Prognostic Value of Right Ventricular Dysfunction in Heart Failure With Reduced Ejection Fraction

Superiority of Longitudinal Strain Over Tricuspid Annular Plane Systolic Excursion

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Background—In heart failure (HF) with reduced ejection fraction, right ventricular (RV) impairment, as defined by reduced tricuspid annular plane systolic excursion, is a predictor of poor outcome. However, peak longitudinal strain of RV free wall (RVFWS) has been recently proposed as a more accurate and sensitive tool to evaluate RV function. Accordingly, we investigated whether RVFWS could help refine prognosis of patients with HF with reduced ejection fraction in whom tricuspid annular plane systolic excursion is still preserved.

Methods and Results—A total of 200 patients with HF with reduced ejection fraction (age, 66±11 years; ejection fraction, 30±7%) with preserved tricuspid annular plane systolic excursion (>16 mm) underwent RV function assessment using speckle-tracking echocardiography to measure peak RVFWS. After a median follow-up period of 28 months, 62 (31%) patients reached the primary composite end point of all-cause death/HF rehospitalization. Median RVFWS was −19.3% (interquartile range, −23.3% to −15.0%). By lasso-penalized Cox-hazard model, RVFWS was an independent predictor of outcome, along with Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure-HF score, Echo-HF score, and severe mitral regurgitation. The best cutoff value of RVFWS for prediction of outcome was −15.3% (area under the curve, 0.68; $P<0.001$; sensitivity, 50%; specificity, 80%). In 50 patients (25%), RVFWS was impaired (ie, ≥−15.3%); event rate (per 100 patients per year) was greater in them than in patients with RVFWS <−15.3% (29.5% [95% confidence interval, 20.4–42.7] versus 9.4% [95% confidence interval, 6.7–13.1]; $P<0.001$). RVFWS yielded a significant net reclassification improvement (0.584 at 3 years; $P<0.001$), with 68% of nonevents correctly reclassified.

Conclusions—In patients with HF with reduced ejection fraction with preserved tricuspid annular plane systolic excursion, RV free-wall strain provides incremental prognostic information and improved risk stratification. (***Circ Cardiovasc Imaging*. 2018;11:e006894. DOI: 10.1161/CIRCIMAGING.117.006894.**)

Key Words: echocardiography, 2D ■ heart failure ■ heart ventricles ■ prognosis

In patients with heart failure and reduced ejection fraction (HFrEF), right ventricular (RV) systolic dysfunction represents a marker of poor prognosis.[1–5]

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In clinical practice, echocardiography is the mainstay of evaluation of RV function. Measurement of tricuspid annular plane systolic excursion (TAPSE) by M-mode echocardiography has long been considered as the simplest, yet the most reliable, indicator of RV dysfunction. Importantly, impaired RV function by TAPSE measurement is common in patients with HFrEF, being found in 35% to 50% of cases,[1,2,4,5] in whom it represents an independent marker of poor prognosis, either when used alone[1,3–5] or combined with pulmonary artery systolic pressure, as an indicator of RV-to-pulmonary circulation coupling.[2]

Recently, 2-dimensional (2D) strain imaging technique, such as speckle-tracking echocardiography (STE), has allowed cardiologists to investigate myocardial mechanics easily and with greater accuracy, being relatively angle independent.[6] Furthermore, this technique is reproducible,[7] and its findings have been validated against cardiac magnetic resonance.[8] Applicability of STE has recently been extended to RV,[9,10] allowing to demonstrate a prognostic role of RV longitudinal strain in different clinical settings,[11,12] including patients with HFrEF in whom RV longitudinal strain showed incremental prognostic value over left ventricular (LV) ejection fraction (EF)[13], being useful in risk stratification of prognosis in patients undergoing cardiac resynchronization therapy[14] or LV assist device implantation.[15]

Because STE has the capability to detect early abnormalities of systolic function in the preclinical stage,[16] this brings about the possibility to explore whether RV longitudinal strain is actually

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able to predict prognosis also in patients with HFrEF deemed to have preserved RV function when assessed by TAPSE. However, this issue has not yet been investigated. Additionally, no studies have quantified net reclassification improvement obtained by RV longitudinal strain–based methods in patients with HFrEF.

Therefore, in the present study, we sought to evaluate whether peak longitudinal strain of RV free wall (RVFWS) would provide additive prognostic information in HFrEF patients with preserved TAPSE.

Methods

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

Population

Consecutive patients with chronic HFrEF (EF ≤40%) were enrolled. Inclusion criteria were heart failure (HF) because of ischemic heart disease, hypertensive heart disease, or idiopathic cardiomyopathy; stable sinus rhythm; stable clinical conditions and optimal medical therapy during the last 3 months; >18 years of age; and good technical quality of echocardiograms. Ischemic heart disease was defined as previous myocardial infarction or significant coronary artery disease at coronary angiography. Exclusion criteria were TAPSE ≤16 mm because this cutoff has been demonstrated to predict poor outcome in large populations of patients with HF[2,5]; moderate-to-severe mitral or aortic stenosis, prosthetic valves, hypertrophic cardiomyopathy, untreated thyroid disease, pericardial disease, amyloidosis, active myocarditis, previous coronary artery bypass graft, recent myocardial infarction (≤6 months), recent (<6 months) implant of cardiac resynchronization device, cor pulmonale, congenital heart diseases, scheduled coronary revascularization, and life expectancy of <1 year because of comorbidities.

The hemoglobin value closest to enrollment visit (±3 months) was used to define anemia (hemoglobin concentration, <13.0 g/dL in men and <12.0 g/dL in women).[17] Estimated glomerular filtration rate was calculated using the last serum creatinine value available at the time of enrollment or the first value post-enrollment (whichever closer) with the MDRD study (Modification of Diet in Renal Disease) equation.[18] Chronic kidney disease was defined as estimated glomerular filtration rate <60 mL/min per 1.73 m^2 for >3 months.[18] Mean blood pressure in the brachial artery was calculated as the diastolic pressure plus one third of the difference between the systolic and diastolic pressures. Our study complies with the Declaration of Helsinki, and the protocol was approved by the local ethics committee. All patients provided written informed consent before entering the study.

Echocardiography

Images were obtained with patients in left-lateral decubitus, using commercially available systems (Vivid 7, Vivid S6; General Electric-Vingmed, Horton, Norway). Data acquisition was performed in the parasternal and apical views using a 3.5-MHz transducer. During breath hold, M-mode and 2D images were obtained, and 3 consecutive beats were saved in cineloop format. Analysis was performed offline by 2 independent observers using dedicated software (EchoPac 112.1.5; General Electric-Vingmed).

Left atrial (LA) volume was measured from apical 4- and 2-chamber views.[19] LV end-diastolic and end-systolic volumes, and EF, were calculated by Simpson biplane method from apical imaging planes.[19] Cardiac chamber volumes were indexed to body surface area.

Severity of mitral regurgitation (MR) was graded semiquantitatively (grades I–IV) from color-flow Doppler jet area and by measuring the width of the vena contract, as follows: mild MR, jet area/LA area <20% and vena contracta width <0.3 cm; moderate MR, jet area/LA area of 20% to 40% and vena contracta width of 0.3 to 0.69 cm; and severe MR, jet area/LA area >40% and vena contracta width ≥0.7 cm[20].

Tricuspid regurgitation severity was graded based on jet/right atrial area ratio. Tricuspid regurgitation was graded as trivial (jet area, <10% of right atrial area), mild (jet area, 10% to <20%), moderate (jet area, 20% to <33%), and severe (jet area, ≥33% of right atrial area).[20] Additionally, diameter of inferior vena cava and its respiratory variation were measured in the subcostal view and used to estimate right atrial pressure.[19] Peak systolic pulmonary artery pressure was estimated by adding right atrial pressure to systolic tricuspid regurgitation gradient.

Pulsed Doppler was used to record transmitral flow in the apical 4-chamber view.[21] Sample volume was placed at the tips of mitral valve leaflets. Peak early diastolic flow velocity (E), peak flow velocity of atrial contraction (A), and their ratio (E/A) were measured at their maximum amplitude. Deceleration time was measured from peak E velocity to the point when the E-wave descent intercepted the zero line: a value ≤140 ms was used to define restrictive LV filling pattern.[21] Pulsed-wave tissue Doppler (PW-TDI) early diastolic annular velocities (E′) were acquired at the septal and lateral annular sites and averaged as described.[21] The ratio between transmitral E velocity and the averaged E′ velocity (E/E′) was calculated.

RV Functional Analysis

RV function was assessed by using an off-axis apical 4-chamber view for better visualization of RV. TAPSE was measured as the systolic displacement of the lateral portion of the tricuspid annulus during systole, recorded on M-mode under 2D echocardiographic guidance.[10]

RV transverse diameter at the base and mid portion of RV, RV end-diastolic, and end-systolic areas were measured in the apical 4-chamber view by tracking the endocardial border of RV. RV fractional area change (FAC) was calculated as (RV end-diastolic area−end-systolic area)/RV end-diastolic area×100.[19]

Tricuspid annular S′ velocity was measured using pulsed-wave tissue Doppler.[10]

RV strain analysis was performed with 2D strain software (EchoPAC) using high frame rate acquisitions (>40 frames per second) of the RVFWS in the apical 4-chamber view (Figure 1).

After tracing the endocardial border of RV, the region of interest was automatically generated and manually adjusted to fit RV myocardial wall thickness, excluding the pericardium (Figure 1). Natural acoustic markers (speckles) were tracked throughout systole, starting from tricuspid valve closure until end systole, defined by pulmonic valve closure. The software automatically divides the RVFWS and the interventricular septum into 3 segments each (basal, mid, and apical), resulting in a 6-segment model. The quality of tracking was automatically validated by software and confirmed visually from the 2D images. Peak strain of RVFWS was then calculated as the arithmetic mean of the strain values in the 3 segments of RVFWS obtained from a 6-segment region of interest.[7,10] Segments were discarded if tracking was of poor quality, as were subjects with >2 segments per ventricle showing persistent inadequate tracking, despite attempts to readjust region of interest position and width.

Intraobserver and interobserver variabilities of RVFWS were evaluated in 15 randomly chosen subjects by 2 investigators and measured by calculating intraclass correlation coefficients. To assess reproducibility, the same observer, blinded to previous results, measured RVFWS for each selected patient again at least 1 week later.

Follow-Up

Patients were regularly followed up at our outpatient HF clinic by both clinical visits, made on a regular basis, and telephone calls, to ascertain readmission for worsening HF. All-cause mortality was recorded by chart review, telephone contact, and inspection of electronic files of death certificates. For the purpose of this study, the primary end point was the composite of death from any cause or rehospitalization for HF. For patients without events, the date of last contact was used for survival analysis.

Statistical Analysis

Continuous variables are expressed as mean±SD, or median (interquartile range [IQR]), and compared using Student *t* test (for normally distributed variables) or Mann–Whitney *U* test (for non-normally distributed variables). Categorical data are expressed as percentage and compared using χ^2 test or Fisher exact test, when appropriate. Brain natriuretic peptide

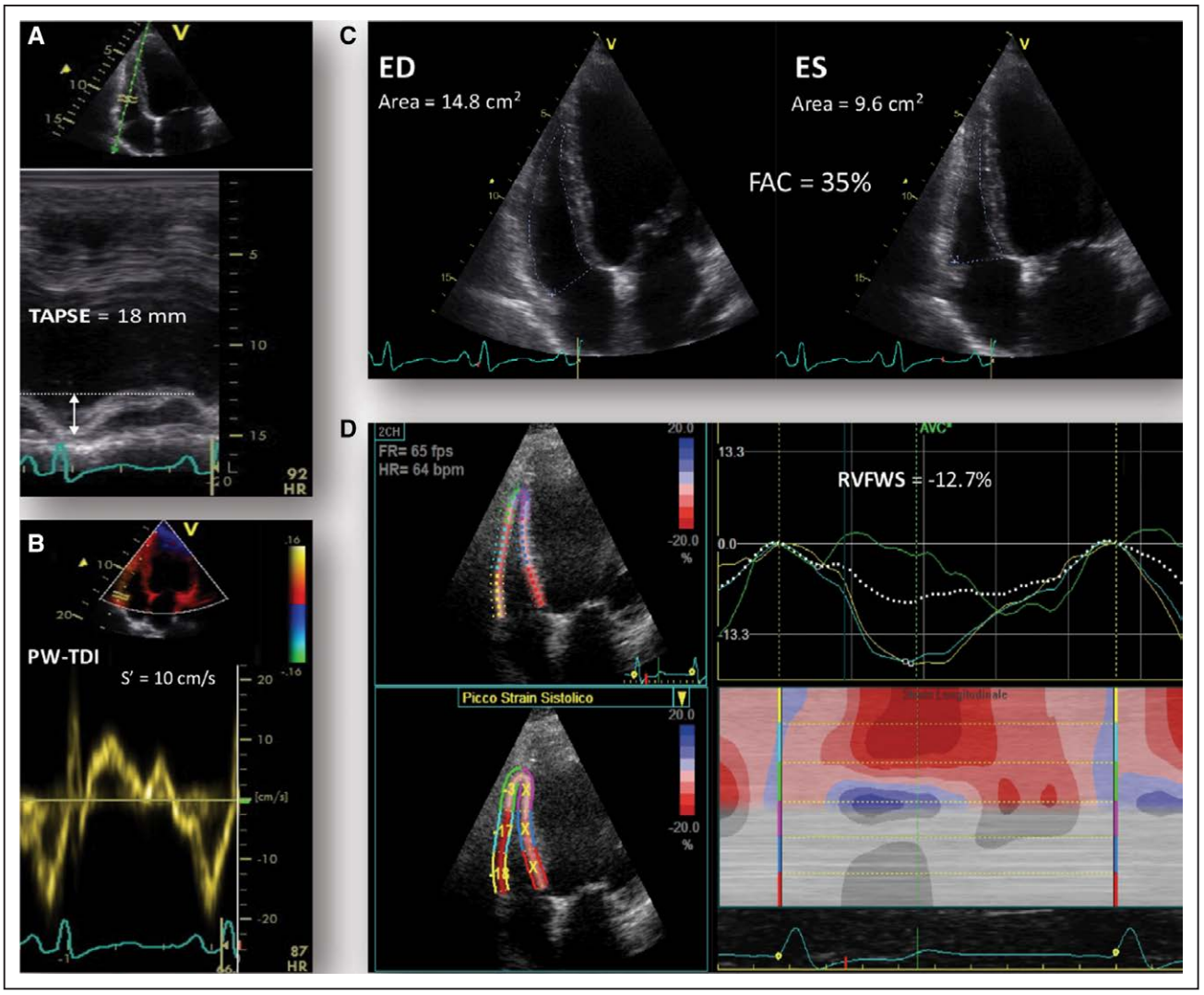

Figure 1. Determination of right ventricular (RV) systolic function in a typical patient. RV function was normal by (**A**) tricuspid annular plane systolic excursion (TAPSE) and (**B**) S′ by Pulsed-wave Tissue Doppler Imaging, slightly reduced by (**C**) RV fractional area change (FAC=35%) and clearly reduced by (**D**) longitudinal RV strain (RVFWS, −12.7%). ED indicates end-diastolic; ES, end-systolic; FR, frame rate; and HR, hazard ratio.

was logarithmically transformed for statistical analyses. Correlation between continuous variables was assessed using Spearman correlation coefficient.

Time-dependent receiver operator characteristic curves were used to determine the optimal prognostic RVFWS cutoff value (Youden method) for the primary end point at 2 years of follow-up. Using this cutoff, the study population was divided into 2 groups. Event rates (per 100 patients per year) were calculated. Survival curves were obtained using the Kaplan–Meier method and compared by log-rank statistic. Univariable Cox proportional-hazards model was used to analyze relationship between baseline covariables and end points. Results are reported as hazard ratios with 95% confidence intervals. Variables with P <0.1 at univariable analysis were further tested in multivariable Cox regression analysis. To avoid overfitting issues because of high dimensionality, we applied least absolute shrinkage and selection operator (lasso) penalization with the penalty parameter selected by 10-fold cross-validation (R package hdnom). Penalized regression is a flexible shrinkage approach that is effective when the number of events per variable is low (<10).[22] Because lasso coefficients are good for prediction but are not straightforward, multivariate Cox proportional hazard model is also presented. Two multivariable models were constructed based on inclusion of RVFWS either as a continuous variable or as binary categorical variable.

To further reduce the number of predictors in the final multivariable model, clinical predictors were aggregated into the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS)-HF risk score[23] (a risk score for patients with HFrEF, including age, sex, systolic blood pressure, estimated glomerular filtration rate, diabetes mellitus, prior HF hospitalization, hemoglobin, prior myocardial infarction/coronary artery bypass graft, body mass index, and heart rate). Then, 3 groups of low (0–4), medium (5–6), and high (7–12) risk were identified.[23] Similarly, the Echo-HF score—a recently developed echocardiographic risk score for mortality in HFrEF,[24] which incorporates 5 echocardiographic variables (left atrial volume index, end-systolic volume index, deceleration time of transmittal E velocity, TAPSE, and systolic pulmonary artery pressure)—was calculated and used instead of each individual predictor.

The incremental prognostic value of RVFWS at 3 years was assessed by adding RVFWS to a base model containing EMPHASIS-HF score and Echo-HF score. We assessed reclassification of event risk using continuous net reclassification improvement because it does not require a prior definition of strata risk, thus considering change in the estimation prediction as a continuous variable. In addition, the discriminative ability of various survival models was compared using Harrell C index.[25]

Analyses were performed with STATA 13 (StataCorp LP), R (version 3.4.0), and SAS University Edition (SAS Institute, Inc, Cary, NC). A 2-tailed *P* value <0.05 was considered statistically significant.

Results

From 222 eligible patients initially screened, 13 (6%) with RVFWS not suitable for strain analysis were excluded, and 9 (4%) were lost to follow-up, leaving a final study population of 200 patients. Tables 1 and 2 summarize their clinical and echocardiographic characteristics, respectively. Age averaged 66±11 years, and most patients were men (76%). Sixty-five patients (33%) were in New York Heart Association class ≥3. Ischemic heart disease was the underlying pathogenesis in 33% of cases.

In the whole population, median LVEF, TAPSE, and RVFWS were 30% (IQR, 25%–35%), 20 mm (IQR, 18–23), and −19.3% (IQR, −22.3% to −15.0%), respectively. A restrictive filling pattern was found in 31% of patients, whereas 16% had severe MR (Table 2). RVFWS worsened with increasing New York Heart Association class (*P*<0.0001 for trend), but it was not associated with brain natriuretic peptide levels (ρ=0.11; *P*=0.1258). There was a weak but significant correlation between RVFWS and LVEF (ρ=−0.28; *P*=0.001), end-diastolic volume index (ρ=0.18; *P*=0.0124), end-systolic volume index (ρ=0.23; *P*=0.001), and pulmonary artery systolic pressure (ρ=0.19; *P*=0.007).

Table 1. Baseline Clinical Characteristics

	All Patients (n=200)	Events (n=62)	No Event (n=138)	*P* Value
Age, y	66±11	68±10	65±11	0.065
Male sex (%)	151 (76)	54 (87)	97 (70)	0.011
Body mass index, kg/m^2	26.5±4.2	25.9±3.6	27.1±4.4	0.069
Mean blood pressure, mm Hg	87.1±10.4	84.2±8.6	88.3±10.9	0.009
Heart rate, bpm	71.7±11.1	71.6±10.9	71.7±11.2	0.918
NYHA class III–IV	65 (33)	28 (45)	37 (27)	0.010
Diabetes mellitus, (%)	46 (25)	16 (26)	33 (24)	0.773
COPD, (%)	55 (28)	18 (29)	37 (27)	0.745
Ischemic pathogenesis, (%)	65 (33)	23 (37)	42 (30)	0.352
Prior HF hospitalization (%)	24 (12)	7 (11)	17 (12)	0.836
eGFR, mL/min per 1.73 m^2	71.1±25.4	63.7±20.8	74.4±26.6	0.0053
Hemoglobin, gr/dL	13.3±1.6	13.1±1.7	13.4±1.5	0.104
EMPHASIS-HF score, median (IQR)	4 (3–5)	5 (4–6)	4 (3–5)	0.0001
BNP, median (IQR)	391 (197–634)	506 (297–698)	327 (180–603)	0.009
Diuretics, (%)	182 (91)	59 (95)	123 (89)	0.168
β-Blockers (%)	159 (80)	48 (77)	111 (80)	0.625
ACE inhibitors/ARBs (%)	176 (88)	55 (89)	121 (88)	0.836
Aldosterone antagonists (%)	90 (45)	32 (52)	58 (42)	0.208

EMPHASIS score includes age, sex, systolic blood pressure, eGFR, diabetes mellitus, and prior HF hospitalization; hemoglobin; history of coronary artery disease; and body mass index and heart rate. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blockers; BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; EMPHASIS, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; HF, heart failure; IQR, interquartile range; and NYHA, New York Heart Association.

Table 2. Baseline Echocardiographic Characteristics

	All Patients (n=200)	Events (n=62)	No Event (n=138)	*P* Value
EDVI, mL/m^2	108±37	126±46	99±29	0.0001
ESVI, mL/m^2	77±33	93±42	69±24	0.0001
Ejection fraction, %; median (IQR)	30 (25–35)	28 (25–34)	31 (26–35)	0.0198
LAVI, mL/m^2	53±18	64±16	48±17	0.0001
E/A ratio	1.55±1.291	2.01±1.27	1.33±1.11	0.0001
Deceleration time, ms	199±84	175±85	210±82	0.0056
Restrictive filling pattern (%)	61 (31)	28 (45)	33 (24)	0.003
E/E′$_{averg}$ median (IQR)	13.7 (10.3–17.7)	16.0 (12.2–21.3)	12.8 (9.6–16.7)	0.0006
PASP, mm Hg	34.2±15.2	41.2±15.5	31.1±13.9	0.0001
Severe mitral regurgitation (%)	32 (16)	18 (29)	14 (10)	0.001
Echo-HF score, median (IQR)	1 (0–2)	2 (1–3)	1 (0–2)	0.0001
TAPSE, mm	21.1±3.7	20.7±3.8	21.1±3.6	0.461
S′ tricuspid, cm/s	11.9±2.6	11.4±2.5	12.2±2.6	0.0810
RVFAC, %; median (IQR)	39 (28–47)	35 (25–41)	41 (30–50)	0.0022
RVFWS, %	−19.6±6.2	−16.7±5.6	−20.9±5.9	0.0001
RVDb, cm	3.8±0.7	4.0±0.7	3.7±0.6	0.0052
RVDm, cm	2.7±0.7	2.6±0.6	2.7±0.8	0.487
RVDA, cm^2	19.2±8.4	20.3±5.8	18.7±9.3	0.0043
RVSA, cm^2	11.8±5.0	13.7±5.1	10.9±4.8	0.0002

Echo-HF score includes ESVI, LAVI, deceleration time, TAPSE, and PASP. EDVI indicates end-diastolic volume index; ESVI, end-systolic volume index; HF, heart failure; IQR, interquartile range; LAVI, left atrial volume index; PASP, pulmonary artery systolic pressure; RVDA, right ventricular end-diastolic area; RVDb, right ventricular transverse diameter at the base; RVDm, right ventricular transverse diameter at the mid portion; RVFAC, right ventricular fractional area change; RVFWS, strain of right ventricular free wall; RVSA, right ventricular end-systolic area; and TAPSE, tricuspid annular plane systolic excursion.

RV Free-Wall Strain and Outcome

During a median follow-up of 28 months (IQR, 13–44), 62 patients (31%) reached the composite end point: 25 patients died (13%), and 54 patients (27%) were hospitalized for worsening HF. Compared with patients without events, patients who reached the composite end point were older and prevalently men (Table 1; *P*<0.05). They also showed more advanced New York Heart Association class, higher brain natriuretic peptide levels, lower mean blood pressure, and more severe renal dysfunction

(*P*<0.01 for all; Table 1). Accordingly, the EMPHASIS-HF risk score was higher in patients with events compared with those without (*P*=0.0001; Table 1).

Patients with events also showed higher LV volumes, lower EF, increased left atrial volume index (LAVI), more advanced diastolic dysfunction, increased pulmonary artery systolic pressure, and higher prevalence of severe MR than event-free patients (Table 2). Accordingly, Echo-HF score was greater in patients with events (*P*=0.0001; Table 2). Diastolic RV basal diameter and areas were also significantly greater in this group.

Because by protocol, we enrolled only patients with TAPSE >16 mm, this parameter did not differ between patients with and without events (Table 2). Similarly, tricuspid S′ velocity was only slightly reduced in patients with events compared with those without events. However, both RVFWS and RV FAC were significantly impaired in patients with events (Table 2).

Table 3. Univariable Predictors of the Composite End Point

	Univariable	
	HR (95% CI)	*P* Value
Age, y (per 10 y increase)	1.31 (0.99–1.71)	0.051
Male sex (yes/no)	2.36 (1.12–4.96)	0.024
NYHA class	1.86 (1.18–2.93)	0.008
Mean BP (per 5 mm Hg increase)	0.83 (0.73–0.94)	0.004
eGFR (per 10 mL·m^{-2}·min^{-1})	0.85 (0.76–0.95)	0.003
LogBNP (per unit increase)	1.64 (1.22–2.20)	0.001
Hemoglobin (per unit increase)	0.86 (0.73–1.02)	0.088
EMPHASIS score (per unit increase)	1.27 (1.13–1.43)	<0.0001
LAVI (per 10 mL/m^2 increase)	1.45 (1.29–1.64)	<0.0001
ESVI (per 10 mL/m^2 increase)	1.15 (1.08–1.22)	<0.0001
Ejection fraction (per 5% increase)	0.86 (0.71–1.03)	0.099
Severe mitral regurgitation (yes/no)	3.62 (2.05–6.38)	<0.0001
DT of E velocity (per 25 ms increase)	0.87 (0.79–0.94)	0.001
E/E′ ratio (per 5 U increase)	1.29 (1.14–1.46)	<0.0001
PASP (per 10 mm Hg increase)	1.48 (1.27–1.72)	<0.0001
Echo-HF score (per unit)	1.73 (1.43–2.09)	<0.0001
RVDb (per unit)	1.79 (1.25–2.57)	0.001
RVDA (per unit, cm^2)	1.02 (0.99–1.04)	0.057
RVSA (per unit, cm^2)	1.09 (1.05–1.14)	<0.0001
RVFAC (per unit, %)	0.97 (0.96–0.99)	0.002
Tricuspid S′ (cm/s, per unit)	0.91 (0.83–1.00)	0.069
RVFWS (per 1% increase)	1.09 (1.05–1.15)	<0.0001
RVFWS ≥−15.3% (yes/no)	2.96 (1.79–4.89)	<0.0001

Ischemic pathogenesis, diabetes mellitus, COPD, the absence of β-blockers or ACEI/ARBs therapy, TAPSE, mid-RV diastolic diameter, and cardiac resynchronization therapy during follow-up (time-dependent variable) were not significant. ACE indicates angiotensin-converting enzyme; ARB, Angiotensin receptor blockers; BP, blood pressure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DT, deceleration time; eGFR, estimated glomerular filtration rate; EMPHASIS, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; ESVI, end-systolic volume index; HF, heart failure; HR, hazard ratio; LAVI, left atrial volume index; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; RV, right ventricular; RVDA, right ventricular end-diastolic area; RVDb, right ventricular transverse diameter at the base; RVFAC, right ventricular fractional area change; RVFWS, strain of right ventricular free wall; RVSA, right ventricular end-systolic area; and TAPSE, tricuspid annular plane systolic excursion.

Table 3 shows results of univariable Cox regression analysis. In addition to clinical characteristics and echocardiographic measurements of LV function, RV function parameters (RV FAC, tricuspid S′ velocity, and RVFWS) significantly predicted the composite end point. RV dimension parameters were also univariable predictors of events.

The most regularized and parsimonious model (penalized lasso–Cox regression model) with a cross-validated error within 1 standard error of the minimum included 4 variables: EMPHASIS-HF score (penalized coefficient, 0.01 600 574), Echo-HF score (penalized coefficient, 0.26 074 073), MR severity (penalized coefficient, 0.13 501 567), and RVFWS (penalized coefficient, 0.01 168 053). Thus, after adjusting for RV dimension and other univariable predictors, only RVFWS independently predicted the composite end point, either when assessed as a continuous variable or as a categorical variable, whereas RV FAC and S′ no longer remained significant (Table 4). The model yielded a C index of 0.76, and the proportional-hazards assumption test was not significant (χ^2=4.07; *P*=0.5392).

The best cutoff value of RVFWS for the prediction of outcome was ≥−15.3% (area under the curve, 0.68; *P*<0.001; sensitivity, 50%; specificity, 80%). In 50 patients (25%), RVFWS resulted impaired (≥−15.3%). Incidence rate (per 100 patients per year) of the composite end point in these patients was significantly higher than in patients in whom RVFWS was not impaired (Figure 2B; *P*<0.0001). Kaplan–Meier survival curves showed lower survival rates in patients with impaired RVFWS than in those with RVFWS <−15.3% (Figure 2A).

When added to a base model, including EMPHASIS-HF score and Echo-HF score, RVFWS yielded a slight increase in C index (from 0.73 to 0.75; *P*=0.082). However, it provided a significant continuous net reclassification improvement of 0.584 (95% confidence interval, 0.308–0.861; *P*<0.001), suggesting marked improvement in reclassification of event risk, with 68% of nonevents correctly reclassified.

Reproducibility of RV Longitudinal Strain

Interobserver variability of RVFWS was small (intraclass correlation coefficient, 0.86; 95% confidence interval, 0.39–0.99; *P*<0.0001), as was intraobserver variability (0.87; 95% confidence interval, 0.77–0.97; *P*<0.0001).

Discussion

The present study shows that, in patients with chronic HFrEF, detailed assessment of RV function through measurement of longitudinal strain of RVFWS is able to predict outcome during follow-up, independently of, and incrementally to, TAPSE and other recognized clinical and echocardiographic predictors of events. In particular, for the first time, we demonstrated that among patients with preserved TAPSE, there still is a proportion of patients in whom longitudinal function of RV may actually be impaired when assessed by using strain analysis through STE. A value of RVFWS ≥−15.3% in patients with preserved TAPSE was associated with an adjusted 2-fold increased risk of events. Furthermore, assessment of RVFWS longitudinal

Table 4. Multivariable Cox Regression Model by Penalized (Lasso) Cox Regression

	RVFWS as Continuous Variable		RVFWS as Categorical Variable	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
EMPHASIS-HF score				
Low risk (0–4)	Reference		Reference	
Intermediate risk (5–6)	2.08 (1.07–4.05)	0.031	2.10 (1.08–4.09)	0.028
High risk (≥7)	3.28 (1.31–8.20)	0.011	3.45 (1.38–8.60)	0.008
Echo-HF score (per unit)	1.38 (1.10–1.72)	0.005	1.43 (1.14–1.78)	0.002
Severe MR (yes/no)	1.75 (0.93–3.29)	0.084	1.54 (0.81–2.94)	0.187
RVFWS (per unit increase)	1.06 (1.01–1.11)	0.014		
RVFWS ≥–15.3% (yes/no)			1.93 (1.13–3.31)	0.016

CI indicates confidence interval; EMPHASIS, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; HF, heart failure; HR, hazard ratio; MR, mitral regurgitation; and RVFWS, strain of right ventricular free wall.

strain was able to increase the prognostic ability of the model, further improving reclassification of patients' risk.

RV failure is a detrimental condition that is associated with significant morbidity and mortality, not only in patients with HFrEF but also in HF with preserved EF[3,26] and other cardiac diseases.[11,12] Recognition of the prognostic importance of RV function has recently stimulated the development of imaging techniques capable of reliably assessing RV function. Although RV assessment by conventional 2D imaging is difficult because of the complex shape of this chamber, the simple measurement of TAPSE has been recognized as a predictor of prognosis in HF, either when used alone[1,5] or adjusted for the estimated systolic pulmonary artery pressure, as a measure of ventricular arterial coupling.[2,3] However, it must be kept in mind that TAPSE represents the longitudinal contraction of the basal segment of RVFWS only and not of the entire RV. Furthermore, the intercept angle between the Doppler cursor and the tricuspid annulus is also critical in accurately measuring TAPSE.

Recently, myocardial mechanics have been easily studied by 2D strain imaging techniques—that is, STE—which have the advantage of being non-Doppler based and, therefore, relatively angle independent.[6] STE has the ability to discriminate between normal, active myocardial segmental deformation, versus passive displacement of a dysfunctional myocardium because of adjacent segment tethering and global cardiac motion.[6,27] Although initially developed to study LV mechanics, STE has recently been extended to the study of RV,[9,10] making possible to demonstrate the prognostic utility of RV longitudinal strain in different clinical settings, including HF.[11–14,28,29] Therefore, strain imaging may provide a nongeometric approach to RV assessment, and it has been validated against cardiac magnetic resonance.[30]

Comparison With Previous Studies

In 171 patients with systolic HF, Motoki et al, using the vector-velocity imaging technique, showed that RV global strain was

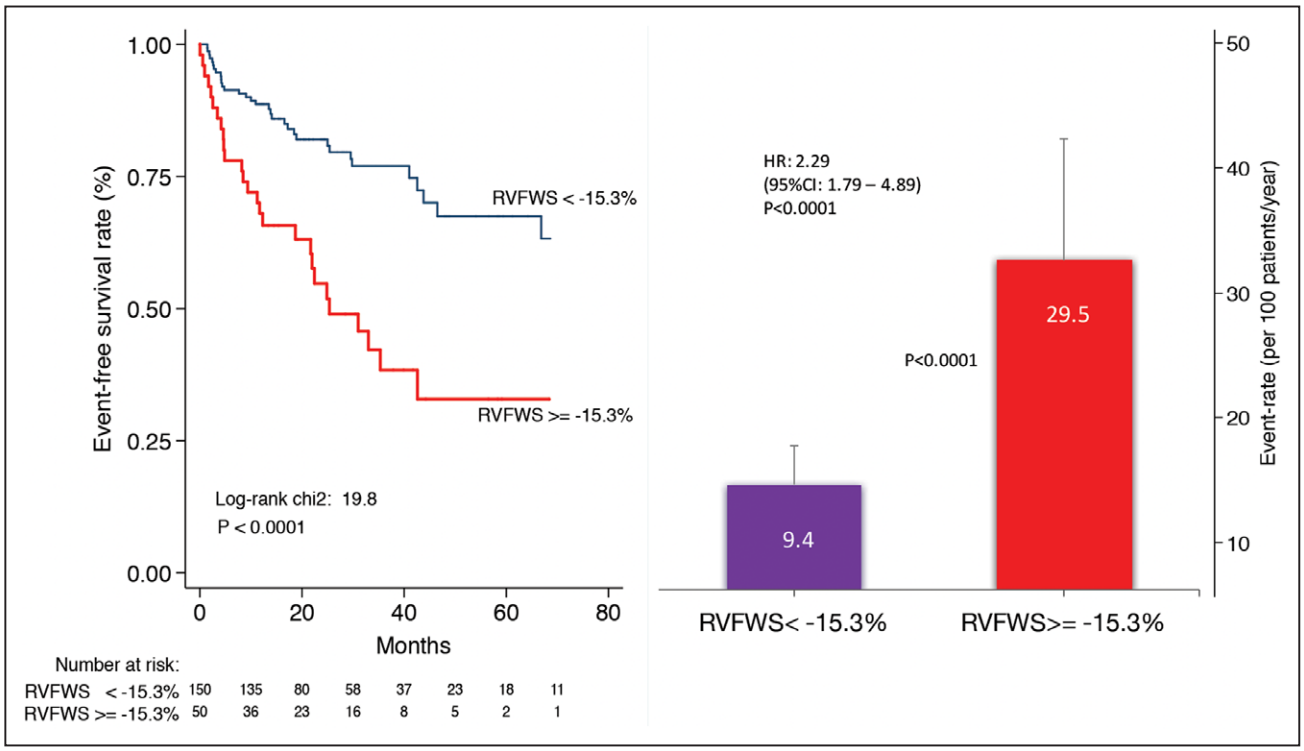

Figure 2. Survival Analysis. **Left**, Kaplan–Meier analysis for patients stratified by strain of right ventricular free wall (RVFWS): heart failure and reduced ejection fraction patients with preserved tricuspid annular plane systolic excursion but impaired RVFWS (≥–15.3%) had poorer outcome (log-rank *P*<0.0001). **Right**, incidence rates (per 100 patients/y) are shown for patients stratified by RVFWS. CI indicates confidence interval; and HR, hazard ratio.

independently associated with cardiac events during follow-up. However, in that study, RV strain was analyzed retrospectively, and although it provided incremental prognostic value with respect to LVEF, its accuracy to predict cardiac events was modest when the multivariable Cox regression adjustment included age, ischemic pathogenesis, and NTproBNP (N-terminal pro-B-type natriuretic peptide), suggesting insufficient statistical power to detect incremental prognostic value over other indexes, including TAPSE.[13]

In 120 HF patients undergoing cardiac resynchronization therapy implant, 2D longitudinal strain of RVFWS also emerged as a significant predictor of cardiac events independently of ischemic pathogenesis, QRS duration, left bundle-branch block, use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, excessive LV dilatation, MR, and absence of mechanical dyssynchrony.[14] Although in that study, TAPSE was also a significant predictor of events by univariable analysis, it was not retained in the multivariable model; therefore, the prognostic role of RV longitudinal strain relative to TAPSE remained undetermined.

To our knowledge, this is the first study demonstrating the presence of RV dysfunction (assessed by 2D longitudinal strain of the free wall) in patients with preserved TAPSE (>16 mm; 25% of our population), suggesting that the use of TAPSE as a sole descriptor of RV function might be questionable. In fact, despite preserved TAPSE, in the present study, impaired RVFWS was associated with a 3-fold increase in the risk of events, which remained significant after adjusting for clinical and echocardiographic confounders. Because it has been demonstrated a close negative correlation between RV longitudinal strain and RV stroke work index,[31] which represents the hemodynamic parameter usually used to evaluate RV function in patients waiting for heart transplant, RV longitudinal strain seems a reliable method for the assessment of RV function.

Clinical Implications

By demonstrating a strong and independent prognostic role of RVFWS in the presence of preserved TAPSE, our data may have important clinical implications because they suggest that in HFrEF, assessment of RV function by traditional measurements (ie, TAPSE and FAC) should be complemented by analysis of longitudinal strain, to improve the identification of patients who are at risk for adverse events. Our results are in line with previous reports demonstrating the potential of RV strain in several populations to detect subtle changes in RV function.[12,32]

Study Limitations

This is a single-center experience with a relatively small sample size. Speckle-tracking requires user experience and high-quality images, and it is not currently recommended for routine RV assessment. However, feasibility and reproducibility of RVFWS in our study was good, with excellent levels of agreement, as in previous studies in HFrEF patients.[13,14] Our cutoff value for RVFWS for discrimination between patients with and without events was chosen using time-dependent receiver operator characteristic relative to our population because reference limits of RV strain derived from larger HF populations are currently lacking. Therefore, the cutoff value of −15.3% for RVFWS needs to be further tested in larger HF studies. There is no consensus about which RV strain parameter should be used in clinical practice: we used free-wall longitudinal strain instead of global RV strain because it demonstrated the highest diagnostic accuracy to predict a depressed RV stroke work index in a simultaneous echocardiographic-catheterization study,[31] suggesting that the free wall might better reflect function of RV than global RV strain.

Conclusions

This study confirms that RV dysfunction is an independent determinant of outcomes in patients with HFrEF. Two-dimensional strain imaging by STE seems to be a reliable quantification tool for this purpose, emerging as a more accurate predictor of outcomes than TAPSE. Therefore, assessment of RV function should be implemented by analysis of longitudinal strain in patients with HFrEF, to improve identification of patients who are at risk for adverse events.

Disclosures

None.

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CLINICAL PERSPECTIVE

In patients with heart failure and reduced ejection fraction, reduced tricuspid annular plane systolic excursion represents a marker of poor prognosis. However, peak longitudinal strain of right ventricular (RV) free wall has recently been proposed as a more accurate and sensitive tool to evaluate RV function. In the present study, analyzing 200 consecutive heart failure and reduced ejection fraction patients with preserved RV function by tricuspid annular plane systolic excursion (>16 mm), RV function was also quantified with RV fractional area change, S′ velocity by Pulsed-wave Tissue Doppler Imaging, and strain of RV free wall. The present study first demonstrates the presence of RV dysfunction (assessed by 2-dimensional longitudinal strain of the free wall) in patients deemed to have preserved RV function when assessed by tricuspid annular plane systolic excursion. During a median follow-up period of 28 months, 62 patients reached the primary composite end point of all-cause death/heart failure rehospitalization. Strain of RV free wall was an independent predictor of outcome. Furthermore, strain of RV free wall provided incremental prognostic value to baseline clinical and echocardiographic information. Our data may have important clinical implications, suggesting that assessment of RV function with traditional measurements should be implemented by analysis of longitudinal strain in patients with heart failure and reduced ejection fraction, to improve risk stratification.

Prognostic Value of Right Ventricular Dysfunction in Heart Failure With Reduced Ejection Fraction: Superiority of Longitudinal Strain Over Tricuspid Annular Plane Systolic Excursion

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