Right Ventricular Global Longitudinal Strain and Outcomes in Heart Failure with Preserved Ejection Fraction

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Background: Right ventricular (RV) strain has emerged as an accurate tool for RV function assessment and is a powerful predictor of survival in patients with heart failure with reduced ejection fraction. However, its prognostic impact in patients with heart failure with preserved ejection fraction (HFpEF) remains unclear. The aim of this study was to compare the prognostic value of RV global longitudinal strain (RVGLS) by two-dimensional speckle-tracking echocardiographic (STE) imaging in patients with HFpEF against conventional RV function parameters.

Methods: Patients with HFpEF were prospectively recruited, and 149 of 183 (81%) with analyzable STE RVGLS images constituted the final study population (mean age, 78 ± 9 years; 61% women), compared with 28 control subjects of similar age and sex. All control subjects and 120 patients also underwent cardiac magnetic resonance imaging. Patients were followed up for a primary end point of all-cause mortality and first heart failure hospitalization, and Cox regression analysis was performed.

Results: Mean STE RVGLS was significantly altered in patients with HFpEF compared with control subjects (−21.7 ± 4.9% vs −25.9 ± 4.2%, $P < .001$). STE RVGLS correlated well with RV ejection fraction by cardiac magnetic resonance ($r = -0.617$, $P < .001$). Twenty-eight patients with HFpEF (19%) had impaired STE RVGLS (>−17.5%). During a mean follow-up period of 30 ± 9 months, 91 patients with HFpEF (62%) reached the primary end point. A baseline model was created using independent predictors of the primary end point: New York Heart Association functional class III or IV, hemoglobin level, estimated glomerular filtration rate, and the presence of moderate or severe tricuspid regurgitation. Impaired STE RVGLS provided significant additional prognostic value over this model (χ^2 to enter = 7.85, $P = .005$). Impaired tricuspid annular plane systolic excursion and fractional area change, however, did not.

Conclusions: In patients with HFpEF, impaired RVGLS has strong prognostic value. STE RVGLS should be considered for systematic evaluation of RV function to identify patients at high risk for adverse events. (J Am Soc Echocardiogr 2020;■:■-■.)

Keywords: Heart failure, Preserved ejection fraction, Right ventricle, Speckle-tracking echocardiography, Prognosis

The role of the right ventricle in the pathophysiology of cardiac diseases has been underestimated for many years and has only recently emerged as an independent predictor of morbidity and mortality in patients with heart failure (HF).[1-3] Few studies have evaluated the prognostic impact of right ventricular dysfunction (RVD) specifically in HF with preserved ejection fraction (HFpEF).[4-8] Although different parameters were used to measure right ventricular (RV) function, those studies all found that patients with RVD had a worse prognosis, and it now seems clear that RVD is associated with the progression of HFpEF

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Abbreviations

2D = Two-dimensional

AF = Atrial fibrillation

CMR = Cardiac magnetic resonance

eGFR = Estimated glomerular filtration rate

eSPAP = Estimated systolic pulmonary artery pressure

FAC = Fractional area change

HF = Heart failure

HFpEF = Heart failure with preserved ejection fraction

ICC = Intraclass correlation coefficient

LV = Left ventricular

NT-proBNP = N-terminal pro–brain natriuretic peptide

NYHA = New York Heart Association

RV = Right ventricular

RVD = Right ventricular dysfunction

RVEF = Right ventricular ejection fraction

RVFWLS = Right ventricular free wall longitudinal strain

RVGLS = Right ventricular global longitudinal strain

STE = Speckle-tracking echocardiographic

TAPSE = Tricuspid annular plane systolic excursion

through multiple mechanisms not yet completely understood. Despite growing interest in RV function, its evaluation remains challenging. The right ventricle has a unique crescent shape, which adds complexity to the quantification of its function. Therefore, the current recommendations for cardiac chamber quantification of the American Society of Echocardiography and the European Association of Cardiovascular Imaging favor a multiparametric approach, including fractional area change (FAC), Doppler tissue imaging–derived tricuspid lateral annular systolic velocity wave (S′) and tricuspid annular plane systolic excursion (TAPSE), while cardiac magnetic resonance (CMR)–derived RV ejection fraction (RVEF) remains the gold standard for RV evaluation.[9] Yet echocardiography is more readily available in daily practice, and new techniques are currently being developed using myocardial deformation imaging to guide diagnosis.[10] RV global longitudinal strain (RVGLS) by two-dimensional (2D) speckle-tracking echocardiographic (STE) imaging is emerging as a new reliable tool for the assessment of RV mechanical changes with acceptable variability and less angle dependency than other parameters.[11-14] Additional prognostic value of RV strain for the prediction of survival in patients with HF with reduced ejection fraction[15,16] and in those with pulmonary hypertension[17] has recently been highlighted, but data for HFpEF remain scarce. Accordingly, we aimed to evaluate the prognostic significance of different parameters of RVD in HFpEF, with data from both echocardiography and CMR.

METHODS

Study Population

Between December 2015 and June 2017, patients diagnosed with HFpEF were prospectively evaluated for inclusion in the study until obtaining a sample size calculated to achieve 80% power with $\alpha = 0.05$. The diagnosis of HFpEF was made according to the latest European Society of Cardiology guidelines[18]: presence of symptoms and/or signs of HF, preserved left ventricular (LV) ejection fraction (>50%), elevated levels of N-terminal pro–brain natriuretic peptide (NT-proBNP; >125 pg/mL), and echocardiographic evidence of cardiac functional and structural alterations (LV hypertrophy, left atrial enlargement, and/or diastolic dysfunction). The exclusion criteria were severe valvular disease (except secondary tricuspid regurgitation), infiltrative or hypertrophic cardiomyopathy, acute coronary syndrome in the previous 30 days, chronic obstructive pulmonary disease with a Global Initiative for Chronic Obstructive Lung Disease stage 3 or 4, congenital heart disease, pericardial disease, and atrial fibrillation (AF) with a ventricular response >140 beats/min. A total of 183 patients satisfied the inclusion criteria, but STE RVGLS analysis was feasible in 149 patients, which constituted the final study population (Figure 1). The main characteristics of the 34 excluded patients did not differ from those of our final study population. Continuous H_2FPEF score (heavy, hypertensive, AF, pulmonary hypertension, elder, and filling pressure)[19] was retrospectively calculated to confirm the high probability of HFpEF in the population.

To constitute a control group of similar age and sex, asymptomatic volunteers aged 60 to 90 years were screened by advertisement in the local community. They all underwent a full clinical examination, electrocardiography, echocardiography, and exercise stress testing. Exclusion criteria were (1) any evidence of heart disease as indicated by clinical history, physical examination, presence of abnormal findings on rest or stress electrocardiogram, or presence of abnormal cardiac function or valve disease on echocardiography; (2) contraindications to CMR; and (3) diabetes. Twenty-eight subjects satisfied the inclusion criteria.

Control subjects and patients underwent blood sampling, complete transthoracic echocardiography, and CMR (in the absence of following contraindications: pacemaker, claustrophobia, and estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2). The local ethics committee approved the study, and all patients gave written informed consent before study enrollment (ClinicalTrials.gov identifier NCT03197350). The investigation conformed to the principles outlined in the Declaration of Helsinki.

Clinical Data

Patients' medical histories and treatments were prospectively recorded. Other information was retrieved from medical files and from review of hospital records. All subjects underwent a full clinical examination.

Transthoracic Echocardiography

Standardized complete transthoracic echocardiographic examinations were performed according to established guidelines[20] using iE33 ultrasound systems (Philips Medical Systems, Andover, MA) equipped with a 3.5/1.75-MHz phased-array transducer and stored on an Xcelera 2.1 picture archiving and communication system server (Philips Medical Systems). TAPSE, FAC, and S′ velocity were measured according to established guidelines in four-chamber views oriented to the right ventricle. Estimated systolic pulmonary artery pressure (eSPAP) was calculated on the basis of the Bernoulli simplified equation on continuous-wave Doppler imaging of tricuspid regurgitation maximum jet velocity, added to estimated right atrial pressure on the basis of inferior vena cava diameter and collapsibility.

Global LV and RV strains were computed using 2D STE software (TomTec Imaging Systems, Unterschleissheim, Germany). At an end-systolic frame, a region of interest was traced on the endocardial

HIGHLIGHTS

- Myocardial deformation is a useful tool to assess cardiac function.
- Echocardiographic strain is particularly valuable to evaluate the right ventricle.
- RV function is altered in HFpEF.
- RV dysfunction by strain has a strong prognostic value in HFpEF.

cavity interface by using a point-and-click approach. The region of interest was automatically selected to approximate the myocardium between the endocardium and epicardium. The region of interest was adjusted further to ensure that all myocardial regions were included. Then the software captured the myocardium, automatically tracking its motion and thickening on the subsequent frames. For the assessment of RV strain, we evaluated the peak global strain of the whole myocardium, including the septum (RVGLS), and of the free wall (RV free wall longitudinal strain [RVFWLS]) in the apical four-chamber view focused on the right ventricle. LV global longitudinal strain was computed by averaging four-, three-, and two-chamber views. Images with poor-quality tracking were excluded. RVGLS and LV global longitudinal strain are negative values, where a lower (more negative) value indicates better function. For patients in AF at the time of the echocardiography, all measurements were computed by averaging measures over three beats.

CARDIAC MAGNETIC RESONANCE

CMR was performed using a 3-T system (Ingenia; Philips Medical Systems, Best, the Netherlands). The different sequences have been previously described.[21] Briefly, 10 to 12 consecutive short-axis images covering the entire left ventricle and one-, two-, three-, and four-chamber long-axis cine steady-state free precession images were acquired for assessment of myocardial function. Ten to 15 min after the injection of 0.2 mmol/kg gadolinium-based contrast, identical prescriptions of short- and long-axis slices were acquired using a 2D or three-dimensional inversion recovery sequence allowing the assessment of myocardial viability. CMR studies were analyzed using the freely available software Segment version 2.2 (Medviso, Lund, Sweden). RV and LV volumes and ejection fractions were computed from the short-axis cine images by semiautomatically tracing the endo- and epicardial contours in the end-diastolic and end-systolic phases. Values were indexed to body surface area. To minimize the effect of AF on CMR measurements, sequences with arrhythmia rejection were used, tolerating 20% variation of R-R interval.

Follow-Up

Patients were prospectively followed by ambulatory visits and phone calls at 6-month intervals for ≥1 year. Clinical and survival status was obtained by follow-up visits and by phone contact with the patients, their relatives, or their physicians if necessary. The primary end point was a composite of all-cause mortality or hospitalization for HF, whichever came first. Vital status was ascertained by medical record review. First HF hospitalization was defined as patients requiring intravenous diuretics, either treated in the emergency department or admitted to the hospital. Patients had at least one symptom and two signs of HF (peripheral edema, pulmonary crackles, high NT-proBNP level, radiologic signs of pulmonary congestion, or hemodynamic evidence). The secondary end point was overall mortality.

Statistical Analysis

Statistical analyses were performed using SPSS version 25 (SPSS, Somers, NY). All tests were two sided, and P values $< .05$ were considered to indicate statistical significance. Continuous variables are expressed as mean ± SD and categorical variables as counts and proportions. For FAC, TAPSE, S′, and CMR-derived RVEF, RVD was determined according to cutoff described in the literature.[9] For RV strain measurements, cutoffs were defined as the means of the control population plus 2 SDs (−17.5% for RVGLS and −18.1% for RVFWLS). Patients with and those without RVD according to STE RVGLS were compared. Comparison between groups was performed using χ^2 tests or unpaired t tests as appropriate. Bonferroni correction for multiple-variable testing was applied, and significant P values after correction are marked with asterisks. The correlation between CMR-derived RVEF versus echocardiographic measures of RV function was examined using the Pearson correlation coefficient. Interobserver and intraobserver reproducibility of measurement of RV function were evaluated in 30 randomly selected subjects in sinus rhythm and 20 subjects in AF, using intraclass correlation coefficient (ICCs). ICC estimates were based on a single-rating, absolute-agreement, two-way mixed-effects model.

To determine independent predictors of the primary and secondary end points, uni- and multivariate Cox proportional-hazards models were used. Hazard ratios are expressed as mean and 95% CI. All clinical and echocardiographic parameters were proposed for inclusion in the univariate model. Then a stepwise forward model including significant ($P < .05$) clinical and echocardiographic univariate correlates of survival was used to construct a baseline model predicting either the primary end point (a composite of hospitalization for HF and overall survival) or the secondary end point (overall survival). When two significant covariates were correlated (Pearson $r > 0.6$), only the variable with the strongest impact (lowest P value) was included in the model. To assess the additive prognostic value of RV function measurements, the ability of each RV parameter to improve the prediction of the primary and secondary end points from the baseline model was tested using likelihood-ratio tests (χ^2 to enter). When the χ^2 to enter was significant, the interest of adding a parameter to the model was confirmed using the Bayesian information criterion. In addition, bootstrapping was used to test the model stability. Ninety-five percent CIs associated with the hazard ratios in the models presented were all obtained after bootstrapping.

Unadjusted and adjusted Kaplan-Meier curves were used to illustrate the difference in prognosis (overall survival and event-free survival) between patients with and those without RVD, according to RV myocardial deformation (STE RVGLS).

RESULTS

Baseline Characteristics

Demographic, clinical, and imaging characteristics of the 149 patients are summarized in Table 1. Median H_2FPEF score[19] was 95.8 (interquartile range: 86.5–98.1). The characteristics of the control group can be found in Supplemental Table 1. Patients with HFpEF were

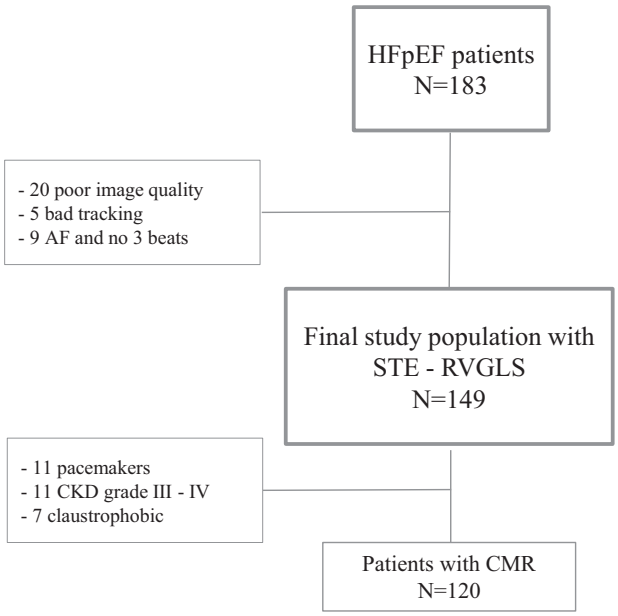


Figure 1 Flowchart of the study population. *CKD*, Chronic kidney disease.

78 ± 9 years old, and 61% were women. They had a high incidence of cardiovascular risk factors and comorbidities. History of AF was particularly prevalent among patients (58%). Fifteen patients (10%) had low-stage chronic obstructive pulmonary disease and 16 (11%) had obstructive sleep apnea treated with continuous positive airway pressure. Thirteen patients (9%) had undergone previous valve surgery (11 aortic bioprostheses, one transcatheter aortic valve replacement, and one Starr mitral valve), all with normal morphology and function at the time of inclusion. Patients with HFpEF also had low hemoglobin, low eGFR, and high NT-proBNP.

As expected, patients with HFpEF had echocardiographic signs of LV diastolic dysfunction (higher left atrial volume, higher E-wave velocity, higher E/e′ ratio), higher LV mass, and higher pulmonary pressures. Interestingly, RV systolic function was depressed in patients with HFpEF: FAC and TAPSE, as well as RVGLS and RVFWLS, were all significantly altered (Figure 2). Among 86 patients with histories of AF, 58 (39% of all patients) were in AF at time of echocardiography. Notably, those patients also had altered RV function compared with those in sinus rhythm (FAC 38 ± 9% vs 44 ± 8%, TAPSE 16 ± 5 vs 21 ± 5 mm, RVGLS −20 ± 4% vs −23 ± 5, and RVFWLS −22 ± 5% vs −26 ± 7%, $P < .001$ for all).

Table 1 shows the characteristics of the study population according to the presence of RVD defined by STE RVGLS less negative than −17.5%, corresponding to the mean RVGLS of the control subjects plus 2 SDs. There was no significant difference in age or sex between the two groups or in severity of symptoms. Patients with RVD more often had sleep apneas. Other comorbidities and cardiovascular risk factors, however, were equally prevalent in both groups. As expected, other indicators of RVD (FAC, TAPSE, S′, RVFWLS, and CMR-derived RVEF) were significantly lower in patients with the most depressed RVGLS.

RV Function Parameters: Correlations with CMR-Derived RVEF and Reproducibility

Among the study population, 120 of 149 patients (81%) and all control subjects underwent CMR. The correlations of RV functional parameters versus CMR-derived RVEF are shown in Figure 3. All RV echocardiographic parameters correlated significantly with CMR-derived RVEF, with $P < .001$ for Pearson linear correlation. Among all parameters, STE RVGLS had the best correlation with CMR-derived RVEF ($r = -0.617$) while RVFWLS showed a moderate correlation ($r = -0.509$). Inter- and intraobserver reproducibility was satisfactory for all parameters. STE RVGLS was more reproducible than FAC but slightly less than TAPSE and showed similar variability to CMR-derived RVEF (Table 2). STE RVFWLS had higher variability than RVGLS. Of note, AF did not alter inter- and intraobserver reproducibility of RVGLS (ICCs calculated among 20 randomly selected patients in AF at time of the echography were 0.82 and 0.96, respectively).

Predictors of Hospitalization and Survival

Two patients were lost to follow-up (1.3%). Over a mean follow-up period of 30 ± 9 months, 40 patients (27%) died and 74 patients (50%) were hospitalized for HF. A total of 91 patients (62%) reached the primary end point of all-cause mortality and/or first HF hospitalization, whichever came first.

In univariate Cox regression analysis, low hemoglobin, low eGFR, high E/e′ ratio, high eSPAP, and the presence of moderate to severe tricuspid insufficiency were predictors of both the primary and secondary end points (Table 3).

New York Heart Association (NYHA) functional classes III and IV, diabetes, loop diuretic medications, high NT-proBNP, and high E wave velocity were the only predictors of the primary composite end point, while lower body mass index was associated with the secondary end point of overall mortality (Table 3).

With regard to RVD parameters, only STE RVGLS > −17.5% was a predictor of both the composite end point and overall mortality. CMR-derived RVEF < 45% and FAC < 35% were predictors of the composite end point, whereas TAPSE < 17 mm and RVFWLS > −18.1% were predictors of overall mortality.

In multivariate Cox regression analysis, NYHA functional classes III and IV, low eGFR, low hemoglobin, and moderate to severe tricuspid insufficiency were independent predictors of the primary end point. These parameters were used to construct a baseline model predicting the composite end point of death or HF hospitalization. NT-proBNP level was not included in the model, as it did not contribute significantly. Figure 4 shows the additional prognostic value of different RV function parameters over the baseline model for prediction of the primary end point. STE RVGLS was the only parameter found to have a significant additional value.

The baseline model for prediction of the secondary end point was based on independent clinical and echocardiographic predictors of overall mortality, which were low body mass index, low hemoglobin, and high eSPAP. STE RVGLS > −17.5% and STE RVFWLS > −18.1% were found to provide significant additional value for prediction of overall mortality (Figure 5).

Unadjusted and adjusted Kaplan-Meier event-free survival and overall survival curves stratified by STE RVGLS are shown in Figures 6 and 7. They clearly demonstrate that both event-free and overall survival significantly declined with worsening RV function.

DISCUSSION

This study demonstrates the prognostic significance of RVD in patients with HFpEF and, most important, shows that STE RVGLS

Table 1 Baseline characteristics and imaging parameters of patients with HFpEF with or without RVD according to STE RVGLS

	Total population (*N* = 149)	STE RVGLS < −17.5% (*n* = 121)	STE RVGLS > −17.5% (*n* = 28)	*P*
Baseline characteristics				
Age, y	78 ± 9	78 ± 9	77 ± 8	.56
Female	91 (61)	75 (62)	16 (57)	.64
Body mass inde, kg/m^2	28.5 ± 6.2	28.3 ± 6.2	29.5 ± 6.3	.35
Systolic blood pressure, mm Hg	138 ± 22	138 ± 23	135 ± 16	.39
Diastolic blood pressure, mm Hg	73 ± 13	74 ± 13	73 ± 12	.73
NYHA functional class III or IV	70 (47)	58 (48)	12 (43)	.63
Medical history				
AF	86 (58)	69 (57)	17 (61)	.72
Ischemic cardiomyopathy	51 (34)	13 (11)	3 (11)	.99
Previous HF episode	100 (67)	79 (65)	21 (75)	.32
Previous valvular surgery	13 (9)	11 (9)	2 (7)	.74
Chronic obstructive pulmonary disease	15 (10)	13 (11)	2 (7)	.57
Sleep apnea	16 (11)	11 (9)	6 (23)	.045
Cardiovascular risk factors				
Smoking	65 (44)	53 (44)	12 (43)	.90
Hypertension	138 (93)	112 (93)	26 (93)	.92
Diabetes	61 (41)	47 (39)	14 (50)	.28
Family history of CV disease	26 (17)	22 (18)	4 (14)	.61
Hypercholesterolemia	96 (64)	78 (65)	18 (64)	.94
Medication				
Loop diuretic	99 (66)	79 (66)	20 (71)	.57
Biology				
Hemoglobin, g/dL	11.8 ± 2.0	11.7 ± 2	12.2 ± 2	.20
Total cholesterol, mg/dL	158 ± 47	158 ± 46	157 ± 34	.92
GFR, mL/min/1.73 m^2 by CK-EPI	57 ± 24	58 ± 24	51 ± 21	.22
NT-proBNP, pg/mL	1,747 (923–3,521)	1,645 (852–3,256)	2,148 (1,058–7,410)	.06
Echocardiography				
LA volume index, mL/m^2	45 ± 19	45 ± 19	47 ± 17	.63
LV EDV index, mL/m^2	67 ± 18	66 ± 18	70 ± 16	.32
LVEF, %	63 ± 7	63 ± 7	59 ± 7	.01
STE LVGLS, %	−16.7 ± 3.1	−17.1 ± 3	−14.9 ± 3	.001*
E-wave velocity, m/sec	92 ± 30	93 ± 30	90 ± 30	.71
Septal e′, m/sec	5.2 ± 1.3	5.2 ± 1.3	5.1 ± 1.0	.66
E/e′ septal ratio	18.7 ± 7.8	18.8 ± 8.0	18.5 ± 7.3	.85
RV FAC, %	42 ± 9	44 ± 8	33 ± 7	<.001*
TAPSE, mm	19 ± 5	20 ± 5	15 ± 4	<.001*
S′ velocity, m/sec	11.2 ± 2.9	11.7 ± 2.8	9.4 ± 2.7	<.001*
Moderate to severe TR	14 (9)	9 (7)	5 (18)	.092
SPAP, mm Hg	43 ± 13	42 ± 12	48 ± 16	.069
STE RVGLS, %	−21.7 ± 4.9	−23.5 ± 3.6	−14.4 ± 2.2	<.001* by design
STE RVFWLS, %	−24.2 ± 6.3	−26.0 ± 5.4	−16.4 ± 2.8	<.001*
CMR study	**(*n* = 120)**	**(*n* = 102)**	**(*n* = 18)**	
LVEF, %	63 ± 8	63 ± 8	62 ± 10	.64
LV mass index, g/m^2	67 ± 14	66 ± 15	73 ± 12	.047
RV EDV index, mL/m^2	80 ± 25	79 ± 25	84 ± 23	.39
RVEF, %	56 ± 7	58 ± 7	48 ± 5	<.001*

Data are expressed as mean ± SD, number (percentage), or median (interquartile range). Across-group *P* value is for the difference between patients with HFpEF with and those without RVD, evaluated using χ^2 tests or unpaired *t* tests as appropriate.
CK-EPI, Chronic Kidney Disease Epidemiology Collaboration; *CV*, cardiovascular; *EDV*, end-diastolic volume; *GFR*, glomerular filtration rate; *LVEF*, LV ejection fraction; *LVGLS*, LV global longitudinal strain; *LA*, left atrial; *SPAP*, systolic pulmonary artery pressure; *TR*, tricuspid regurgitation.
**P* value was still significant after Bonferroni correction for multivariate testing.

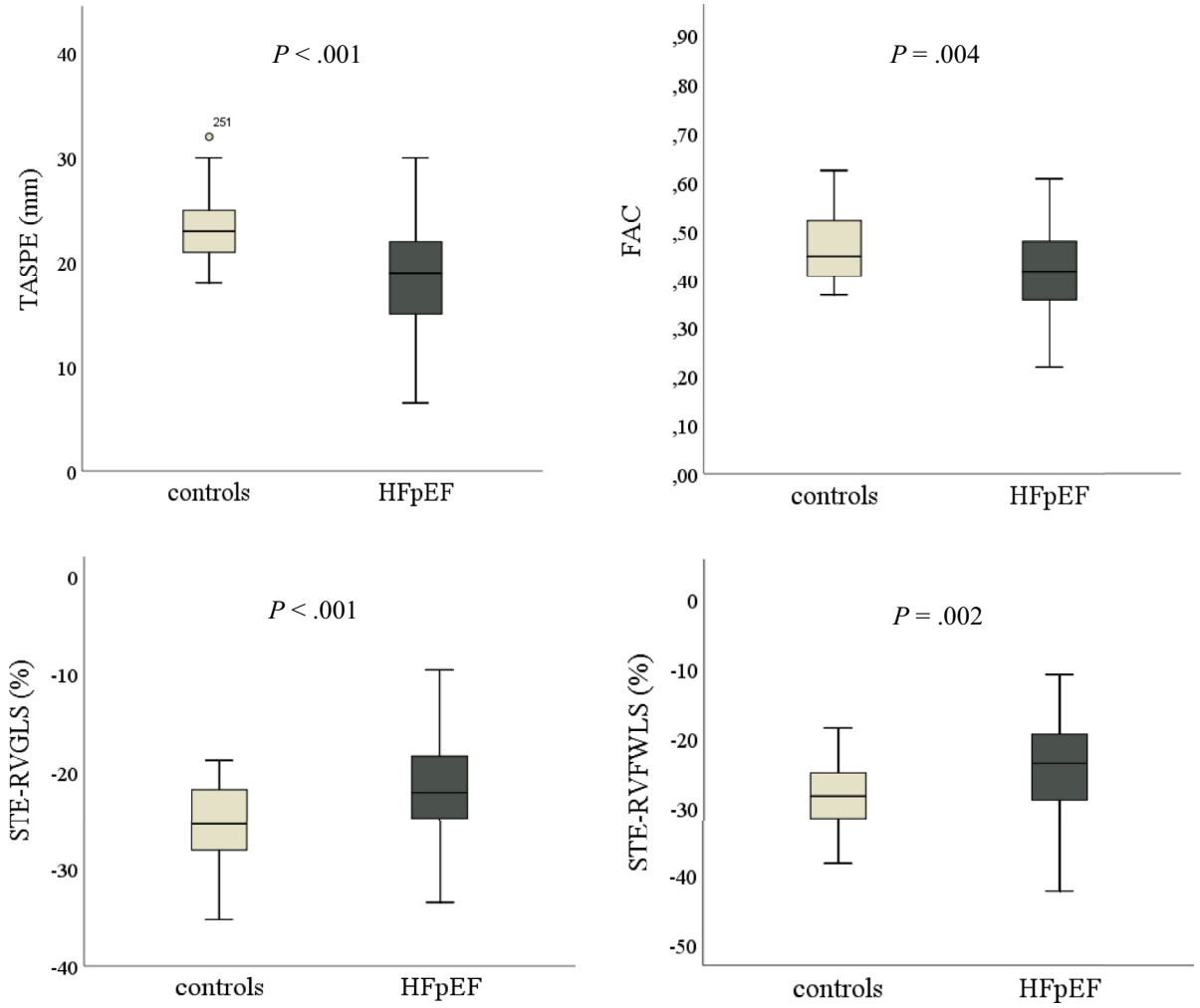


Figure 2 Boxplot of parameters of RV function in patients with HFpEF and in control subjects.

was superior to commonly used RV function parameters such as FAC, TAPSE, and S′ for predicting both the combined outcome and overall mortality.

Assessment of RV Function by Echocardiography

Although its prognostic significance has recently been highlighted, accurate assessment of RV function in daily practice remains challenging. Indeed, the complex shape of the right ventricle and its localization behind the sternum makes echocardiographic evaluation arduous, and no optimal parameter for RV functional measurements has been identified. Hence, CMR-derived RVEF remains the gold standard, while echocardiography is more readily available and would be better suited for risk stratification of patients with HFpEF. Currently, a multiparametric approach is recommended for the evaluation of RV function by echocardiography,[9] including FAC and TAPSE. TAPSE has the important advantage of being easily measurable even when image quality is poor but reflects only the longitudinal function of the RV free wall and is angle dependent. RV FAC, on the other hand, may better reflect RV global function but was found to have high interobserver and intraobserver variability.[9,22]

More recently, 2D STE RVGLS has been proposed for echocardiographic evaluation of RV function and has been validated in an animal study with sonomicrometry[23] and in human studies with CMR.[12,24-26] In previous work, STE RVGLS was found to be significantly correlated with CMR-derived RVEF (Pearson correlation coefficient = −0.50 to −0.80), TAPSE ($r = -0.547$ to -0.83), and RV FAC ($r = -0.213$ to -0.73).[27] Because it is a global parameter of RV systolic function, it correlates better with CMR RVEF than other conventional parameters and has more prognostic power.

However, an important limitation to using STE RVGLS in clinical practice is the intervendor variability in terms of strain value estimates and the lack of standardized normal values. Furthermore, several studies showed sex and age differences in strain.[28,29] To overcome these limitations, we defined RVD with a cutoff derived from a control population of similar age and sex, using the same software for all analysis. In this control population, the mean RVGLS was −25.9 ± 4.2%, which is consistent with data published in the literature.[27,30,31]

Prevalence of RVD in Patients with HFpEF

In recent years, few studies have examined the right ventricle in HFpEF. A recent meta-analysis found large variability in the prevalence of RVD.[30] The prevalence of TAPSE < 16 mm ranged from 26% to 49% and the prevalence of FAC < 35% from 4% to 33%. The majority of studies were performed before the publication of the new recommendations, and consequently they used the previous recommended cutoff of <16 mm for TAPSE. In a magnetic resonance

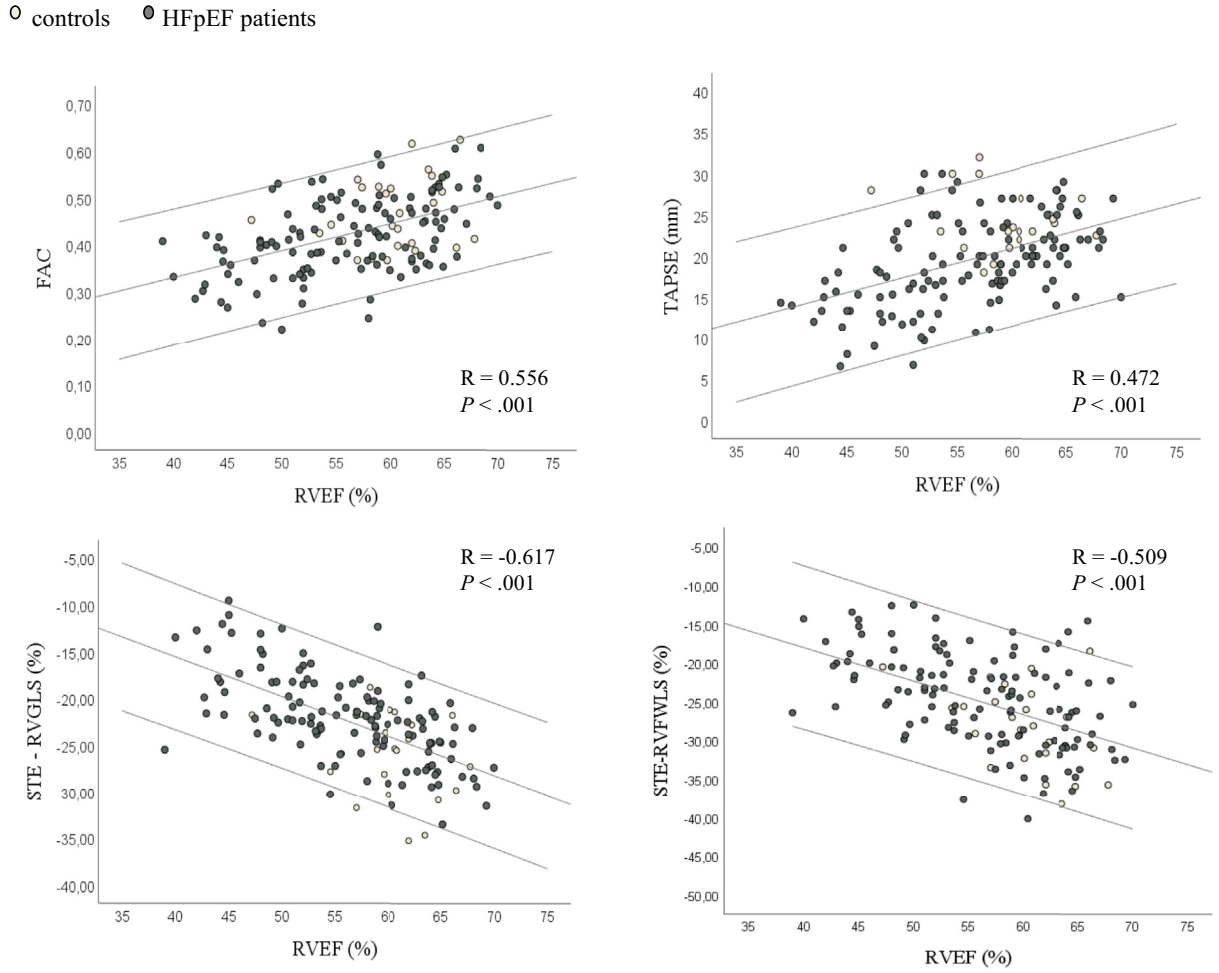


Figure 3 Correlation of RV function parameters with CMR-derived RVEF.

Table 2 RV function parameters: Pearson linear correlations with CMR-derived RVEF and evaluation of reproducibility by ICC

Variables	Pearson correlation (*r*)	*P*	Intraobserver ICC	Interobserver ICC
RV FAC	0.556	<.001	0.682	0.506
TAPSE	0.472	<.001	0.957	0.858
S′ velocity	0.349	<.001	0.908	0.838
STE RVGLS	−0.617	<.001	0.856	0.766
STE RVFWLS	−0.509	<.001	0.809	0.635
CMR-derived RVEF	—	—	0.946	0.773

ICC, Intraclass correlation coefficient.

study, Aschauer *et al*[7] assessed RV function in 171 patients with HFpEF and found a prevalence of RVD (RVEF < 45%) of 19%. Thus despite variable reports, methods, and criteria, the best available current data indicate that RVD is present in at least 20% and potentially up to 30% to 50% of patients with HFpEF.[32]

In our study, the prevalence of RVD in patients with HFpEF varied on the basis of its definition, with 37% having TAPSE < 17 mm, 26% having FAC < 35%, 25% having RVFWLS > −18.1%, and 19% having impaired RVGLS > −17.5%. Only 10% of patients had CMR-derived RVEFs < 45%. This discrepancy was also observed in other studies using multiple parameters for the evaluation of RV function.[6,30,33] TAPSE is limited to longitudinal function, using only tricuspid annular excursion, and will be the first to be altered. Preliminary evidence suggests that at the first stage of RVD, there may be a change in the contraction pattern of the right ventricle, with reduced longitudinal shortening but enhanced transverse contraction.[34] This pattern would be more suited for increased afterload to preserve global systolic function. Consequently, TAPSE may be reduced while FAC is enhanced. RVGLS is also mainly a reflection of longitudinal function, but unlike TAPSE, it is not limited to analysis of the RV free wall but also includes the septum, which contributes to RV systolic function through biventricular interactions.

Physiopathology of RVD in Patients with HFpEF

Several mechanisms have been associated with the development of RVD in patients with HFpEF, essentially the increase of pulmonary pressures, subtle LV dysfunction, and AF.[4] Passive backward transmission of LV filling pressures induces an increase in venous pulmonary pressures and hence in RV afterload. A precapillary component has

Table 3 Univariate predictors of the primary end point (composite of all-cause mortality and first HF hospitalization) and secondary end point (overall mortality)

Variables	Primary end point (composite)			Secondary end point (mortality)		
	HR	95% CI	*P*	HR	95% CI	*P*
Age	1.007	0.982–1.033	.57	1.017	0.979–1.057	.38
Female sex	1.314	0.852–2.026	.22	0.976	0.518–1.840	.94
BMI	0.973	0.939–1.009	.14	0.900	0.847–0.956	.001
NYHA functional class III or IV	1.524	1.008–2.305	.046	0.863	0.458–1.628	.65
Loop diuretic medication	1.777	1.099–2.872	.019	1.813	0.833–3.945	.13
Diabetes	1.615	1.068–2.443	.023	1.593	0.854–2.973	.14
COPD	1.788	0.969–3.299	.063	0.804	0.247–2.618	.72
Sleep apnea	0.562	0.266–1.189	.13	0.146	0.020–1.076	.059
AF	1.144	0.751–1.742	.53	0.723	0.388–1.347	.31
NT-proBNP	1.226	1.008–1.490	.041	1.265	0.946–1.691	.11
GFR	0.978	0.967–0.990	<.001	0.982	0.966–0.998	.032
Hemoglobin	0.831	0.741–0.932	.002	0.755	0.635–0.897	.001
STE LVGLS	1.019	0.951–1.093	.59	1.066	0.964–1.178	.22
E-wave velocity	1.010	1.004–1.016	.002	1.006	0.996–1.016	.22
E/e′ ratio	1.032	1.009–1.054	.005	1.030	0.995–1.066	.089
Moderate to severe TI	2.254	1.191–4.267	.013	2.550	1.121–5.800	.026
SPAP	1.017	1.002–1.033	.030	1.027	1.005–1.050	.018
RV FAC < 35%	1.603	1.034–2.487	.035	1.384	0.714–2.684	.34
S′ velocity < 9.5 cm/sec	1.280	0.814–2.013	.28	1.675	0.868–3.232	.12
TAPSE < 17 mm	1.364	0.896–2.078	.15	2.133	1.136–4.005	.018
STE RVGLS > −17.5%	1.664	1.020–2.713	.041	2.338	1.202–4.550	.012
STE RVFWLS > −18.1%	1.310	0.762–2.254	.34	2.476	1.231–4.979	.011

BMI, Body mass index; *COPD*, chronic obstructive pulmonary disease; *GFR*, glomerular filtration rate; *HR*, hazard ratio; *LVGLS*, LV global longitudinal strain; *SPAP*, systolic pulmonary artery pressure; *TI*, tricuspid insufficiency.

also been incriminated, with local modification of the pulmonary vasculature secondary to the systemic proinflammatory state associated with HFpEF[35] or to concomitant comorbidities (i.e., chronic obstructive pulmonary disease and sleep apneas).[36]

However, RV function is not only altered through the elevation of pulmonary pressures. Indeed, RVD and pulmonary hypertension are not well correlated and do not always coexist, especially in patients with HFpEF.[6,37] It is well established that the left ventricle actively contributes to RV systolic performance through the shared ventricular septum.[38,39] Although global LV ejection fraction is by definition preserved in HFpEF, there is evidence of subtle LV contractile dysfunction,[40] reducing the direct contribution of LV contraction to RV function.[4,7] This explains why RVGLS might be a better reflection of RV function and have a stronger prognostic value than RVFWLS or TAPSE. However, the prognostic impact of RVD seems independent of LV function, as studies have found that in patients with HFpEF, LV function was not significantly associated with outcome, while RV function was.[4,5,7]

Several studies have also indicated a link between AF, highly prevalent among patients with HFpEF, and the presence of RVD.[4,41] Both may relate to worsening HFpEF, in which increased LV filling pressures leads to left atrial stretch and remodeling and to increased pulmonary pressures. AF might also directly impair RV function via altered longitudinal performance. Indeed, it was demonstrated that cardioversion from AF to sinus rhythm was associated with enhanced RV longitudinal contraction,[42] and RV shortening is worse in patients with HFpEF with AF for any given pulmonary artery pressure load.[4] Our study corroborates these findings, as patients in sinus rhythm had better RVGLS and RVFWLS than those in AF at the time of the echocardiography.

Prognosis

Data on the prognostic value of RVD in patients with HFpEF are conflicting. Melenovsky *et al*[4] demonstrated that RVD by transthoracic echocardiography (defined as FAC < 35%) was the strongest predictor of death in an overweight population with advanced HF (96 patients with HFpEF, mean body mass index 34 kg/m^2, and 71% in NYHA functional class III or IV). This was not the case in a less advanced HF population (i.e., in clinical trials such as PARAGON, with 28% of patients in NYHA class III or IV and only 9% of patients with FAC < 35%).[33] In a study investigating a community-based HFpEF cohort, RVD defined by semiquantitative assessment was associated with poorer outcomes even after adjustment for comorbidities.[5] However, those studies included only clinical characteristics in their multivariate analyses. They did not account for echocardiographic parameters of diastolic dysfunction or for the presence of tricuspid regurgitation, although the impact of tricuspid regurgitation

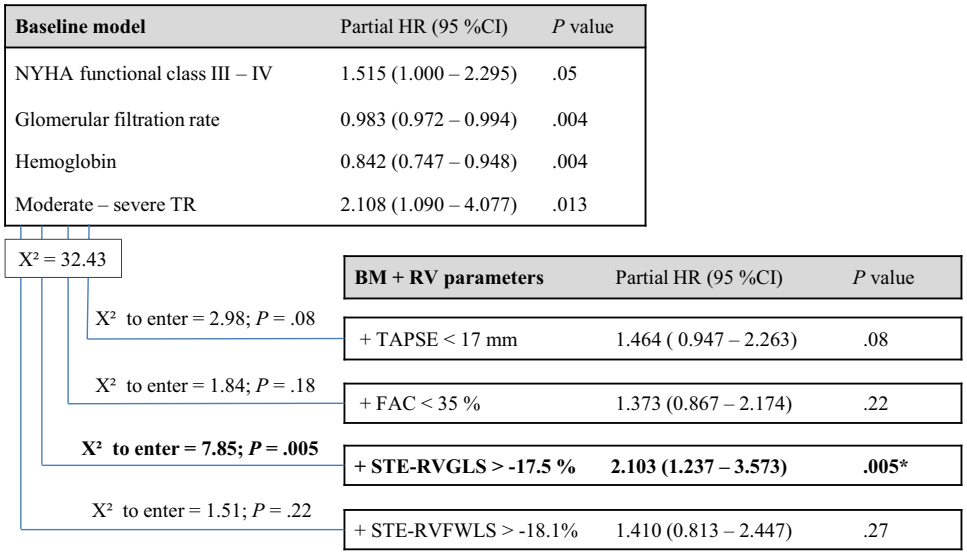


Figure 4 Multivariate Cox regression, model for prediction of the primary end point (composite of HF hospitalization and all-cause mortality). *HR*, Hazard ratio. **P* value was still significant after Bonferroni correction for multivariate testing.

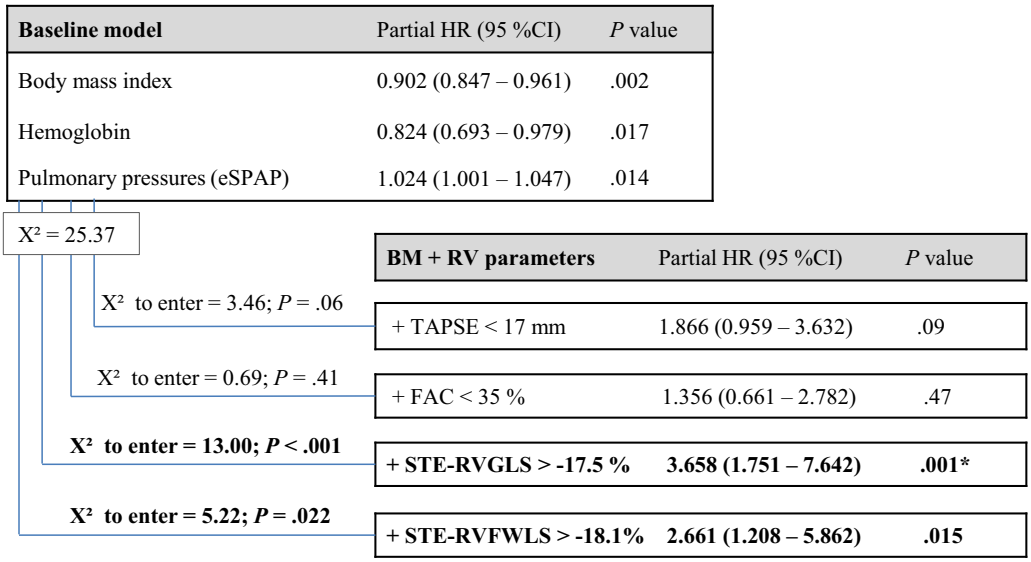


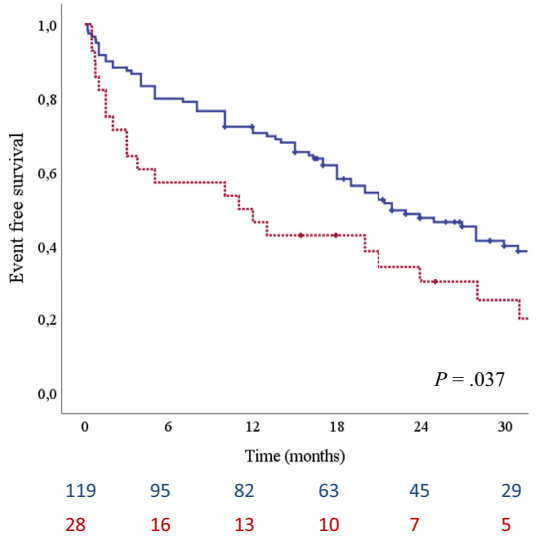
Figure 5 Multivariate Cox regression, model for prediction of the secondary end point (all-cause mortality). **P* value was still significant after Bonferroni correction for multivariate testing.

on survival has been demonstrated in HF with reduced ejection fraction.[43] In other studies, FAC and TAPSE were associated with prognosis in univariate analysis but were not independent predictors of outcome.[4,6,44] Burke *et al*[45] found that lower LV compliance and increased RV remodeling were both independently associated with the composite outcome of cardiovascular hospitalization or death. CMR studies also produced conflicting results regarding the predictive value of CMR-derived RVEF.[7,8] Overall, results from different studies vary depending on the selected population and the parameters studied but all agree that RVD has an important prognostic value in patients with HFpEF.

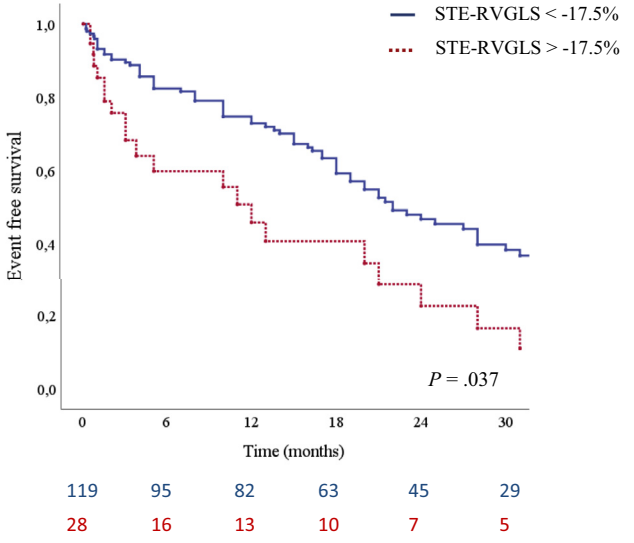
The predictive value of RV deformation imaging in patients with HFpEF has been assessed in only one study, conducted by Bosch *et al*[6] in 219 patients. RVGLS was found to predict the combined outcome of all-cause mortality and first HF hospitalization, even after multivariable adjustment. Our study confirms these data and further emphasizes the additional value of RVGLS over conventional echocardiographic parameters. Indeed, we showed that when we accounted for indirect signs of RVD assessed in daily practice, such as the presence of moderate to severe tricuspid regurgitation or elevated eSPAP, STE RVGLS was the only RV function parameter with additional prognostic significance over clinical characteristics.

Clinical Implications and Perspective

Only a few studies have evaluated prognostic markers in patients with HFpEF.[8,45,46] Our study underlines the importance of considering

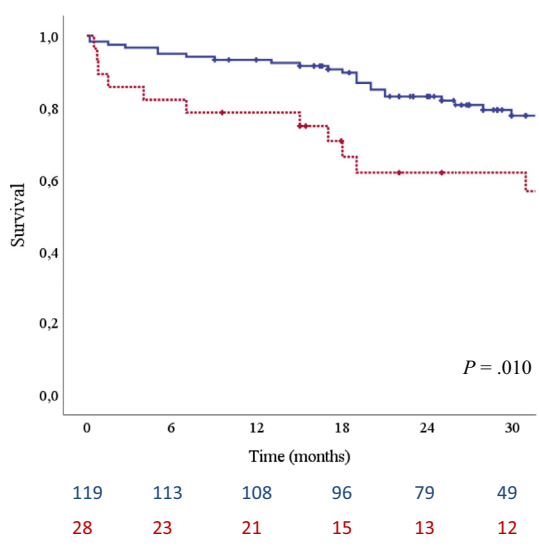


A. Non adjusted Kaplan Meier curves of event free survival.

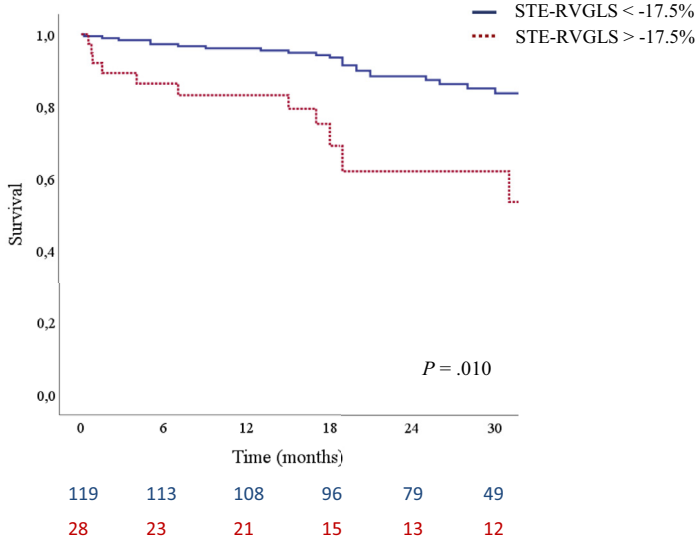


B. Adjusted Kaplan Meier curves of event free survival. Adjustments were made for NYHA functional class, renal function, hemoglobin levels and tricuspid regurgitation ≥ 2

Figure 6 Kaplan-Meier curves for the primary end point of event-free survival in patients with HFpEF, according to RV function by STE RVGLS.



A. Non adjusted Kaplan Meier curves of survival.



B. Adjusted Kaplan Meier curves of survival. Adjustments were made for body mass index, hemoglobin levels and estimated pulmonary pressures.

Figure 7 Kaplan-Meier curves for the secondary end point of overall survival in patients with HFpEF, according to RV function by STE RVGLS.

RVD as a risk marker of poor prognosis and suggests that RV function assessment should be part of the comprehensive evaluation of patients with HFpEF. Even though there are currently no treatments improving prognosis in patients with HFpEF, those at high risk for events should benefit from closer monitoring and intensive treatment of comorbidities and congestion. The best parameter to evaluate RVD is yet to be defined, but our study suggests that STE RVGLS could be of interest. Indeed, it is well correlated to CMR-derived RVEF; it is reproducible and has prognostic significance over clinical and echocardiographic parameters. However, extra effort should be put into the standardization of software to implement strain analysis in clinical practice.

Better discrimination of patients at high risk for events could also be valuable in the setting of clinical trials. The mixed results of the PARAGON trial[47] highlight the importance of good phenotyping of patients with HFpEF to match the therapeutic mechanism of an agent with the patient subgroup most likely to benefit. Exclusion criteria implemented in clinical trials led to underrepresentation of patients at

high risk (the prevalence of RVD is generally lower than in community-based studies), who would perhaps benefit more from new treatments.

Study Limitations

The present data were collected at a single center. Patients did not undergo invasive measurement of filling pressures; hence the contribution of HFpEF to the elevation of pulmonary pressure could not be assessed with precision. Also, echocardiographic measurements were averaged over only three beats in patients in AF at the time of echocardiography. The impact of AF on the quality of the measurements is difficult to assess, but in our rate-controlled patients (mean heart rate, 75 ± 13 beats/min), a three-beat average seems acceptable, as the beat-to-beat variability of RVGLS measurements was equivalent to intraobserver variability (ICCs of 0.862 and 0.856, respectively). Excluding patients in AF would introduce an important bias given the high prevalence of AF among patients with HFpEF. Strain analysis was performed using TomTec software, and specific cutoff values reported in this study may not apply to other software or other populations. We excluded 18.5% of patients because of poor image quality precluding STE imaging. Indeed, a significant limitation of STE strain remains the need for high-quality images and frame rate dependency.

CONCLUSION

Our study demonstrates that in patients with HFpEF, RVD assessed by STE RVGLS is a strong independent predictor of overall mortality and HF hospitalization, providing additional prognostic value over clinical parameters. Importantly, STE RVGLS was found to have higher predictive value than FAC and TAPSE. Hence, effort should be put into the standardization of myocardial deformation software to implement STE RVGLS in daily practice. Systematic evaluation of RV function by STE RVGLS could help identify patients with HFpEF at high risk for adverse events, who should benefit from closer monitoring and intensive treatment of comorbidities and congestion.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.echo.2020.02.016.

REFERENCES

1. Meyer P, Filippatos GS, Ahmed MI, Iskandrian AE, Bittner V, Perry GJ, et al. Effects of right ventricular ejection fraction on outcomes in chronic systolic heart failure. Circulation 2010;121:252-8.
2. Gulati A, Ismail TF, Jabbour A, Alpendurada F, Guha K, Ismail NA, et al. The prevalence and prognostic significance of right ventricular systolic dysfunction in nonischemic dilated cardiomyopathy. Circulation 2013;128:1623-33.
3. Pouleur AC, Rousseau MF, Ahn SA, Amzulescu M, Demeure F, de Meester C, et al. Right ventricular systolic dysfunction assessed by cardiac magnetic resonance is a strong predictor of cardiovascular death after coronary bypass grafting. Ann Thorac Surg 2016;101:2176-84.
4. Melenovsky V, Hwang SJ, Lin G, Redfield MM, Borlaug BA. Right heart dysfunction in heart failure with preserved ejection fraction. Eur Heart J 2014;35:3452-62.
5. Mohammed SF, Hussain I, AbouEzzeddine OF, Takahama H, Kwon SH, Forfia P, et al. Right ventricular function in heart failure with preserved ejection fraction: a community-based study. Circulation 2014;130:2310-20.
6. Bosch L, Lam CSP, Gong L, Chan SP, Sim D, Yeo D, et al. Right ventricular dysfunction in left-sided heart failure with preserved versus reduced ejection fraction. Eur J Heart Fail 2017;19:1664-71.
7. Aschauer S, Kammerlander AA, Zotter-Tufaro C, Ristl R, Pfaffenberger S, Bachmann A, et al. The right heart in heart failure with preserved ejection fraction: insights from cardiac magnetic resonance imaging and invasive haemodynamics. Eur J Heart Fail 2016;18:71-80.
8. Goliasch G, Zotter-Tufaro C, Aschauer S, Duca F, Koell B, Kammerlander AA, et al. Outcome in heart failure with preserved ejection fraction: the role of myocardial structure and right ventricular performance. PLoS One 2015;10:e0134479.
9. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233-70.
10. Tabassian M, Sunderji I, Erdei T, Sanchez-Martinez S, Degiovanni A, Marino P, et al. Diagnosis of heart failure with preserved ejection fraction: machine learning of spatiotemporal variations in left ventricular deformation. J Am Soc Echocardiogr 2018;31:1272-84.e9.
11. de Groote P, Fertin M, Goeminne C, Petyt G, Peyrot S, Foucher-Hossein C, et al. Right ventricular systolic function for risk stratification in patients with stable left ventricular systolic dysfunction: comparison of radionuclide angiography to echoDoppler parameters. Eur Heart J 2012;33:2672-9.
12. Park JH, Negishi K, Kwon DH, Popovic ZB, Grimm RA, Marwick TH. Validation of global longitudinal strain and strain rate as reliable markers of right ventricular dysfunction: comparison with cardiac magnetic resonance and outcome. J Cardiovasc Ultrasound 2014;22:113-20.
13. Tadic M, Pieske-Kraigher E, Cuspidi C, Morris DA, Burkhardt F, Baudisch A, et al. Right ventricular strain in heart failure: clinical perspective. Arch Cardiovasc Dis 2017;110:562-71.
14. Il'Giovine ZJ, Mulder H, Chiswell K, Arges K, Tomfohr J, Hashmi A, et al. Right Ventricular longitudinal strain reproducibility using vendor-dependent and vendor-independent software. J Am Soc Echocardiogr 2018;31:721-32.e5.
15. Houard L, Benaets MB, de Meester de Ravenstein C, Rousseau MF, Ahn SA, Amzulescu MS, et al. Additional prognostic value of 2D right ventricular speckle-tracking strain for prediction of survival in heart failure and reduced ejection fraction: a comparative study with cardiac magnetic resonance. JACC Cardiovasc Imaging 2019;12:2373-85.
16. Carluccio E, Biagioli P, Alunni G, Murrone A, Zuchi C, Coiro S, et al. Prognostic value of right ventricular dysfunction in heart failure with reduced ejection fraction: superiority of longitudinal strain over tricuspid annular plane systolic excursion. Circ Cardiovasc Imaging 2018;11:e006894.
17. Shukla M, Park JH, Thomas JD, Delgado V, Bax JJ, Kane GC, et al. Prognostic value of right ventricular strain using speckle-tracking echocardiography in pulmonary hypertension: a systematic review and meta-analysis. Can J Cardiol 2018;34:1069-78.
18. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:891-975.

19. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. Circulation 2018;138:861-70.
20. Mitchell C, Rahko PS, Blauwet LA, Canaday B, Finstuen JA, Foster MC, et al. Guidelines for performing a comprehensive transthoracic echocardiographic examination in adults: recommendations from the American Society of Echocardiography. J Am Soc Echocardiogr 2019;32:1-64.
21. Roy C, Slimani A, de Meester C, Amzulescu M, Pasquet A, Vancraeynest D, et al. Associations and prognostic significance of diffuse myocardial fibrosis by cardiovascular magnetic resonance in heart failure with preserved ejection fraction. J Cardiovasc Magn Reson 2018;20:55.
22. Hoette S, Creuze N, Gunther S, Montani D, Savale L, Jais X, et al. RV fractional area change and TAPSE as predictors of severe right ventricular dysfunction in pulmonary hypertension: a CMR study. Lung 2018;196:157-64.
23. Jamal F, Bergerot C, Argaud L, Loufouat J, Ovize M. Longitudinal strain quantitates regional right ventricular contractile function. Am J Physiol Heart Circ Physiol 2003;285:H2842-7.
24. Lu KJ, Chen JX, Profitis K, Kearney LG, DeSilva D, Smith G, et al. Right ventricular global longitudinal strain is an independent predictor of right ventricular function: a multimodality study of cardiac magnetic resonance imaging, real time three-dimensional echocardiography and speckle tracking echocardiography. Echocardiography 2015;32:966-74.
25. Wang J, Prakasa K, Bomma C, Tandri H, Dalal D, James C, et al. Comparison of novel echocardiographic parameters of right ventricular function with ejection fraction by cardiac magnetic resonance. J Am Soc Echocardiogr 2007;20:1058-64.
26. Giusca S, Dambrauskaite V, Scheurwegs C, D'Hooge J, Claus P, Herbots L, et al. Deformation imaging describes right ventricular function better than longitudinal displacement of the tricuspid ring. Heart 2010;96:281-8.
27. Lee JH, Park JH. Strain analysis of the right ventricle using two-dimensional echocardiography. J Cardiovasc Imaging 2018;26:111-24.
28. Muraru D, Onciul S, Peluso D, Soriani N, Cucchini U, Aruta P, et al. Sex- and method-specific reference values for right ventricular strain by 2-dimensional speckle-tracking echocardiography. Circ Cardiovasc Imaging 2016;9:e003866.
29. Park JH, Choi JO, Park SW, Cho GY, Oh JK, Lee JH, et al. Normal references of right ventricular strain values by two-dimensional strain echocardiography according to the age and gender. Int J Cardiovasc Imaging 2018;34:177-83.
30. Gorter TM, Hoendermis ES, van Veldhuisen DJ, Voors AA, Lam CS, Geelhoed B, et al. Right ventricular dysfunction in heart failure with preserved ejection fraction: a systematic review and meta-analysis. Eur J Heart Fail 2016;18:1472-87.
31. Morris DA, Krisper M, Nakatani S, Kohncke C, Otsuji Y, Belyavskiy E, et al. Normal range and usefulness of right ventricular systolic strain to detect subtle right ventricular systolic abnormalities in patients with heart failure: a multicentre study. Eur Heart J Cardiovasc Imaging 2017;18:212-23.
32. Gorter TM, van Veldhuisen DJ, Bauersachs J, Borlaug BA, Celutkiene J, Coats AJS, et al. Right heart dysfunction and failure in heart failure with preserved ejection fraction: mechanisms and management. Position statement on behalf of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2018;20:16-37.
33. Shah AM, Cikes M, Prasad N, Li G, Getchevski S, Claggett B, et al. Echocardiographic features of patients with heart failure and preserved left ventricular ejection fraction. J Am Coll Cardiol 2019;74:2858-73.
34. Kind T, Mauritz GJ, Marcus JT, van de Veerdonk M, Westerhof N, Vonk-Noordegraaf A. Right ventricular ejection fraction is better reflected by transverse rather than longitudinal wall motion in pulmonary hypertension. J Cardiovasc Magn Reson 2010;12:35.
35. Ghio S, Raineri C, Scelsi L, Asanin M, Polovina M, Seferovic P. Pulmonary hypertension and right ventricular remodeling in HFpEF and HFrEF. Heart Fail Rev 2020;25:85-91.
36. Stenmark KR, Fagan KA, Frid MG. Hypoxia-induced pulmonary vascular remodeling: cellular and molecular mechanisms. Circ Res 2006;99:675-91.
37. Andersen MJ, Hwang SJ, Kane GC, Melenovsky V, Olson TP, Fetterly K, et al. Enhanced pulmonary vasodilator reserve and abnormal right ventricular: pulmonary artery coupling in heart failure with preserved ejection fraction. Circ Heart Fail 2015;8:542-50.
38. Yamaguchi S, Li KS, Harasawa H, Santamore WP. Acute alterations in systolic ventricular interdependence-mechanical dependence of right ventricle on left ventricle following acute alteration of right ventricular free wall. Basic Res Cardiol 1993;88:350-61.
39. Schwarz K, Singh S, Dawson D, Frenneaux MP. Right ventricular function in left ventricular disease: pathophysiology and implications. Heart Lung Circ 2013;22:507-11.
40. Kraigher-Krainer E, Shah AM, Gupta DK, Santos A, Claggett B, Pieske B, et al. Impaired systolic function by strain imaging in heart failure with preserved ejection fraction. J Am Coll Cardiol 2014;63:447-56.
41. Gorter TM, van Melle JP, Rienstra M, Borlaug BA, Hummel YM, van Gelder IC, et al. Right heart dysfunction in heart failure with preserved ejection fraction: the impact of atrial fibrillation. J Card Fail 2018;24:177-85.
42. Alam M, Samad BA, Hedman A, Frick M, Nordlander R. Cardioversion of atrial fibrillation and its effect on right ventricular function as assessed by tricuspid annular motion. Am J Cardiol 1999;84:1256-8.
43. Neuhold S, Huelsmann M, Pernicka E, Graf A, Bonderman D, Adlbrecht C, et al. Impact of tricuspid regurgitation on survival in patients with chronic heart failure: unexpected findings of a long-term observational study. Eur Heart J 2013;34:844-52.
44. Damy T, Viallet C, Lairez O, Deswarte G, Paulino A, Maison P, et al. Comparison of four right ventricular systolic echocardiographic parameters to predict adverse outcomes in chronic heart failure. Eur J Heart Fail 2009;11:818-24.
45. Burke MA, Katz DH, Beussink L, Selvaraj S, Gupta DK, Fox J, et al. Prognostic importance of pathophysiologic markers in patients with heart failure and preserved ejection fraction. Circ Heart Fail 2014;7:288-99.
46. Freed BH, Daruwalla V, Cheng JY, Aguilar FG, Beussink L, Choi A, et al. Prognostic utility and clinical significance of cardiac mechanics in heart failure with preserved ejection fraction: importance of left atrial strain. Circ Cardiovasc Imaging 2016;9:e003754.
47. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med 2019;381:1609-20.

APPENDIX

Supplemental Table 1 Baseline characteristics and imaging parameters of patients with HFpEF compared with control subjects of similar age and sex

	Control subjects (n = 28)	Patients with HFpEF (n = 149)	*P value*
Baseline characteristics			
Age, y	76 ± 5	78 ± 9	.115
Female	19 (68)	91 (61)	.497
Body mass index, kg/m^2	25.4 ± 3.7	28.5 ± 6.2	.001*
Systolic blood pressure, mm Hg	144 ± 22	138 ± 22	.154
Diastolic blood pressure, mm Hg	82 ± 12	73 ± 13	.003
NYHA functional class III or IV	0	70 (47)	<.001*
Medical history			
AF	1 (4)	86 (58)	<.001*
Ischemic cardiomyopathy	0 (0)	51 (34)	<.001*
Previous HF episode	0 (0)	100 (67)	<.001*
Previous valvular surgery	0 (0)	13 (9)	.104
Chronic obstructive pulmonary disease	0 (0)	15 (10)	.079
Sleep apnea	0 (0)	16 (11)	.064
Cardiovascular risk factors			
Smoking	6 (21)	65 (44)	.026
Hypertension	18 (64)	138 (93)	<.001*
Diabetes	3 (11)	61 (41)	.002
Family history of CV disease	4 (14)	26 (17)	.672
Hypercholesterolemia	25 (89)	96 (64)	.011
Medication			
Loop diuretic	0 (0)	99 (66)	<.001*
Thiazide	2 (7)	31 (21)	.084
Mineralocorticoid receptor antagonist	0 (0)	22 (15)	.030
β-blocker	3 (11)	94 (63)	<.001*
ACE inhibitor or ARB	11 (39)	98 (66)	.008
Antiaggregant	6 (21)	63 (42)	.038
Oral anticoagulant	1 (4)	81 (54)	<.001*
Statin	7 (25)	61 (41)	.09
Biology			
Hemoglobin, g/dL	13.8 ± 1.4	11.8 ± 2.0	<.001*
Total cholesterol, mg/dL	210 ± 41	158 ± 47	<.001*
GFR, mL/min/1.73 m^2 by CK-EPI	69 ± 18	57 ± 24	.003
NT-proBNP, pg/mL	111 (57–156)	1,747 (923–3,521)	<.001*
Echocardiographic study			
LA volume index, mL/m^2	19 ± 6	45 ± 19	<.001*
LV EDV index, mL/m^2	60 ± 10	67 ± 18	.003
LVEF, %	65 ± 5	63 ± 7	.047
STE LVGLS, %	−21.0 ± 2.5	−16.7 ± 3.1	<.001*
E-wave velocity, m/sec	55 ± 10	92 ± 30	<.001*
Septal e′, m/sec	5.8 ± 0.92	5.2 ± 1.3	.015
E/e′ septal ratio	9.6 ± 1.7	18.7 ± 7.8	<.001*
RV FAC, %	47 ± 7	42 ± 9	.004
TAPSE, mm	24 ± 4	19 ± 5	<.001*

(*Continued*)

Supplemental Table 1 (*Continued*)

	Control subjects (*n* = 28)	Patients with HFpEF (*n* = 149)	*P value*
S′ velocity, m/sec	11.6 ± 2.5	11.2 ± 2.9	.566
Moderate to severe TR	0 (0)	14 (9)	.09
eSPAP, mm Hg	24 ± 6	43 ± 13	<.001*
STE RVGLS, %	−25.9 ± 4.2	−21.7 ± 4.9	<.001*
STE RVFWLS, %	−28.2 ± 5.2	−24.2 ± 6.3	.002
CMR study	**(*n* = 28)**	**(*n* = 120)**	
LVEF, %	66 ± 6	63 ± 8	.025
LV mass index, g/m^2	58 ± 12	67 ± 14	.004
RV EDV index, ml/m^2	68 ± 11	80 ± 25	<.001*
RVEF, %	60 ± 5	56 ± 7	<.001*

Data are expressed as mean ± SD, number (percentage), or median (interquartile range). Across-group *P* value is for the difference between patients with HFpEF and age- and sex-matched control subjects evaluated using χ^2 tests or unpaired *t* tests as appropriate.
ACE, *Angiotensin*-converting enzyme; *ARB*, angiotensin receptor blocker; *CK-EPI*, Chronic Kidney Disease Epidemiology Collaboration; *CV*, cardiovascular; *EDV*, end-diastolic volume; *GFR*, glomerular filtration rate; *LA*, left atrial; *LVEF*, LV ejection fraction; *TR*, tricuspid regurgitation.
**P* value was still significant after Bonferroni correction for multivariate testing.