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Short communication

Right ventricular strain in Fabry disease: Prognostic implications☆

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ABSTRACT

Introduction: Left ventricular (LV) hypertrophy is the main feature of cardiac involvement in Anderson-Fabry disease (FD), but the right ventricle (RV) is also frequently affected. Previous studies failed to demonstrate an independent association between conventional parameters of RV performance and outcomes in FD. Nevertheless, if RV free wall strain (RV-FWS), assessed by 2D speckle tracking analysis, may provide a better prognostication is currently unknown.

Methods: We retrospectively evaluated the association between RV-FWS and the occurrence of cardiovascular events in a cohort of 56 patients with FD. The study endpoint comprises cardiovascular mortality, severe heart failure symptoms, new-onset atrial fibrillation and major arrhythmias requiring device implantation.

Results: Reduced RV-FWS, defined by values lower than 23%, was found in 25 (45%) patients. During a median follow-up of 47 months, 16 (29%) patients met the study endpoint. A ROC-curve analysis confirmed the threshold of reduced RV-FWS (<23%) as the best cut-off for predicting cardiovascular events, but with a lower power compared to left-sided parameters. On univariable Cox regression analysis, RV-FWS, expressed as continuous variable, was significantly associated with the study endpoint (HR: 0.795, 95% CI: 0.710–0.889, $p < 0.001$). However, RV-FWS did not retain a significant association with outcomes, after adjustment for LV global longitudinal strain or indexed left atrial volume ($p = 0.340$ and $p = 0.289$ respectively).

Conclusions: RV-FWS was not independently associated with the occurrence of cardiovascular events in FD, confirming previous observations that prognosis is mainly driven by the severity of LV cardiomyopathy.

1. Introduction

Anderson-Fabry disease (FD) is a X-linked lysosomal storage disorder caused by a deficient enzymatic activity of α-galactosidase A, that leads to progressive intracellular accumulation of globotriaosylceramide in different organs, including the heart [1]. Left ventricular hypertrophy (LVH) is the main feature of cardiac involvement, but the right ventricle (RV) is also frequently affected [2,3]. In particular, RV hypertrophy is found in a consistent proportion of patients with FD, but is typically associated with preserved RV systolic function when assessed by conventional echocardiography [2,3]. We previously reported that RV hypertrophy as well as standard parameters of RV performance are not independently associated with the occurrence of cardiac and non-cardiac events in FD, suggesting that RV involvement is an important feature of Fabry cardiomyopathy phenotype but has no additive prognostic value [4]. However, the recent application of two-dimensional speckle tracking analysis (2D-STE) allowed to demonstrate that RV free wall strain (RV-FWS) is often reduced in FD [5–7], unveiling a subclinical impairment of RV longitudinal mechanics. Nevertheless, if RV-FWS may provide a better prognostication in patients with FD is currently unknown. Thus, aim of the present study was to investigate the possible prognostic value of RV-FWS in FD.

☆ All authors take responsibility for all aspects of the reliability and freedom, from bias of the data presented and their discussed interpretation

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2. Methods

We conducted a retrospective analysis of the association between RV-FWS and the occurrence of cardiovascular events in a previously described cohort of patients with FD followed at the Fondazione Policlinico A. Gemelli IRCCS, Rome, Italy [7].

2.1. Echocardiography

Conventional echocardiography and 2D-STE were performed in all study participants at baseline, as previously described [7]. Briefly, 2D-STE analysis was performed using a dedicated software: 2D Cardiac Performance Analysis© by TomTec-Arena TM (TomTec Imaging Systems, Unterschleissheim, Germany). Images obtained in a RV focused apical four-chamber view and with a frame rate between 50 and 90 were used for RV strain measurements [8,9]. RV-FWS was derived by the software as the average of longitudinal peak systolic strain values of the three segments of RV free wall [8,9]. In the present study, the values of strain measurements are reported in absolute values.

According to current evidence [8], we adopted the threshold of 23% to define the impairment of RV-FWS. As secondary analysis, RV global longitudinal strain GLS (RV-GLS), calculated as average of strain values of the six segments of the RV free wall and septal wall, and ΔRV strain defined as the difference between RV-FWS and RV-GLS [7], were also investigated. Excellent intra- and inter-observer agreement of RV strain measurements performed in our echocardiographic laboratory has been previously reported [7].

2.2. Follow-up and study endpoint

All patients underwent clinical evaluation every 6–12 months or earlier if clinically indicated. The study endpoint included the occurrence of cardiovascular mortality, severe heart failure symptoms (new-developed New York Heart Association functional class III/IV), new-onset atrial fibrillation (AF), major brady-arrhythmias or tachy-arrhythmias requiring pacemaker/implantable cardioverter defibrillator implantation.

2.3. Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range [IQR]) and categorical variables are expressed as numbers and percentages. Continuous variables were compared using an unpaired Student *t*-test or Mann–Whitney *U* test, as appropriate, while categorical variables were evaluated using the $\chi 2$ test or Fisher exact test.

Receiver operating characteristic (ROC) curve analysis, Kaplan-Meier analysis and Cox regression models were used to determine the association between RV-FWS and outcomes. Survival analyses were performed evaluating the time to the first event occurrence during the follow-up. Given the limited number of events, multivariable Cox regression analyses were performed adjusting alternatively for one of the following variable: age, QRS duration, indexed LV mass, LV global longitudinal strain (LV-GLS), indexed left atrial volume (LAVi). Significant collinearity between any pairs of covariates included in multivariable models was excluded by a correlation factor analysis (correlation coefficient < 0.70). Statistical analysis was performed using SPSS version 25.0 (IBM Corporation, Armonk, NY, USA) and R version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

The study cohort was composed by 56 patients with genetically-proven FD. Among them, half were considered as having Fabry Cardiomyopathy (FC, $n = 28$) defined as the presence of LVH (LV maximal wall thickness ≥ 13 mm). Clinical and echocardiographic data in the population stratified according to the presence of LVH have been previously published [7]. The median value of RV-FWS in the overall population was 24.0% (IQR:21.0–27.9%). Reduced RV-FWS, defined by values lower than 23%, was found in 25 patients (45%). The comparison of clinical and echocardiographic variables between patients with preserved or impaired RV-FWS is shown in Table 1. Two patients had a history of paroxysmal AF (these events were not accoutered in survival analyses), while at baseline there were no subjects with implanted pacemaker/implantable cardioverter defibrillator.

Table 1
Comparative analysis of baseline characteristics in patients with preserved or impaired RV-FWS.

	Overall cohort ($n = 56$)	Impaired RV-FWS ($n = 25$)	Preserved RV-FWS ($n = 31$)	P-value
Clinical characteristics				
Age (years)	47 ± 16	53 ± 14	42 ± 17	0.008
Female (n,%)	26 (46)	10 (40)	16 (52)	0.386
Disease variant (n, %)				0.400
Classic	37 (66)	13 (52)	6 (19)	
Late-onset	19 (34)	7 (28)	12 (39)	
MSSI	18 (6–29)	27 (18–33)	9 (2–21)	<0.001
NYHA class (n,%)				0.034
I/II	54 (96)	21 (84)	31(100)	
III/IV	4 (7)	4 (16)	0 (0)	
QRS duration (ms)	106 ± 22	116 ± 24	98 ± 16	0.003
PAF (n,%)	2 (4)	2 (8)	0 (0)	0.195
NSTV (n, %)	6 (11)	5 (20)	1 (3)	0.061
Hypertension (n, %)	17 (30)	11 (44)	6 (19)	0.046
eGFR<60 mL/min/1.73m^2	6 (11)	4 (16)	2 (7)	0.391
ERT/Chaperon therapy (n,%)	27(48)/1(2)	13(52)/1(4)	14(45)/0(0)	0.428
Echocardiographic characteristics				
Indexed LV mass (g/m^2)	112 (78–167)	152 (113−222)	93 (68–120)	0.001
Indexed LVEDV (ml/m^2)	48 (41–56)	52 (40–60)	47 (42–51)	0.150
LVEF (%)	63 ± 4	62 ± 4	64 ± 3	0.045
LV-GLS (%)	17.5 ± 4.1	15.0 ± 4.2	19.5 ± 2.6	<0.001
Indexed LAV (ml/m^2)	32 (26–50)	46 (31–60)	29 (24–35)	<0.001
E/E' ratio	8.0 (5.8–10.4)	10.1 (7.0–13.4)	6.5 (5.5–8.6)	<0.001
RVWT (mm)	4.3 (3.5–7.0)	6.0 (3.6–8.4)	4.0 (3.5–5.5)	0.013
TAPSE (mm)	22 ± 4	20 ± 4	23 ± 2	0.007
RVFAC (%)	48 ± 8	45 ± 8	51 ± 7	0.001
RV S′ velocity (cm/s)	12.3 ± 2.7	11.4 ± 3.5	13.0 ± 1.6	0.034
RV-FWS (%)	24.0 (21.0–27.9)	20.1 (16.8–22.0)	27.4 (25.0–29.7)	<0.001
TR jet velocity (m/s)	2.3 (2.0–2.5)	2.5 (2.0–2.8)	2.3 (2.0–2.4)	0.193

Abbreviations. ERT: enzyme replacement therapy; eGFR: estimated glomerular filtration rate (by the formula of Cockcroft-Gault); LAV: left atrial volume; LV: left ventricular; LVEDV: LV end-diastolic volume; LVEF: LV ejection fraction; LV-GLS: LV global longitudinal strain; MSSI: Mainz Severity Score Index; NYHA: New York Heart Association; PAF: paroxysmal atrial fibrillation; RV: right ventricular; RVFAC: RV fractional area change; RV-FWS: RV free wall strain; RVWT: RV wall thickness; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation; TVNS: non sustained ventricular tachycardia.

During a median follow-up of 47 (IQR: 24–51) months, 16 (29%) patients met the study endpoint. The most common events weres the development of severe heart failure symptoms ($n = 6$) or new-onset AF (n = 6), followed by major arrhythmias ($n = 5$) and cardiovascular death ($n = 1$).

A ROC-curve analysis showed the previously defined threshold of impaired RV-FWS (<23%) as the best cut-off for predicting cardiovascular outcomes at 4 years (area under curve [AUC]: 0.809; 95% confidence interval [CI]: 0.672–0.946; *p*-value<0.001, sensitivity: 81%;

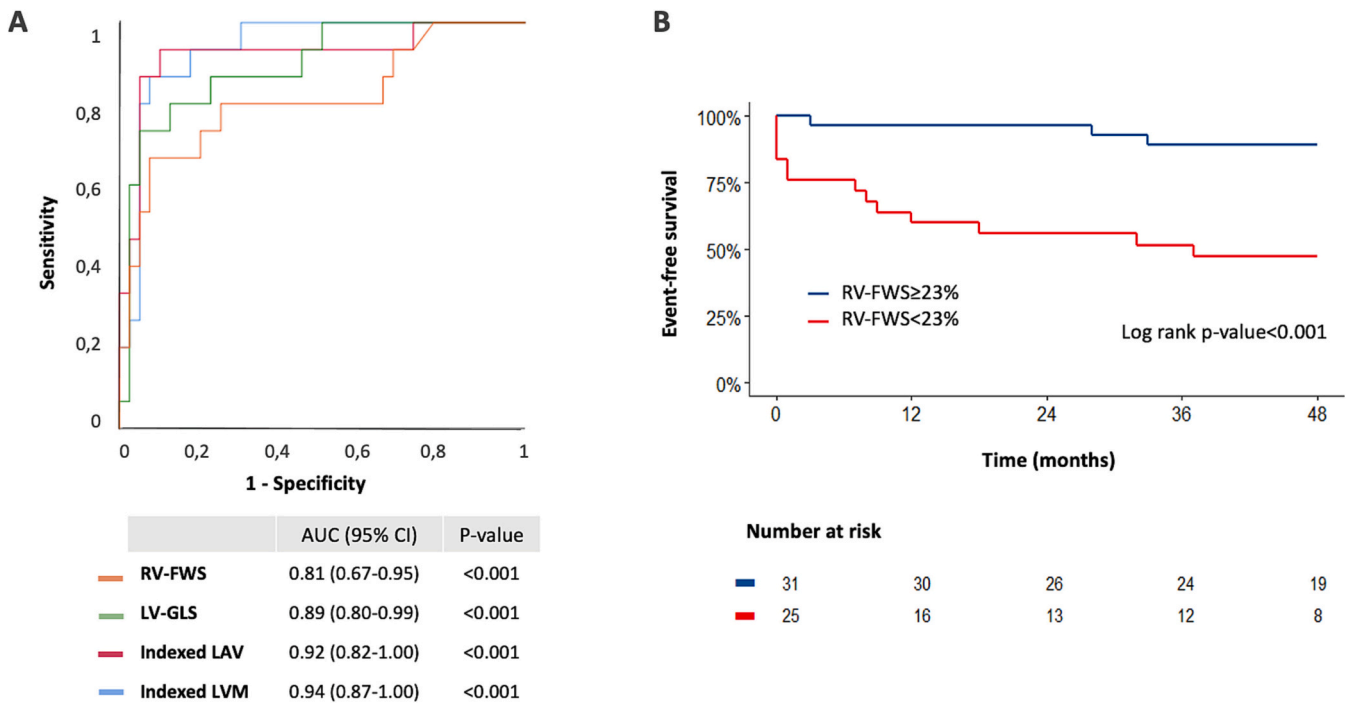

Fig. 1. A) ROC curves for cardiovascular events at 4 years according to RV-FWS and left-sided parameters; B) Kaplan-Meier curves showing the event-free survival according to RV-FWS.
Abbreviations. LAV: left atrial volume; LV: left ventricular; LV-GLS: LV global longitudinal strain; LVM: LV mass; RV: right ventricular; RV-FWS: RV free wall strain.

specificity: 73%), but with a lower predictive value in comparison to left-sided parameters, including indexed LV mass, LV-GLS and LAVi (Fig. 1A).

Kaplan-Meier survival curves demonstrated significantly lower event-free survival at 4 years in patients with impaired RV-FWS (<23%) as compared to patients with preserved RV-FWS (≥23%) (47% versus 89%; log rank $p < 0.001$) (Fig. 1B). On univariable Cox regression analysis, RV-FWS expressed as continuous variable was significantly associated with the study endpoint (Hazard ratio [HR]: 0.795, 95% CI 0.710–0.889, p < 0.001). This association was confirmed both in male and female patients (HR: 0.764, 95% CI 0.655–0.891, $p = 0.001$ and HR: 0.815, 95% CI 0.667–0.997, $p = 0.046$; respectively). RV-FWS retained an independent association with outcomes after alternative adjustment for age (HR: 0.860, 95% CI 0.767–0.965, $p = 0.010$), QRS duration (HR: 0.820; 95% CI 0.710–0.948; $p = 0.007$), or indexed LV mass (HR: 0.882, 95% CI 0.788–0.987, $p = 0.029$). Conversely, RV-FWS was not significantly associated with cardiovascular events, after correcting for LV-GLS or LAVi (HR: 0.937, 95% CI 0.821–1.071, $p = 0.340$ and HR: 0.930, 95% CI 0.812–1.064, $p = 0.289$; respectively). These findings were confirmed when only patients with FC were considered (HR: 0.933, 95% CI 0.793–1.097, $p = 0.401$ and HR: 0.920, 95% CI 0.808–1.048, $p = 0.208$, respectively). Of note, similar results were obtained when investigating conventional parameters of RV systolic performance (TAPSE, RV fractional area change, RV S′ velocity) or RV-GLS (data not shown). Conversely, ΔRV strain was not significantly related to cardiac outcomes at univariable analysis (HR: 0.964, 95% CI 0.721–1.28, $p = 0.803$).

4. Discussion

This is the first study evaluating the prognostic value of RV-FWS in FD. We found that RV-FWS does not retain an independent association with cardiovascular outcomes after adjustment for LV-GLS and LAVi in patients with FD. This evidence suggests that RV-FWS does not provide an incremental prognostic value over markers reflecting the severity of LV cardiomyopathy.

Our observations are in contrast with those reported in the setting of other cardiomyopathies with hypertrophic phenotype [10,11]. Indeed, RV strain has been shown as a strong prognostic marker in patients with hypertrophic cardiomyopathy (HCM) [9] and cardiac amyloidosis (CA) [10,11]. This difference might be possibly explained by the peculiar pathophysiology of RV impairment in FD, as compared to other cardiomyopathies with hypertrophic phenotype [4]. As previously hypothesized [7], RV-FWS reduction may be primarily due to intramyocardial storage in FD, with a minor role played by ventricular interdependence and/or afterload increase that usually take place in HCM and CA [4,10,11]. In this scenario, it is reasonable that RV-FWS do not provide an additive role in the prognostic stratification of patients with FD, as compared to parameters associated with the severity of LV cardiomyopathy.

Our results are in line with a large body of evidence showing LVH as a strong predictor of cardiovascular outcome in FD [4,12], as demonstrated by the highest AUC of indexed LV mass. Moreover, our findings corroborate recent data showing that LV-GLS may not only be a surrogate marker of myocardial fibrosis but also a prognostic marker in FD [13].

The present study is limited by its retrospective nature and the small sample size; the latter, however is a common issue in rare diseases. Indeed, the statistical power might not have been sufficient to detect an independent association between RV-FWS and outcomes. Moreover, the observational nature and the limited number of events did not allow to adjust for the effect of enzyme replacement therapy initiation or other potentially relevant clinical factors (i.e. age at onset of cardiac manifestations, hypertension). Thus, our results need to be confirmed in larger, specifically-designed studies. RV-FWS was calculated using a vendor-independent software (Tomtec), however the use of different software still represents an issue for the reproducibility of strain measurements and should be taken into consideration. Finally, cardiac magnetic resonance imaging was not systematically available and therefore we could not compare the prognostic impact of echocardiographic strain measurements and myocardial tissue characterization.

In conclusion, impaired RV-FWS was not independently associated with the occurrence of cardiovascular events in patients with FD,

confirming previous observations that prognosis is mainly driven by the severity of LV cardiomyopathy.

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