

Original Article

Left ventricular myocardial strain in ventricular arrhythmia without structural heart disease using cardiac magnetic resonance

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Abstract: Ventricular arrhythmia (VA) in structurally normal heart is considered as benign. However, these arrhythmias have been recently reported to induce left ventricular (LV) dysfunction. Up to now, there is no efficacious method to detect abnormal myocardial systolic function in VA patients. Therefore, in the current study, we used cardiac magnetic resonance feature tracking (CMR-FT) on balanced steady state free precession (SSFP) cine images to investigate LV myocardial strain in 42 VA patients without known heart disease as well as in 29 normal volunteers. As compared with controls, VA patients had lower peak values of radial and circumferential strain (RS, CS) in both basal and middle parts of LV and the peak value of longitudinal strain (LS) in VA patients was also decreased in middle LV. Moreover, as revealed by LV myocardial segmental peak strain, reduced RS, CS and LS peaks in VA were more significant in anterior, inferoseptal and anterolateral segments, especially for the patients with frequent premature ventricular complexes. Our results suggested that VA in normal heart is associated with abnormal segmental wall motion, which can be efficaciously detected by CMR-FT derived strain analysis. And early clinical management should be considered to prevent further significant symptoms in these patients.

Keywords: Ventricular arrhythmia, cardiac magnetic resonance

Introduction

Ventricular arrhythmia (VA) in the absence of structural heart disease predominantly originates from ventricular outflow tract, which accounts for about 10% of all VA cases with most of the patients experiencing a benign course and developing favorable prognosis [1, 2]. However, in some cases, VA in normal heart can lead to severe symptoms and sudden death. Recent studies have reported that VA in patients without overt cardiovascular disease can cause adverse left ventricular (LV) remodeling and dysfunction, especially in those with frequent premature ventricular complexes (PVCs) [3, 4]. These evidences indicate a potential abnormal LV myocardial function associated with VA. Theoretically, disorders of electrical activation initiated by VA may result in significant ventricular systolic dyssynchrony [5, 6]. However, most of VA patients without structural

heart diseases have normal LV ejection fraction (LVEF), and a more efficacious method is thus in need to evaluate the myocardial systolic function for VA in normal hearts.

Cardiac magnetic resonance feature tracking (CMR-FT) has been recently proposed to quantitatively evaluate myocardial function [7]. It allows the tracking of tissue voxel motion through CMR balanced steady state free precession (SSFP) cine images, and myocardial mechanisms derived from CMR-FT don't rely on additional sequences, which largely reduces post-processing time [8]. Recently, CMR-FT has been successfully applied to detect the abnormalities of regional ventricular wall motion in patients with cardiac diseases, such as ischemic heart diseases and cardiomyopathies [9-13], however, little evidence is available regarding the feasibility of CMR-FT in detecting myocardial deformation in VA patients without

structural heart diseases. In the current study, we therefore aim to evaluate whether CMR-FT is sensitive enough to detect abnormal LV myocardial strains as well as regional wall systolic dyssynchrony in VA patient with normal LVEF.

Methods

Patient population

The study population included 42 consecutive VA subjects without structural heart disease, which were diagnosed by cardiovascular physicians in the Second Affiliated Hospital of Nanchang University from 2012 to 2016. The following inclusion and exclusion criteria were applied: 1) VA patients were diagnosed by invasive radiofrequency catheter ablation and intracardiac electrophysiological examinations; 2) PVCs and VT were determined by 24-h Holter monitoring. Frequent PVC was defined as more than 1000 PVCs over 24 hours, and non-sustained VT was defined as three or more consecutive ventricular arrhythmias with tachycardia frequency more than 100 times/min; 3) patients had malignant or congenital idiopathic ventricular arrhythmia without overt cardiovascular disease were excluded, such as polymorphic VT, Brugada wave; 4) patients with structural heart diseases, ischemic cardiomyopathy and significant coronary atherosclerosis were excluded; 5) patients with familial history of heart diseases, particularly the arrhythmogenic right ventricular cardiomyopathy, were excluded; 6) patients with familial history of sudden death were; 7) patients with renal impairment, systemic hypertension, or diabetes mellitus were excluded.

As a control, 29 healthy volunteers were also recruited from medical examinations. None of the healthy controls had history of cardiovascular diseases, valvular heart disease, renal impairment, systemic hypertension, or diabetes mellitus. All controls had normal electrocardiography (ECG) or sinus tachycardia or sinus bradycardia.

All procedures in the present study were performed with the approval of the institutional review board and ethics committee of the Second Affiliated Hospital of Nanchang University in accordance with the 1964 Helsinki declaration. Written informed consent was obtained from all participating individuals prior to the study.

Cardiac magnetic imaging

All CMR examinations were performed on a 1.5T and 3.0T scanner (GE Signa Excite HD Twinspeed) with a cardiac phased-array 8 channel coil. ECG was used for cardiac gating and breath holding [14]. Following a three-plane or real-time localizer, balanced steady state free precession (SSFP) cines were acquired in the short-axis (SAX) and long axis (vertical and horizontal planes, LAX). Contiguous short axis cines extending from the atrioventricular valve plane to the apex were obtained to cover the entire left and right ventricles (6 mm parallel slices with 2 mm gap). The four-chamber planes were acquired to cover the LV and RV chambers (5 mm slice thickness with 1 mm gap). Typical scan parameters were applied: 1) 1.5T: NEX 1, FOV 35 cm, a matrix of 224×224, TR/TE 3.8/1.6 ms, 20 phases per cardiac cycle; 2) 3.0T: NEX 1, FOV 35 cm, a matrix of 224×160, TR/TE 3.5/1.6 ms, 20 phases per cardiac cycle [15].

Image analysis

CMR-FT analysis was performed on Circle Cardiovascular Imaging (Tissue Tracking, CVI42, Circle Cardiovascular Imaging, Calgary, Alberta, Canada). SAX and LAX cine images were uploaded into the software which reconstructed a 3D model and derived peak radial, circumferential and longitudinal strain [16]. End-diastolic and end-systolic phases were selected, endo/epi contours were drawn manually, and papillary muscles were excluded from the endocardial contour. Then the software automatically tracked the defined LV slices through the cardiac cycle. The segmental peak strain values were displayed in a modified 16-segment LV model according to the standard 17-segment model of the American Heart Association [17]. As a global functional evaluation, LVEF was also assessed via standardized protocols using a semi-automated commercially available software (CVI42) [14, 17, 18].

Reproducibility

Previous studies demonstrated that the circumferential global strain and peak strain values displayed excellent reproducibility [19-21]. Therefore, in the present study, we randomly selected CMR images from 14 subjects for the assessment of inter- and intra-observer variability of strain values.

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Table 1. Patient demographics and the LV function parameters

Variable	VA group (n=42)	Control group (n=29)	p-value
Demographic data			
Age, y	36±15.5	35±16.8	0.797
Male/Female, n (%)	26 (62)/16 (38)	16 (55)/13 (45)	0.571
Heart rate (/min)	77.45±15.61	79.36±13.92	0.598
LV function			
Cardiac Output (ml/min)	6.21±1.33	6.57±1.65	0.313
End-diastolic volume (ml)	124.13±28.10	132.67±30.49	0.228
LVEF (%)	66.45±7.27	69.84±7.52	0.061
Clinical Symptom	Palpitation, chest distress	NA	
Arrhythmia type, n (%)			
Frequent PVCs	22/(52.5)	NA	
Non-sustained VT	11 (26)	NA	
Other	9 (21.5)	NA	
Catheter ablation, n (%)	20 (48)	NA	
Ectopic origin type, n (%)			
Right ventricular outflow tract	13 (31)	NA	
Left ventricular outflow tract	2 (5)	NA	
Other	5 (12)	NA	

distress. 52.5% of them (22 patients) had frequent premature ventricular complexes (PVCs), 26% (11 patients) had non-sustained ventricular tachycardias (VT), and the rest 21.5% (9 patients) had both or others. Through catheter ablation and electrophysiological examinations, ectopic origin was confirmed in 20 VA patients, including 13 patients originating from right ventricular outflow tract, 2 from left outflow tract and 5 from other positions (**Table 1**).

Statistical analysis

Continuous variables were assessed for normality distribution using the one sample Kolmogorov-Smirnov test and presented as mean ± SD. Comparisons of CMR parameters between controls and VA patients, frequent PVC and non-sustained VT were performed using independent samples t-Test or Wilcoxon signed-rank test, as appropriate. One-way ANOVA was applied to compare the regional LV peak strain in VA patients as well as in healthy controls. Agreement was tested by calculating mean bias from Bland-Altman analysis. All statistical analysis was performed using the SPSS v20.0 (SPSS Inc., Chicago, IL, USA) and Bland-Altman analysis was performed with Medcalc v 16.4.1 (MedCalc Software bvba, Ostend, Belgium). A two-sided P<0.05 was considered statistically significant.

Results

Patient characteristics

29 healthy controls and 42 VA patients were enrolled in the current study. As shown in **Table 1**, no significant difference was observed in age, gender and heart rate between VA patients and controls, and LV function indexes (Cardiac Output, End-diastolic volume, LVEF) also remained normal in VA patients. All VA patients had clinical symptoms, such as palpitation, chest

LV CMR-FT

Representative LV CMR-FT images were shown in **Figure 1A-C**. Circumferential strain (CS) was determined from LV short-axis at end-diastole (**Figure 1A**), while longitudinal strain (LS) was defined from both 4- and 2-chamber cines (**Figure 1B and 1C**). The distribution of segmental CS and LS from a 38-year old male volunteer and a 39-year old male VA patients were also shown in **Figure 1D-I**. In healthy condition, the distribution CS and LS curves from different segments are consistent (**Figure 1D and 1E**), while in VA patient, the CS and LS curves varied a lot from different segments, with most of the segments displaying a reduced strain value (**Figure 1G and 1H**). As shown in the 16-segment maps of peak LS, VA patient had much reduced peak LS at basal level, especially at basal anterior segment, which displayed a reserved value (**Figure 1F and 1I**). These results suggested reduced myocardial strain at different LV levels and at different segments. And our next step is to figure out the deregulated levels and segments.

Distribution of peak strain in the LV levels

As shown in **Figure 2**, both healthy controls and VA patients had the highest radial strain (RS) peak existed at apical levels of LV and lowest

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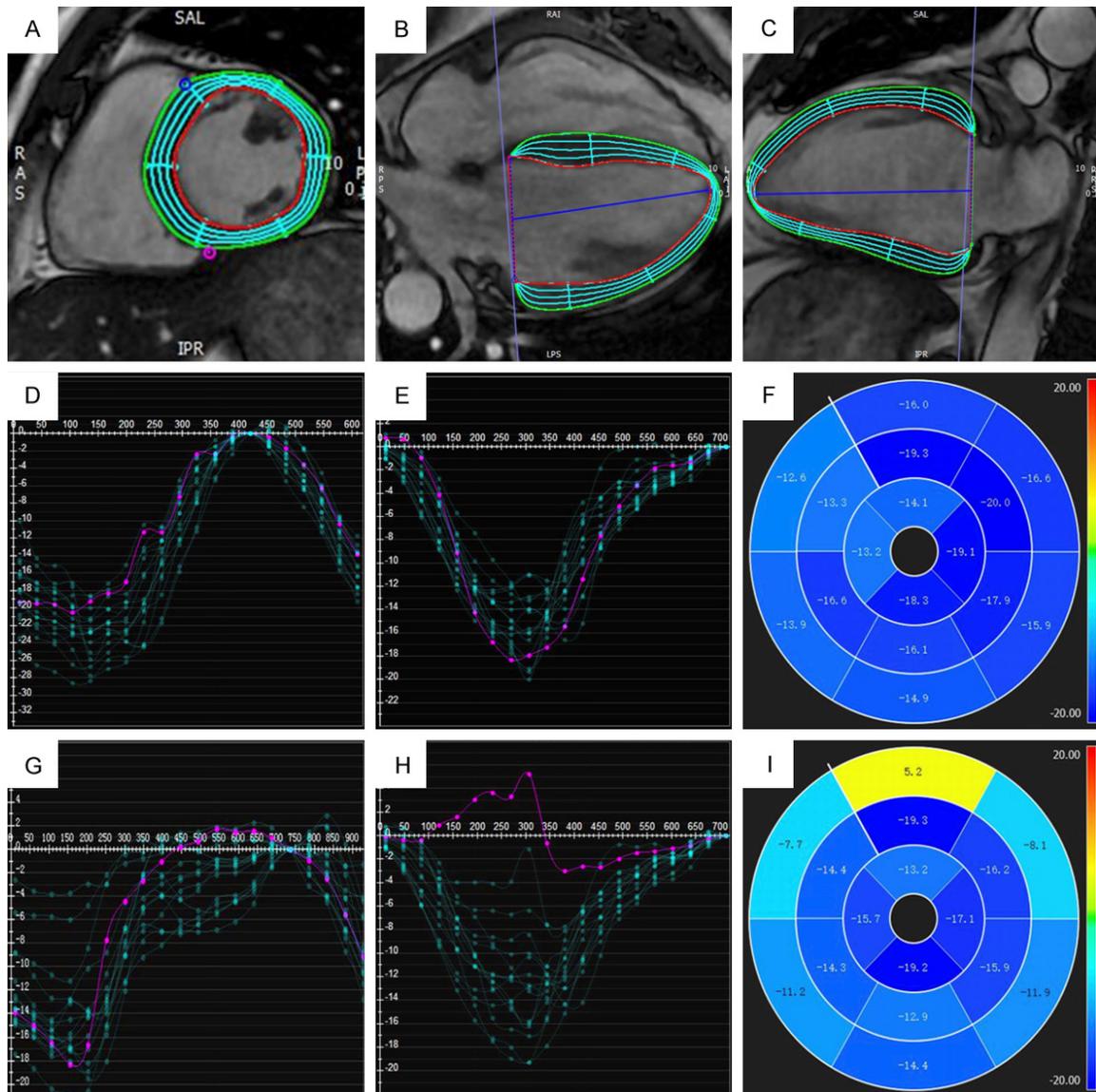


Figure 1. LV CMR-FT. (A) Circumferential strain from LV short-axis. Longitudinal strain from 4-chamber (B) and 2-chamber (C) cines. (D-F) are the representative segmental CS curves (D), LS curves (E) and 16-segmental map of peak LS (F) from a healthy volunteer, while (G-I) are segment CS curves (G), LS curves (H) and 16-segmental map of peak LS (I) from a VA patient.

peak RS at middle levels. In contrast, the highest peaks of CS and LS existed at middle levels, while apical levels had the lowest CS and LS peaks. As compared with controls, VA patients had significantly lower RS and CS peaks at both basal and middle levels of LV (RS-basal: $35.63 \pm 13.57\%$ vs. $42.61 \pm 10.32\%$, $P=0.022$; RS-mid: $28.69 \pm 10.43\%$ vs. $36.04 \pm 7.54\%$, $P=0.002$; CS-basal: $-15.23 \pm 3.38\%$ vs. $-17.50 \pm 1.95\%$, $P=0.001$; CS-mid: $-15.38 \pm 4.19\%$ vs. $-18.05 \pm 2.61\%$, $P=0.002$), and the LS peak in the middle was also decreased in VA (LS-mid: $-14.59 \pm 4.44\%$ vs. $-17.64 \pm 2.64\%$, $P=0.001$). No

differential myocardial strains were observed at apical levels.

16-segment LV myocardial peak strain

Through modified 16-segment LV model, the peak of radial, circumferential and longitudinal strain can be acquired for each single LV segment (basal segments: 1~6; mid segments: 7~12; apical segments: 13~16). As listed in **Table 2**, VA patients had significantly reduced peak PS in segments 1, 6, 7, 9, 10, 12, 13 as compared with healthy controls, and peak CS of segments 1, 5, 6, 7, 9, 12 and peak LS of

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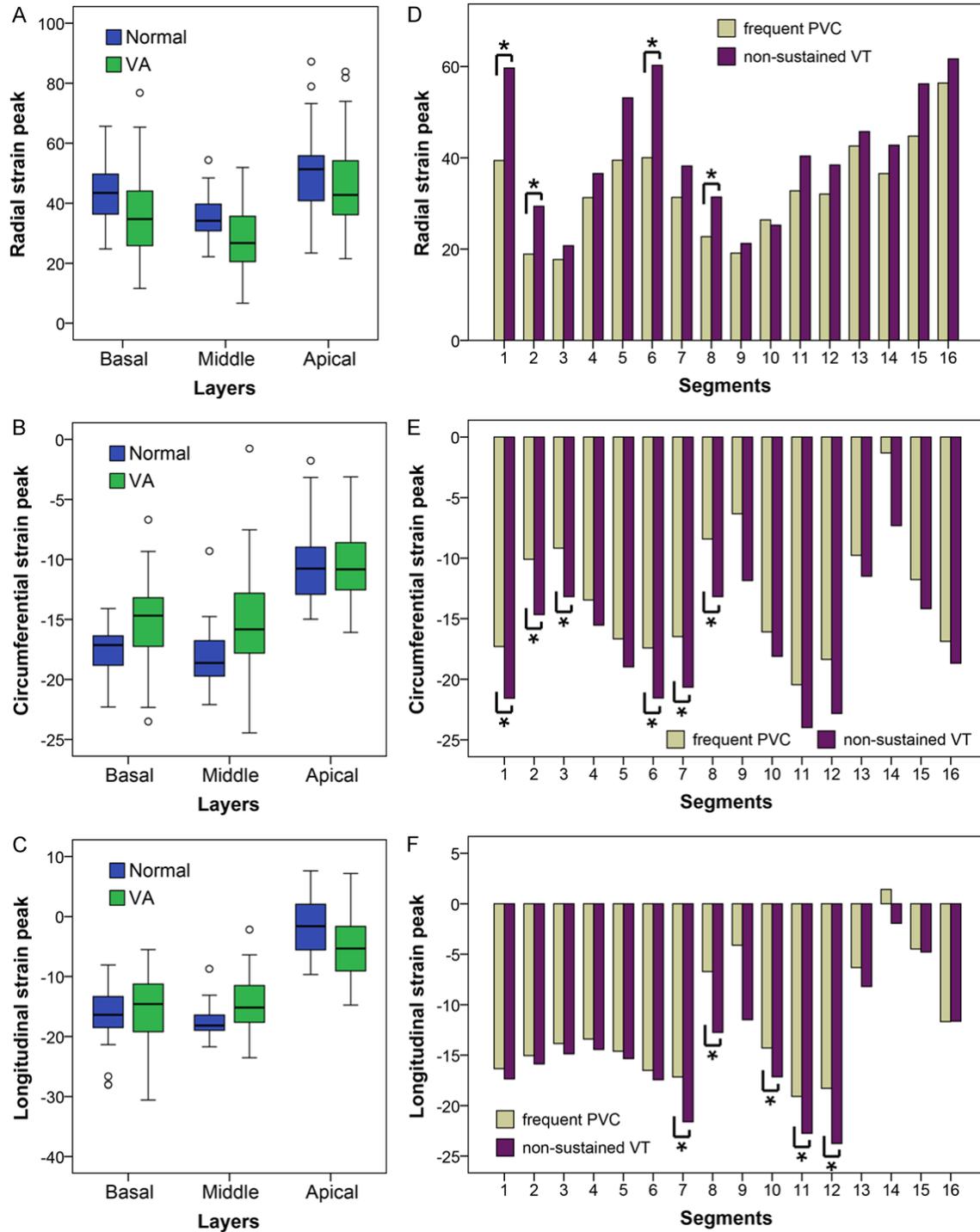


Figure 2. The distribution of regional peak strain by groups in the radial (A), circumferential (B) and longitudinal (C) directions. Blue and green boxplots correspond to control subjects and VA cohorts respectively. Bar charts represented the segmental peak radial (D), circumferential (E) and longitudinal (F) strain values of frequent PVCs (brown) and non-sustained VT (purple).

segments 7, 12, 13 were also dramatically decreased in VA patients ($P < 0.05$). These results suggested abnormal motion within anterior, septal and anterolateral walls in VA patients without structural heart diseases.

Notably, reduced myocardial strain peak is more pronounced in patients with frequent PVCs. As shown in **Figure 2D-F**, as compared with non-sustained VT, VA patients with frequent PVCs had lower peak RS in segments 1,

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Table 2. 3D segmental peak strain for controls and VA cohorts (S, %)

Segments	RS			CS			LS		
	Controls	VA	P	Controls	VA	P	Controls	VA	P
Basal									
1 anterior	64.02±18.40	45.53±23.64	0.001	-20.90±3.17	-18.33±5.36	0.014	-17.41±5.81	-16.96±6.49	0.768
2 anteroseptal	26.18±10.80	22.51±11.53	0.181	-13.21±3.27	-11.02±6.94	0.08	-16.72±5.41	-15.55±6.18	0.46
3 inferoseptal	20.33±8.60	19.51±11.28	0.742	-12.47±3.39	-10.65±5.16	0.1	-15.48±4.87	-14.31±5.38	0.35
4 inferior	34.94±12.32	34.15±16.44	0.825	-15.71±2.75	-14.31±4.13	0.115	-14.88±5.24	-13.94±6.13	0.505
5 inferolateral	46.83±16.95	44.74±24.89	0.674	-20.02±3.52	-17.86±4.69	0.039	-16.94±5.37	-15.57±6.87	0.373
6 anterolateral	63.36±23.09	47.32±24.20	0.007	-22.69±3.67	-19.24±6.35	0.01	-17.87±5.20	-17.36±6.22	0.72
Middle									
7 anterior	47.75±18.28	32.63±14.21	<0.001	-20.47±3.38	-17.05±7.57	0.012	-21.32±3.20	-18.23±6.74	0.012
8 anteroseptal	27.62±10.14	24.25±13.05	0.247	-10.93±5.81	-8.86±9.11	0.283	-10.16±6.19	-7.53±10.06	0.178
9 inferoseptal	23.06±3.95	19.65±6.97	0.011	11.49±8.48	-7.87±10.42	0.013	-10.46±8.01	-6.21±11.53	0.058
10 inferior	32.33±9.29	27.01±10.99	0.037	-18.30±3.22	-16.91±4.28	0.142	-16.87±2.84	-14.78±5.83	0.079
11 inferolateral	42.53±15.64	35.39±17.40	0.081	-23.74±4.31	-21.63±5.58	0.091	-23.05±4.34	-20.42±5.70	0.04
12 anterolateral	42.95±13.44	33.20±18.01	0.016	-23.34±4.65	-19.99±7.26	0.032	-23.99±4.86	-20.37±7.69	0.028
Apical									
13 anterior	52.54±15.81	42.58±17.40	0.016	-10.42±2.90	-9.61±5.01	0.434	-2.58±6.68	-5.88±5.29	0.023
14 septal	40.11±11.24	37.55±13.43	0.403	-1.93±8.71	-7.13±8.35	0.562	5.43±5.82	0.57±7.57	0.003
15 inferior	49.20±19.92	48.45±21.34	0.881	-11.29±7.06	-12.28±6.38	0.539	-0.46±7.74	-4.48±7.75	0.035
16 lateral	60.32±26.73	56.54±26.81	0.56	-18.38±5.24	-17.44±5.30	0.461	-8.79±5.88	-11.10±4.90	0.077

2, 6, 8 (1: 39.40±17.57% vs. 59.65±27.67%, P=0.015; 2: 18.89±11.09% vs. 29.40±11.74%, P=0.017; 6: 40.03±20.32% vs. 60.26±22.52%, P=0.014; 8: 22.72±10.99% vs. 31.42±14.83%, P=0.042), lower peak CS in segments 1~3, 6~8 (1: -17.29±5.81% vs. -21.57±3.42%, P=0.037; 2: -10.09±7.29% vs. -14.66±4.73%, P=0.022; 3: -9.18±5.72% vs. -13.18±5.03%, P=0.022; 6: -17.41±7.63% vs. -21.55±3.95%, P=0.044; 7: -16.48±5.11% vs. -20.66±2.17%, P=0.008; 8: -8.42±7.06% vs. -13.18±5.15%, P=0.041) and lower peak LS in segments 7, 8, 10~12 (7: -17.15±5.43% vs. -21.61±1.80%, P=0.005; 8: -6.71±9.31% vs. -12.74±4.81%, P=0.029; 10: -14.30±3.91% vs. -17.15±4.26%, P=0.032; 11: -19.09±5.14% vs. -22.75±5.53%, P=0.045; 12: -18.29±8.70% vs. -23.76±5.11%, P=0.027), whereas no difference was identified for any peak strain in apical segments (segments 13~16).

Reproducibility

Fourteen randomly selected cases were reanalyzed for the intra- and inter-observer feasibility and reproducibility. As shown in **Figure 3C** and **3E**, segmental peak CS and LS had excellent agreement between measurement from intra observers (CS: ICC=0.859, 95% CI: 0.561~0.955, P=0.001; LS: ICC=0.845, 95% CI: 0.738~0.973, P<0.001), with minimal to mod-

erate difference according to Bland-Altman analysis (**Figure 3C**, CS: -1.5±2.1%, 95% CI: -5.7~2.6; **Figure 3E**, LS: -1.7±3.0%, 95% CI: -7.6~4.1). For the measurement from different observers, segmental peak RS had excellent agreement (ICC=0.888, 95% CI: 0.653~0.964, P<0.001) with minimal difference of -0.4±8.7% (**Figure 3B**, 95% CI: -17.5 to 16.7).

Discussion

Myocardial strain analysis is a quantitative measurement of myocardial deformation in response to an applied force. During a cardiac cycle, the changes of myocardial fiber structure are associated with myocardial deformation in three directions: negative strain represents the myocardial segment shortening circumferentially and longitudinally, while positive strain represents radial thickening [22]. Various techniques have been used for strain analysis, including speckling tracking imaging, strain-encoding and myocardial tagging with CMR [23, 24]. In the current study, we used new CMR-FT approach to detect the regional wall motion abnormalities. CMR-FT is a technique that can quantify left ventricular deformation directly from SSFP cine CMR images and agrees well with other techniques. More importantly, as compared with other myocardial imaging techniques, such as cardiac computed tomog-

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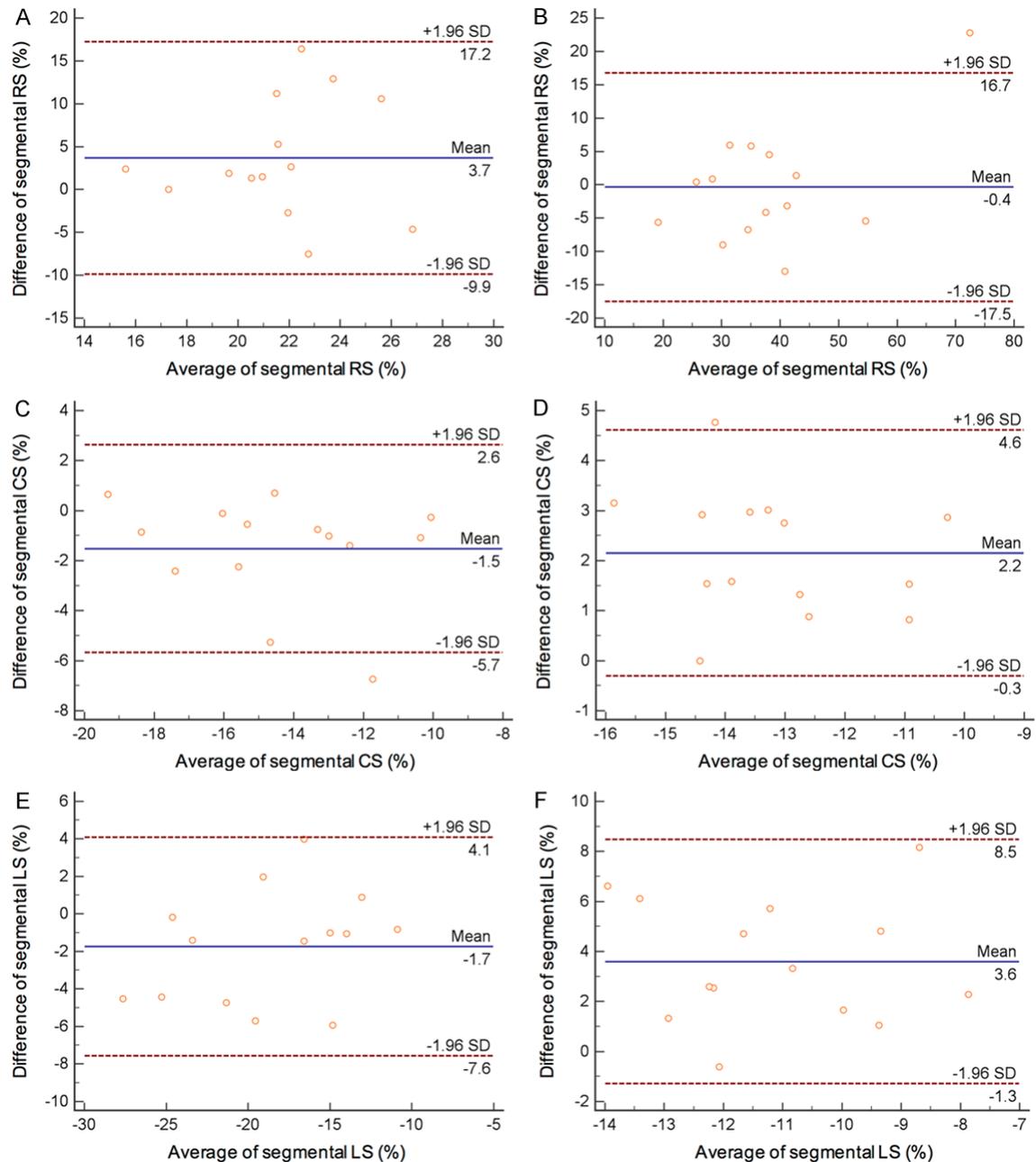


Figure 3. Bland-Altman analysis for peak segmental RS (A), CS (C) and LS (E) from intra-observers, and peak segmental RS (B), CS (D) and LS (F) of inter-observer.

raphy (CCT), echocardiograph, CMR has high reproducibility, high spatial, temporal resolution, no radiation exposure, and provides superior detection and quantification of segmental function [25-27]. In recent years, CMR-FT has found widespread applications in various myocardial disorders and has provided incremental values over conventional CMR imaging. To our knowledge, our study is the first to assess the feasibility of CMR-FT in detecting segmental

wall motion abnormalities in VA patients without structural heart diseases.

The results from this study can be summarized as follow: 1) In general, VA with structurally normal hearts had significantly reduced 3D peak strain at the basal and middle layers of LV, while the distribution of peak strain in apical layers is similar to controls; 2) In VA patients, the 3D peak segmental strain were principally

reduced in the anterior, inferoseptal and anterolateral segments, especially in the anterior segments of patients with frequent PVCs. These results indicate deregulated myocardial function in VA patients with normal global cardiac function, especially in those with frequent PVC, and also suggested careful cardiac imaging may help to detect function abnormalities in ventricular arrhythmias and aid treatment decisions.

Abnormal regional wall motion in VA has been documented in previous echocardiographic studies, occurring primarily in the early-activated regions. With strain data based on speckle tracking imaging, Yao et al evaluated circumferential strain in idiopathic frequent PVCs and found that peak CS was reduced significantly in the anterior, anteroseptal and septal segments, and the distribution of peak CS in the various layers exhibited a similar trend as that in controls [28]. Leeters et al reported the assessment of LV regional contraction abnormalities in combined right bundle with left anterior fascicular block (RBBB+LAFB) by echocardiographic, and demonstrated wall motion abnormalities between inferior and anterior LV walls as well as between septal and lateral walls in patients with left bundle branch block [29]. All these studies supported our findings that abnormal motion was associated with anterior and septal walls in VA patients without structural heart disease. Anterior, anteroseptal and septal walls are close to ventricular outflow track which was the major origin of ectopic pacemaker in VA without structural heart diseases. The reduction of peak strain values in these walls can be explained by the contraction pattern altered in patients with arrhythmia. Moreover, as compared with non-sustained VT, the strain peaks of anterior and septal segments decreased dramatically in patients with frequent PVCs, which indicate frequent PVC might originate from right ventricular outflow tract and is consistent with previous reports. Besides, we also found abnormality involved in anterolateral segment. Considering that ectopic pacemaker can cause the alteration in electrophysiological activation patterns and electrical wave conducts throughout the myocardium, our result might indicate deregulated ventricular function from other region, which deserves to be explore in the future.

Moreover, our study demonstrated that the segmental peak strain values were lower in patients with frequent PVCs than in those with non-sustained VT, so was the LVEF. Previous studies revealed a correlation between PVC frequency and LV dysfunction. Yao et al reported that patients with frequent PVCs had more significantly greater asynchronous segments compared with controls and a positive correlation existed between PVC frequency with asynchronous segments [28]. Markowitz et al demonstrated that patients with frequent PVC had more advanced LV remodeling than those with monomorphic VT [8]. To our knowledge, the arrhythmia can cause deregulated electrophysiological activation, but the mechanism of the relationship between contraction dyssynchrony and PVC frequency remains to be elucidated.

Besides, several limitations in this study should be acknowledged. First, the sample size in the study is small. Only 42 VA patients were enrolled and only 20 of them (47.6%) received radiofrequency catheter ablation to prove the origin. Therefore, we didn't have enough power to compare CMR-FT with catheter ablation in detecting the origin of ectopic rhythm. A large-scale study with expanded patient cohort is still undergoing to systematically to evaluate the feasibility of CMR-FT in clinic. Second, VT also occurs in some patients with early-phase arrhythmogenic right ventricular cardiomyopathy (ARVC). In present study, we excluded the ARVC simply based on the absence of myocardial scar and fat infiltration. In our further study, we will take RV function into consideration in accordance with 2010 Task Force Criteria for ARVC. Third, all CMR examinations in the study were performed on a 1.5T and 3.0T scanner. No significant difference was identified between these two scanners, which is consistent with previous reports [30]. However, it is still possible that the independence of cardiac strain on CMR field strengths might be caused by small study population, and an in-depth study with large cohort is still undergoing. Fourth, the influence of age on myocardial strain hasn't been considered in the current study mainly due the small range of age in control group and the small sample size. And the influence of age will be adjusted in the following large-scale study.

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Disclosure of conflict of interest

None.

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