Advanced echocardiographic techniques in hereditary cardiac diseases

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Chapter 4

Prevalence and Prognostic Implications of Right Ventricular Dysfunction in Patients With Hypertrophic Cardiomyopathy

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Abstract

Right ventricular (RV) dysfunction is a well-known prognostic factor in several cardiac diseases. However, the prevalence of RV dysfunction in hypertrophic cardiomyopathy (HC) is unclear and its prognostic value is unknown. This study aims at addressing these issues assessing RV function with speckle tracking echocardiography. In 267 HC patients (52±15 years, 68% male), standard and advanced echocardiographic measurements of RV function were performed including RV 4-chamber longitudinal strain (RV4CLS) and RV free wall longitudinal strain (RVFWLS). The primary endpoint was all-cause mortality and heart failure development. RV dysfunction was observed in 9% of patients based on tricuspid annular plane systolic excursion (TAPSE ≤17mm), 5% based on fractional area change (FAC<35%), 23% based on RVFWLS ≥-19%, 39% based on RVFWLS ≥-23% and 55% based on RV4CLS ≥-20%. In total 59(22%) patients reached the primary endpoint during a median follow-up of 6.7(IQR 4.2-9.8) years. Kaplan-Meier survival curve showed a significant worse survival free of the endpoint for patients with impaired RV4CLS ≥-20% vs. patients with preserved RV4CLS <-20% (log-rank 7.0,p=0.008) and for patients with impaired RVFWLS ≥-19% vs. patients with preserved RVFWLS <-19% (log-rank 4.4,p=0.037). Multivariable Cox regression analysis showed that E/E' (HR 2.26(1.30-3.92),p=0.004), left ventricular global longitudinal strain LV GLS (HR 1.08(1.01-1.17),p=0.034) and RV4CLS (HR 1.08(1.02-1.15),p=0.007) were independently associated with the primary endpoint. In conclusion, RV dysfunction as measured by longitudinal strain is relatively frequent in HC patients. Impaired RV4CLS is –together with LV GLS and E/E'– associated with adverse outcome, which may indicate a more severe form of HC.

Keywords: Hypertrophic cardiomyopathy; Right ventricular function; Speckle tracking echocardiography; Prognosis

Introduction

Hypertrophic cardiomyopathy (HC) is the most common inherited heart disease, primarily characterised by left ventricular (LV) hypertrophy,[1, 2] but frequently involves also the right ventricle (RV).[3-6] Data on RV function in HC patients is limited, partially because the accuracy of standard echocardiographic measurements is challenged by the complex shape and geometry of the RV. Initial studies showed a low prevalence of RV dysfunction in HC patients, when assessed with conventional RV parameters.[7, 8] RV longitudinal strain measured by two-dimensional (2D) speckle tracking analysis might better reflect RV contractility and few studies demonstrated a subtle, RV dysfunction in a substantial amount of HC patients.[6, 9, 10] However, different parameters with different cut-off values have been proposed, including RV four chamber longitudinal strain (RV4CLS) and RV free wall longitudinal strain (RVFWLS).[11] Importantly, the prognostic value of RV dysfunction assessed by longitudinal strain has not been studied in HC patients. The objectives of this study were therefore to evaluate the prevalence of RV dysfunction in a large cohort of HC patients, including the assessment of RV longitudinal strain parameters and their correlation with LV function and to assess the prognostic value of impaired RV4CLS and RVFWLS for all-cause mortality or heart failure (HF) development.

Methods

Patients with a clinical diagnosis of HC were identified from an ongoing clinical registry in the Leiden University Medical Center (LUMC), Leiden, the Netherlands. HC was defined according to current guidelines: maximal LV thickness ≥15mm (or ≥13mm in case of an affected first-degree relative), which could not be explained by abnormal loading conditions.[1] Clinical evaluation included demographic characteristics, cardiovascular risk factors, New York Heart Association (NYHA) functional class, genetic status, medication use and the parameters of the HC sudden cardiac death (SCD) risk score: family history of SCD at young age, previously documented non-sustained ventricular arrhythmias (nsVT) and unexplained syncope[12]. Also septal interventions and implantable cardioverter defibrillator (ICD) implantation were noted. A complete echocardiographic assessment was performed at the initial evaluation in the LUMC. Patients were excluded when the echocardiogram was of insufficient quality to perform RV measurements. These data were prospectively collected in the departmental cardiology information system (EPD-Vision®; Leiden University Medical Center, Leiden, The Netherlands) and retrospectively analysed. The study complied with the Declaration of Helsinki. Due to the retrospective design of this study, the Medical Ethical Committee declared that no formal ethical approval was needed and waived the need of written informed consent.

A commercially available ultrasound machine (Vivid 5, Vivid 7 and E9, GE-Vingmed, Milwaukee, WI) was used to perform standard 2D transthoracic echocardiography at rest. Images were digitally stored and analyzed offline using EchoPAC (version 112, GE Medical Systems, Horten, Norway). As recommended, LV diameters, LV septal thickness, LV posterior wall thickness and left atrial (LA) diameter were assessed on the parasternal long-axis view. Maximum LV wall thickness (LVWT) was assessed from a short-axis view at different levels from base to apex. LV volumes and LV ejection fraction (LVEF) were measured using Simpson's method and indexed for body surface area (BSA).[13] LV diastolic function was assessed using Doppler mitral inflow peak velocities of E divided by the peak early diastolic velocity (E') of the lateral mitral annulus, calculating the E/E' ratio.[14] The presence of systolic anterior movement (SAM) of the mitral valve was evaluated on the parasternal long-axis view and from apical 3- and 5-chamber acquisitions and grade of mitral regurgitation (MR) was assessed according to current recommendations.[15] LV outflow-tract (LVOT) peak gradient at rest was quantified by continuous wave Doppler. RV function was evaluated from the 4-chamber apical view according to current recommendations[10] and including RV fractional area change (FAC) and tricuspid annular plane systolic excursion (TAPSE). RV wall thickness (RVWT) was evaluated from the subcostal view measuring the RV free wall during end-diastole. Systolic pulmonary artery pressure (sPAP) was calculated by combining the peak velocity of the tricuspid regurgitation jet and the right atrial (RA) pressure estimated by the diameter and inspiratory collapse of the vena cava inferior.[16] 2-D speckle tracking analysis was performed to measure LV global longitudinal strain (LV-GLS), RV4CLS and RVFWLS. For LV-GLS the 2-, 3- and 4-chamber apical views acquired at a frame rate >40 fps were used and the region of interest was automatically created and manually adjusted when appropriate. LV-GLS was then calculated by averaging the peak longitudinal strain in 17 LV segments from the 3 different views. For RV4CLS and RVFWLS, a dedicated RV apical view was used to trace the RV free wall and the RV part of the intraventricular septum at end-systole and the region of interest manually adjusted to secure proper tracking of the myocardium. RV4CLS was then calculated as the average of the 6 segments (figure 1) and RVFWLS was calculated as the average of the 3 segments of the RV free wall.

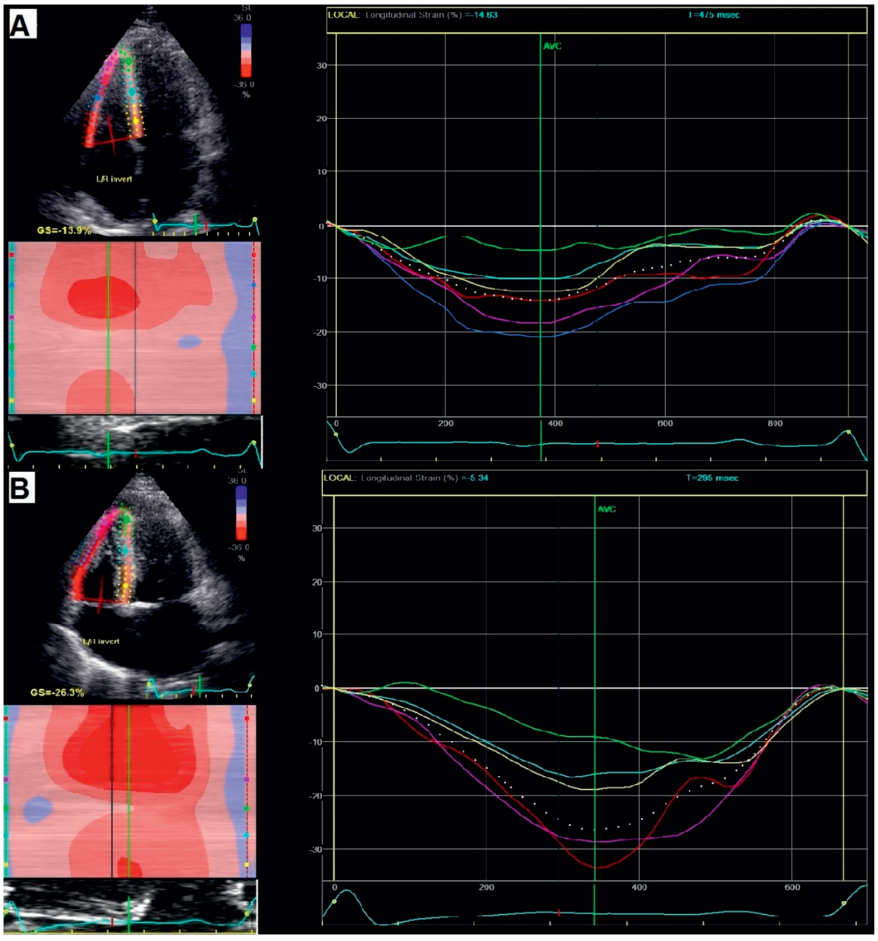

Figure 1. Assessment of right ventricular four chamber longitudinal strain (RV4CLS) by 2D speckle-tracking echocardiography. **Panel A.** 51-year old patient with impaired RV4CLS of -13.9% who developed severe HF symptoms 3 years later. **Panel B.** 56-year old patient with preserved RV4CLS of -26.3% who did not experience an event during 8 years follow-up.

Primary endpoint of the study was a combined endpoint of all-cause mortality or HF development. HF was defined as: new onset of any HF symptoms,[17] progression of HF symptoms to NYHA functional class III/IV or HF hospitalization. Specifically, new onset of HF was defined in patients who never had HF symptoms, but developed at least NYHA functional class II during follow-up. Progression of HF was defined when patients were already at NYHA functional class II symptoms at baseline, but progressed to NYHA functional class III or IV at follow-up. The occurrence of events was obtained by review of medical charts and/or contact with the general practitioner of the patients. Survival status was also retrieved through the municipal civil registries. The secondary endpoint

included (aborted) SCD or appropriate ICD therapy, defined as anti-tachycardia pacing and/or shock for ventricular tachycardia or ventricular fibrillation.

Continuous variables are presented as mean±standard deviation, when normally distributed or as median(interquartile range) when not normally distributed. Categorical variables are presented as absolute numbers and percentages. The relation of RV4CLS and RVFWLS with other clinical and echocardiographic parameters was assessed using Pearson's method or Spearman's method. The percentage of patients with RV dysfunction was calculated according to different cut-off values of RV4CLS and RCFWLS. Current recommendations and the study of Muraru et al.[18] propose RV4CLS ≥ -20% and RVFWLS ≥ -23% as abnormal. However, other studies showed that RVFWLS ≥ -19% was associated with poor prognosis.[19, 20] Therefore, Kaplan-Meier curves were constructed for the different cut-off values to estimate the survival free from the endpoint and compared by log-rank test for patients with RV4CLS <-20% vs. RV4CLS ≥-20%, RVFWLS <-19% vs. RVFWLS ≥-19% and RVFWLS <-23% vs. RVFWLS ≥-23%. For the primary endpoint, univariable and multivariable Cox regression analysis were used to identify predictors of this endpoint and hazard ratios (HR) and 95% confidence interval (CI) were calculated. Because of the relatively low number of events, the multivariable analysis was performed in separate steps including clinical and echocardiographic parameters. To avoid collinearity, 2 separate multivariate analyses were performed to assess the independent prognostic value of RV4CLS and RVFWLS. For the secondary endpoint only univariable analysis was performed. Statistical analysis was performed with the SPSS software package (version 23, IBM Corp, Armonk, NY). P-values <0.05 were considered statistically significant.

Results

A total of 267 HC patients (52±15 years, 68% male) were included out of a cohort of 436 patients; 169 patients were excluded because of insufficient quality or incomplete images for the RV assessment (RV free wall not eligible for strain analysis). Clinical and echocardiographic characteristics of the overall population are summarized in Table 1. Most patients were asymptomatic (81% in NYHA class I) and a known HC genetic mutation was found in 58% of tested patients. Already at baseline evaluation, 7(3%) patients had a septal intervention, 27 (10%) underwent a PCI and 59 (22%) patients had an ICD. Although LVEF was within normal values, LV-GLS was significantly impaired (-15±5%).[13] 15% of the patients showed obstructive HC with a significant LVOT gradient. Interestingly, mean RVWT was 6±1mm, mean RV4CLS was -19±5% and mean RVFWLS was -24±7%.

Table 1. Baseline clinical and echocardiographic characteristics of the overall population.

Clinical characteristics	
Age (years)	52±15
Men	182(68%)
Hypertension	98(37%)
Atrial fibrillation	27(10%)
NYHA class ≥ II	51 (19%)
Septal intervention*	7(3%)
PCI*	27(10%)
ICD implanted*	59(22%)
Genetic mutation†	96(58%)
Beta-blocker	96(36%)
Calcium-antagonist	46(18%)
Family history of SCD	112(42%)
Unexplained syncope	27(10%)
Prior nsVT	70(27%)
Echocardiographic characteristics	
LVEDD (mm)	44±7
LVEF (%)	65±9
LV-GLS (%)	-15±5
Maximum LVH (mm)	20(17-24)
Peak LVOT (mmHg)	9(6-19)
LA diameter (mm)	41±7
E/E'	10(8-15)
MR > grade 2	54(21%)
SAM	94(35%)
RV4CLS (%)	-19±5
RVFWLS (%)	-24±7
TV annulus (mm)	30±5
TAPSE (mm)	24±5
RV FAC (%)	48±7
RV wall thickness (mm)	6±1
TR ≥ grade 2	27(10%)
sPAP (mmHg)	25(22-28)

FAC fractional area change; LA left atrial; LVEDD left ventricular end diastolic diameter; LVEF left ventricular ejection fraction; LV-GLS left ventricular global longitudinal strain; LVH left ventricular hypertrophy; LVOT left ventricular outflow tract; ICD implantable cardioverter defibrillator; MR mitral regurgitation; nsVT non-sustained ventricular tachycardia; NYHA New York Heart Association; PCI percutaneous coronary intervention; RV right ventricular; RV4CLS right ventricular four chamber longitudinal strain; RVFWLS right ventricular free wall longitudinal strain; SAM systolic anterior motion; SCD sudden cardiac death; sPAP systolic pulmonary artery pressure; TAPSE tricuspid annular plane systolic excursion; TV tricuspid valve

** interventions before baseline echocardiography*

† *only genetically tested patients (N=165)*

In Table 2 the correlation of RV4CLS and RVFWLS and other clinical and echocardiographic characteristics are shown. RV4CLS showed a weak but significant correlation with maximum LVWT,

LA diameter, E/E', LVEF, TAPSE, RV FAC and RVWT. The correlation between RV4CLS and LV-GLS was moderate. RVFWLS also showed a correlation with maximum LVWT, LA diameter, LVEF, TAPSE, RV FAC and RVWT, but not with E/E'. The correlation between RVFWLS and LV-GLS was moderate.

Table 2. Correlation of right ventricular four chamber longitudinal strain (RV4CLS) and right ventricular free wall longitudinal strain (RVFWLS) with other echocardiographic parameters.

Variable	RV4CLS		RVFWLS	
	P-value	**R**	**P-value**	**R**
Age	0.264	-0.069	0.302	-0.063
Maximum LVH (mm)	<0.001	0.278	0.003	0.181
LVEDD (mm)	0.197	-0.079	0.441	-0.047
LA diameter (mm)	0.001	0.209	0.041	0.126
E/E'	0.019	0.155	0.414	0.054
Peak LVOT (mmHg)	0.364	-0.056	0.139	-0.091
MR > grade 2	0.173	0.084	0.693	0.025
LVEF (%)	<0.001	-0.223	0.001	-0.198
LV-GLS (%)	<0.001	0.459	<0.001	0.352
TAPSE (mm)	<0.001	-0.349	<0.001	-0.302
RV FAC (%)	<0.001	-0.253	<0.001	-0.243
sPAP (mmHg)	0.065	0.120	0.376	0.058
RV wall thickness (mm)	0.021	0.143	0.010	0.160

FAC fractional area change; LA left atrial; LVEDD left ventricular end diastolic diameter; LVEF left ventricular ejection fraction; LV-GLS left ventricular global longitudinal strain; LVH left ventricular hypertrophy; LVOT left ventricular outflow tract; MR mitral regurgitation; RV right ventricular; RV4CLS right ventricular four chamber longitudinal strain; RVFWLS right ventricular free wall longitudinal strain; sPAP systolic pulmonary artery pressure; TAPSE tricuspid annular plane systolic excursion

Figure 2 presents the percentages of patients with RV dysfunction based on the different echocardiographic parameters and according to different cut-off values.

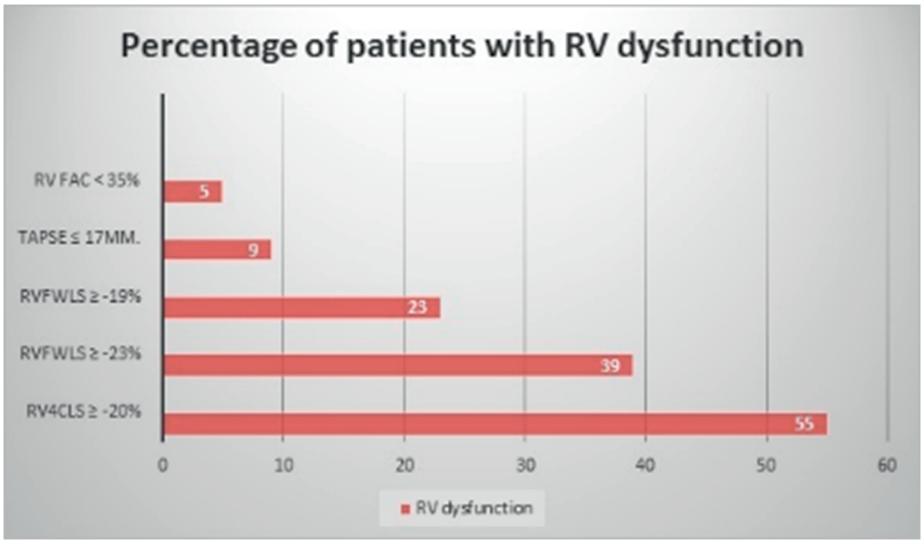

Figure 2. Prevalence of right ventricular dysfunction
RV4CLS right ventricular four chamber longitudinal strain; RV FAC right ventricular fractional area change; RVFWLS right ventricular free wall longitudinal strain; TAPSE tricuspid annular systolic plane excursion

During a median follow-up of 6.7(IQR 4.2-9.8) years, 59 patients reached the primary endpoint of all-cause mortality or HF development. Specifically, 41/59 patients reached the HF endpoint: 22 patients developed HF symptoms (NYHA class ≥2) and 19 patients showed progressive HF (to NYHA class III/IV), 13 of those patients were also hospitalized for HF. A total of 18 patients died and the cause of death was unknown in 7 patients, SCD in 3 patients, 1 patient died of complications after cardiac surgery and cause of death was non-cardiac in 7 patients. 32 patients reached the secondary endpoint: 3 patients experienced SCD, 4 patients had aborted SCD and 25 patients received appropriate ICD therapy (15 ICD shocks and 10 ATP).

In patients with preserved RV4CLS (<-20%), the cumulative survival rates free of the primary endpoint at 2, 5 and 8 years follow-up were 93%, 90% and 84% respectively. In contrast, patients with impaired RV4CLS (≥-20%) showed significantly worse outcome with survival rates free of the primary endpoint of 90% at 2 years, 82% at 5 years and 68% after 8 years (log-rank 8.3,p=0.004) (Figure 3A). When using RVFWLS of -19% as a cut-off value, patients with preserved RVFWLS (<-19%) showed cumulative survival rates of 94%, 88% and 78% at 2, 5 and 8 years follow-up respectively, whereas patients with impaired RVFWLS (≥-19%) showed worse outcome with survival rates of 90% at 2 years, 80% at 5 years and 68% after 8 years (log-rank 4.4, p=0.037) (Figure 3B).

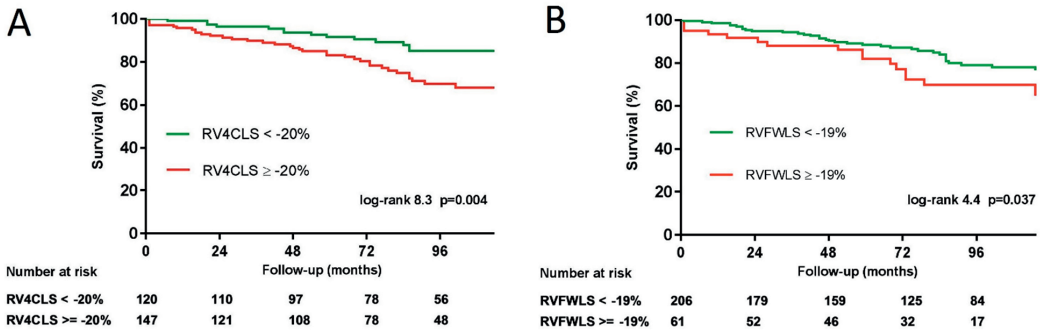

Figure 3. Kaplan-Meier analyses to evaluate the survival free of experiencing the endpoint (all-cause mortality or heart failure (HF) development). **(A)** Patients with right ventricular four chamber longitudinal strain (RV4CLS) <-20% compared to patients with RV4CLS ≥-20% **(B)** Patients with right ventricular free wall longitudinal strain (RVFWLS) <-19% compared to patients with RVFWLS ≥-19%

When using -23% as a cut-off value for RVFWLS, no differences in survival rates were observed between patients with normal RVFWLS (<-23%) as compared to patients with abnormal RVFWLS (≥-23%). Univariable Cox regression analysis showed that age, NYHA class ≥2, nsVT, LA diameter, E/E', MR>grade 2, LVEF, LV-GLS, RV4CLS, RVFWLS, TV annulus, TAPSE, TR≥grade 2 and sPAP were all significantly associated with the primary endpoint. Concerning the secondary endpoint, only unexplained syncope, LA diameter, maximum LVWT and LV-GLS were associated with this endpoint. Specifically, the echocardiographic measurements of the RV were not associated with the secondary endpoint (Table 3).

Table 3. Univariable Cox proportional hazard regression analysis to identify parameters associated with the primary and secondary endpoints.

Univariable analysis	Primary endpoint: all-cause mortality + HF development		Secondary endpoint: (aborted) SCD + appropriate ICD therapy	
Parameter	**HR (95%CI)**	**P-value**	**HR (95%CI)**	**P-value**
Age	1.04(1.02-1.05)	<0.001	0.99(0.97-1.01)	0.431
NYHA class≥2	2.14(1.23-3.73)	0.008	0.97(0.37-2.53)	0.955
Ventricular septal intervention	1.07(0.46-2.49)	0.879	2.04(0.78-5.31)	0.144
Beta-blockers	1.38(0.83-2.31)	0.218	1.29(0.64-2.62)	0.479
nsVT	1.78(1.05-3.00)	0.033	1.81(0.90-3.68)	0.099
Family history of SCD	1.16(0.69-1.93)	0.583	1.79(0.89-3.60)	0.105
Syncope	1.19(0.54-2.63)	0.664	2.57(1.05-6.29)	0.039
LA diameter (mm)	1.06(1.03-1.09)	<0.001	1.07(1.03-1.11)	<0.001
E/E'	3.49(2.15-5.65)	<0.001	1.41(0.69-2.85)	0.344
Maximum LVH (mm)	1.03(0.99-1.07)	0.094	1.06(1.02-1.11)	0.004
Peak LVOT(mmHg)	1.03(0.78-1.38)	0.817	1.28(0.91-1.82)	0.159
MR > grade 2	2.41(1.41-4.11)	0.001	1.01(0.44-2.33)	0.980
LVEF (%)	0.93(0.90-0.95)	<0.001	0.99(0.95-1.02)	0.449
LV GLS (%)	1.16(1.09-1.24)	<0.001	1.12(1.03-1.21)	0.007
RV4CLS (%)	1.11(1.06-1.17)	<0.001	1.05(0.97-1.13)	0.215
RVFWLS (%)	1.05 (1.01-1.09)	0.013	1.01 (0.96-1.06)	0.700
TV annulus (mm)	1.06(1.00-1.11)	0.044	1.07(0.99-1.14)	0.073
TAPSE (mm)	0.93(0.87-0.98)	0.009	1.02(0.94-1.10)	0.653
RV FAC (%)	0.97(0.94-1.00)	0.067	0.97(0.93-1.02)	0.207
RV wall thickness (mm)	1.01(0.81-1.27)	0.916	1.08(0.79-1.47)	0.639
TR ≥ grade 2	2.76(1.46-5.21)	0.002	0.55(0.13-2.32)	0.418
sPAP (mmHg)	1.05(1.02-1.09)	0.003	1.03(0.99-1.09)	0.178

CI confidence interval; FAC fractional area change; HF heart failure; HR hazard ratio; LA left atrial; LVEF left ventricular ejection fraction; LV GLS left ventricular global longitudinal strain; LVH left ventricular hypertrophy; LVOT left ventricular outflow tract; ICD implantable cardioverter defibrillator; MR mitral regurgitation; nsVT non-sustained ventricular tachycardia; NYHA New York Heart Association; RV right ventricular; RV4CLS right ventricular four chamber longitudinal strain; RVFWLS right ventricular free wall longitudinal strain; SCD sudden cardiac death; sPAP systolic pulmonary artery pressure; TAPSE tricuspid annular plane systolic excursion; TV tricuspid valve

In Table 4 the results of the multivariable analysis for the primary endpoint are shown. Step 1, including clinical characteristics, showed that age (HR1.03(1.01-1.05),p=0.011) is independently associated with the primary endpoint. In step 2, the most important left-sided echocardiographic variables were tested and the analysis showed that E/E' (HR 2.39(1.39-4.11),p=0.002) and LV-GLS (HR 1.11(1.03-1.20),p=0.006) were associated with the primary endpoint. Step 3 and 4 were separately performed for RV4CLS and RVFWLS. In step 3a the standard RV parameters were tested combined with RV4CLS and of those only RV4CLS was associated (HR 1.10(1.04-1.17),p=0.002) with the primary endpoint. In step 4a, significant variables from the previous steps were combined,

revealing E/E' (HR 2.26(1.30-3.92),p=0.004), LV-GLS (HR 1.08(1.01-1.17),p=0.034) and RV4CLS (HR 1.07(1.02-1.15),p=0.007) to be independently associated with the primary endpoint.
In step 3b the standard RV parameters were tested combined with RVFWLS and of those, none were significantly associated with the primary endpoint, although RVFWLS was borderline significant (HR 1.04(0.99-1.09), p=0.060). In step 4b RVFWLS was combined with the significant variables from the previous steps, and revealed only E/E' and LV-GLS to be significantly associated with the endpoint, while RVFWLS was not (HR 1.03(0.99-1.08), p=0.121).

Table 4. Step-wise multivariable Cox regression analyses to evaluate whether right ventricular four chamber longitudinal strain (RV4CLS) and right ventricular free wall longitudinal strain (RVFWLS) are independently associated with the primary endpoint.

Parameter	**Multivariable analysis HR (95% CI)**	**P-value**		
Step 1: clinical characteristics				
Age	1.03(1.01-1.05)	0.011		
NYHA ≥ 2	1.54(0.85-2.79)	0.155		
nsVT	1.64(0.96-2.79)	0.068		
Step 2: echocardiographic LV parameters				
LA diameter (mm)	1.03(0.99-1.07)	0.078		
E/E'	2.39(1.39-4.11)	0.002		
MR > grade 2	1.67(0.87-3.19)	0.121		
LV GLS (%)	1.11(1.03-1.20)	0.006		
Parameter	**Multivariable analysis HR (95% CI)**	**P-value**	**Multivariable analysis HR (95% CI)**	**P-value**
Step 3: echocardiographic RV parameters	*Step 3a*		*Step 3b*	
TV annulus (mm)	1.04(0.98-1.10)	0.189	1.04 (0.98-1.10)	0.168
TAPSE (mm)	0.99(0.92-1.06)	0.735	0.96 (0.90-1.03)	0.262
TR ≥ grade 2	1.93(0.89-4.20)	0.096	1.81 (0.85-3.84)	0.125
sPAP (mmHg)	1.02(0.99-1.06)	0.233	1.03 (0.99-1.07)	0.128
RV4CLS (%)	1.10(1.04-1.17)	0.002		
RVFWLS (%)			1.04 (0.99-1.09)	0.060
Step 4: all combined	*Step 4a*		*Step 4b*	
Age	1.01(0.99-1.04)	0.069	1.02 (0.99-1.04)	0.058
E/E'	2.26(1.30-3.92)	0.004	1.04 (1.01-1.07)	0.004
LV GLS (%)	1.08(1.01-1.17)	0.034	1.10 (1.03-1.19)	0.007
RV4CLS (%)	1.08(1.02-1.15)	0.007		
RVFWLS (%)			1.03 (0.99-1.08)	0.121

CI confidence interval; HR hazard ratio; LA left atrial; LV GLS left ventricular global longitudinal strain; MR mitral regurgitation; nsVT non-sustained ventricular tachycardia; NYHA New York Heart Association; RV right ventricular; RV4CLS right ventricular four chamber longitudinal strain; RVFWLS right ventricular free wall longitudinal strain; sPAP systolic pulmonary artery pressure; TAPSE tricuspid annular plane systolic excursion; TV tricuspid valve

Discussion

The present study showed that 1) RV dysfunction, reflected by impaired RV4CLS or RVFWLS, is a common finding in patients with HC and is correlated to LV dysfunction as assessed by LV-GLS, and 2) impaired RV4CLS is independently associated with worse outcome in terms of all-cause mortality and HF development together with LV-GLS and E/E'. Several studies already showed that HC is a biventricular disease although the clinical definition is based on LV thickness and function. McKenna et al.[5] for example showed that RVWT >5-7 mm is commonly observed in HC patients (44%) and associated with presence of HF symptoms and supraventricular arrhythmias. Similarly, Maron et al.[3] used magnetic resonance imaging to study the RV in HC patients and found an increased RVWT (7±2mm), which was significantly correlated with LVWT (R^2=0.4,p<0.001). In the present study, a mean RVWT of 6±1mm was observed, confirming the presence of biventricular hypertrophy. Few other studies focused on RV function assessment in HC patients, using different echocardiographic methods such as TAPSE, RV FAC or tissue Doppler imaging.[7, 8] However, these parameters often remain within the normal range until RV function significantly impairs and therefore might not reflect subtle RV dysfunction. Finocchiaro et al.[7] for example reported a prevalence of RV dysfunction of 6% in 324 HC patients, measured by RV FAC <35%, and 11% defined by TAPSE <17mm; however, an abnormal RV myocardial performance index (>0.4) was found in 71% and sPAP >35 mmHg in 24% of the patients. The low prevalence of RV dysfunction, defined by impaired RV FAC or TAPSE, is comparable to the present study and suggests the limited sensitivity of these parameters to detect subtle RV dysfunction.

GLS has been suggested as more sensitive measure of myocardial dysfunction and several studies evaluated the clinical value of LV-GLS in HC patients.[21-25] However, RV longitudinal strain has been studied less extensively in these patients and there is no consensus on which parameter should be used between RV4CLS and RVFWLS. Recent guidelines suggest to use RVFWLS when assessing RV function, yet this recommendation is not specifically for HC patients and without a clear proposed cut-off value.[11] Muraru et al.[18] evaluated 276 healthy volunteers and defined the reference value as -20% for RV4CLS and -23% for RVFWLS. However, other studies in patients with pulmonary hypertension suggested that a lower cut-off value of RVFWLS (-19%) is associated with prognosis.

Initial studies in HC patients[6] used RV4CLS and showed that this parameter was significantly impaired in patients as compared to controls (-19.4±4.4% vs. -23.8±2.7%), with a significant correlation of RV4CLS with LV mass and LV-GLS. The present study included a larger group of HC patients and showed a relatively high prevalence (55%) of impaired RV4CLS (when using -20% as cut-off value), but also a high prevalence (39%) of impaired RVFWLS (when using -23% as cut-off value),

and still 23% of impaired RVFWLS when applying a more strict cut-off value of -19%. Furthermore, RV4CLS and RCFWLS were both associated mainly with impaired LV-GLS, but also with increased LVWT and RVWT, although not with elevated sPAP. These observations suggest a primary involvement of the RV in HC patients together a significant inter-ventricular dependency.

Current study also evaluated the prognostic value of RV4CLS and RVFWLS in HC patients, while only few studies with small patient populations studied the prognostic value of RV function.[7, 26, 27]. Rosca et al. demonstrated an association between RVWT and ventricular arrhythmias in these patients, while both LV-GLS and RV4CLS were not independently associated with this endpoint probably due to the small sample size.[6] The present study demonstrated in a large group of HC patients the association of RV4CLS and RVFWLS with the endpoint of all-cause mortality and HF development. However in the multivariate analysis, RV4CLS performed better than RVFWLS and showed an independent association with the primary endpoint, together with LV-GLS and E/E', while RVFWLS was only associated on a univariate level. This might be due to the fact that RV4CLS better reflects the interventricular dependence, still remaining associated with the outcome after correction for LVGLS in the multivariate analysis and therefore not being explained solely by LV (septal) dysfunction). With the secondary endpoint of appropriate ICD therapy, both RV4CLS and RVFWLS showed no significantly association, which partially confirms the findings by Rosca et al.[6] These results suggest that echocardiographic evaluation of RV function including RV longitudinal strain should be considered in the standard assessment of HC patients and might be helpful in risk stratification. Particularly, impaired RV4CLS seems to identify patients with a more severe HC profile with important biventricular systolic and diastolic dysfunction, who might deserve closer monitoring and/or more aggressive treatment to avoid HF development. In turn, the use of RV4CLS and RVFWLS for risk prediction of SCD in HC patients has not been proven.

Several limitations of this study need to be mentioned. Due to the retrospective design, a relatively large group of patients was excluded because RV longitudinal strain could not be measured or a dedicated view was not available. Furthermore, RV longitudinal strain measurements were performed only with GE software and therefore the absolute values of RV longitudinal strain might not be generalizable to other vendors. Particularly, the software used in this study was originally developed to measure LV-GLS and still has to be validated for RV longitudinal strain measurements. However, several studies showed the accuracy of this parameter to assess RV dysfunction in patients with different cardiomyopathies.[9, 28, 29] Also, when using the septal segments in the calculation of RV4CLS, an accurate distinction of the LV part from the RV part is not possible and therefore the correlation between LV-GLS and RV4CLS might have been overestimated. Finally, prospective studies

with comprehensive assessment of the RV function are needed to validate these results and to define which parameter – RV4CLS or RVFWLS – and which cut-off values should be used to identify HC patients at risk for adverse outcome.

In conclusion, RV dysfunction is relatively common in HC patients either assessed by RV4CLS or RVFWLS. Importantly, an impaired RV4CLS is associated with all-cause mortality and HF development together with LV-GLS and E/E', possibly identifying patients with a more severe form of HC.

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