International Journal of Cardiology 294 (2019) 43–49

Contents lists available at ScienceDirect

International Journal of Cardiology

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

The prognostic value of biventricular long axis strain using standard cardiovascular magnetic resonance imaging in patients with hypertrophic cardiomyopathy

Fuyao Yang [a,1,2], Jie Wang [a,1,2], Yuancheng Li [a,2], Weihao Li [a,2], Yuanwei Xu [a,2], Ke Wan [c,2], Jiayu Sun [b,2], Yuchi Han [e,2], Yucheng Chen [a,b,d,*,2]

[a] Department of Cardiology, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China
[b] Department of Radiology, West China Hospital, Sichuan University, Chengdu, 610041, Sichuan Province, China
[c] Department of Geriatrics, West China Hospital, Sichuan University, Chengdu, 610041, Sichuan Province, China
[d] Center of Rare Diseases, West China Hospital, Sichuan University, Chengdu, 610041, Sichuan Province, China
[e] Department of Medicine (Cardiovascular Division), University of Pennsylvania, Philadelphia, PA, USA

ARTICLE INFO

Article history:
Received 26 May 2019
Received in revised form 26 July 2019
Accepted 2 August 2019
Available online 3 August 2019

Keywords:
Hypertrophic cardiomyopathy
Long axis strain
Prognosis
Cardiovascular magnetic resonance imaging

ABSTRACT

Background: Long axis strain (LAS) is a parameter derived from standard cardiovascular magnetic resonance imaging. However, the prognostic value of biventricular LAS in hypertrophic cardiomyopathy (HCM) is unknown.

Methods: Patients with HCM (n = 384) and healthy volunteers (n = 150) were included in the study. Left ventricular (LV)-LAS was defined as the percentage change in the length measured from the epicardial border of the LV apex to the midpoint of a line connecting the mitral annulus at end-systole and end-diastole. Right ventricular (RV)-LAS represented the percentage change of length between epicardial border of the LV apex to the midpoint of a line connecting the tricuspid annulus at end-systole and end-diastole. The primary endpoint was a combination of all-cause death and sudden cardiac death aborted by appropriate implantable cardioverter-defibrillator discharge and cardiopulmonary resuscitation after syncope. The secondary endpoint was a combination of the primary endpoint and hospitalization for congestive heart failure.

Results: Twenty-nine patients (7.6%) achieved the primary endpoint, and the secondary endpoint occurred in 66 (17.2%) patients. In multivariate Cox regression analysis, RV-LAS was an independent prognostic factor for the primary (hazard ratio (HR), 1.13) and secondary (HR, 1.11) endpoints. In the subgroup of patients with a normal RV ejection fraction (EF) (>45.0%, n = 345), impaired RV-LAS was associated with adverse outcomes and might add incremental prognostic value to RVEF and tricuspid annular plane systolic excursion (TAPSE) ($p < 0.01$).

Conclusions: RV-LAS is an independent predictor of adverse prognosis in HCM in addition to RVEF and TAPSE.

1. Introduction

Hypertrophic cardiomyopathy (HCM), the most common hereditary cardiovascular disease, is characterized by a thickened left ventricular (LV) wall and normal chamber size. The prevalence of HCM is approximately 1:500 people in the general population [1]. HCM causes heart failure (HF) and death at any age, and is the main explanation for sudden cardiac death (SCD) in young people [2,3]. Recently, the SHaRe study of 4591 patients with HCM showed that 8% of patients died, 3% of patients experienced resuscitated cardiac arrest, and up to 20% of patients suffered from HF during the mean follow-up of 5.4 years [4]. Therefore, early identification of high-risk patients with HCM is critical to guide individualized treatment and management.

Cardiovascular magnetic resonance (CMR) is recognized as the gold standard for non-invasive diagnosis and evaluation of ventricular function in patients with HCM [5]. Late gadolinium enhancement (LGE) and

Abbreviations: CMR, cardiovascular magnetic resonance; HCM, hypertrophic cardiomyopathy; LAS, long axis strain; LGE, late gadolinium enhancement; SCD, sudden cardiac death; TAPSE, tricuspid annular plane systolic excursion.

* Corresponding author at: Cardiology Division, Department of Cardiology, West China Hospital, Sichuan University, Guoxue Xiang No. 37, Chengdu, Sichuan 610041, China.
E-mail address: chenyucheng2003@126.com (Y. Chen).

[1] Both authors contributed equally to this study.
[2] All author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

https://doi.org/10.1016/j.ijcard.2019.08.010
0167-5273/

ventricular dysfunction are associated with adverse prognosis in patients with HCM [6–8]. Recently, long axis strain (LAS), a new parameter that can be derived rapidly from CMR cine images without additional pulse sequences and special post-processing software, has proven to be feasible and has shown good inter- and intra-observer agreement in patients with different cardiomyopathies [9,10]. LV-LAS was reported as a powerful predictor of cardiovascular disease and congestive HF occurrence in the Multi-Ethnic Study of Atherosclerosis [11]. Subsequent studies demonstrated that reduced LV-LAS and right ventricular (RV)-LAS values were associated with increased risk of cardiac death, transplant, aborted SCD caused by appropriate implantable cardioverter defibrillator (ICD) shock, and hospitalization because of HF in patients with non-ischemic dilated cardiomyopathy [12–14]. However, there is no data on the prognostic value of biventricular LAS in patients with HCM. Therefore, the present study aimed to investigate whether CMR LV-LAS and RV-LAS have prognostic value in patients with HCM.

2. Materials and methods

2.1. Research population and design

This study comprised healthy volunteers from our database [15,16] and consecutive patients with HCM who underwent a baseline CMR assessment from August 2011 to October 2017 at West China Hospital, Sichuan University. We collected clinical data retrospectively from our electronic medical records, including basic information, clinic history, and cardiac medication. The study was approved by the Institutional Ethics Committee of West China Hospital, Sichuan University. All patients with HCM and the healthy volunteers provided written informed consent.

The diagnosis of HCM was based on the latest European Society of Cardiology (ESC) criteria [17]. The inclusion criteria were: Normal LV size with maximal LV wall thickness (Max LVWT) ≥15 mm or LVWT ≥13 mm with a family history of HCM that was not explained by loading conditions. The obstructive HCM was defined as an LV out flow gradient ≥30 mmHg at rest or with provocation [17].

2.2. Cardiovascular magnetic resonance protocol

A 3.0 T MRI scanner (Magnetom Tim Trio; Siemens Medical Solutions, Erlangen, Germany) was used to perform the CMR using a dedicated 32-channel phased array cardiac coil. Cardiac cine images were obtained using steady-state free procession with retrospective electrocardiogram gating during breath-holds in the three long-axis planes and the continuous short-axis planes. The CMR imaging parameters were: Field-of-view, 320–340 mm; flip angle, 50°; echo time, 1.3 ms; matrix size, 256 × 144; repetition time, 3.4 ms; slice thickness, 8 mm with no gap; spatial resolution, 1.4 × 1.3 mm; and temporal resolution, 42 ms. LGE images were acquired at 10–15 min after intravenous bolus injection of gadopentetate dimeglumine (0.15 mmol per kilogram of body weight, Magnevist; Bayer Schering Pharma, Berlin, Germany) during breath-holds and using an inversion recovery turbo fast low-angle shot sequence with phase-sensitive reconstruction.

2.3. CMR data analysis

Images were analyzed on a commercially available workstation (Qmass 8.1; Medis Medical Imaging Systems, Leiden, Netherlands). Ventricular function and mass were assessed according to our previous study [18]. Max LVWT was defined as the maximum thickness of the LV myocardium in all short-axis slices. Two independent observers, who were blinded to all patient information, assessed the presence of LGE visually. Semi-automatic quantification of LGE was performed using the myocardium signal intensity of 6 standard deviations (SD) from the normal myocardium, and expressed as the percentage of the LV myocardium, which was consistent with previous studies [19]. The tricuspid annular plane systolic excursion (TAPSE) was defined as the distance of the tricuspid annulus from end-diastole to end-systole in a 4-chamber image [20]. Other indexed parameters were divided by the body surface area (BSA).

2.4. LV- and RV- LAS

Left ventricular LAS was assessed on the 2-chamber and 4-chamber view. The percentage change in length between the epicardial border of the LV apex and the mid-point of a line connecting the mitral annulus at end-diastole and end-systole defined LV-LAS. Similarly, RV-LAS was expressed as the percentage change in length between the epicardial border of the LV apex and the mid-point of a line connecting the tricuspid annulus at end-diastole and end-systole [10] (Supplementary Fig. S1). All values were measured using RadiAnt DICOM Viewer 4.1.6 software (RadiAnt, Poznan, Poland).

The LAS value was acquired according to the following formula:

$$LAS = 100 * \left(Length_{end-systole} - Length_{end-diastole}\right) / Length_{end-diastole}$$

Finally, mean values of LV-LAS in 2- and 4-chamber views were calculated for further analysis [9].

2.5. Reproducibility

The observers who measured the biventricular LAS were blinded to the clinical data. Thirty patients and 30 controls were selected randomly to assess variability. For intra-observer variability, the same observer measured the biventricular LAS of the selected sample at one month later. Another observer, who was blinded to the first observer results and the clinical information, performed analysis for inter-observer variability on the selected sample.

2.6. Clinical follow-up

The end of follow-up was October 2018. The patients' follow-up information was collected using standardized questionnaires during telephone interviews or clinical interviews with the patients or their family members. The time of the first CMR was considered as the initial time of follow-up. The primary endpoint was a combination of all-cause death, SCD aborted by appropriate ICD discharge due to ventricular tachycardia (VT) or fibrillation (VF), and cardiopulmonary resuscitation after syncope. The secondary endpoint was a combination of the primary endpoint and hospitalization because of congestive HF, which was defined as hospitalization resulting from the presence of symptoms of decompensated HF after the first CMR.

2.7. Statistical analysis

Statistical analysis was performed using SPSS (version 17.0; IBM Corp., Armonk, NY, USA) and MedCalc (MedCalc Software version 13.0; Ostend, Belgium). Categorical variables were expressed as N (%); continuous variables were expressed as the mean ± SD. The mean values between groups were compared using a two-tailed Student's *t*-test. A chi-squared test and Fisher's exact test were used to compare the proportions of categorical variables. Survival curves were constructed using the Kaplan–Meier method and compared using the log-rank test between groups. The optimal cut-off values were determined using receiver operating curve analysis (ROC). Pearson's correlation coefficient was used to analyze the relationships between LGE and bi-ventricular LAS. Univariate and multivariate Cox proportional hazards regression analysis were used to calculate hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs). All variables with a $p < 0.1$ in the univariate Cox regression were included in the stepwise multivariate Cox regression analysis. The incremental predictive value of different models was evaluated using the performance of global chi-squared value of each model and a p value <0.05 was considered statistically significant. For the reproducibility of LAS analysis, the coefficient of variation (COV) and the intraclass correlation coefficient (ICC) were calculated.

3. Results

3.1. Baseline characteristics

A total of 386 patients with HCM and 150 healthy volunteers were enrolled. Two patients were excluded from the study because of poor 4-chamber images. All baseline characteristics and CMR data of the patients with HCM and healthy volunteers are presented in Table 1. In terms of CMR functional parameters, the mean values for the patients were significantly different from those of the volunteers (all $p < 0.05$). The mean values of max LVT and LGE in the patients were 22.5 (SD 5.7) mm and 8.6 (SD 8.9) %, respectively. Most patients were treated with β blockers (66.9%). Among the patients, LV-LAS and RV-LAS were also impaired significantly ($p < 0.001$). There was a significant correlation between LGE and LV-LAS and RV-LAS ($r = 0.11$, $p = 0.04$; $r = 0.19$, $p < 0.001$; respectively).

3.2. Intra- and inter-observer reproducibility of LAS

The intra-observer variability and inter-observer variability of the biventricular LAS value are shown in Supplementary Table S1. Right ventricular-LAS and LV-LAS both exhibited high ICC and low COV value, indicating excellent reproducibility of biventricular LAS.

3.3. Follow-up results

During the follow-up period of 33.4 ± 17.8 months, 29 (7.5%) patients reached the primary endpoint, including 19 (5.0%) who experienced cardiovascular death, 5 (1.3%) who experienced SCD aborted by appropriate ICD discharge because of VT or VF, 1 (0.3%) who experienced resuscitation after syncope, and 4 (1.0%) non-cardiac deaths. In addition, 66 (17.2%) patients reached the secondary endpoint.

Patients achieving the primary endpoint were older, had a lower systolic blood pressure (SBP), a lower incidence of syncope, lower left and right ventricular function, and higher LGE% (all $p < 0.05$). Among the patients who achieved the secondary endpoint, they were older, mostly female and mainly had obstructive HCM, with lower RV function, higher incidence of syncope, and higher LGE% (all $p < 0.05$). LV-LAS, TAPSE, and RV-LAS values were statistically significantly different among all groups (Table 1).

3.4. Survival analysis

For the primary endpoint, ROC analysis showed an LV-LAS cut-off value of −7.6% (AUC of 0.73, sensitivity of 55.2%, and specificity of 78.9%), and −12.1% for the secondary endpoint (AUC of 0.71, sensitivity of 89.4%, and specificity of 41.2%). For RV-LAS, the cut-off value was −10.9% for the primary endpoint (AUC of 0.76, sensitivity of 69.0%, and specificity of 78.0%), and −13.3% for the secondary endpoint (AUC of 0.72, sensitivity of 77.3%, and specificity of 58.2%). The Kaplan–Meier curves demonstrated that impaired LV-LAS and RV-LAS significantly increased the risk of adverse events (Fig. 1).

3.5. Uni- and multivariate cox regression analysis

Table 2 shows the results of univariate Cox regression analysis for the clinical parameters. In the stepwise multivariate Cox regression analysis, only age (HR, 1.04; CI, 1.01–1.07; $p = 0.017$), LGE (HR, 1.08; CI, 1.05–1.12; $p < 0.001$), and RV-LAS (HR, 1.13; CI, 1.03–1.25; $p = 0.013$) remained independent predictors for the primary endpoint (Supplementary Table S2). In terms of the secondary endpoint, age (HR, 1.05; CI, 1.03–1.07; $p < 0.001$), SBP (HR, 0.98; CI, 0.97–1.00; $p = 0.021$), obstructive HCM (HR, 1.89; CI, 1.09–3.25; $p = 0.022$), right ventricular ejection fraction (RVEF) (HR, 0.96; CI, 0.94–0.99; $p = 0.003$), and RV-LAS (HR, 1.11; CI, 1.04–1.18; $p = 0.002$) remained independent indicators (Supplementary Table S2).

3.6. RV-LAS based subgroup survival analysis

Late gadolinium enhancement was detected in 209 patients. The primary and secondary endpoints occurred in 25 patients with LGE and 44 patients with LGE, respectively. Kaplan-Meier curves for the primary and secondary endpoints demonstrated a significantly higher rate of reaching an endpoint in patients with decreased RV-LAS values, regardless of the presence of LGE (both $p < 0.05$, Supplementary Fig. S2).

A total of 345 patients had normal RV systolic function, defined as RVEF >45%. The cut-off value of RV-LAS was −10.9% for the primary endpoint (AUC of 0.74, $p < 0.001$) and −12.8% for the secondary endpoint (AUC of 0.70, $p < 0.001$). The subgroup survival analysis showed that reduced RV-LAS was significantly associated with poor prognosis in patients with normal RVEF (Supplementary Fig. S3).

Table 1
Baseline characteristics of all patients with HCM and healthy volunteers.

Variable	Healthy volunteers (n = 150)	HCM (n = 384)	p	HCM without primary endpoint (n = 355)	Patients with primary endpoint (n = 29)	p	Patients without secondary endpoint (n = 318)	Patients with secondary endpoint (n = 66)	p
Clinical data									
Age, y	45.8 ± 17.6	48.5 ± 16.3	0.063	47.7 ± 16.1	58.4 ± 15.0	<0.001*	46.4 ± 15.8	58.6 ± 14.5	<0.001*
Male gender, n (%)	64 (42.7)	207 (53.9)	0.020*	194 (54.7)	13 (44.8)	0.308	181 (56.9)	26 (39.4)	0.009*
BMI (kg/m^2)	22.5 ± 2.6	23.6 ± 3.7	<0.001*	23.6 ± 3.7	23.8 ± 3.5	0.861	23.6 ± 3.7	23.7 ± 3.6	0.998
BSA (m^2)	1.6 ± 0.2	1.7 ± 0.2	<0.001*	1.7 ± 0.2	1.6 ± 0.2	0.584	1.7 ± 0.2	1.6 ± 0.2	0.018*
SBP (mmHg)	119.5 ± 10.0	123.2 ± 18.4	0.037*	123.7 ± 17.9	117.6 ± 22.1	0.015*	123.9 ± 17.7	120.0 ± 21.0	0.112
DBP (mmHg)	77.5 ± 8.7	74.6 ± 12.1	<0.001*	74.8 ± 11.9	72.1 ± 14.0	0.252	75.0 ± 11.9	72.6 ± 12.6	0.140
HR (beat/min)	73.2 ± 12.0	73.1 ± 11.8	0.495	72.9 ± 11.3	74.8 ± 17.3	0.542	72.8 ± 11.1	74.1 ± 14.9	0.510
Diabetes mellitus, n (%)	–	26 (6.8)	–	24 (6.8)	2 (6.9)	0.978	22 (6.9)	4 (6.1)	0.801
Hypertension, n (%)	–	91 (23.7)	–	85 (23.9)	6 (20.7)	0.692	69 (21.7)	22 (33.3)	0.043*
Obstructive HCM, n (%)	–	147 (38.3)	–	135 (38.0)	12 (3.4)	0.721	109 (34.3)	38 (57.6)	<0.001*
Family history of SCD, n (%)	–	52 (13.5)	–	47 (13.2)	5 (1.4)	0.545	41 (12.9)	11 (16.7)	0.415
History of syncope, n (%)	–	71 (18.5)	–	61 (17.2)	10 (2.8)	0.021*	52 (16.4)	19 (28.8)	0.018*
CAD, n (%)	–	28 (7.3)	–	26 (7.3)	2 (6.9)	0.932	21 (6.6)	7 (10.6)	0.256
Cardiac medications									
β blocker, n (%)	–	257 (66.9)	–	234 (65.9)	23 (24.9)	0.140	204 (64.2)	53 (16.7)	0.011*
CMR data									
LVEF (%)	65.0 ± 5.4	62.7 ± 10.1	0.048*	63.2 ± 9.5	55.6 ± 14.9	0.013*	63.2 ± 9.4	59.8 ± 13.0	0.167
LVEDVi (mL/m^2)	74.2 ± 12.4	82.0 ± 22.2	<0.001*	80.9 ± 18.3	96.3 ± 49.1	0.255	80.9 ± 18.0	87.5 ± 36.9	0.189
LVESVi (mL/m^2)	26.2 ± 7.1	31.6 ± 17.3	0.001*	30.4 ± 13.5	46.6 ± 40.7	0.049*	30.5 ± 13.4	37.5 ± 29.8	0.200
RVEF (%)	59.2 ± 6.6	60.8 ± 9.4	0.008*	61.1 ± 9.2	56.3 ± 11.1	0.011*	61.5 ± 8.7	57.1 ± 11.8	0.009*
RVEDVi (mL/m^2)	70.5 ± 15.4	65.5 ± 15.7	0.001*	65.8 ± 15.3	61.1 ± 19.4	0.030*	66.6 ± 14.9	59.6 ± 18.4	<0.001*
RVESVi (mL/m^2)	29.0 ± 8.4	25.7 ± 9.4	<0.001*	25.6 ± 9.0	26.9 ± 13.8	0.992	25.8 ± 8.8	25.5 ± 12.0	0.288
LV massi (g/m^2)	48.1 ± 8.6	98.9 ± 36.4	<0.001*	97.8 ± 34.9	113.5 ± 50.5	0.198	97.5 ± 35.5	106.0 ± 40.1	0.113
Max LVT (mm)	–	22.5 ± 5.7	–	22.5 ± 5.8	22.7 ± 5.2	0.593	22.5 ± 5.9	22.6 ± 4.6	0.425
LGE (%)	–	8.6 ± 8.9	–	7.9 ± 8.2	17.2 ± 12.4	<0.001*	7.9 ± 8.2	11.8 ± 11.0	0.003*
TAPSE (mm)	–	25.5 ± 6.4	–	21.4 ± 8.1	25.8 ± 6.2	0.007	21.8 ± 7.5	26.2 ± 5.9	<0.001*
LV-LAS (%)	−17.0 ± 2.7	−10.8 ± 3.9	<0.001*	−11.1 ± 3.9	−8.0 ± 3.1	<0.001*	−11.3 ± 3.9	−8.5 ± 3.2	<0.001*
RV-LAS (%)	−19.4 ± 4.1	−13.8 ± 4.6	<0.001*	−14.1 ± 4.4	−9.4 ± 4.2	<0.001*	−14.4 ± 4.4	−10.7 ± 4.2	<0.001*

Data are expressed as mean ± SD, or as a percentage for categorical variables. HCM, hypertrophic cardiomyopathy; BMI, body mass index; BSA, body surface area; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; EF, ejection fraction; SCD, sudden cardiac death; CAD, coronary artery disease; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; LV massi, LV mass index; Max LVWT, maximal LV wall thickness; LGE, late gadolinium enhancement; LV, left ventricular; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; LV-LAS, left ventricular-long axis strain; RV-LAS, right ventricular-long axis strain.

* $p < 0.05$.

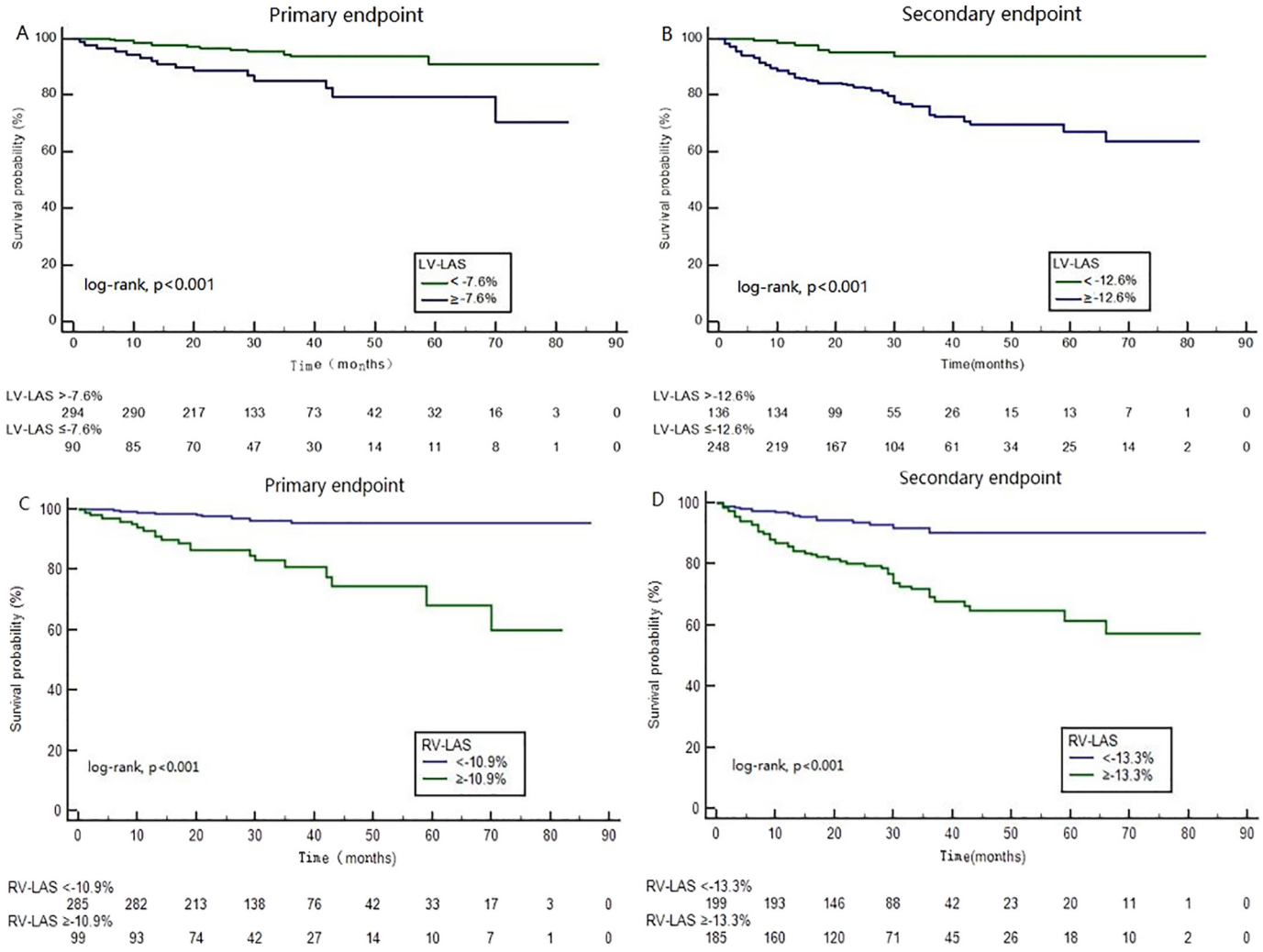

Fig. 1. Kaplan–Meier curves demonstrating the cumulative event free survival according to long axis strain (LAS) groups. A and B were grouped according to the cut-off value of LV-LAS. C and D were grouped according to the cut-off value of RV-LAS. LV-LAS and RV-LAS were both associated with an increased risk of adverse cardiac events. LV-LAS, left ventricular long axis strain, RV-LAS, right ventricular long axis strain.

3.7. Incremental predictive value of RV-LAS

Using a sequential multi-variable Cox regression analysis, the incremental predictive value of RV-LAS was observed as superior to RVEF and TAPSE for the primary and secondary endpoints in the model with LVEF ($p < 0.05$, Fig. 2). In model 1 (including LVEF and TAPSE) or model 2 (including LVEF and RVEF), RV-LAS addition increased the prognostic value over that of TAPSE and RVEF ($p < 0.05$, Fig. 2). In general, RV-LAS offered incremental value beyond RVEF and TAPSE, and the predictive power of RV-LAS was superior to RVEF and TAPSE in HCM.

4. Discussion

This study investigated the relationship between the outcome of patients with HCM and biventricular global longitudinal function using standard CMR cine sequences. The results confirmed that RV-LAS is an independent prognostic factor for patients with HCM.

Kaplan–Meier survival analysis and univariate Cox regression analysis showed that a lower LV-LAS increased the risk of achieving the primary and secondary endpoints. However, LV-LAS was not retained in the multivariate Cox regression analysis of primary and secondary endpoints. Contrastingly, impaired RV-LAS was associated with an increased risk of adverse events in patients with HCM. Multivariate Cox regression analysis showed that RV-LAS remained an independent prognostic factor for the primary and secondary endpoints. In the present study, in approximately 90% of patients with normal RVEF, impaired RV-LAS was statistically associated with poor prognosis.

With the recent rapid development of genetic testing and imaging technology, the current estimate of the incidence of HCM is 1/200 [21]. Patients with HCM have a high risk of HF and death at end-stage, characterized by systolic dysfunction and extensive scarring [22]. Previous studies demonstrated that semi-quantitative assessment of LGE could be used in clinical practice, and that the extent of LGE value was associated with adverse outcomes in patients with HCM [23,24]. In the present study, LGE was also an independent prognostic factor for the primary endpoint in patients with HCM.

Previous studies demonstrated that impaired LV longitudinal function correlated with poor outcome of patients with HCM [8,25]. In the present study, LV-LAS was not retained in the multivariate model, mainly because LGE was associated with long-term prognosis [24], and LV-LAS was correlated with the degree of LV LGE [8]. Therefore, it was possible that LGE was superior to LV-

Table 2
Univariate analysis of all patients (n = 384) for primary and secondary endpoints.

Variable	Primary endpoint			Secondary endpoint		
	HR	95% CI	*p*	HR	95% CI	*p*
Age, years	1.05	1.02–1.07	0.001*	1.05	1.03–1.07	<0.001*
Gender	1.45	0.70–3.02	0.317	1.90	1.16–3.12	0.011*
BSA (m^2)	0.66	0.13–3.47	0.626	0.43	0.16–1.16	0.096*
BMI (kg/m^2)	1.01	0.99–1.11	0.916	1.00	0.93–1.07	0.963
SBP (mmHg)	0.98	0.96–1.00	0.075*	0.99	0.97–1.00	0.097*
DBP (mmHg)	0.98	0.95–1.02	0.293	0.98	0.96–1.01	0.158
HR (beat/min)	1.01	0.98–1.04	0.402	1.01	0.99–1.03	0.470
Diabetes mellitus	0.96	0.23–4.03	0.951	0.85	0.31–2.34	0.756
Obstructive HCM	1.10	0.52–2.29	0.811	2.31	1.42–3.76	0.001*
Family history of SCD	1.43	0.55–3.76	0.465	1.36	0.71–2.60	0.352
History of syncope	2.34	1.09–5.03	0.030*	1.89	1.11–3.22	0.020*
CAD	1.08	0.26–4.53	0.919	1.63	0.75–3.58	0.220
β blocker	0.60	0.24–1.48	0.265	0.54	0.29–0.98	0.044*
LVEF (%)	0.95	0.93–0.98	0.001*	0.98	0.96–1.00	0.035*
LVEDVi (mL/m^2)	1.02	1.01–1.03	<0.001*	1.01	1.00–1.02	0.018*
LVESVi (mL/m^2)	1.03	1.01–1.04	<0.001*	1.02	1.01–1.03	0.002*
RVEF (%)	0.96	0.93–0.99	0.026*	0.96	0.94–0.98	0.001*
RVEDVi (mL/m^2)	0.99	0.96–1.01	0.217	0.98	0.96–0.99	0.003*
RVESVi (mL/m^2)	1.02	0.98–1.06	0.455	1.00	0.97–1.03	0.966
LV massi (g/m^2)	1.01	1.00–1.02	0.038*	1.01	1.00–1.01	0.136
Max LVT (mm)	1.00	0.94–1.07	0.898	1.00	0.96–1.04	0.975
LGE (%)	1.08	1.05–1.12	<0.001*	1.04	1.02–1.06	<0.001*
TAPSE (mm)	0.92	0.87–0.96	0.001*	0.91	0.88–0.95	<0.001*
LV-LAS (%)	1.24	1.10–1.39	<0.001*	1.20	1.11–1.29	<0.001*
RV-LAS (%)	1.26	1.15–1.39	<0.001*	1.17	1.10–1.26	<0.001*

HCM, hypertrophic cardiomyopathy; BMI, body mass index; BSA, body surface area; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; EF, ejection fraction; SCD, sudden cardiac death; CAD, coronary artery disease; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; LV massi, LV mass index; Max LVWT, maximal LV wall thickness; LGE, late gadolinium enhancement; LV, left ventricular; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; LV-LAS, left ventricular-long axis strain; RV-LAS, right ventricular-long axis strain.

* $p < 0.1$.

LAS to predict the outcome and LGE maintained its value as an independent risk factor in the multivariate analysis, rather than LV-LAS.

The evaluation of RV function includes RVEF, TAPSE, or RV strain. TAPSE is easy to use [26]; however, the study of TAPSE from CMR in patients with HCM showed poor correlation with RV function [27]. Other studies showed that RV function was impaired in patients with HCM [28–30]. TAPSE from conventional echocardiography and RV-global longitudinal strain (GLS) from two-dimensional echocardiography strain analysis are significantly impaired in patients with HCM [31,32]. Finocchiaro et al. reported that TAPSE <16 mm was an independent prognostic marker in patients [33]. A subsequent CMR study involving 245 patients with HCM confirmed that RVEF and RV systolic dysfunction (RVEF <45%) are independent prognostic factors for cardiovascular events [6]. These findings support our results on the prognostic value of RV longitudinal function. In our study, univariate Cox regression analysis showed that decreased TAPSE and RV-LAS increased the risk of achieving the primary and secondary endpoints; however, only RV-LAS remained an independent predictor of adverse prognosis. Importantly, the predictive power of RV-LAS was superior to that of RVEF and TAPSE for poor outcome in patients with HCM. Right ventricular-LAS differs from RV-GLS or TAPSE because the definition is the length change from the LV apex to the tricuspid annulus, rather than the RV apex. Thus, RV-LAS likely incorporates both LV and RV longitudinal function. In addition, RV-LAS may be associated with the parameter of RV fibrosis, which is currently unmeasured. Even in patients without LGE or with normal RVEF (>45%), impaired RV-LAS was significantly associated with poor prognosis.

Currently, mature and practical techniques exist to assess myocardial strain, including tagging, feature tracking, and strain-encoded magnetic resonance (SENC). Studies have confirmed that myocardial deformation can apply to the risk stratification of patients with HF or ischemic heart disease, and provides significant prognostic value in those patients [34–36]. In previous studies, tissue tagging is normally considered the gold standard to quantify myocardial strain [37]. However, extra imaging acquisition and time-consuming image post-processing limit its clinical application. Additionally, SENCE is a validated CMR technique and has the advantage on evaluating layer-specific strain [38], but it also need extra sequence to acquire imaging, which is similar to tissue tagging. In comparison with tagging and SENCE techniques, feature tracking strain or the studied long axis strain is based on conventional cine images, and have the advantage of wide availability and easy feasibility. The advantage of LAS is that it can be assessed online without the need for additional software tools. In our present study, it highlighted the importance of RV-LAS for prognosis in patients with HCM, in which it could be measured simply without the need for extra post-processing software and contrast agents, and added value to RVEF and TAPSE.

4.1. Study limitations

There are several limitations of our study. First, we did not include all CMR parameters, such as native T1, extracellular volume fraction (ECV), and circumferential or radial strain. Native T1 and ECV were not available in all patients because not all patients underwent tissue mapping during the early data acquisition period. Second, this was a single-center study, and the participants came from a single geographical region of China. Third, the optimal cut-off value of RV-LAS should be validated in further prospective studies with larger sample.

5. Conclusions

Right ventricular-LAS is a more sensitive indicator of RV dysfunction than RVEF and TAPSE, and can be quickly obtained from standard CMR images without the need for contrast agents and special post-processing software. Impaired RV-LAS is an independent prognostic marker of adverse outcomes in patients with HCM, and adds value to RVEF and TAPSE.

Contributors

Conception and drafting the article: FY and JW. Data collection, analysis, and interpretation: FY, JW, YL, WL, YX, KW, JS, YH, and YC. Revising the article: FY, JW, WL, YX, YH, and YC. Final approval of the manuscript to be published: all authors.

Acknowledgement of grant support

This study was supported by the National Natural Science Foundation of China (contract grant numbers: 81571638 and 81271531) and 1·3·5 project for disciplines of excellence, West China Hospital, Sichuan University (No: ZYJC18013).

Conflicts of interest

No.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.08.010.

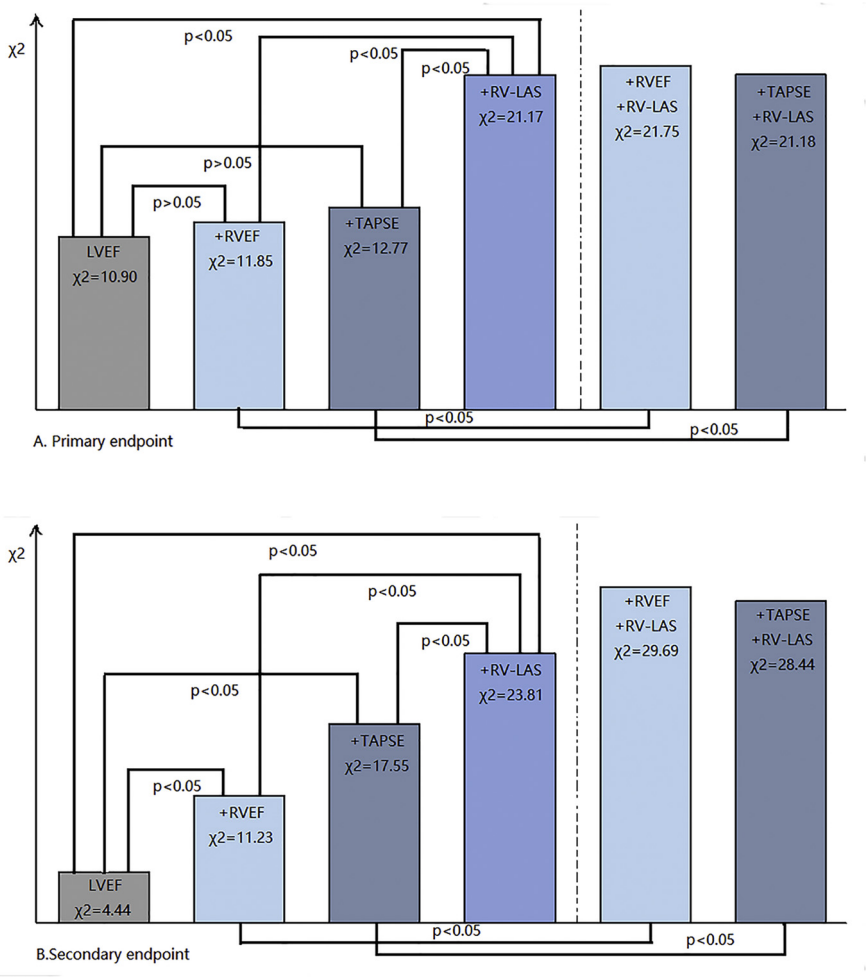

Fig. 2. Association between RV-LAS and outcome in patients with HCM. The χ^2 value was calculated using a sequential multi-variable Cox regression analysis in a series of models: the addition of TAPSE, RVEF, and RV-LAS to LVEF. A and B show the incremental predictive value of RV-LAS for the primary and secondary endpoints in patients with HCM, respectively. Model 1 included LVEF and RVEF. Model 2 included LVEF and RV-LAS. HCM, hypertrophic cardiomyopathy; CMR, cardiovascular magnetic resonance; LVEF, right ventricular ejection fraction, LGE, late gadolinium enhancement, RVEF, right ventricular ejection fraction, RV-LAS, right ventricular long axis strain, TAPSE, tricuspid annular plane systolic excursion.

References

[1] B.J. Maron, J.M. Gardin, J.M. Flack, S.S. Gidding, T.T. Kurosaki, D.E. Bild, Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA study. Coronary Artery Risk Development in (Young) Adults, Circulation 92 (1995) 785–789.
[2] B.J. Maron, Clinical course and management of hypertrophic cardiomyopathy, N. Engl. J. Med. 379 (2018) 655–668.
[3] M.S. Maron, E.J. Rowin, I. Olivotto, et al., Contemporary natural history and management of nonobstructive hypertrophic cardiomyopathy, J. Am. Coll. Cardiol. 67 (2016) 1399–1409.
[4] C.Y. Ho, S.M. Day, E.A. Ashley, et al., Genotype and lifetime burden of disease in hypertrophic cardiomyopathy: insights from the Sarcomeric Human Cardiomyopathy Registry (SHaRe), Circulation 138 (2018) 1387–1398.
[5] A.R. Patel, C.M. Kramer, Role of cardiac magnetic resonance in the diagnosis and prognosis of nonischemic cardiomyopathy, JACC Cardiovasc. Imaging 10 (2017) 1180–1193.
[6] J.P. Shah, Y. Yang, S. Chen, et al., Prevalence and prognostic significance of right ventricular dysfunction in patients with hypertrophic cardiomyopathy, Am. J. Cardiol. 122 (2018) 1932–1938.
[7] D. He, M. Ye, L. Zhang, B. Jiang, Prognostic significance of late gadolinium enhancement on cardiac magnetic resonance in patients with hypertrophic cardiomyopathy, Heart Lung 47 (2018) 122–126.
[8] R. Hinojar, C. Fernández-Golfín, A. González-Gómez, et al., Prognostic implications of global myocardial mechanics in hypertrophic cardiomyopathy by cardiovascular magnetic resonance feature tracking. Relations to left ventricular hypertrophy and fibrosis, Int. J. Cardiol. 249 (2017) 467–472.
[9] J.H. Riffel, F. Andre, M. Maertens, et al., Fast assessment of long axis strain with standard cardiovascular magnetic resonance: a validation study of a novel parameter with reference values, J. Cardiovasc. Magn. Reson. 17 (2015) 69.
[10] N. Arenja, J.H. Riffel, C.N. Djiokou, et al., Right ventricular long axis strain-validation of a novel parameter in non-ischemic dilated cardiomyopathy using standard cardiac magnetic resonance imaging, Eur. J. Radiol. 85 (2016) 1322–1328.
[11] O. Gjesdal, K. Yoneyama, N. Mewton, et al., Reduced long axis strain is associated with heart failure and cardiovascular events in the multi-ethnic study of atherosclerosis, J. Magn. Reson. Imaging 44 (2016) 178–185.
[12] N. Arenja, J.H. Riffel, T. Fritz, et al., Diagnostic and prognostic value of long-axis strain and myocardial contraction fraction using standard cardiovascular MR imaging in patients with nonischemic dilated cardiomyopathies, Radiology. 283 (2017) 681–691.
[13] N. Arenja, J.H. Riffel, M. Halder, et al., The prognostic value of right ventricular long axis strain in non-ischaemic dilated cardiomyopathies using standard cardiac magnetic resonance imaging, Eur. Radiol. 27 (2017) 3913–3923.
[14] J.H. Riffel, M.G. Keller, F. Rost, et al., Left ventricular long axis strain: a new prognosticator in non-ischemic dilated cardiomyopathy? J. Cardiovasc. Magn. Reson. 18 (2016) 36.
[15] W. Li, K. Wan, Y. Han, et al., Reference value of left and right atrial size and phasic function by SSFP CMR at 3.0 T in healthy Chinese adults, Sci. Rep. 7 (1) (2017) 3196.
[16] Y. Dong, D. Yang, Y. Han, et al., Age and gender impact the measurement of myocardial interstitial fibrosis in a healthy adult Chinese population: a cardiac magnetic resonance study, Front. Physiol. 9 (2018) 140.
[17] P.M. Elliott, A. Anastasakis, M.A. Borger, et al., 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC), Eur. Heart J. 35 (2014) 2733–2779.
[18] K. Wan, J. Sun, D. Yang, et al., Left ventricular myocardial deformation on cine MR images: relationship to severity of disease and prognosis in light-chain amyloidosis, Radiology. 288 (1) (2018) 73–80.
[19] C.J. Harrigan, D.C. Peters, C.M. Gibson, et al., Hypertrophic cardiomyopathy: quantification of late gadolinium enhancement with contrast-enhanced cardiovascular MR imaging, Radiology. 258 (1) (2011) 128–133.
[20] S. Hoette, N. Creuzé, S. Günther, et al., RV fractional area change and TAPSE as predictors of severe right ventricular dysfunction in pulmonary hypertension: a CMR study, Lung 196 (2) (2018) 157–164.
[21] C. Semsarian, J. Ingles, M.S. Maron, B.J. Maron, New perspectives on the prevalence of hypertrophic cardiomyopathy, J. Am. Coll. Cardiol. 65 (2015) 1249–1254.

[22] E.J. Rowin, S. Mohanty, C. Madias, B.J. Maron, M.S. Maron, Benefit of cardiac resynchronization therapy in end-stage nonobstructive hypertrophic cardiomyopathy, JACC Clin. Electrophysiol. 5 (1) (2019) 131–133.
[23] R.H. Chan, B.J. Maron, I. Olivotto, et al., Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy, Circulation 130 (2014) 484–495.
[24] Z. Weng, J. Yao, R.H. Chan, et al., Prognostic value of LGE-CMR in HCM: a meta-analysis, JACC Cardiovasc. Imaging 9 (2016) 1392–1402.
[25] P. Reant, M. Mirabel, G. Lloyd, et al., Global longitudinal strain is associated with heart failure outcomes in hypertrophic cardiomyopathy, Heart 102 (2016) 741–747.
[26] E. Aloia, M. Cameli, F. D'Ascenzi, C. Sciaccaluga, S. Mondillo, TAPSE: an old but useful tool in different diseases, Int. J. Cardiol. 225 (2016) 177–183.
[27] C. Doesch, C. Zompolou, F. Streitner, et al., CMR-derived TAPSE measurement: a semi-quantitative method of right ventricular function assessment in patients with hypertrophic cardiomyopathy, Neth. Hear. J. 22 (2014) 557–564.
[28] A. D'Andrea, P. Caso, E. Bossone, et al., Right ventricular myocardial involvement in either physiological or pathological left ventricular hypertrophy: an ultrasound speckle-tracking two-dimensional strain analysis, Eur. J. Echocardiogr. 11 (6) (2010) 492–500.
[29] M. Roşca, A. Călin, C.C. Beladan, et al., Right ventricular remodeling, its correlates, and its clinical impact in hypertrophic cardiomyopathy, J. Am. Soc. Echocardiogr. 28 (2015) 1329–1338.
[30] E.D. Pagourelias, G.K. Efthimiadis, D.G. Parcharidou, et al., Prognostic value of right ventricular diastolic function indices in hypertrophic cardiomyopathy, Eur. J. Echocardiogr. 12 (2011) 809–817.
[31] S. Morner, P. Lindqvist, A. Waldenstrom, E. Kazzam, Right ventricular dysfunction in hypertrophic cardiomyopathy as evidenced by the myocardial performance index, Int. J. Cardiol. 124 (2008) 57–63.
[32] A. D'Andrea, G. Limongelli, L. Baldini, et al., Exercise speckle-tracking strain imaging demonstrates impaired right ventricular contractile reserve in hypertrophic cardiomyopathy, Int. J. Cardiol. 227 (2017) 209–216.
[33] G. Finocchiaro, J.W. Knowles, A. Pavlovic, et al., Prevalence and clinical correlates of right ventricular dysfunction in patients with hypertrophic cardiomyopathy, Am. J. Cardiol. 113 (2014) 361–367.
[34] M. Neizel, G. Korosoglou, D. Lossnitzer, et al., Impact of systolic and diastolic deformation indexes assessed by strain-encoded imaging to predict persistent severe myocardial dysfunction in patients after acute myocardial infarction at follow-up, J. Am. Coll. Cardiol. 56 (13) (2010) 1056–1062.
[35] G. Korosoglou, S. Giusca, N.P. Hofmann, et al., Strain-encoded magnetic resonance: a method for the assessment of myocardial deformation, ESC Heart Fail. (2019) 584–602.
[36] R.Y. Kwong, C.M. Kramer, Y. Chandrashekhar, CMR global longitudinal strain: a better tool for unraveling the links to heart failure mortality, JACC Cardiovasc. Imaging 11 (10) (2018) 1554–1555.
[37] M.Y. Jeung, P. Germain, P. Croisille, G.S. El, C. Roy, A. Gangi, Myocardial tagging with MR imaging: overview of normal and pathologic findings, Radiographics 32 (2012) 1381.
[38] E. Altiok, M. Neizel, S. Tiemann, et al., Layer-specific analysis of myocardial deformation for assessment of infarct transmurality: comparison of strain-encoded cardiovascular magnetic resonance with 2D speckle tracking echocardiography, Eur. Heart J. Cardiovasc. Imaging 14 (6) (2013) 570–578.