The American Journal of Cardiology 241 (2025) 61–68

Contents lists available at ScienceDirect

The American Journal of Cardiology

journal homepage: www.elsevier.com/locate/ajc

Arrhythmogenic Right Ventricular Cardiomyopathy: The Importance of Biventricular Strain in Risk-Stratification

Aileen Paula Chua, MD[a], Dorien Laenens, MD[a], Camille Sarrazyn, MD[a], Maria Pilar Lopez-Santi, MD[a], Takeru Nabeta, MD[a], Rinchyenkhand Myagmardorj, MD[a], Marianne Bootsma, MD, PhD[a], Daniela Q.C.M. Barge-Schaapveld, MD, PhD[b], Jeroen J. Bax, MD, PhD[a,c], Nina Ajmone Marsan, MD, PhD[a*]

[a] Department of Cardiology, Heart Lung Center, Leiden University Medical Center, Leiden, The Netherlands
[b] Department of Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands
[c] Department of Cardiology, Turku Heart Center, University of Turku and Turku University Hospital, Turku, Finland

ARTICLE INFO

Article History:
Received 28 August 2024
Revised 2 January 2025
Accepted 9 January 2025

Keywords:
arrhythmogenic right ventricular cardiomyopathy
biventricular involvement
biventricular strain
free wall strain and global longitudinal strain

Despite arrhythmogenic right ventricular cardiomyopathy (ARVC) being predominantly a right ventricular (RV) disease, concomitant left ventricular (LV) involvement has been recognized. ARVC is diagnosed by the RV-centric 2010 Task Force Criteria(TFC) using routine echocardiography, but previous studies have suggested that strain imaging may be more sensitive to detect RV and LV dysfunction. No data however are available regarding the additional value of combining biventricular strain for risk stratification. This study aims to assess the prognostic value of both LV global longitudinal strain (GLS) and RV free wall strain (FWLS) in patients with ARVC. To accomplish this, 204 patients who met the TFC for the ARVC spectrum were included. Patients (age 41 ± 17 years,55% men) were divided into impaired(n = 33), discordant (RV or LV impaired, n = 70), and normal (n = 101) strain groups based on a value of ≥18% for both ventricles. During a follow-up of 87 [24–136] months, 57 (28%) experienced the composite outcome of all-cause mortality, arrhythmic events, implantable cardioverter defibrillator therapy and heart failure events, and a significant difference in event-free survival was observed (p <0.001) between the 3 groups. In the multivariable analysis, the strain groups remained associated with outcomes (p = 0.014) after adjusting for age, sex, history of syncope and definite ARVC diagnosis. A subanalysis including only definite and borderline diagnosed ARVC confirmed that the strain groups were independently predictive of the endpoint (p = 0.023). In conclusion, biventricular involvement by strain analysis may help risk stratification in ARVC patients, with the worst outcomes of patients with both RV and LV impaired strain.

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy characterized by progressive myocardial atrophy and replacement with fibrous and fatty tissue, causing a predisposition for ventricular arrhythmias, sudden cardiac death, and ventricular dysfunction.[1,2] While it is predominantly a right ventricular (RV) disease, involvement of the left ventricle (LV) has frequently been observed;[1,3] accordingly, the inclusion of LV abnormalities has been considered in a more encompassing diagnosis of Arrhythmogenic Cardiomyopathy.

Currently however, the diagnosis of ARVC is still based on the 2010 revised Task Force Criteria (TFC). This system incorporates 6 components (structural, depolarization, repolarization, arrhythmia, tissue and family history), with a combination of major and minor criteria leading to the diagnosis of either definite, borderline or possible ARVC.[4] The structural component is mainly determined by imaging (echocardiography or cardiac magnetic resonance imaging, CMR), which includes the presence of RV dilation or RV dysfunction (using fractional area change or ejection fraction to assess RV dysfunction), and RV wall motion abnormalities. However, these criteria are mostly present when structural damage is already severe. Since the introduction and wide application of echocardiographic strain imaging, various studies[1,5–9] have explored the value of 2D longitudinal strain in patients with ARVC to detect ventricular involvement earlier or

Abbreviations: ARVC, Arrhythmogenic right ventricular cardiomyopathy; EDV, End-diastolic volume; EF, Ejection fraction; ESV, End-systolic volume; FAC, Fractional area change; FH, Family history; FWLS, Free wall longitudinal strain; GLS, Global longitudinal strain; ICD, Implantable cardioverter defibrillator; LV, Left ventricle; LVMI, Left ventricular mass index; MR, Mitral regurgitation; PLAX, Parasternal long-axis; PSAX, Parasternal short-axis; RV, Right ventricle; RVOT, Right ventricular outflow tract; TAPSE, Tricuspid annular plane systolic excursion; TFC, Task Force Criteria; TR, Tricuspid regurgitation

*Corresponding author.
E-mail address: n.ajmone@lumc.nl (N.A. Marsan).

https://doi.org/10.1016/j.amjcard.2025.01.006

more accurately before regional wall motion abnormalities or myocardial aneurysms occur. These studies demonstrated that reduced RV free wall longitudinal strain (FWLS) was associated with worse clinical outcomes or structural disease progression, with cut-off values of FWLS varying from 18% to 23%.[1,5–9] The recognition that the LV may be involved in these patients (despite a normal LVEF), has also promoted assessment of LV global longitudinal strain (GLS). Previous studies demonstrated that reduced LV GLS (<18%) in patients with ARVC was associated with worse prognosis.[9–11] The growing evidence of the prognostic value of GLS is also reflected in the proposed Padua criteria, and in recent recommendations advocating the use of RV FWLS and LV GLS to assess ventricular involvement in patients with suspected and diagnosed ARVC.[1,12]

However, the prognostic value of concomitant biventricular involvement (assessed by RV and LV strain) has not been studied extensively. Accordingly, the aim of the current study is to assess the frequency of biventricular involvement in patients with ARVC using LV GLS and RV FWLS, as well as to assess the long-term prognostic value of these parameters.

Material and Methods

Patients examined at the Leiden University Medical Center (LUMC), The Netherlands, for ARVC either due to symptoms, structural findings or family history were screened for inclusion in this retrospective study. Only individuals aged ≥16 years, who met the revised 2010 TFC for at least possible ARVC diagnosis, were included.[4] Patients without adequate echocardiographic images for strain analysis were excluded. Of the initial 256 patients, 52 patients were excluded (17 with inadequate image quality and 35 with insufficient ARVC criteria). The final study population consisted of 204 patients.

Data on clinical characteristics, 12-lead electrocardiograms (ECG), 24-hour Holter monitoring, signal-averaged ECG, exercise stress test, CMR, endocardial biopsy, and genetic testing were obtained (when available) through the departmental Cardiology Information system (EPD-Vision; Leiden University Medical Center, Leiden, The Netherlands) and the Hospital Information System (Hix 6.3; Leiden University Medical Center, Leiden, The Netherlands). The first echocardiographic study available served as baseline, and the diagnosis was assessed based on the available data at that time. The institutional review board of the LUMC approved the retrospective analysis of the clinically acquired data, and the need for written informed consent was waived.

Transthoracic echocardiography was performed using commercially available ultrasound systems (Vivid 7, Vivid E9 and E95; General Electric Healthcare, Horten, Norway) equipped with 3.5 MHz or M5S-D transducers. Parasternal, apical, subcostal and suprasternal views were obtained following current recommendations.[13] Data were digitally stored in DICOM cine-loop format for analysis using commercially available software (Caas Qardia 2.0, Pie Medical Imaging, Maastricht, the Netherlands), and were retrospectively analyzed.

Measurement of RV outflow tract dimensions involved assessment of the parasternal long-axis and short-axis at the level of the aortic valve views, which were then indexed to body surface area calculated with the Dubois method. RV dimensions were assessed from the RV focused view: the basal diameter was measured as the maximal transverse dimension of the basal one third of the RV at end-diastole, and the mid-cavity diameter as the transverse diameter of the middle third of the RV, halfway between the maximal basal diameter and apex, at end-diastole. Fractional area change (FAC) was calculated as the difference in percentage between the end-diastolic and end-systolic areas, and tricuspid annular plane systolic excursion (TAPSE) from M-mode recordings of the lateral tricuspid annulus.[13]

LV dimensions were obtained from the parasternal long-axis view, and used to calculate LV mass index using Devereux's formula and relative wall thickness. LV end-systolic and end-diastolic volumes were measured from the apical four- and two-chamber views, and LV ejection fraction was derived using the Simpson's biplane method.[13] The presence of significant valvular regurgitation was determined through a multiparametric approach, in accordance with current guidelines.[14] Systolic pulmonary artery pressure was determined by the application of the Bernoulli equation on the TR jet peak velocity and adding RA pressure. RA pressure was estimated based on the inferior vena cava diameter and respiratory collapsibility.[13]

RV and LV strain were assessed using speckle-tracking (Caas Qardia 2.0) from the apical RV focused or four-chamber, and the apical two-, three- and four-chamber views, respectively (Figure 1), in accordance with current recommendations.[13] The region of interest was automatically determined but manually adjusted when necessary. For RV function, FWLS was calculated from the average peak longitudinal strain of the 3 free-wall segments. LV GLS was calculated as the average peak longitudinal strain of 16 LV segments. All strain results were reported as absolute (i.e. positive) values. Patients were classified as having impaired RV or LV strain based on a previously proposed cut-off value of 18%.[6,11]

The study endpoint comprised a composite of all-cause mortality, ventricular arrhythmic events, appropriate Implantable cardioverter defibrillator (ICD) therapy, and heart failure events. Mortality data were obtained through the departmental Cardiology Information System, which is linked to the governmental death registry database. Ventricular arrhythmic events included aborted cardiac arrest or documented sustained ventricular arrhythmias. Appropriate ICD therapy was defined as either shocks or antitachycardia pacing for ventricular tachycardia or fibrillation, as documented by device interrogation records in the department information system. Lastly, heart failure events were recorded as either consultation, emergency room visit or hospitalization for symptoms and/or signs of heart failure, supported by objective evidence of cardiogenic pulmonary or systemic congestion and/or elevated natriuretic peptides.[15]

For the statistical analysis, continuous variables were reported as mean and standard deviation or median and interquartile range, while categorical variables were presented as frequencies and percentages. Group comparisons were done using the ANOVA test or chi-square test, as appropriate. For parameters with significant differences, a Bonferroni test was conducted to identify which groups were different.

The correlation between LV GLS and RV FWLS was assessed using the Pearson correlation test. To define impaired ventricular strain, the previously proposed cut-off value of 18% was applied for both the LV and RV.[6,11] However, to validate the applicability of the cut-off values to the study population, spline curve and ROC analyses were performed to confirm which strain cut-off values were associated with increased risk of adverse outcomes. Subsequently, patients were categorized into three groups: (1) Patients with impaired strain, comprising patients with both RV and LV strain <18%; (2) Patients with discordant strain, consisting of patients with either RV or LV strain <18%; and (3) Patients with normal strain, including patients with biventricular strain ≥18%.

Survival curves were plotted using the Kaplan-Meier analysis, stratified according to the strain groups, and were compared for significant differences through the log-rank test. To determine the association between clinical and echocardiographic factors with outcomes, Cox proportional hazards regression univariable analysis was initially performed. Variables with a p-value <0.05, and which were clinically relevant and not collinear with other factors, were selected for inclusion into a multivariable model. The proportional hazard assumption was verified based on Schoenfeld residuals. Several clinical and diagnostic parameters were excluded because they are already part of the TFC for ARVC diagnosis. To ascertain if the strain groups remain to be significantly associated with outcomes, a

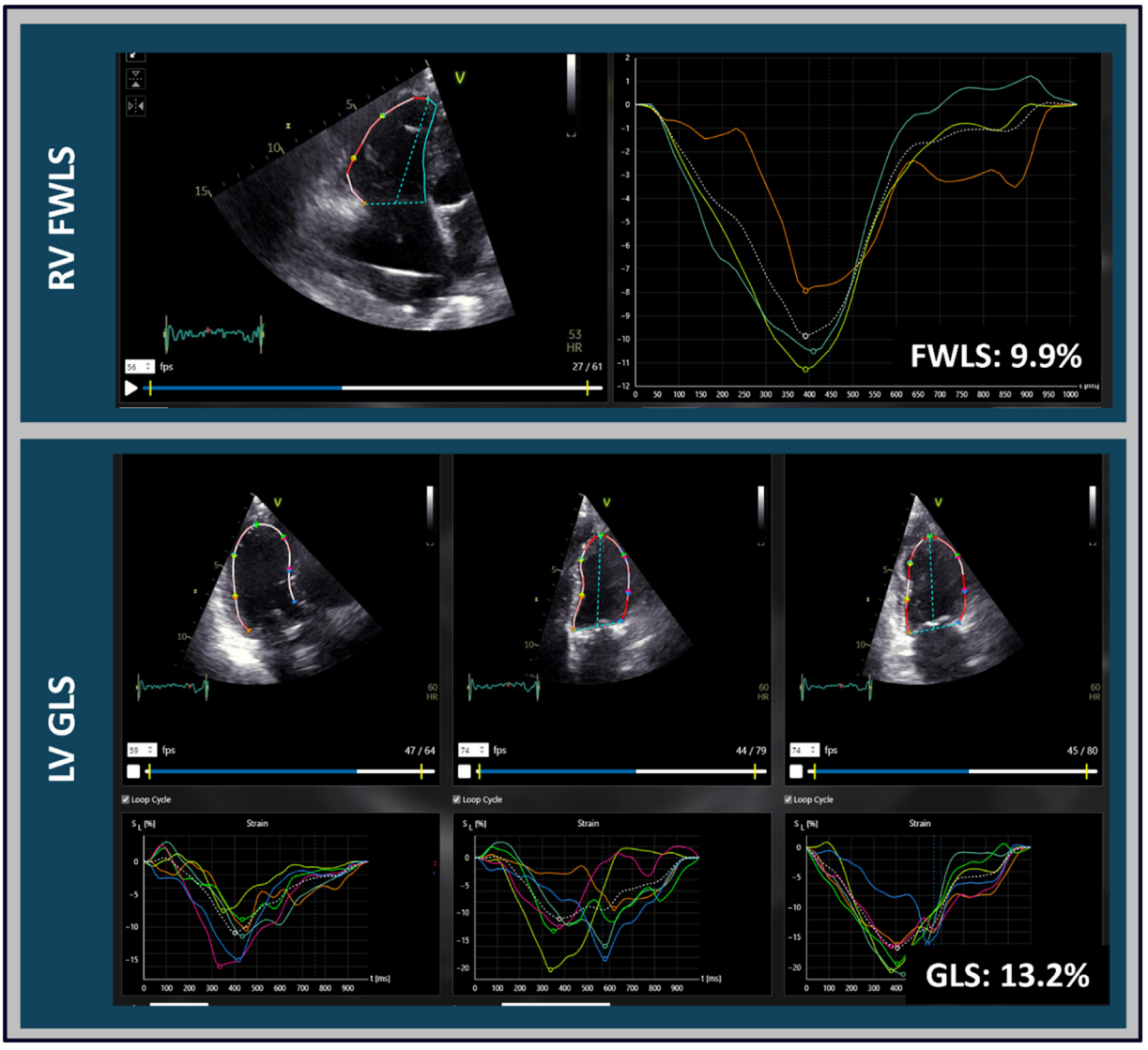

Figure 1. Measurements for RV FWLS and LV GLS for a patient diagnosed with definitive ARVC. *ARVC = arrhythmogenic right ventricular cardiomyopathy; FWLS = free wall longitudinal strain; GLS = global longitudinal strain; LV = left ventricle; RV = right ventricle. Images obtained from Caas Qardia 2.0 (Pie Medical Imaging, Maastricht, the Netherlands).*

sub-analysis on definite and borderline ARVC patients was also performed.

Furthermore, to determine the value of adding biventricular strain to ARVC diagnosis for risk stratification, likelihood ratios were calculated for a baseline model of age, sex and the ARVC diagnosis categories, then adding either RV FWLS, LV GLS or the strain groups. Both strain measures were treated as categorical variables based on a threshold of 18%.

Intraclass correlation coefficients (ICC) were calculated to assess intra- and inter-observer variability of the RV FWLS and LV GLS in a subset of 30 patients, of which 20 randomly selected, and 10 from the discordant strain group. Mean bias and mean absolute error were likewise determined. Analyses were done using SPSS for windows, version 25 (SPSS, Armonk, NY) and RStudio version 2022.02.3 (R Foundation for Statistical Computing, Vienna, Austria). A p-value <0.05 was considered statistically significant.

Results

A total of 204 patients were included in the study, with a mean age of 41 years, and a slight male predominance (55%). The most frequently reported symptoms were palpitations and syncope or near-syncope (Table 1). At the time of first echocardiography at LUMC, 19 patients (9%) already had an ICD. Genetic test results were available for only 126 patients (62%). Among these, (likely) pathogenic variants in PKP2 gene were the most common, followed by those in the DSP gene and the PLN founder variant, in accordance with the list of genes with definitive or moderate evidence of pathogenicity for ARVC.[16] Diagnosis of definite, borderline and possible ARVC was based on the TFC criteria, applied at the time of the initial analyzable echocardiographic study. Figure S1 illustrates the distribution and breakdown of these parameters.

The ICC for RV FWLS and LV GLS showed excellent correlation for both intra-observer and inter-observer reliability. Mean bias and mean absolute error were also negligible, making reclassification between the groups non-significant. Values are listed in Supplemental Table 1.

The correlation between RV FWLS and LV GLS revealed a modest positive correlation between RV and LV strain ($r = 0.674$, $p < 0.001$; Figure S1). To confirm whether the cut-off values proposed in previous literature[6,11] were also associated with an increased hazard ratio in this study cohort, spline curves were generated for both

Table 1
Clinical characteristics of the study population

	Total population (N = 204)
Age, years	41 ± 17
Male, n (%)	112 (55)
BMI, kg/m^2	21.2 ± 3.6
History of palpitations, n (%)	44 (22)
History of syncope/ near-syncope, n (%)	17 (8)
ICD, n (%)	19 (9)
Gene variants, n (%)	
PKP2	71 (35)
DSP	12 (6)
PLN	12 (6)
DSC2	7 (3)
DSG2	6 (3)
TMEM43	2 (1)
DES	2 (1)
Genes not associated with ARVC/ No variant found	20 (15)

Values are mean ± SD, median (IQR), or n(%). *ARVC= Arrhythmogenic Right Ventricular Cardiomyopathy; BMI = Body mass index; DSC2 = desmocollin-2; DSG2 = desmoglein-2; DSP = desmoplakin; ICD = Implantable cardiac defibrillator; DES = desmin; PKP2 = plakophilin-2; PLN = phospholamban; TMEM43 = transmembrane protein 43.*

parameters, confirming an increase in risk for values <18% (Figure 2). The optimal cut-off value by Youden index was also 18% based on ROC analysis (AUC of 0.702).

According to the abovementioned cut-off values, the 204 patients included were stratified as follows: impaired strain (n = 33), discordant strain (n = 70), and normal strain (n = 101) groups. Table 2 lists the clinical characteristics based on this strain grouping, and Table 3 shows a comparison of their echocardiographic parameters. Significant differences were observed in RV dimensions (mid-cavity and basal diameter) and measures of function (FAC, TAPSE, and FWLS) for the impaired and discordant groups compared to the normal group. Similarly, LV ejection fraction and GLS were both lower in the impaired and discordant groups.

Over a median follow-up of 87 (IQR 32–138) months, 57 (28%) patients experienced the composite end-point. During follow-up, 72 patients (35%) had an ICD. The most common outcome was appropriate ICD therapy (56%), followed by heart failure (21%), ventricular arrhythmias (18%) and death (5%). Kaplan-Meier survival analysis (Central illustration—lower left panel) showed a significant difference in the combined event-free survival when the patients were stratified according to the strain group (log-rank ^{2} = 51.17, p

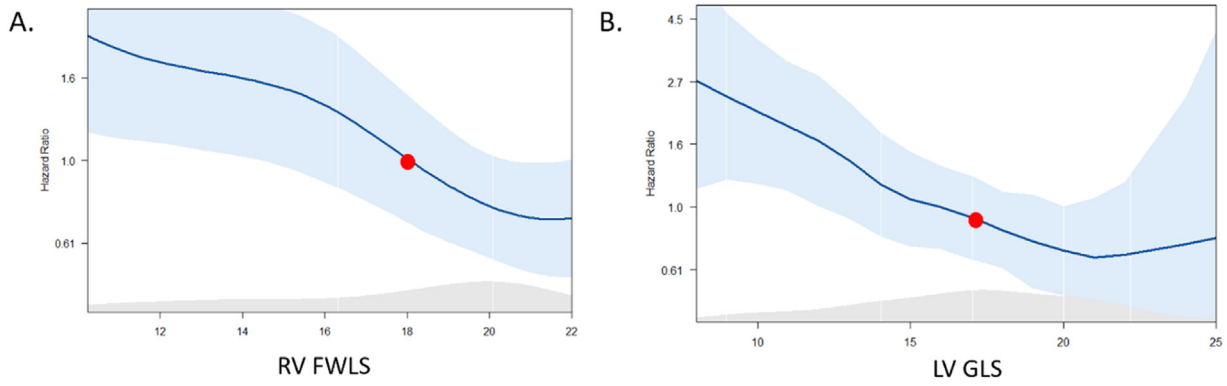

Figure 2. Spline curves for right ventricular free wall longitudinal strain (FWLS) (panel A) and left ventricular global longitudinal strain (GLS) (panel B), showing the applicability of the cut-off values published in literature.[6,11] *FWLS = free wall longitudinal strain; GLS = global longitudinal strain; LV = Left ventricle; RV = Right ventricle.*

Table 2
Baseline clinical characteristics according to the strain groups

	Impaired strain (n = 33)	Discordant strain (n = 70)	Normal strain (n = 101)	P- value
Males (n,%)	23 (70)	49 (70)	40 (40) $^{\alpha\beta}$	**<0.001**
Age, years	49 ± 17	43 ± 16	38 ± 17 $^{\alpha}$	**0.004**
BMI (kg/m^2)	23 ± 4	22 ± 4	20 ± 3$^{\alpha\beta}$	**<0.001**
History of palpitations, n (%)	2 (6)	20 (29) $^{\alpha}$	22 (22)$^{\alpha}$	**0.035**
History of syncope, n (%)	8 (24)	7 (10)	2 (2)$^{\alpha}$	**<0.001**
ICD, n(%)	6 (26)	10 (31)	3 (18)	0.589
Diagnosis by TFC criteria, n (%)				**<0.001**
Definite	26 (79)	35 (50)	17 (17)	
Borderline	6 (18)	14 (20)	19 (19)	
Possible	1 (3)	21 (30)	65 (64)	
Clinical and ECG parameters, n (%)				
T wave inversion V1-V3	16 (48)	20 (29)	9 (9) $^{\alpha\beta}$	**<0.001**
Any T wave inversion	22 (67)	28 (41) $^{\alpha}$	12 (12) $^{\alpha\beta}$	**<0.001**
Epsilon waves in V1-V3	6 (18)	0 $^{\alpha}$	0 $^{\alpha}$	**<0.001**
NSVT or VT of LBBB morphology with superior axis	7 (21)	14 (20)	8 (8) $^{\beta}$	**0.038**
NSVT or VT of any morphology	26 (79)	40 (57)	23 (23) $^{\alpha\beta}$	**<0.001**
>500 Ventricular extrasystoles in 24 hours	15 (68)	31 (48)	25 (26) $^{\alpha\beta}$	**<0.001**
ARVC in first degree relative	5 (15)	26 (37) $^{\alpha}$	64 (63) $^{\alpha\beta}$	**<0.001**
ARVC in first degree relative or presence of pathogenic variant	22 (67)	48 (69)	86 (85) $^{\alpha\beta}$	**0.015**

Values are mean ± SD, median (IQR), or n(%). P-values <0.05 were considered statistically significant and are shown in bold.
α p<0.05 on Bonferroni correction vs. impaired strain group; β p<0.05 on Bonferroni correction vs. discordant strain group.
ARVC = arrhythmogenic right ventricular cardiomyopathy; BMI = body mass index; ECG = electrocardiogram; LBBB = left bundle branch block; NSVT = non-sustained ventricular tachycardia; TFC = task force criteria; VT = ventricular tachycardia.

Table 3
Echocardiographic characteristics according to strain groups

	Impaired strain (n = 33)	Discordant strain (n = 70)	Normal strain (n = 101)	P- value
ECHOCARDIOGRAPHY: RV				
RVOTprox PLAX indexed (mm/m^2)	20 ± 5	17 ± 3 $^{\alpha}$	17 ± 3 $^{\alpha}$	**<0.001**
RVOTprox PSAX indexed (mm/m^2)	20 ± 5	17 ± 3 $^{\alpha}$	17 ± 3 $^{\alpha}$	**0.001**
Basal diameter (mm)	47 ± 9	40 ± 7$^{\alpha}$	38 ± 6 $^{\alpha\beta}$	**<0.001**
Mid-cavity diameter (mm)	38 ± 9	32 ± 7$^{\alpha}$	29 ± 5 $^{\alpha\beta}$	**<0.001**
FAC (%)	31 ± 8	40 ± 7$^{\alpha}$	47 ± 7 $^{\alpha\beta}$	**<0.001**
TAPSE (mm)	17 ± 5	22 ± 5$^{\alpha}$	24 ± 4 $^{\alpha\beta}$	**<0.001**
FWLS (%)	13.1 ± 3.2	21.6 ± 3.6$^{\alpha}$	25.6 ± 3. 4 $^{\alpha\beta}$	**<0.001**
Significant TR, n (%)	10 (30)	4 (6) $^{\alpha}$	1 (1) $^{\alpha}$	**<0.001**
SPAP (mmHg)	29 ± 10	25 ± 9	25 ± 7	0.065
ECHOCARDIOGRAPHY: LV				
LVMI (g/m^2)	88 ± 23	84 ± 26$^{\alpha}$	74 ± 19 $^{\alpha\beta}$	**0.001**
RWT	0.37 ± 0.12	0.35 ± 0.08	0.35 ± 0.08	0.448
EDV (ml)	129 ± 46	136 ± 31	131 ± 31	0.476
ESV (ml)	64 ± 37	56 ± 14$^{\alpha}$	48 ± 13 $^{\alpha\beta}$	**<0.001**
EF (%)	52 ± 9	58 ± 4$^{\alpha}$	64 ± 4 $^{\alpha\beta}$	**<0.001**
EF< 50%, n(%)	10 (30)	2 (3) $^{\alpha}$	0 (0) $^{\alpha\beta}$	**<0.001**
GLS (%)	12.3 ± 3.1	16.0 ± 2.2$^{\alpha}$	20.7 ± 1.7 $^{\alpha\beta}$	**<0.001**
Significant MR, n(%)	1 (3)	1 (1)	2 (2)	0.861

Values are mean ± SD, median (IQR), or n(%). P-values <0.05 were considered statistically significant and are shown in bold.
α p<0.05 on Bonferroni correction vs. impaired strain group; β p<0.05 on Bonferroni correction vs. discordant strain group.
EDV = end diastolic volume; ESV = end-systolic volume; EF = ejection fraction; FAC = fractional area change; FWLS = free-wall longitudinal strain; GLS = global longitudinal strain; LV = left ventricle; LVMI = left ventricular mass index; MR = Mitral regurgitation; PLAX = parasternal long-axis; PSAX = parasternal short-axis; RV = right ventricle; RVOT = right ventricular outflow tract; RWT = relative wall thickness; SPAP = systolic pulmonary artery pressure; TAPSE = tricuspid annular plane systolic excursion; TR = Tricuspid regurgitation.

<0.001), indicating worse outcomes when either one or both ventricles are involved. Event-free survival at 10 years was 36%, 67% and 84% for the impaired, discordant and normal strain groups, respectively.

Table 4 presents the univariable and multivariable Cox regression analyses for the composite outcome. In the univariable analysis, the discordant and normal groups had significantly better outcomes as compared to the impaired strain group. Correcting for age, sex,

Table 4
Univariable and multivariable cox regression analysis for the combined study endpoint

	Univariable Analysis		Multivariable Analysis	
	Hazard Ratio (95% CI)	P- Value	Hazard Ratio (95% CI)	P- Value
Age	1.023 (1.007- 1.039)	**0.004**	1.006 (0.990- 1.023)	0.464
Male sex	2.446 (1.372- 4.363)	**0.002**	1.721 (0.908- 3.262)	0.096
History of Palpitations	0.573 (0.271- 1.210)	0.144		
History of Syncope	4.555 (2.444- 8.492)	**<0.001**	1.547 (0.759- 3.154)	0.230
Definite ARVC diagnosis	5.508 (3.085- 9.832)	**<0.001**	3.526 (1.849- 6.723)	**<0.001**
Strain groups				
Impaired	Reference	**<0.001**	Reference	**0.014**
Discordant	0.311 (0.171- 0.563)	**<0.001**	0.436 (0.221- 0.858)	**0.016**
Normal	0.116 (0.058- 0.232)	**<0.001**	0.316 (0.135- 0.741)	**0.008**
T wave inversion in V1-V3	3.386 (2.004- 5.719)	**<0.001**		
T wave inversion (any)	4.361 (2.565- 7.417)	**<0.001**		
NSVT or VT of LBBB superior axis	2.209 (1.208- 4.039)	**0.010**		
NSVT or VT of any morphology	9.040 (4.430- 18.448)	**<0.001**		
FH first degree relative or pathogenic mutation	0.593 (0.339- 1.038)	0.067		
RVOTprox PLAX/BSA	1.192 (1.115- 1.274)	**<0.001**		
RVOTprox PSAX/BSA	1.190 (1.112- 1.274)	**<0.001**		
RV basal diameter	1.117 (1.082- 1.152)	**<0.001**		
RV mid-cavity diameter	1.098 (1.065- 1.131)	**<0.001**		
RV FAC	0.920 (0.896- 0.944)	**<0.001**		
RV FWLS	0.879 (0.841- 0.919)	**<0.001**		
Significant TR	6.479 (3.461- 12.128)	**<0.001**		
SPAP	1.039 (1.006- 1.073)	**0.019**		
LVMI	1.021 (1.012- 1.029)	**<0.001**		
LV EDV	1.003 (0.995- 1.011)	0.510		
LV ESV	1.020 (1.011- 1.030)	**<0.001**		
LVEF	0.911 (0.887- 0.936)	**<0.001**		
LV GLS	0.831 (0.783- 0.883)	**<0.001**		
Significant MR	2.691 (0.653- 11.085)	0.171		

ARVC = Arrhythmogenic Right Ventricular Cardiomyopathy; BSA = Body Surface Area; EDV = end diastolic volume; ESV; end-systolic volume; EF = ejection fraction; FAC = fractional area change; FH = family history; FWLS = free-wall longitudinal strain; GLS = global longitudinal strain; LV = left ventricle; LVMI = left ventricular mass index; MR = Mitral regurgitation; PLAX = parasternal long-axis; PSAX = parasternal short-axis; RV = right ventricle; RVOT = right ventricular outflow tract; SPAP = systolic pulmonary artery pressure; TAPSE = tricuspid annular plane systolic excursion; TR = Tricuspid regurgitation.

symptoms and definite ARVC diagnosis on multivariable analysis, the strain groups remained independently associated with the composite outcome (p = 0.014), together with ARVC diagnosis by TFC criteria.

To confirm these findings in a population with more definitive ARVC diagnosis, a sub-analysis on definite and borderline ARVC patients (n = 117) was performed. These patients were stratified into impaired (n = 32), discordant (n = 49), and normal (n = 36) strain groups. During a median follow-up period of 56 months (IQR 9-124 months), 45% (n = 53) patients experienced events. Univariable cox regression analysis showed that along with male sex, indexed proximal RVOT diameter, and the presence of T wave inversion and ventricular tachycardia of any morphology, the strain groups were associated with the combined outcome. After including these variables in a multivariable cox regression analysis, the strain groups remained independently associated with adverse outcomes (Table S2).

To evaluate the additional utility of measuring biventricular strain when the ARVC diagnosis is already known, likelihood ratios were obtained (Central illustration—lower right panel) ad showed the significant additional value (chi-square change of 21.41, p = 0.012) of the strain groups in establishing prognosis for these patients.

Discussion

This study was able to demonstrate the value of analyzing both RV and LV strain in patients with ARVC, since the involvement defined through strain of either one or both ventricles was significantly associated with outcomes. Since the ARVC diagnosis based on the TFC is a strong prognosticator, the additional prognostic value of this biventricular strain grouping demonstrated across the spectrum of ARVC diagnosis (from borderline to definite ARVC) further suggests that this approach may help improve risk stratification in these patients.

Assessment of myocardial involvement and dysfunction is crucial in ARVC patients both for diagnosis and risk-stratification purposes. For the RV, conventional echocardiographic and CMR parameters are currently applied; however, several echocardiographic strain measures have been proposed, including longitudinal strain, but also mechanical dispersion, deformation patterns, and post-systolic shortening.[17] Although all these parameters were associated with outcomes in these patients, we opted to use specifically FWLS as the simplest and most standardized parameter for clinical application.[1] The choice of cut-off value for the definition of RV involvement was made at 18% based on a previous study assessing the association of this parameter with outcomes,[6] which was confirmed by the spline curve analysis in the current cohort.

As for LV involvement, our approach using LV GLS (with a cut-off value of 18% as well) is in line with the specific recommendations for ARVC patients, which propose this measure as more sensitive than LVEF; the choice is also in line with previous studies exploring the association of this parameter with outcomes.[1,11] However, the use of longitudinal strain to define both RV and LV involvement has not been explored extensively in ARVC patients. Pinamonti et al. introduced the concept of “ordinal dysfunction” when both ventricles were affected in these patients, but used only conventional echocardiographic parameters (LVEF <50% and FAC <33%), which are known to have low sensitivity.[18] Conversely, the work of Mast et al. also considered the concept of biventricular involvement in ARVC patients, but only in terms of LV involvement according to GLS on top of isolated RV involvement defined by the TFC structural criteria, but the study included a limited number of patients (38 definite and 16 possible ARVC patients).[10] They also performed a subanalysis in 27 patients with CMR, and showed that regional deformation abnormalities in the LV corresponded to the areas with late gadolinium enhancement; however, subtle myocardial dysfunction was detected by strain also in patients without enhancement, suggesting other possible myocardial abnormalities such as interstitial fibrosis or fatty replacement. A recent study by Navasivayam et al.[9] examined the diagnostic and prognostic utility of LV and RV strain in 109 patients with suspected ARVC, but considered RV GLS, FWLS and LV GLS as separate measures, to compare their accuracy for diagnosis and prognosis. Their analysis was able to show that RV strain, both as global strain and FWLS, had more diagnostic value, while LV GLS showed superior prognostic value.[9] However, the effect of the interplay of both strains was not considered, and the sample size was rather small. In the current study, using both strain measures for LV and RV involvement, we aimed at identifying (in the most sensitive but easily applicable manner) patients at risk for adverse events, and including a large cohort of patients across the spectrum of ARVC diagnosis (from borderline to definite ARVC). In addition, we chose to categorize patients into groups based on the impairment of one (discordant) or both (impaired) ventricles, with the recognition that it may be possible to exhibit worse LV than RV involvement. This study in fact identified a significant number of discordant patients, some of whom only met the cut-off value for LV involvement, highlighting the need for assessing both ventricular strains once a patient meets the criteria for at least possible ARVC. Further studies are advocated to monitor progression of biventricular involvement and to further characterize these discordant patients.

Similar to other cardiomyopathies,[19–21] initial studies have shown the prognostic value of a combined biventricular impairment in ARVC patients, although using only conventional echocardiographic parameters and therefore possibly being late in the disease stage when performing risk-stratification. Our current study confirmed these findings, but using strain measures as a more advanced and possibly more sensitive approach, and therefore reinforcing the concept of systematically assessing both ventricular functions (RV and LV) in these patients. In addition, the current study uniquely showed that the discordant strain group was characterized by a different event-rate than those with normal strain or biventricular impairment. This may suggest different patterns of involvement in these patients, which could be related to specific clinical (or genetic) characteristics or to the disease stage, but nevertheless underlines the importance of monitoring this discordant group to potentially adjust management in a timely manner.

Diagnosis and risk stratification of ARVC poses significant challenges. While advances in imaging (e.g. CMR) have provided novel and possibly more accurate measures to define ventricular involvement, these parameters are more difficult to implement in clinical practice, often requiring advanced imaging techniques not widely accessible, and specific expertise not always available. ARVC risk scores have been proposed and were proven to be useful, although these risk scores are still not systematically implemented, mainly due to the number and complexity of variables included. The relatively simple approach of measuring both LV and RV strain (on top of parameters such as age, sex and ARVC diagnosis) proposed in the current study may be considered a screening tool especially in centers which do not have the diagnostic capabilities that other risk stratification criteria necessitate. This study also demonstrates that classifying patients into these strain groups is useful since outcomes may differ if one or both ventricles are involved, even among patients with borderline and definite ARVC, further helping in risk stratifying these patients and selecting follow-up and management strategies.

This study has several limitations. First, the analyses were performed in a relatively small population from a single tertiary center. Although studies on ARVC are often small in size, larger studies are needed to validate the reported findings. Given the variability of cut-offs used in current literature, further research in larger cohorts of patients are needed to make more definitive conclusions, especially to establish standardized thresholds. In addition, agreement between

echocardiography and other imaging modalities will be of value, particularly the difference in RV or LV involvement when conventional echocardiography, strain, and CMR findings are examined. This will greatly help in decision-making in terms of the diagnostics needed, and for patient prognostication.

Second, clinical and diagnostic data were analyzed at the time of the first echocardiogram. Since the true onset of the disease in a patient is unknown, the evaluation may have been performed at different stages of the disease for each patient. Future studies should therefore consider examining patients from a specific stage to assess whether the current findings can be confirmed. Third, as a retrospective study, the available information is constrained by the diagnostic tests conducted at the time and the data recorded in medical records. Some patients were diagnosed before the 2010 TFC criteria, potentially leading to incomplete diagnostic evaluations based on this criterion. CMR, for example, was not systematically performed. Lastly, although inter- and intra-observer agreement was excellent for the RV and LV strain measurements and bias was minimal, patients with borderline values may be reclassified into different strain groups even with the acceptable variation of <2% for strain measurements.[22] This is a limitation inherent to dichotomization of continuous measures.

In conclusion, strain imaging is a useful parameter to detect biventricular involvement in patients within the whole spectrum of ARVC diagnosis. A significant impairment of either one or both ventricles in strain, is independently associated with worse outcomes and may therefore help improve patient management and risk stratification.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

J.J.B. reports financial support was provided by Pie Medical Imaging BV. N.A.M. reports a relationship with Abbott Vascular Inc that includes: speaking and lecture fees. N.A.M. reports a relationship with Philips Ultrasound, Inc. that includes: speaking and lecture fees. N.A.M. reports a relationship with Omron Healthcare that includes: speaking and lecture fees. N.A.M. reports a relationship with Pfizer Inc that includes: speaking and lecture fees. N.A.M. reports a relationship with GE Healthcare that includes: speaking and lecture fees. J.J.B. reports a relationship with Abbott Vascular Inc that includes: speaking and lecture fees. J.J.B. reports a relationship with Edwards Lifesciences Corporation that includes: speaking and lecture fees. J.J.B. reports a relationship with Omron Healthcare that includes: speaking and lecture fees. A.P.C. reports a relationship with Turku PET Centre that includes: funding grants. D.L. reports a relationship with Turku PET Centre that includes: funding grants. C.S. reports a relationship with Turku PET Centre that includes: funding grants. P.L.S. reports a relationship with Turku PET Centre that includes: funding grants. T. N. reports a relationship with Turku PET Centre that includes: funding grants. R.M. reports a relationship with Turku PET Centre that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Aileen Paula Chua: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Dorien Laenens:** Writing – review & editing, Methodology, Investigation, Data curation. **Camille Sarrazyn:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Maria Pilar Lopez-Santi:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Takeru Nabeta:** Methodology, Investigation, Formal analysis. **Rinchyenkhand Myagmardorj:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Marianne Bootsma:** Data curation, Conceptualization. **Daniela Q.C.M. Barge-Schaapveld:** Writing – review & editing, Investigation, Data curation. **Jeroen J. Bax:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Formal analysis. **Nina Ajmone Marsan:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Data Availability Statement

The data that support the results of this study are available upon reasonable request from the corresponding author.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2025.01.006.

References

1 Haugaa KH, Basso C, Badano LP, Bucciarelli-Ducci C, Cardim N, Gaemperli O, et al. Comprehensive multi-modality imaging approach in arrhythmogenic cardiomyopathy-an expert consensus document of the European association of cardiovascular imaging. Eur Heart J Cardiovasc Imaging 2017;18(3):237–53.
2 Arbelo E, Protonotarios A, Gimeno JR, Arbustini E, Barriales-Villa R, Basso C, et al. 2023 ESC Guidelines for the management of cardiomyopathies. Eur Heart J 2023;44(37):3503–626.
3 Bos TA, Piers SRD, Wessels MW, Houweling AC, Bokenkamp R, Bootsma M, et al. The arrhythmogenic cardiomyopathy phenotype associated with PKP2 c.1211dup variant. Neth Heart J 2023;31(7-8):315–23.
4 Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. Circulation 2010;121(13):1533–41.
5 Teske AJ, Cox MG, De Boeck BW, Doevendans PA, Hauer RN, Cramer MJ. Echocardiographic tissue deformation imaging quantifies abnormal regional right ventricular function in arrhythmogenic right ventricular dysplasia/cardiomyopathy. J Am Soc Echocardiogr 2009;22(8):920–7.
6 Teske AJ, Cox MG, Te Riele AS, De Boeck BW, Doevendans PA, Hauer RN, et al. Early detection of regional functional abnormalities in asymptomatic ARVD/C gene carriers. J Am Soc Echocardiogr 2012;25(9):997–1006.
7 Malik N, Win S, James CA, Kutty S, Mukherjee M, Gilotra NA, et al. Right ventricular strain predicts structural disease progression in patients with arrhythmogenic right ventricular cardiomyopathy. J Am Heart Assoc 2020;9(7):e015016.
8 Pieles GE, Grosse-Wortmann L, Hader M, Fatah M, Chungsomprasong P, Slorach C, et al. Association of echocardiographic parameters of right ventricular remodeling and myocardial performance with modified task force criteria in adolescents with arrhythmogenic right ventricular cardiomyopathy. Circ Cardiovasc Imaging 2019;12(4):e007693.
9 Namasivayam M, Bertrand PB, Bernard S, Churchill TW, Khurshid S, Marcus FI, et al. Utility of left and right ventricular strain in arrhythmogenic right ventricular cardiomyopathy: a prospective multicenter registry. Circ Cardiovasc Imaging 2023;16(12):e015671.
10 Mast TP, Teske AJ, vd Heijden JF, Groeneweg JA, Te Riele AS, Velthuis BK, et al. Left ventricular involvement in arrhythmogenic right ventricular dysplasia/cardiomyopathy assessed by echocardiography predicts adverse clinical outcome. J Am Soc Echocardiogr 2015;28(9):1103-13 e9.
11 Lie OH, Chivulescu M, Rootwelt-Norberg C, Ribe M, Bogsrud MP, Lyseggen E, et al. Left ventricular dysfunction in arrhythmogenic cardiomyopathy: association with exercise exposure, genetic basis, and prognosis. J Am Heart Assoc 2021;10(8):e018680.
12 Corrado D, Perazzolo Marra M, Zorzi A, Beffagna G, Cipriani A, Lazzari M, et al. Diagnosis of arrhythmogenic cardiomyopathy: the Padua criteria. Int J Cardiol 2020;319:106–14.
13 Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American society of echocardiography and the European association of cardiovascular imaging. J Am Soc Echocardiogr 2015;28(1):1-39 e14.

14 Lancellotti P, Pibarot P, Chambers J, La Canna G, Pepi M, Dulgheru R, et al. Multi-modality imaging assessment of native valvular regurgitation: an EACVI and ESC council of valvular heart disease position paper. Eur Heart J Cardiovasc Imaging 2022;23(5):e171–232.
15 Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, et al. Universal definition and classification of heart failure: a report of the heart failure society of america, heart failure association of the European society of cardiology, Japanese heart failure society and writing committee of the universal definition of heart failure: endorsed by the Canadian heart failure society, heart failure association of india, cardiac society of Australia and new Zealand, and Chinese heart failure Association. Eur J Heart Fail 2021;23(3):352–80.
16 James CA, Jongbloed JDH, Hershberger RE, Morales A, Judge DP, Syrris P, et al. International evidence based reappraisal of genes associated with arrhythmogenic right ventricular cardiomyopathy using the clinical genome resource framework. Circulation: Genomic and Precision Medicine 2021;14(3):e003273.
17 Kirkels FP, Lie OH, Cramer MJ, Chivulescu M, Rootwelt-Norberg C, Asselbergs FW, et al. Right ventricular functional abnormalities in arrhythmogenic cardiomyopathy: association with life-threatening ventricular arrhythmias. JACC Cardiovasc Imaging 2021;14(5):900–10.
18 Pinamonti B, Dragos AM, Pyxaras SA, Merlo M, Pivetta A, Barbati G, et al. Prognostic predictors in arrhythmogenic right ventricular cardiomyopathy: results from a 10-year registry. Eur Heart J 2011;32(9):1105–13.
19 Park JH, Park JJ, Park JB, Cho GY. Prognostic value of biventricular strain in risk stratifying in patients with acute heart failure. J Am Heart Assoc 2018;7(19):e009331.
20 Seo J, Hong YJ, Kim YJ, Lkhagvasuren P, Cho I, Shim CY, et al. Prevalence, functional characteristics, and clinical significance of right ventricular involvement in patients with hypertrophic cardiomyopathy. Sci Rep 2020;10(1):21908.
21 Manca P, Nuzzi V, Cannata A, Castrichini M, Bromage DI, De Luca A, et al. The right ventricular involvement in dilated cardiomyopathy: prevalence and prognostic implications of the often-neglected child. Heart Fail Rev 2022;27(5):1795–805.
22 Kouris NT, Kostopoulos VS, Psarrou GA, Kostakou PM, Tzavara C, Olympios CD. Left ventricular ejection fraction and global longitudinal strain variability between methodology and experience. Echocardiography 2021;38(4):582–9.