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CLINICAL RESEARCH

Right ventricular mechanical dispersion is related to malignant arrhythmias: a study of patients with arrhythmogenic right ventricular cardiomyopathy and subclinical right ventricular dysfunction

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Aims We evaluated if right ventricular (RV) mechanical dispersion by strain was related to ventricular arrhythmias (VT/VF) in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) and if mechanical dispersion was increased in so far asymptomatic mutation carriers.

Methods and results We included 69 patients, 42 had symptomatic ARVC and 27 were mutation positive asymptomatic family members. Forty healthy individuals served as controls. Myocardial strain was assessed in 6 RV and 16 left ventricular (LV) segments. Contraction duration (CD) in 6 RV and 16 LV segments were measured as the time from onset R on electrocardiogram to maximum myocardial shortening in each segment. The standard deviation of CD was defined as mechanical dispersion. Mechanical dispersion was more pronounced in ARVC patients with arrhythmias compared with asymptomatic mutation carriers and healthy individuals in RV [52(41,63) vs. 35(23,47) vs. 13(9,19) ms, $P < 0.001$]. Mechanical dispersion was more pronounced in asymptomatic mutation carriers compared with healthy individuals ($P < 0.001$). Right ventricular mechanical dispersion predicted VT/VF in a multivariate logistic regression analysis [odds ratio (OR), 1.66 (95% confidence interval (CI) 1.06–2.58), $P < 0.03$]. Right ventricular and LV function by strain were reduced in symptomatic ARVC patients and correlated significantly ($R = 0.81$, $P < 0.001$). Right ventricular and LV strain were reduced in asymptomatic mutation carriers compared with healthy individuals ($P < 0.001$).

Conclusion Right ventricular mechanical dispersion was pronounced in patients with ARVC with VT/VF. Right ventricular mechanical dispersion was present in asymptomatic mutation carriers and may be helpful in risk stratification. Right ventricular and LV function correlated in ARVC patients implying that ARVC is a biventricular disease.

Keywords ARVC • Echocardiography • Ventricular arrhythmia • Myocardial contraction • Dispersion

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a chronic, progressive, heritable cardiomyopathy and is one of the leading causes of sudden unexpected cardiac death in previously healthy young individuals.[1,2] The first clinical symptom may present as life-threatening arrhythmias.

Arrhythmogenic right ventricular cardiomyopathy was initially recognized as a disease of the right ventricular (RV) myocardium, but involvement of the left ventricular (LV) myocardium is now

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commonly recognized.[3–6] Four clinical stages have been documented: an early concealed phase, overt electrical disorder, isolated right heart failure, and biventricular pump failure.[2,4]

Recent molecular genetic reports have revealed ARVC as mainly an autosomal dominant inherited desmosomal disease,[7] leading to progressive loss of cardiac myocytes, followed by fibrofatty replacement. Penetrance is age and gender dependent and the progressive clinical picture is highly variable.[8] Importantly, life-threatening arrhythmias can occur with only discrete or even absent myocardial structural changes.[9,10] Risk stratification of malignant arrhythmias in so far asymptomatic mutation carriers is therefore challenging.

Echocardiographic studies of the RV in ARVC patients have shown that RV dilatation and reduced regional or global RV function are traits of the disease. Quantitative assessment of RV function is difficult due to complicated anatomy and load dependency. Reviewed guidelines for diagnosing ARVC from 2010 have improved quantitative assessment of RV dysfunction, including measures of right ventricular outflow tract (RVOT) and RV area.[11]

Strain by echocardiography has been introduced as an accurate tool for assessment of regional[12] and global myocardial function,[13] and recent reports have shown that RV function can be accurately assessed by this method.[14]

Electrical conduction delay with consequent electrical dispersion has been suggested as a mechanism of ventricular arrhythmias (VT/VF) in ARVC patients.[15,16] Mechanical dispersion (heterogeneous contraction) assessed by myocardial strain may reflect electrical dispersion and has recently been demonstrated to relate to malignant VT/VF in patients with long QT syndrome[17] and in patients after myocardial infarction.[18]

We hypothesized that pronounced mechanical dispersion by myocardial strain is associated with susceptibility to ventricular arrhythmia in patients with ARVC and, therefore, may be an additional tool for arrhythmia risk stratification. Furthermore, we aimed to investigate to what extent LV function assessed by strain echocardiography was reduced along with RV function in patients with ARVC diagnosis and in asymptomatic mutation carriers.

Methods

In total, 69 patients (*Table 1*) were included. Of these, 42 were index patients referred to our centre for ventricular tachycardia (VT) or ventricular fibrillation (VF) evaluation and in whom the diagnosis of ARVC was originally made based on the International Task Force criteria from 1994. After the revision of the International Task Force criteria in 2010,[11] the diagnosis of all ARVC patients was reviewed (*Table 1*). First-degree relatives of mutation positive ARVC index patients underwent cascade genetic screening. Of all screened individuals, 27 tested positive for the ARVC mutation found in the index patient (*Table 1*). Importantly, none of the included mutation positive family members had symptoms of the disease in terms of palpitations, syncopes, arrhythmias, or heart failure and were defined as asymptomatic mutation carriers.

The medication received at the time of the echocardiographic study and the presence of an implanted cardioverter defibrillator (ICD) were recorded.

The control group consisted of 30 healthy individuals from the hospital staff. Ten healthy mutation negative family members were included after family cascade genetic screening. They were added to explore if RV mechanical dispersion was attributed to the familiar ARVC-related genetic mutation or to other unidentified familiar factors. All individuals in the control group had normal electrocardiogram (ECG), physical examination, and echocardiographic study and were free from disease with potential impact on the cardiovascular system.

Written informed consent was given by all study participants. The study complies with the Declaration of Helsinki and is approved by the Regional Committee for Medical Research Ethics.

Table 1 Clinical characteristics

	Healthy individuals ($n = 40$)	Asymptomatic mutation carriers ($n = 27$)	ARVC patients with arrhythmia ($n = 42$)	*P*-value ANOVA F-test
Age (years)	38.9 ± 16.0	38.4 ± 17.7	43.7 ± 15.9	0.31
Male *n* (%)	20 (50)	15 (56)	26 (62)	0.63
Heart rate (b.p.m.)	67 ± 11	65 ± 13	60 ± 14*	0.04
ARVC Task Force Criteria (2010)[a]				
Family history (none/minor/major)		0/0/27	2/13/27	
Depolarization abnormality (none/minor/major)		20/6/1	14/19/9	
Repolarization abnormality (none/minor/major)		26/1/0	20/4/18	
Arrhythmia (none/minor/major)		27/0/0	0/14/28	
RV functional/anatomical abnormality (none/minor/major)		24/3/0	4/15/23	

Mean ± SD, Numbers. Right column shows *P*-values for ANOVA and χ^2 tests. Flags for significance are obtained from the post hoc pair-wise comparison using the Bonferroni correction when comparing three groups.
ANOVA, analysis of variance.
[a]Histology not performed.
*$P < 0.05$ compared with healthy individuals.

Genetic analyses

Genomic DNA was isolated from peripheral blood in patients with ARVC phenotype. The individual exons with flanking intron sequences of the genes *plakophilin-2* (*PKP2*), *desmoglein-2*, and *desmoplakin* (*DSP*), and 29 of the 105 exons of the *ryanodine receptor-2* (*RYR2*) gene were sequenced by polymerase chain reaction amplification in combination with direct sequencing. Cascade genetic screening was performed in family members of mutation positive ARVC patients.

Two-dimensional echocardiography

Patients and control subjects underwent an echocardiographic study (Vivid 7, GE, Vingmed, Horten, Norway). Cineloops from three standard apical views (four-chamber, two-chamber, and apical long-axis) were recorded using grey-scale harmonic imaging. Data were digitally stored for off-line analysis using software (EchoPac, GE, Vingmed). The echocardiographic data were analysed blinded to all clinical information.

From two-dimensional (2D) echocardiography, the following parameters were assessed: RVOT diameter in the parasternal short axis view, right ventricular end-diastolic (RVED) area, right ventricular end-systolic (RVES) area, and right ventricular fractional area change (RVFAC) from the apical four-chamber view.[11]

Two-dimensional strain and dispersion

The endocardial borders were traced in the end-systolic frame of the 2D images from the three apical views for LV strain and from the four-chamber view for RV strain. Speckles were tracked frame by frame throughout the LV and RV wall during the cardiac cycle. Segments that failed to track were manually adjusted by the operator. Any segments that subsequently failed to track were excluded. The peak systolic myocardial strain by 2D speckle tracking echocardiography was assessed in 16 LV segments and averaged to LV global longitudinal strain (LVGLS). Peak systolic strain from three RV free wall segments was averaged as a measure of RV function (RV strain). Contraction duration (CD; *Figure 1*) was measured as the time from onset R on ECG to maximum LV and RV shortening by strain. Standard deviation (SD) of CD was calculated as a parameter of mechanical dispersion, in a 16 LV segment and a 6 RV segment model.

We used a six RV segment model (three RV free wall segments plus three septal segments) when assessing mechanical dispersion which includes the usually less affected interventricular septum[11] to elucidate dispersion of contraction between affected and non-affected segments.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) was performed using 1.5 Tesla units (Magnetom Vision Plus or Magnetom Sonata, Siemens, Erlangen, Germany) and a phased array body coil. Axial and sagittal T1 turbo spin echo images, multiple axial images, and one sagittal cineloop covering the RV and LV were recorded. Right ventricular and LV chamber dimensions, wall thickness, and myocardial function were assessed. A negative MRI study was defined as normal RV and LV dimensions, normal global and regional wall motion, no fatty infiltration, and no aneurysm formation.

Signal-averaged electrocardiogram

Signal-averaged electrocardiogram (SAECG) was performed using a MAC® 5000-analysing system (GE Medical Systems, Milwaukee, WI, USA). Time domain analysis was obtained in the band-pass filter 40–250 Hz. The SAECG was considered positive for late potentials when at least two of the following parameters were abnormal: total filtered QRS duration (fQRSd) $>$ 114 ms, the terminal (last 40 ms) QRS root-mean-square voltage (RMS) $<$20 μV, and the low amplitude ($<$40 μV) late potential duration (HFLA) $>$38 ms.

Statistical analyses

Analyses were carried out using a standard statistical software program (SPSS version 16, SPSS Inc., Chicago, IL, USA). Data were presented as mean ± SD, numbers and percentages, and the median and inter-quartile range, respectively. The χ^2 test (categorical variables) and Student's *t*-test (continuous variables) were used to determine differences between two groups. Comparisons of means for normally distributed variables were performed by analysis

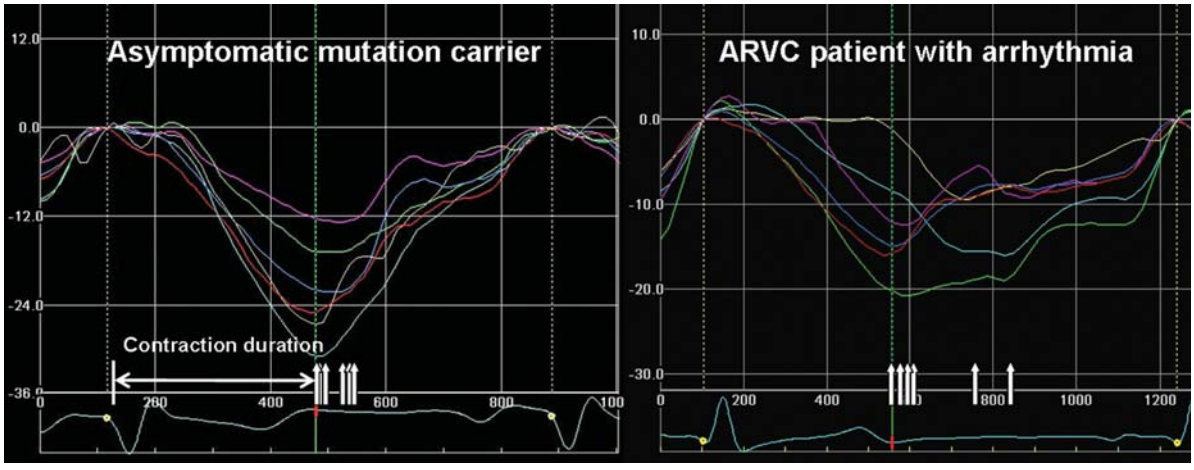


Figure 1 Mechanical dispersion in an asymptomatic mutation carrier (left panel) and an arrhythmogenic right ventricular cardiomyopathy patient with recurrent arrhythmias (right panel). Horizontal white arrow indicates contraction duration defined as the time from onset R to maximum myocardial shortening. Vertical arrows indicate the timing of maximum myocardial shortening in each segment. Right panel shows more pronounced mechanical dispersion.

of variance (ANOVA) with the Bonferroni post hoc correction for multiple comparisons. For non-normally distributed variables, the Kruskal–Wallis test (multiple groups) and Mann–Whitney U-test (two groups) were used. Logistic regression analysis was performed to determine the independent prognostic value of RV dispersion for predicting arrhythmias in ARVC patients and asymptomatic mutation carriers. The left ventricular ejection fraction (LVEF), LVGLS, RVFAC, RV strain, and RV dispersion plus the categorical variable positive SAECG were selected for inclusion in a multivariate logistic regression analysis. The selection of variables was based on statistical significance of $P < 0.05$ in the univariate logistic regression analysis in addition to the LVEF which was forced in. The area under the receiver-operating characteristic (ROC) curve (AUC) was calculated for the LVEF, LVGLS, RV strain, RVFAC, and RV mechanical dispersion. Comparisons between AUCs were performed with the Analyse-it software including all study participants. The value closest to the upper left corner of the ROC curve determined the optimal sensitivity and specificity for the ability of the parameters to discriminate between those with and without arrhythmic events. Correlation between the RV and LV strain was assessed by linear regression analysis. Reproducibility was expressed as the intraclass correlation coefficient. *P*-values were two-tailed and values <0.05 were considered significant.

Table 2 Electrocardiogram and signal-averaged electrocardiogram findings

	Asymptomatic mutation carriers ($n = 27$)	ARVC patients with arrhythmia ($n = 42$)	*P*-value
QRS (ms)	92 ± 11	104 ± 22	0.01
QTc (ms)	422 ± 24	440 ± 37	0.02
SAECG fQRSd (ms)	112 ± 12	125 ± 26	0.02
SAECG HFLA (ms)	36 ± 10	46 ± 28	0.08
SAECG RMS (μV)	36 ± 17	26 ± 22	0.09
SAECG positive (*n*)	6 (24%)	19 (56%)	0.01

Mean ± SD. Right column shows *P*-values for Student's *t*-test and χ^2 tests. fQRSd, filtered QRS duration; HFLA, low amplitude (<40 μV) late potential duration; QTc, QT interval corrected for heart rate; RMS, terminal (last 40 ms) QRS root-mean-square voltage.

Results

Among 69 patients in this study, 42 (61%) had symptomatic ARVC, while 27 (39%) were asymptomatic mutation carriers, diagnosed by cascade genetic screening. Six asymptomatic mutation carriers had minor depolarization abnormalities and three had minor echocardiographic/MRI findings without fulfilling clinical criteria for ARVC (*Table 1*).

Arrhythmogenic right ventricular cardiomyopathy-related mutations were confirmed in 54 (78%) of all patients, [47 (68%) *PKP2*, 6 (9%) *DSP*, and 1 (1%) *RYR2*]. In ARVC patients with arrhythmias, 27 (64%) had ARVC-related mutations [23 (55%) *PKP2*, 3 (7%) *DSP*, and 1 (2%) *RYR2*]. No mutations were found in 15 (36%) ARVC patients. In asymptomatic mutation carriers, 24 (89%) had *PKP2* and 3 (11%) had *DSP* mutations.

Ventricular arrhythmias were documented in all 42 ARVC patients and 32 (76%) of the ARVC patients received antiarrhythmic medical therapy at the time of the echocardiographic study. An ICD was implanted in 39 (93%) of the symptomatic ARVC patients. Three patients did not receive ICD. Two of these were successfully treated with Sotalol. On the basis of a clinical decision, they did not receive an ICD. One patient refused ICD treatment.

Magnetic resonance imaging studies were completed in 19 (70%) asymptomatic mutation carriers and in 31 (71%) ARVC patients. Negative MRI study regarding ARVC phenotype was found in 24 (89%) asymptomatic mutation carriers and in 4 (10%) symptomatic ARVC patients (*Table 1*).

A pathological SAECG was more frequent in symptomatic ARVC patients compared with asymptomatic mutation carriers ($P = 0.01$). QRS and QTc duration assessed by ECG and fQRSd assessed by SAECG were prolonged in ARVC patients compared with asymptomatic mutation carriers ($P = 0.01$, 0.02, and 0.02, respectively; *Table 2*).

Holter recordings were performed in 23 of the 27 asymptomatic mutation carriers. None of the asymptomatic mutation carriers had >500 ventricular premature beats per 24 h, and none had recorded VT or non-sustained VT.

Mechanical dispersion in arrhythmogenic right ventricular cardiomyopathy patients

Arrhythmogenic right ventricular cardiomyopathy patients with arrhythmias showed a marked increase in RV and LV mechanical dispersion compared with asymptomatic mutation carriers (both $P < 0.001$) and healthy controls (both $P < 0.001$; *Table 3*). Importantly, asymptomatic mutation carriers showed significantly increased RV and LV mechanical dispersion compared with healthy controls (both $P < 0.001$), indicating subclinical myocardial alterations.

Right ventricular dispersion and RVFAC were significant predictors of arrhythmia in a multivariate logistic regression analysis (*Table 4*).

The ROC analysis demonstrated that RV mechanical dispersion of 29 ms was the optimal cut-off value to identify arrhythmic events among the study participants (*Figure 2*).

Arrhythmogenic right ventricular cardiomyopathy patients with arrhythmias and *PKP2* mutations had similar RV mechanical dispersion [52(41,63) ms] compared with ARVC patients with arrhythmia and no identified mutation [50(35,62) ms, $P = 0.52$]. Asymptomatic mutation carriers had significantly greater RV mechanical dispersion compared with mutation negative family members [35(23, 47) vs. 13(10,17) ms, $P < 0.001$]. Right ventricular mechanical dispersion in healthy controls and in mutation negative family members was similar [15(9,21) vs. 13(10,17) ms, $P = 0.44$].

Table 3 Echocardiographic results

	Healthy individuals ($n = 40$)	Asymptomatic mutation carriers ($n = 27$)	ARVC patients with arrhythmia ($n = 42$)	*P*-value Kruskal-Wallis
LVEF (%)	64(61,65)	61(60,65)	60(55,67)	0.16
LVGLS (%)	−22(−21,−24)	−20(−18,−21)*	−17(−16,−19)*,**	<0.001
RV strain (%)	−25(−23,−27)	−22(−20,−24)*	−19(−16,−21)*,**	<0.001
LV dispersion (ms)	20(16,25)	38(33,49)*	60(48,70)*,**	<0.001
RV dispersion (ms)	13(9,19)	35(23,47)*	52(41,63)*,**	<0.001
PSAX RVOT (mm)	28(26,30)	27(26,28)	31(29,37)*,**	<0.001
RVED area (cm^2)	22(20,24)	24(22,27)	29(25,36)*,**	<0.001
RVES area (cm^2)	12(11,14)	14(12,15)	18(15,25)*,**	<0.001
RVFAC (%)	44(39,48)	43(40,48)	38(27,43)*,**	<0.001

Data expressed as median (inter-quartile range). Right column shows *P*-values for Kruskal–Wallis test when comparing all three groups. Flags for significance are obtained from pair-wise comparison using Mann–Whitney U-test.
LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; PSAX, parasternal short axis; RVOT, right ventricular outflow tract; ED, end-diastolic; ES, end-systolic; FAC, fractional area change.
*$P < 0.001$ compared with healthy individuals.
**$P < 0.01$ compared with asymptomatic mutation carriers.

Table 4 Predictors of arrhythmia in symptomatic arrhythmogenic right ventricular cardiomyopathy patients ($n = 42$) and asymptomatic mutation carriers ($n = 27$)

	Univariate logistic regression			Multivariate logistic regression		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
SAECG positive (*n*) (yes vs. no)	4.01	1.28–12.5	0.02	2.27	0.53–9.79	0.27
LVEF (per 5% decrease)	1.31	0.96–1.78	0.09	1.15	0.68–1.96	0.60
LVGLS (%)	1.41	1.12–1.76	0.003	1.22	0.89–1.67	0.22
RV strain (%)	1.25	1.08–1.44	0.003	0.98	0.76–1.26	0.85
RV dispersion (per 10 ms increase)	1.71	1.22–2.39	0.002	1.66	1.06–2.58	0.03
RVFAC (per 5% decrease)	2.33	1.44–3.76	0.001	2.16	1.04–4.47	0.04

SAECG, signal-averaged ECG; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; RVFAC, right ventricular fractional area change.

Right ventricular and left ventricular function

Arrhythmogenic right ventricular cardiomyopathy patients with arrhythmias showed significantly reduced RV and LV function assessed by myocardial strain compared with asymptomatic mutation carriers (both $P < 0.01$) and healthy controls (both $P < 0.01$). Left ventricular ejection fraction was within normal range in all groups and without significant differences (*Table 3*).

Left ventricular and RV function by strain were correlated in symptomatic ARVC patients ($R = 0.81$, $P < 0.001$; *Figure 3*) and healthy individuals ($R = 0.52$, $P = 0.01$). Importantly, this relationship was present in symptomatic ARVC patients with reduced RV function by visual assessment, indicating biventricular disease in patients with 'classic' RV involvement. There was, however, no correlation between LV and RV function in asymptomatic mutation carriers.

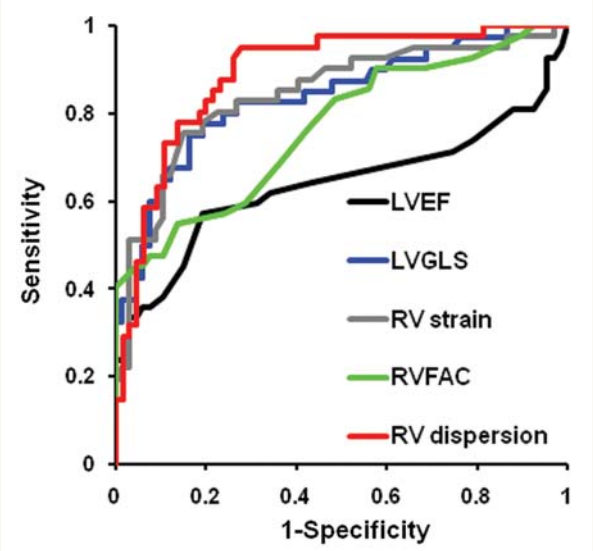
Asymptomatic mutation carriers had LV strain within normal range [−20(−18,−21)%], but importantly, RV and LV function assessed by strain were significantly reduced compared with healthy individuals ($P < 0.001$), indicating subclinical myocardial impairment (*Table 3*).

Intra-observer and inter-observer intra-class correlation was performed in 10 patients and was 0.96 and 0.95 for RV strain measurements, 0.94 and 0.94 for LVGLS measurements, 0.85 and 0.84 for RV time measurements, and 0.93 and 0.88 for LV time measurements, respectively.

Arrhythmogenic right ventricular cardiomyopathy patients with arrhythmias had increased RVOT diameter, RVED area, and RVES area and reduced RVFAC ($P < 0.001$) compared with asymptomatic mutation carriers. However, there were no differences in these variables between asymptomatic mutation carriers and healthy controls (*Table 3*).

Discussion

This study demonstrates that mechanical dispersion assessed by speckle tracking echocardiography is pronounced in patients with



	AUC	95% CI	Optimal cut-off	Sensitivity (%)	Specificity (%)
LVEF (%)	0.64	0.51-0.76	63	62	66
LVGLS (%)	0.84	0.76-0.92	-20	83	73
RV strain (%)	0.84	0.76-0.93	-22	83	73
RVAF (%)	0.77	0.67-0.86	42	69	64
RV dispersion (ms)	0.89	0.83-0.95	29	88	77

AUC, area under the curve; LVEF, left ventricular ejection fraction; LVGLS, left ventricular global longitudinal strain; RVFAC, right ventricular fractional area change

Figure 2 Receiver-operating characteristic curve for left ventricular and right ventricular parameters in arrhythmogenic right ventricular cardiomyopathy patients, asymptomatic mutation carriers, and healthy controls ($n = 109$).

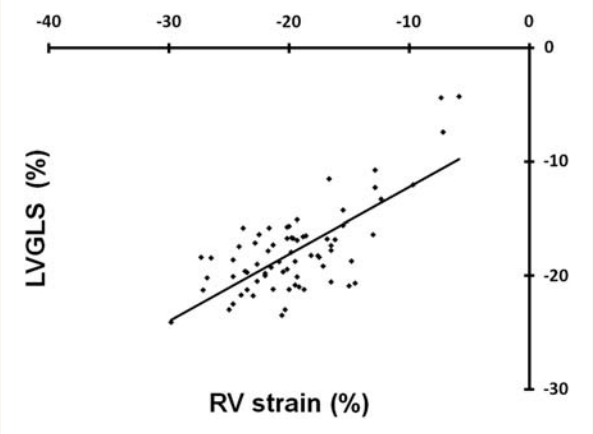


Figure 3 Right ventricular vs. left ventricular strain in 42 arrhythmogenic right ventricular cardiomyopathy patients with arrhythmias ($R = 0.81$, $P < 0.001$).

ARVC and arrhythmias. Increased mechanical dispersion and reduced myocardial strain in both ventricles were present in asymptomatic mutation carriers, indicating subclinical myocardial alterations. These findings indicate that mechanical dispersion may be evaluated as a marker of arrhythmias and may be helpful in risk stratification of so far asymptomatic mutation carriers.

The relationship between mechanical dispersion and arrhythmias

The diagnosis of ARVC is challenging and the prediction as to which patients will develop arrhythmias is even more so. No single test is sufficient to diagnose or exclude ARVC and to predict arrhythmias. The Task Force criteria from 1994[19] are highly specific but lack sensitivity for early stages and familial forms of ARVC. Overall sensitivity has been enhanced by the 2010 revision.[11] However, risk assessment of malignant arrhythmias in asymptomatic mutation carriers remains a challenge.

The occurrence of malignant arrhythmias can precede structural myocardial changes shown by traditional imaging techniques. An accurate assessment of myocardial function is therefore particularly important in early ARVC and in so far asymptomatic mutation carriers. Myocardial strain by echocardiography has been demonstrated to be a sensitive tool for assessing ventricular function and timing.[13]

In our study, we demonstrate that evaluation of regional timing in terms of mechanical dispersion may add important diagnostic and prognostic information in ARVC, particularly in the early stages of the disease. We demonstrate a significant increase in mechanical dispersion in both ventricles in asymptomatic mutation carriers who apparently have structurally and functionally normal LV and RV by traditional echocardiography and MRI. More importantly, these findings may be used for risk prediction of life-threatening arrhythmias in these individuals.

Interestingly, reduced myocardial strain and increased mechanical dispersion in both ventricles showed significant differences between healthy controls and asymptomatic mutation carriers. These findings suggest biventricular involvement also in the concealed phase of the disease when structural and functional changes are not apparent if assessed by traditional echocardiography or MRI.

We have recently demonstrated mechanical dispersion to be related to VT/VF in patients with the long QT syndrome.[17] Furthermore, we have introduced mechanical dispersion as a predictor of VT/VF in patients after myocardial infarction.[18] The mechanisms of arrhythmogenesis in infarcted tissue and in ARVC have similarities in terms of fibrosis and delayed electrical conduction. Altered electrical conduction is present in ARVC in the phase of overt electrical disorder, while fibrosis may develop later.[9,10] Dispersion of ventricular depolarization-repolarization has been regarded as a strong arrhythmogenic factor, although non-invasive assessment of these electrical abnormalities have been challenging.[16] Electrical abnormalities in diseased myocardium may be translated into mechanical alterations. Mechanical dispersion by strain echocardiography appears to be a sensitive tool for assessing subtle changes in the timing of myocardial contraction.

Ventricular arrhythmias in ARVC are believed to originate from different mechanisms at different stages of the disease. In the concealed phase, inflammatory processes due to apoptosis, derangements in cell-to-cell adhesion, and altered nuclear signalling are reported to be arrhythmogenic.[9,10] A study using

immunohistochemistry has shown reduced levels of gap junction protein connexin 43, important for myocardial electrical propagation, in a patient homozygous for ARVC mutations, but without visible structural alterations.[10] Our study may support these findings, indicating subtle contraction heterogeneity in asymptomatic mutation carriers. In later stages of the disease, islands of surviving myocytes surrounded by fibrofatty tissue provide a substrate for re-entry VT/VF.[2,16] The novelty of the present study is the identification of myocardial abnormalities in asymptomatic mutation carriers and the potential for prediction of arrhythmias. However, these findings have to be confirmed in a prospective and longitudinal study.

Multivariate logistic regression analysis showed that RV dispersion and RVFAC, which integrates both RV dimensions and function, were independent predictors of arrhythmias. However, RVFAC was within normal range in most of asymptomatic mutation carriers and was not different from healthy controls. This was even more evident by ROC analyses (*Figure 2*) where RV dispersion was superior to RVFAC to identify arrhythmias ($P < 0.02$). Right ventricular fractional area change has therefore an uncertain value in risk assessment in asymptomatic mutation carriers.

Right ventricular mechanical dispersion was present in asymptomatic ARVC mutation positive family members, but not in mutation negative family members. This finding suggests that increased RV mechanical dispersion is due to the ARVC-related mutation in the affected individuals.

Right ventricular and left ventricular dysfunction or biventricular disease

Initially, ARVC was believed to be a predominant RV disease. New subtypes of arrhythmogenic cardiomyopathy with LV or biventricular predilection have been recognized.[4] Importantly, progression from left dominant to biventricular involvement has also been documented.[20]

Left ventricular involvement was first suggested in 1983[3] and has been confirmed in several studies.[6,20,21] A recent study using echocardiographic tissue Doppler imaging (TDI) showed signs of LV involvement in patients with only mildly decreased RV function.[22] Our study showed similar results. Decreased myocardial strain and increased mechanical dispersion in both ventricles in asymptomatic mutation carriers and in symptomatic ARVC patients diagnosed by current guidelines[11] suggest frequent involvement of the LV. Furthermore, LV and RV strain were correlated in our ARVC patients. Biventricular impairment is probably a result of biventricular ARVC affection, but mutual dependency of RV and LV haemodynamics may be considered. There was no correlation between the RV and LV function in asymptomatic mutation carriers. This might be explained by the fact that the initial myocardial dysfunction in ARVC is of regional character. Ventricular dysfunction may proceed to affect both ventricles as the disease progresses.

Current diagnostic tools

The diagnosis of ARVC is based on the criteria outlined by the International Task Force in 1994[19], and revised in 2010.[11] Criteria for structural abnormalities are based on 2D echocardiographic and MRI findings. Since the establishment of these criteria, several studies have confirmed the ability of MRI to detect structural abnormalities in patients with ARVC.[23,24] Despite the excellent ability of MRI to diagnose ARVC, our study demonstrates that novel echocardiographic methods were able to detect ventricular abnormalities in asymptomatic mutation carriers with normal MRI findings. Novel echocardiographic methods such as TDI and strain echocardiography are at present not widely used in the diagnostic and prognostic work-up of patients with ARVC. However, they might be promising tools for detecting RV and LV abnormalities in patients with ARVC.

The most significant development in ARVC research in recent years is the identification of mutations in genes encoding desmosomal and extradesmosomal proteins.[2] Pathogenic mutations in the gene encoding the desmosomal protein *PKP2* are particularly prevalent and have been identified in up to 43% of cases.[4,25,26]

Clinical implications

Since the disease is inherited in at least 50% of cases, the screening of relatives is important. Cascade genetic screening helps to identify affected family members and to focus resources; however, risk stratification of asymptomatic mutation positive family members is challenging and emphasized by the fact that the first manifestation of the disease in 20–50% of cases may be cardiac arrest.[27] Guidelines for treatment of asymptomatic mutation carriers are sparse.[26] The novel methods presented in this study demonstrated subclinical myocardial impairments which were associated with the risk of VT/VF. These methods may, therefore, be of help in risk stratification of so far asymptomatic mutation carriers.

Study limitations

The echocardiographic data were analysed blinded to all clinical information. However, ICD leads are visible on echocardiography, thus de-masking the disease status of the patients.

We assessed global longitudinal strain but not radial or circumferential strain. This measure was chosen because longitudinal strain has been best validated. Measurements are reproducible and are easily obtained with only a minor increase in procedure duration. Radial and circumferential strains from the RV are more difficult to obtain due to the complicated anatomy.

Conclusions

This study demonstrates that mechanical dispersion assessed by speckle tracking echocardiography is pronounced in patients with ARVC and arrhythmias, suggesting that mechanical dispersion could be implicated in the genesis of VT/VF. Mechanical dispersion was present in asymptomatic mutation carriers, indicating subclinical myocardial involvement. These findings indicate that mechanical dispersion may serve as a risk stratification tool in asymptomatic mutation carriers, and be helpful in decisions regarding prophylactic treatment.

Right ventricular and LV function correlated in ARVC patients, which implies that ARVC is a biventricular disease. Left ventricular involvement was present in so far asymptomatic mutation carriers and in a majority of ARVC patients. Echocardiographic evaluation

by strain measurements appears to be a sensitive marker of subclinical LV involvement.

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