. Sixteen patients (59.3%) were treated with beta-blockers, for example sotalol (n = 4) and metoprolol (n = 12).

Segmentation of the RV endocardium in the four- and two-chamber views was successful in all participants. Segments that tracked poorly according to visual inspection were excluded (11 in ARVC patients [3-4%] and 10 in controls [3.6%]). In total, 591 RV segments were analysed, including the septum. The longitudinal strain values and their aggregate in terms of regional and global longitudinal strain are displayed in Table 2.

The SD of the TTP in RV segments was prolonged in ARVC patients to 48 ms (range 21–74) vs 35 ms (range 13–66) in controls (P = 0.023).

Analysis of strain amplitude and TTP at the three levels of the RV displayed a significant delay at the RV base in the ARVC group (P<0.001), while the mid and apex segments showed no significant difference in TTP compared to the reference group (P = 0.088 resp. 0.786) (Table 3).

Patients with a mutation known to be associated with ARVC showed no statistically significant changes in RV strain (-24.5 vs -25.2, P = 0.86) or contraction delay (TTP RV 47.2 vs 34.8, P = 0.13).

| Parameter | ARVC (n = 27) | Controls (n = 24) | Difference P-value* |
|-----------|---------------|------------------|---------------------|
| RVEDV (ml) | 190.6 (59.0)  | 172.7 (31.9)     | 0.218               |
| Mean (SD)  | 190 (95–303)  | 180 (94–212)     |                     |
| RVEDVI (ml/m2) | 101.9 (31.3) | 90.1 (16.3)      | 0.112               |
| Mean (range) | 100.5 (58–714)| 93.0 (53–112)   |                     |
| RVESV (ml) | 90.9 (25.8)   | 94.7 (17.2)      | 0.518               |
| Mean (SD)  | 84 (45–140)   | 100 (59–117)     |                     |
| RVEF (%)   | 49.4 (10.9)   | 56.3 (4.2)       | 0.012               |
| Mean (range) | 53 (26–65)  | 57 (49–64)       |                     |
| RV strain lateral wall (%) | -24.3 (7.3) | -31.4 (5.2)      | <0.001              |
| Mean (SD)  | -26.0 (41–6–12.4) | -10.9 (40–0–22.2) |                     |
| RV strain anterior wall (%) | -26.3 (7.2) | -30.0 (7.2)      | 0.103               |
| Mean (SD)  | -26.4 (42–13) | -29.0 (45–19)    |                     |
| RV strain inferior wall (%) | -25.3 (7.3) | -26.8 (6.9)      | 0.394               |
| Mean (SD)  | -24.3 (42–13) | -25.0 (52–18)    |                     |
| Septum strain (%) | -1.87 (5.2) | -2.29 (5.7)      | 0.011               |
| Mean (range) | -1.78 (10–0–10.4) | -2.29 (10–5.1–12.6) |                     |
| RVGLS (%)  | 22.0 (47)     | 26.4 (3.2)       | <0.001              |
| Mean (SD)  | 20.9 (36–5–14.7) | 26.3 (32.5–20.6) |                     |
| RV strain RV base (%) | -25.3 (6.9) | -33.0 (5.9)      | <0.001              |
| Mean (SD)  | -22.8 (41–4–15.8) | -31.7 (42–9–22.5) |                     |
| RV strain RV mid (%) | -22.7 (6.2) | -26.0 (5.4)      | 0.019               |
| Mean (SD)  | -21.6 (41–1–12.2) | -25.0 (10–18–17.7) |                     |
| RV strain RV apex (%) | -21.5 (6.3) | -21.5 (4.1)      | 0.844               |
| Mean (SD)  | -20.8 (36–5–10.7) | -20.8 (30–1–13.5) |                     |
| LV strain lateral wall (%)* | -21.8 (5.6) | -24.4 (12.0)     | 0.014               |
| Mean (SD)  | -20.6 (35–9.1–11.5) | -26.3 (41–9–21.0) |                     |

ARVC, arrhythmogenic right ventricular cardiomyopathy; LV, left ventricle; RV, right ventricle; RVEDV, RV end-diastolic volume; RVGLS, RV end-diastolic volume index; RVEF, RV ejection fraction; RVESV, RV end-systolic volume; RVGLS, RV global longitudinal strain; SD, standard deviation.

*Included for comparison purposes.

*Mann–Whitney U-test for the continuous variables.

(RV_TTP_lat_100*6-680 + RV_SD_TTP_average*0.097 + RVGLS *0.264). This index had an area under the curve (AUC) of 0.94 for the detection of ARVC. The three components of the index all contributed significantly to the detection of ARVC (strain amplitude P<0.001, TTP strain P<0.001 and strain mechanical dispersion P = 0.023 Fig. 4i). The sensitivity for detection of ARVC, at 80% specificity, was 78% for RV TTP lateral wall, 70% for RVGLS, 41% for RV SD TTP and 93% for the composite index. If only information from the four-chamber view was considered, an index based on similar components was calculated and had the same AUC of 0.94.
In 10 patients (37.0%), an ICD was implanted 1 to 6 yrs after MRI (mean 3.5 ± 1.7 yrs). In nine of the 10 ICD carriers, at least one episode of ATP was recorded, and in two patients, appropriate defibrillator shocks were registered. Holter recording was available in 13 patients without ICD (48.1%), and in six, NSVT was recorded (46.1%). The remaining four patients had neither ICD nor Holter recordings. Among 15 patients with documented arrhythmia (ATP/shock on ICD or NSVT on Holter recording), only two had a normal ECG and seven (47%) had pathologic late potentials on the signal-averaged ECG.

Patients with arrhythmia had lower ejection fractions compared to those without arrhythmia (46% [range 26–57] vs 55% [range 45–65]; P = 0.008). Global longitudinal RV strain amplitude and RV mechanical dispersion (SD of TTP) were not statistically significant when comparing the two groups, amplitude P = 0.073, TTP P = 0.86, (Table 4).

Inter- and intraobserver reproducibility, as calculated by ICC, for segmentation and strain measurements were high for RV walls (lateral inter 0.84 and intra 0.91; inferior 0.9 vs 0.87; anterior 0.72 vs 0.83) as well as for the septum and the lateral LV wall (septum inter 0.84 and septum intra 0.89; lateral 0.73 vs 0.86).

Discussion

We found that patients with a definite diagnosis of ARVC had lower absolute values of longitudinal strain amplitude, a prolonged TTP in segmental strain curves, and a larger variation in the TTP (mechanical dispersion) compared to healthy volunteers. All three components contributed significantly when a diagnostic index was created. The basal subtricuspid RV showed significantly lower strain and mechanical dispersion compared to the apical part in ARVC patients. Furthermore, ARVC patients with arrhythmia detected on ICD telemetry or Holter compared to those without arrhythmia had a lower RV ejection fraction, but global strain was not reduced neither was mechanical dispersion increased.

The current TFC (2010) rely on the subjective estimation of wall motion abnormality in the RV (Marcus et al., 2010).
which is in agreement with previous studies that have shown mechanical dispersion compared with the mid and the apex that the basal, subtricuspid portion showed significantly

Several studies have shown that the qualitative estimation of RV function and wall motion abnormalities in ARVC is dependent on the experience of the observer and that the prevalence of RV dysfunction in ARVC may easily be underestimated (Sen-Chowdhry et al., 2010; Hunold, 2013; Rastegar et al., 2014). Thus, adding reproducible quantitative measures of RV wall deformation to RV volume could possibly increase the reliability of cardiac MRI features in ARVC.

Quantitative strain analysis has been previously used primarily in the LV, but strain measurements of the thin-walled RV have also been reported (Aneq et al., 2012; Toro et al., 2016; Morris et al., 2017). In healthy subjects, longitudinal shortening contributes to the major part of global RV function, which longitudinal strain calculations exploit (Brown et al., 2011). While echocardiography may not visualize all parts of the RV, MRI may offer more comprehensive RV coverage by displaying the anterior and inferior RV walls as well. We found that the RV inferior and lateral free walls had low strain amplitude while the anterior wall was spared in agreement with Corrado et al. (Corrado et al., 2000).

When analysing the different levels of the RV, we found that the basal, subtricuspid portion showed significantly lower absolute values of longitudinal strain and increased mechanical dispersion compared with the mid and the apex which is in agreement with previous studies that have shown

| Table 3 | Strain curve time-to-peak measurements |
|----------------|-----------------|------------------|-----------------|
| Parameter | ARVC (n = 27) | Controls (n = 24) | Difference | P-value* |
| RV TTP lateral (ms) | 327.3 (17.2) | 326.1 (28.9) | <0.001 | |
| Median (range) | 367.7 (113.2–483.1) | 329.1 (261–390.0) | |
| RV TTP anterior (ms) | 360.6 (44.0) | 342.5 (36.0) | 0.145 | |
| Mean (SD) | 361 (252–452) | 346 (260–402) | |
| RV TTP inferior (ms) | 372.2 (18.9) | 336.9 (35.8) | 0.003 | |
| Mean (SD) | 375 (293–447) | 346 (267–383) | |
| TTP septum (ms) | 363.7 (47.7) | 337.1 (25.2) | 0.021 | |
| Mean (SD) | 355.0 (277.3–493.0) | 335.0 (297.0–383.0) | |
| LV TTP lateral (ms) | 359.1 (17.1) | 329.1 (32.9) | 0.005 | |
| Mean (SD) | 359 (290–446) | 325 (278–386) | |
| RV SD TTP global (ms) | 46.9 (15.2) | 36.7 (12.9) | 0.023 | |
| Mean (SD) | 48 (21–74) | 35 (13–66) | |
| RV SD TTP base (ms) | 47.6 (21.6) | 28.5 (13.8) | <0.001 | |
| Mean (SD) | 49.1 (0.9–105.1) | 27.1 (0.6–58.1) | |
| RV SD TTP mid (ms) | 43.1 (20.8) | 33.5 (20.7) | 0.088 | |
| Mean (SD) | 41.8 (9.6–91.2) | 30.1 (1–80.3) | |
| RV SD TTP apex (ms) | 37.2 (19.6) | 40.0 (24.0) | 0.786 | |
| Mean (SD) | 34.4 (11.1–83.4) | 38.3 (9.8–86.5) | |

ARVC, arrhythmogenic right ventricular cardiomyopathy; LV, left ventricle; RV, right ventricle; SD, standard deviation; TTP, time-to-peak.

*Mann–Whitney U-test for the continuous variables.

| Table 4 | Parameters analysed for their relationship to ventricular arrhythmia |
|----------------|-----------------|-----------------|-----------------|
| Parameter | Arrhythmia (n = 15) | No arrhythmia (n = 9) | Difference | P-value* |
| RV EDV (ml) | 203.1 (54.1) | 188.3 (66.7) | 0.599 | |
| Mean (SD) | 207 (115–303) | 190 (95–289) | |
| RV ESV (ml) | 116.7 (45.7) | 86.3 (39.4) | 0.108 | |
| Mean (SD) | 109 (47–207) | 85 (35–158) | |
| RVEF (%) | 43.7 (10.4) | 55.6 (7.2) | 0.008 | |
| Mean (SD) | 46 (26–57) | 55 (45–65) | |
| RV GLS (%) | -20.1 (3.7) | -23.9 (5.7) | 0.073 | |
| Mean (SD) | -19.5 (-2.8–0.14.7) | 21.0 (36.5–19.2) | |
| RV SD TTP global (ms) | 48.8 (37–161) | 47.3 (34–160) | 0.861 | |
| Mean (SD) | 49 (21–74) | 48 (22–67) | |
| RV SD TTP base (ms) | 50 (17.7) | 49.9 (25.4) | 0.770 | |
| Mean (SD) | 50 (18–89) | 50 (16–105) | |
| RV SD TTP mid (ms) | 40.7 (20.3) | 46.3 (24.5) | 0.519 | |
| Mean (SD) | 41.2 (9.6–81.7) | 48.5 (13.6–91.2) | |
| RV SD TTP apex (ms) | 40.1 (20.8) | 34.7 (19.4) | 0.682 | |
| Mean (SD) | 36.8 (12.2–83.4) | 34.4 (11.1–72.0) | |
| RV strain lateral wall(%) | -22.2 (6.9) | -25.4 (7.0) | 0.482 | |
| Mean (SD) | -20 (-33–12) | -26 (42–18) | |
| Septum strain (%) | -17.1 (4.1) | -21.0 (6.7) | 0.138 | |
| Mean (SD) | -17 (-25–10) | -20 (-33–12) | |

*Mann–Whitney U-test for the continuous variables.

RV, right ventricle; RV EDV, RV end-diastolic volume; RVEF, RV ejection fraction; RV ESV, RV end-systolic volume; RV GLS, RV global longitudinal strain; SD, standard deviation; TTP, time-to-peak.

The basal RV to be the most frequently involved part, whereas the apex is involved later (te Riele et al., 2015; Vigneault et al., 2016). Furthermore, the LV lateral wall was significantly affected in our patients, similar to findings of Te Riele (Te Riele et al., 2013). These findings challenge the traditional description of ‘the ARVC triangle of dysplasia’ involving the inflow, the outflow and the apex of the RV and could necessitate a review of the morphological description of early disease (van der Wall et al., 2000). In the ARVC group, some patients had an advanced form of the disease while others had only discrete structural abnormalities, which could complicate the use of single measures to diagnose. Parameters based on strain curves, identified in logistic regression analysis as independently related to the diagnosis of ARVC, had moderately high AUC values in ROC but showed a very high AUC when combined and maximum sensitivity and specificity were achieved when both mechanical function and timing parameters were included. Interestingly, an index based on measurements from the four-chamber view performed just as well as the global index.
implicating that most information was present in the segments of the RV free wall. However, the suggested index of mechanics and timing needs to be prospectively validated in larger cohorts.

Strain amplitude and the presence of mechanical dispersion by FT have been studied in several disease processes in addition to ARVC (Hor et al., 2011a,b; Kawakubo et al., 2013; Moon et al., 2015). Some of these studies suggest that dispersion may be related to arrhythmia and cardiac events (Sarvari et al., 2011; Leren et al., 2016) while other studies could not confirm this relationship (Kutüfya et al., 2013; Moon et al., 2015). We were also unable to find such an association, possibly due to the limited sample size.

Individuals with a mutation known to be associated with ARVC may have a comparatively low expression of morphological features of ARVC. In our study, the presence and type of a pathogenic genetic variation showed no correlation with RV strain nor with the presence of mechanical dispersion.

Limitations
The number of patients in the subgroup with arrhythmic events is rather low which, together with slight differences in age and gender between groups may have precluded the demonstration of a relationship between functional parameters and arrhythmia. To obtain sufficient sample size, pooling of registry data may be required. The partial phenotypic expression of the disease in patients with a definite ARVC diagnosis could also have diluted the possible relationship between morphological changes and ARVC. The region of interest employed in feature tracking of the RV includes by necessity some extra-cardiac tissue, which could have concealed changes in the contracting myocardium. Despite this presence of extra-cardiac tissue, the tracking algorithm delivered plausible and reproducible results.

Conclusion
Combining timing with strain amplitude increased the diagnostic accuracy for the detection of ARVC using MRI cine. However, neither strain amplitude nor mechanical dispersion could predict arrhythmic events.

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Conflict of Interest
The authors have no conflict of interest.

References
Aneq MA, Nylander E, Ebbes T, et al. Determination of right ventricular volume and function using multiple axially rotated MRI slices. Clin Physiol Funct Imaging (2011); 31 (3): 233–239.
Aneq MA, Engvall J, Brudin L, et al. Evaluation of right and left ventricular function using speckle tracking echocardiography in patients with arrhythmogenic right ventricular cardiomyopathy and their first degree relatives. Cardiovasc Ultrasound (2012); 10: 37.
Breithardt GME, Cain N, el-Sherif N, et al. Standards for analysis of ventricular late potentials using high resolution or signal-averaged electrocardiography. A statement by a Task Force Committee between the European Society of Cardiology, the American Heart Association and the American College of Cardiology. Eur Heart J (1991a); 12(4): 473–480.
Breithardt G, Cain ME, el-Sherif N. Standards for analysis of ventricular late potentials using high resolution or signal-averaged electrocardiography: a statement by a task force committee of the European Society of Cardiology, the American Heart Association, and the American College of Cardiology. J Am Coll Cardiol (1991b); 17(3): 999–1006.
Brown SB, Raina A, Katz D, et al. Longitudinal shortening accounts for the majority of right ventricular contraction and improves after pulmonary vasodilator therapy in normal subjects and patients with pulmonary arterial hypertension. Chest (2011); 140(1): 27–33.
Corrado D, Basso C, Thiene G. Arrhythmogenic right ventricular cardiomyopathy: diagnosis, prognosis, and treatment. Heart (2000); 83(5): 588–595.
Haugaa KH, Smedsrud MK, Seen T, et al. Mechanical dispersion assessed by myocardial strain in patients after myocardial infarction for risk prediction of ventricular arrhythmia. JACC Cardiovasc Imaging (2010); 3: 247–256.
Heer mann P, Hedderich DM, Paul M, et al. Biventricular myocardial strain analysis in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) using cardiovascular magnetic resonance feature tracking. J Cardiovasc Magn Reson (2014); 16: 75.
Hor KN, Baumann R, Pedrizzetti G, et al. Magnetic resonance derived myocardial strain assessment using feature tracking. J Vis Exp (2011); 48: 22356. doi: 10.3791/22356.
Kutüfya V, Poulleur AC, Knappe D, et al. Dysynchrony and the risk of ventricular arrhythmias. JACC Cardiovasc Imaging (2013); 6(4): 432–444.
Kawakubo M, Nagao M, Kumazawa S, et al. Evaluation of cardiac dys synchrony with longitudinal strain analysis in 4-chamber cine MR imaging. Eur J Radiol (2013); 82 (12): 2212–2216.
Leren IS, Saberniak J, Haland TF, et al. Combination of ECG and Echocardiography for Identification of Arrhythmic Events in Early ARVC. JACC Cardiovasc Imaging (2016); 10(5): 503–513.
Lindstrom L, Nylander E, Larsson H, et al. Left ventricular involvement in arrhythmogenic right ventricular cardiomyopathy - a
scintigraphic and echocardiographic study. Clin Physiol Funct Imaging (2005); 25(3): 171–177.
Lu JC, Ghadimi Mahani M, Agarwal PP, et al. Usefulness of right ventricular free wall strain to predict quality of life in “repaired” tetralogy of Fallot. Am J Cardiol (2013); 111(11): 1644–1649.
Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. Circulation (2010); 121(13): 1533–1541.
Maret E, Todt T, Brudin L, et al. Functional measurements based on feature tracking of cine magnetic resonance images identify left ventricular segments with myocardial scar. Cardiovasc Ultrasound (2009); 7: 53.
Moon TJ, Choueiter N, Geva T, et al. Relation of biventricular strain and dysynchrony in repaired tetralogy of fallot measured by cardiac magnetic resonance to death and sustained ventricular tachycardia. Am J Cardiol (2015); 115(5): 676–680.
Morris DA, Krisper M, Nakatani S, et al. “Normal range and usefulness of right ventricular systolic strain to detect subtle right ventricular systolic abnormalities in patients with heart failure: a multicentre study”. Eur Heart J Cardiovasc Imaging (2017); 18: 212–223.
Prati G, Vitrella G, Allocca G, et al. Right Ventricular Strain and Dyssynchrony Assessment in Arrhythmogenic Right Ventricular Cardiomyopathy: Cardiac Magnetic Resonance Feature-Tracking Study. Circ Cardiovasc Imaging (2015); 8(11): e003647. discussion e003647.
Rastegar N, Burt JR, Corona-Villalobos CP, et al. Cardiac MR findings and potential diagnostic pitfalls in patients evaluated for arrhythmogenic right ventricular cardiomyopathy. Radiographics (2014); 34(6): 1553–1570.
te Riele AS, Marcus FI, James CA, et al. The Value of Cardiac Magnetic Resonance Imaging in Evaluation of Pediatric Patients for Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy. J Am Coll Cardiol (2015); 66(7): 873–874.
Sarvari SI, Haugaa KH, Anfinsen OG, et al. Right ventricular mechanical dispersion is related to malignant arrhythmias: a study of patients with arrhythmogenic right ventricular cardiomyopathy and subclinical right ventricular dysfunction. Eur Heart J (2011); 32(9): 1089–1096.
Schuster A, Hor KN, Kowalcik JT, et al. Cardiovascular magnetic resonance myocardial feature tracking: concepts and clinical applications. Circ Cardiovasc Imaging (2016); 9(4): e004077.
Sen-Chowdhry S, Morgan RD, Chambers JC, et al. Arrhythmogenic cardiomyopathy: etiology, diagnosis, and treatment. Annu Rev Med (2010); 61: 233–253.
Toro KD, Soriano BD, Buddhe S. Right ventricular global longitudinal strain in repaired tetralogy of Fallot. Echocardiography (2016); 33(10): 1557–1562.
Vigneault DM, te Riele AS, James CA, et al. Right ventricular strain by MR quantitatively identifies regional dysfunction in patients with arrhythmogenic right ventricular cardiomyopathy. J Magn Reson Imaging (2016); 43(5): 1132–1139.
van der Wall EE, Kayser HW, Bootsma MM, et al. Arrhythmogenic right ventricular dysplasia: MRI findings. Herz (2000); 25(4): 356–364.