Right Ventricular Function and Pulmonary Coupling in Patients With Heart Failure and Preserved Ejection Fraction

PARAGON-HF Investigators; Inciardi, Riccardo M.; Abanda, Martin; Shah, Amil M.; Cikes, Maja; Claggett, Brian; Skali, Hicham; Vaduganathan, Muthiah; Prasad, Narayana; Litwin, Sheldon

Published in:
Journal of the American College of Cardiology

DOI:
10.1016/j.jacc.2023.05.010

Publication date:
2023

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 82, NO. 6, 2023

PUBLISHED BY ELSEVIER

Right Ventricular Function and Pulmonary Coupling in Patients With Heart Failure and Preserved Ejection Fraction

Riccardo M. Inciardi, MD, PhD,[a,b,*] Martin Abanda, MD,[a,c,*] Amil M. Shah, MD, MPH,[a] Maja Cikes, MD, PhD,[d] Brian Claggett, PhD,[a] Hicham Skali, MD, MSc,[a] Muthiah Vaduganathan, MD, MPH,[a] Narayana Prasad, MD, MPH, RDCS,[a] Sheldon Litwin, MD,[e,f] Bela Merkely, MD,[g] Annamaria Kosztin, MD,[h] Klaudia Vivien Nagy, MD, PhD,[g] Sanjiv J. Shah, MD,[h] Wilfred Mullens, MD, PhD,[i] Michael R. Zile, MD,[e,f] Carolyn S.P. Lam, MD, PhD,[j,k,l] Marc A. Pfeffer, MD, PhD,[a] John J.V. McMurray, MD,[m] Scott D. Solomon, MD,[a] on behalf of the PARAGON-HF Investigators

ABSTRACT

BACKGROUND Limited data exist to characterize novel measures of right ventricular (RV) function and the coupling to pulmonary circulation in patients with heart failure and preserved left ventricular ejection fraction (HFpEF).

OBJECTIVES This study sought to assess the clinical implications of RV function, the association with N-terminal pro-B-type natriuretic peptide, and the risk for adverse events among patients with HFpEF.

METHODS This study analyzed measures of RV function by assessing absolute RV free wall longitudinal strain (RVFWLS) and its ratio to estimated pulmonary artery systolic pressure (PASP) (RVFWLS/PASP ratio) in 528 patients (mean age 74 ± 8 years, 56% female) with adequate echocardiographic images quality enrolled in the PARAGON-HF trial. Associations with baseline N-terminal pro-B-type natriuretic peptide and with total HF hospitalizations and cardiovascular death were assessed, after accounting for confounders.

RESULTS Overall, 311 patients (58%) had evidence of RV dysfunction, defined as absolute RVFWLS <20%, and among the 388 patients (73%) with normal tricuspid annular planar systolic excursion and RV fractional area change, more than one-half showed impaired RV function. Lower values of RVFWLS and RVFWLS/PASP ratios were significantly associated with higher circulating N-terminal pro-B-type natriuretic peptide. With a median follow-up of 2.8 years, there were 277 total HF hospitalizations and cardiovascular deaths. Both absolute RVFWLS (HR: 1.39; 95% CI: 1.05-1.83; $P = 0.018$) and RVFWLS/PASP ratio (HR: 1.43; 95% CI: 1.13-1.80; $P = 0.002$) were significantly associated with the composite outcome. Treatment effect of sacubitril/valsartan was not modified by measures of RV function.

CONCLUSIONS Worsening RV function and its ratio to pulmonary pressure is common and significantly associated with an increased risk of HF hospitalizations and cardiovascular death in patients with HFpEF. (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction [PARAGON-HF]; NCT01920711) (J Am Coll Cardiol 2023;82:489–499) © 2023 by the American College of Cardiology Foundation.

Listen to this manuscript's audio summary by Editor-in-Chief Dr Valentin Fuster on www.jacc.org/journal/jacc.

From the [a]Cardiovascular Division, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA; [b]Division of Cardiology, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy; [c]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA; [d]University of Zagreb School of Medicine and University Hospital Centre, Zagreb, Croatia; [e]Medical University of South Carolina, Charleston, South Carolina, USA; [f]Ralph H. Johnson Veterans Affairs Medical Center, Charleston, South Carolina, USA; [g]Semmelweis University Heart and Vascular Center, Budapest, Hungary; [h]Northwestern University, Chicago, Illinois, USA; [i]Ziekenhuis Oost Limburg, Genk, Belgium; [j]National Heart Centre Singapore and Duke-National University of Singapore, Singapore; [k]University Medical Centre Groningen, Groningen, the Netherlands; [l]The George Institute for Global Health, Newtown, New South Wales, Australia; and the [m]University of Glasgow, Glasgow, United Kingdom. *Drs Inciardi and Abanda contributed equally to this work.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2023.05.010

JACC VOL. 82, NO. 6, 2023
AUGUST 8, 2023:489–499

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CV = cardiovascular

FAC = fractional area change

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

LA = left atrial

LV = left ventricular

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-B-type-brain natriuretic peptide

PASP = pulmonary artery systolic pressure

RV = right ventricular

RVFWLS = right ventricular free wall longitudinal strain

TAPSE = tricuspid annular planar systolic excursion

Right ventricular (RV) dysfunction is a well-known key determinant of functional capacity and marker of adverse clinical outcomes in patients with heart failure (HF).[1,2] Whereas the role of RV function in HF with reduced ejection fraction has been well established, there has been increasing recent interest in the role of the RV in HF with mildly reduced and preserved left ventricular ejection fraction (LVEF).[3-5] The pathophysiology underlying the RV involvement in this population is not entirely elucidated, but it has been hypothesized that increased LV filling pressures adversely affect the pulmonary circulation and eventually RV function because of increased afterload.[3] Because of the importance of loading conditions on global RV performance, noninvasive methods have been developed to index the appropriateness of the coupling between the RV systolic function and the pulmonary vasculature, showing good correlation with prognosis both in HF with reduced ejection fraction and heart failure with preserved ejection fraction (HFpEF).[6,7]

SEE PAGE 500

Assessment of RV function by echocardiography has always been challenging, in part because of the unusual shape of the RV. Assessment of myocardial deformation by strain imaging is a relatively new modality that has been shown to add prognostic value to more commonly used cardiac functional parameters derived from echocardiography.[8] This parameter may show subclinical abnormalities earlier in the course of the RV impairment even before the structural and functional changes that are commonly assessed in clinical practice are identifiable. Nevertheless, limited data exist on the clinical value of RV myocardial deformation imaging in a large HFpEF population. To test the association of right ventricular free wall longitudinal strain (RVFWLS) and its ratio to estimated pulmonary artery systolic pressure (PASP) (RVFWLS/PASP ratio), with circulating biomarkers of HF and its prognostic relevance in terms of total HF hospitalizations and cardiovascular (CV) mortality, we studied patients enrolled in the PARAGON-HF (Prospective Comparison of ARNI With ARB Global Outcomes in HF With Preserved Ejection Fraction) trial who underwent comprehensive echocardiography and RV-dedicated analyses.[9,10]

METHODS

PATIENT POPULATION. PARAGON-HF was a multicenter, international, randomized, double-blind, event-driven trial testing the long-term efficacy and safety of sacubitril/valsartan compared with valsartan alone in patients with signs and symptoms of HF and LVEF ≥45%, as was previously described.[9,11] Briefly, PARAGON-HF enrolled 4,822 patients who met the following key inclusion criteria: 1) age ≥50 years; 2) symptoms of HF requiring treatment with diuretic agents and with current NYHA functional class II-IV symptoms; 3) LVEF ≥45% by echocardiography during the screening epoch or within 6 months prior to the screening visit; 4) left atrial (LA) enlargement (≥1 of the following: LA width ≥3.8 cm, LA length ≥5.0 cm, LA area ≥20 cm^2, LA volume ≥55 mL, or LA volume index ≥29 mL/m^2) or septal thickness or posterior wall thickness ≥1.1 cm by local reading; and 5) ≥1 of the following: a) HF hospitalization within 9 months prior to screening and N-terminal pro-B-type natriuretic peptide (NT-proBNP) >200 ng/L for patients not in atrial fibrillation (AF) or atrial flutter or >600 ng/L for patients in AF on screening electrocardiography, or b) NT-proBNP >300 ng/L for patients not in AF or >900 ng/L for patients in AF on screening electrocardiography. Key exclusion criteria included any prior LVEF <40% by echocardiography, a clinical event within 6 months of screening that may have reduced LVEF unless postevent echocardiography confirmed LVEF ≥45%, isolated right HF, known pericardial constriction or infiltrative or hypertrophic cardiomyopathy, and hemodynamically significant valvular heart disease or congenital heart disease, in the opinion of the investigator. The study was approved by an institutional review committee at each participating site. All patients provided written informed consent.

The echocardiographic substudy was designed for quality control purposes and to better characterize the cardiac phenotype in the trial population, as was previously described.[10]

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received April 10, 2023; revised manuscript received May 8, 2023, accepted May 12, 2023.

The qualifying echocardiogram underwent quantitative analysis at the echocardiography core laboratory at the Brigham and Women's Hospital in a subset of patients. Qualifying echocardiograms were performed within 6 months of the screening visit and were not obtained using a study-specific acquisition protocol. If a qualifying echocardiogram within 6 months of screening was not available, the qualifying echocardiogram was a study performed within the screening epoch, and use of a study-specific imaging protocol was recommended. Consent for review of historical echocardiograms, and for acquisition and review of echocardiograms at the screening visit, was obtained on the main study consent form. Of 1,202 qualifying echocardiograms submitted, image quality was adequate for core laboratory quantification of LVEF in 1,097 (91%), which defined the sample of the overall echocardiographic substudy.

ECHOCARDIOGRAPHY. Echocardiographic studies were transmitted in digital format to the core laboratory, where quantitative analyses of 2-dimensional, Doppler, and tissue Doppler measures were performed in accordance with American Society of Echocardiography guidelines[12,13] by dedicated analysts blinded to clinical information and randomized treatment assignment. Each measure was performed by the same analyst for all study participants. Intraobserver and interobserver variability for key measures of cardiac structure and function in our laboratory have been previously published.[14,15] Measures of RV function included tricuspid annular planar systolic excursion (TAPSE) and RV fractional area change (FAC), measured from tricuspid motion in systole on M-mode and the cavity area at end-diastole and end-systole, respectively. Peak tricuspid regurgitation (TR) velocity was measured, and PASP was estimated as: $4 \times$ (peak TR velocity)^2 + 5. Thresholds for defining abnormal values were based on published American Society of Echocardiography guidelines.[12]

RV myocardial deformation analysis by strain imaging was performed off-line on available echocardiograms at the echocardiography core laboratory at the Brigham and Women's Hospital. Speckle-tracking analysis was conducted using the semiautomated software TOMTEC Imaging systems (Image-Arena version 4.6.6.3). This software is angle-independent and identifies cardiac motion by tracking multiple chamber reference points over time.

Semiautomated tracing of the RV endocardial border of both RV free and septal wall was assessed after identification of 1 cardiac cycle (R-R interval based on QRS waveform) on the simultaneous electrocardiogram, from an RV-focused apical-4-chamber view. Every image was carefully inspected, and tracing was manually adjusted as needed, ensuring that the region of interest overlays the full thickness of the myocardial wall. RV global longitudinal strain was computed as the mean peak longitudinal strain during ventricular systole averaging lateral free wall and interventricular septum. RVFWLS was the mean peak longitudinal strain during ventricular systole of the lateral free wall of RV. For the purposes of this analysis, we explored RVFWLS because this measure is not influenced by the biventricular dependence caused by the interventricular septum. Because of the wall shortening during RV contraction, the RV strain values are negative, but for the purpose of the current analysis, the values were transformed and reported as positive (absolute strain). Absolute RVFWLS <20% was considered abnormal.[4,12] If the RV endocardial border could not be tracked for poor quality images or there was a lack of a full cardiac cycle, missing view, non-DICOM (Digital Imaging and Communications in Medicine) images, or significant foreshortening of the cavity, the measurements were considered unreliable, and the patient was excluded from the analysis. Overall, 527 echocardiograms were analyzed for the assessment of RV myocardial deformation imaging. All RV deformation analyses were performed by an investigator experienced in strain analyses blinded to clinical characteristics and outcome. Reproducibility was assessed by a second blinded investigator using 3 sets of 20 random blinded echocardiograms. The coefficient of variation was <10% and the intraclass correlation coefficient was 0.99% for intraobserver variability, and coefficient of variation was 12% and intraclass correlation coefficient was 0.92% for the interobserver variability.

OUTCOMES. Clinical outcomes included the composite of total (first and recurrent) HF hospitalizations and CV death (PARAGON-HF primary endpoint), total (first and recurrent) HF hospitalizations, and the composite of first HF hospitalization or CV death. All events were reported by the primary site investigator and were independently adjudicated by a clinical endpoints center, as was previously described in detail.[9,11]

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD or as median (IQR) as specified. Comparisons of baseline clinical measures between overall PARAGON-HF echocardiographic patients (n = 1,097) and those with available RV assessment (n = 528) were performed using the Fisher exact test for categorical variables and Student's

TABLE 1 Clinical Characteristics Stratified by RV Function

		Better ↔ Worse			
	Overall Population (N = 528)	1st Tertile Absolute RVFWLS >21.4 % (n = 176)	2nd Tertile Absolute RVFWLS 15.9%-21.4% (n = 176)	3rd Tertile Absolute RVFWLS <15.8% (n = 176)	*P* Value for Trend
Demographics					
Age, y	74.3 ± 7.9	73.3 ± 7.9	74.8 ± 8.0	74.8 ± 7.8	0.08
Female	298 (56.4)	115 (65.3)	91 (51.7)	92 (52.3)	0.013
Race/ethnicity					0.23
White	420 (79.5)	148 (84.1)	133 (75.6)	139 (79.0)	
Asian	82 (15.5)	20 (11.4)	35 (19.9)	27 (15.3)	
Black or African American	22 (4.2)	6 (3.4)	8 (4.5)	8 (4.5)	
Other	4 (0.8)	2 (1.1)	0 (0.0)	2 (1.1)	
Enrollment region					0.22
North America	192 (36.4)	56 (31.8)	52 (29.5)	84 (47.7)	
Western Europe	140 (26.5)	47 (26.7)	49 (27.8)	44 (25.0)	
Central Europe	99 (18.8)	45 (25.6)	32 (18.2)	22 (12.5)	
Asia/Pacific	95 (18.0)	27 (15.3)	43 (24.4)	25 (14.2)	
Latin America	2 (0.4)	1 (0.6)	0 (0.0)	1 (0.6)	
Comorbidities					
Prior MI	108 (20.5)	37 (21.0)	36 (20.5)	35 (19.9)	0.79
Ischemic etiology	153 (29.0)	43 (24.4)	58 (33.0)	52 (29.5)	0.29
Atrial fibrillation	181 (34.4)	35 (20.0)	65 (36.9)	81 (46.3)	<0.001
Prior HF hospitalization	259 (49.1)	79 (44.9)	83 (47.2)	97 (55.1)	0.06
Hypertension	492 (93.2)	162 (92.0)	163 (92.6)	167 (94.9)	0.29
Diabetes	191 (36.2)	51 (29.0)	70 (39.8)	70 (39.8)	0.035
CKD	217 (41.1)	70 (39.8)	79 (44.9)	68 (38.6)	0.83
Stroke	59 (11.3)	15 (8.6)	22 (12.5)	22 (12.7)	0.22
Examination and laboratory values					
NYHA functional class					0.81
I	16 (3.0)	6 (3.4)	5 (2.8)	5 (2.8)	
II	401 (75.9)	131 (74.4)	139 (79.0)	131 (74.4)	
III	110 (20.8)	39 (22.2)	32 (18.2)	39 (22.2)	
IV	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.6)	
SBP, mm Hg	128.30 ± 16.38	130.0 ± 17.2	127.0 ± 14.7	127.9 ± 17.1	0.23
Heart rate, beats/min	69.02 ± 12.20	66.5 ± 12.6	69.4 ± 11.5	71.1 ± 12.1	0.001
BMI, kg/m^2	29.34 ± 4.91	28.7 ± 4.6	29.1 ± 4.6	30.2 ± 5.4	0.003
Creatinine, mg/dL	1.01 ± 0.29	0.97 ± 0.24	1.04 ± 0.33	1.04 ± 0.28	0.017
eGFR, mL/min/1.73 m^2	60.89 ± 18.74	61.2 ± 18.9	61.8 ± 18.6	59.6 ± 18.7	0.41
NT-proBNP, ng/L	907.5 (473.5-1,699.0)	742.0 (431.0-1,384.0)	1,007.0 (474.0-1,719.0)	999.5 (584.0-1,972.0)	<0.001
Site-reported LVEF, %	58.70 ± 7.46	59.8 ± 7.6	58.5 ± 7.8	57.8 ± 6.9	0.01
Medication use					
Diuretics	506 (95.8)	164 (93.2)	170 (96.6)	172 (97.7)	0.033
Mineralocorticoid receptor antagonist	129 (24.4)	41 (23.3)	43 (24.4)	45 (25.6)	0.62
ACE inhibitor or ARB	417 (79.0)	143 (81.3)	137 (77.8)	137 (77.8)	0.43
Beta-blocker	416 (78.8)	142 (80.7)	143 (81.3)	131 (74.4)	0.15

Values are mean ± SD, n (%), or median (IQR).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HF = heart failure; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NT-proBNP = N-terminal pro–B-type natriuretic peptide; PARAGON-HF = Prospective Comparison of ARNI With ARB Global Outcomes in HF With Preserved Ejection Fraction; RV = right ventricular; RVFWLS = right ventricular free wall longitudinal strain; SBP = systolic blood pressure.

t-test or the Wilcoxon rank sum test for continuous variables as specified. Clinical characteristics and echocardiographic measures were stratified by tertiles of RVFWLS. Cross-sectional continuous association of measures of RVFWLS and the RVFWLS/PASP ratio with log-transformed NT-proBNP levels was assessed with restricted cubic splines. The number of knots (3-6 knots assessed) was selected to minimize the Akaike information criterion. The relationship between RVFWLS and the RVFWLS/PASP ratio and the endpoints of: 1) composite of the total (first and recurrent) HF hospitalizations and CV death; and

TABLE 2 Cardiac Structure and Function Stratified by RV Function

		Better ↔ Worse			
	Overall Population (N = 528)	1st Tertile Absolute RVFWLS >21.4% (n = 176)	2nd Tertile Absolute RVFWLS 15.9%-21.4% (n = 176)	3rd Tertile Absolute RVFWLS <15.8% (n = 176)	*P* Value for Trend
LV structure					
LVEDD, cm	4.54 ± 0.68	4.50 ± 0.7	4.55 ± 0.6	4.58 ± 0.7	0.25
LVEDV, mL	101.2 ± 37.7	99.7 ± 35.2	99.6 ± 30.4	104.4 ± 45.9	0.24
LVEDVi, mL/m^2	52.4 ± 16.8	52.6 ± 15.5	52.4 ± 14.9	52.3 ± 19.7	0.89
Septal wall thickness, cm	1.10 ± 0.25	1.07 ± 0.24	1.08 ± 0.22	1.15 ± 0.27	0.001
Posterior wall thickness, cm	0.97 ± 0.21	0.92 ± 0.19	0.97 ± 0.18	1.03 ± 0.23	<0.001
LV mass, g	167.8 ± 59.7	154.4 ± 49.1	165.7 ± 54.7	183.7 ± 70.3	<0.001
LV mass index, g/m^2	89.0 ± 30.0	83.6 ± 25.6	89.3 ± 32.0	94.2 ± 31.1	0.002
LV systolic function					
LVEF, %	59.3 ± 9.3	62.2 ± 8.2	58.9 ± 9.1	56.8 ± 9.9	<0.001
TDI septal s′, cm/s	5.5 ± 1.4	5.7 ± 1.3	5.5 ± 1.2	5.3 ± 1.5	0.003
GLS, %	−16.1 ± 3.7	−17.5 ± 3.3	−16.4 ± 3.4	−14.5 ± 3.7	<0.001
LV diastolic function					
E/A ratio	1.37 ± 0.79	1.32 ± 0.7	1.40 ± 0.8	1.41 ± 0.8	0.42
E wave, cm/s	92.0 ± 27.8	90.2 ± 27.2	90.6 ± 27.3	95.2 ± 28.7	0.10
Average E/e′	15.2 ± 6.5	15.7 ± 6.8	14.2 ± 5.8	15.7 ± 6.9	0.92
LA volume, mL	74.1 ± 31.6	72.6 ± 27.2	73.6 ± 36.9	76.1 ± 29.9	0.30
LA volume index, mL/m^2	39.9 ± 20.6	40.0 ± 14.3	40.0 ± 29.2	39.6 ± 15.5	0.86
RV and pulmonary pressure					
RVEDA, cm^2	20.9 ± 5.8	20.2 ± 5.3	20.9 ± 5.9	21.6 ± 6.3	0.025
RV FAC, %	47.4 ± 9.2	50.6 ± 8.7	47.9 ± 8.6	43.7 ± 8.8	<0.001
TAPSE, cm	1.81 ± 0.42	1.99 ± 0.38	1.74 ± 0.40	1.67 ± 0.40	<0.001
PASP, mm Hg	34.6 ± 11.1	35.1 ± 10.9	34.2 ± 10.9	34.5 ± 11.4	0.71
Absolute RVFWLS, %	19.0 ± 6.8	–	–	–	–
RFWLS/PASP ratio	0.59 ± 0.25	0.81 ± 0.2	0.60 ± 0.2	0.38 ± 0.1	<0.001

Values are mean ± SD.

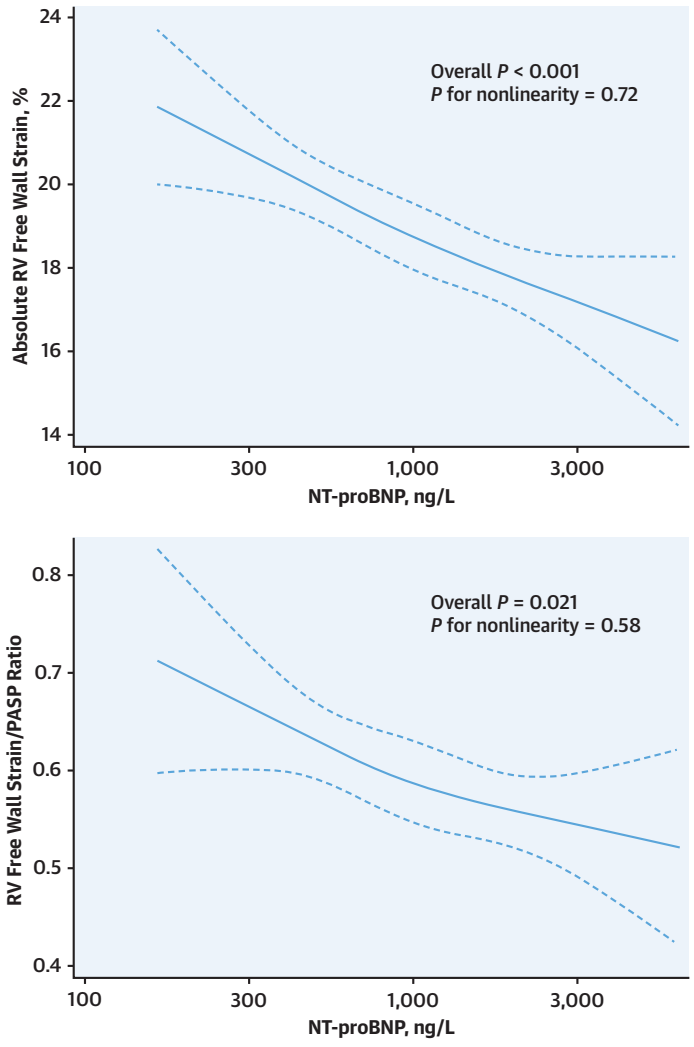
E wave = peak early diastolic transmitral flow velocity; e′ = peak early diastolic mitral annular tissue velocity; FAC = fractional area change; GLS = global longitudinal strain; LA = left atrial; LV = left ventricular; LVEDD = left ventricular end-diastolic dimension; LVEDV = left ventricular end-diastolic volume; LVEDVi = left ventricular end-diastolic volume indexed to body surface area; PASP = pulmonary artery systolic pressure; RVEDA = right ventricular end-diastolic area; s′ = peak systolic mitral annular tissue velocity; TAPSE = tricuspid annular plane systolic excursion; TDI = tissue Doppler imaging; other abbreviations as in Table 1.

2) total (first and recurrent) HF hospitalizations, during the follow-up period was assessed using the semiparametric method of Lin, Wei, Yang, and Ying, which is a modified Anderson-Gill method with a robust variance estimator.[16] This statistical method was used for the primary PARAGON-HF statistical analysis plan.[9,11] It has the benefit of being a recurrent-events model that requires fewer parametric assumptions compared with other approaches to recurrent events, such as the negative binominal model, and is therefore thought to be more robust. The analysis was adjusted for demographics (age, sex, region of enrollment), clinical confounders (body mass index, NYHA functional class, history of AF, heart rate, estimated glomerular filtration rate), measures of LV systolic and diastolic function (global longitudinal strain, E/e′, and PASP) and NT-proBNP. The flexible continuous association of RVFWLS and the RVFWLS/PASP ratio with the composite of the total (first and recurrent) HF hospitalizations and CV death was further assessed using restricted cubic splines with the number of knots selected to minimize the model's Akaike information criteria (3-6 knots tested). A value of $P < 0.05$ was considered statistically significant. All analyses were performed using Stata version 16 (StataCorp).

RESULTS

STUDY POPULATION. Comparison between PARAGON-HF patients not in the echocardiography cohort and those in the echocardiography cohort has been previously reported.[10] Overall, 528 patients (mean age 74.3 ± 7.9 years, 56.4% female, 79.5% White) were included in this analysis. Compared to patients without available RV strain assessment, those included in the current analysis were older, more likely to be female, and had lower body mass index (Supplemental Table 1). Modest differences were observed in comorbidity prevalence, but no

FIGURE 1 Relationship Between Absolute RVFWLS and RVFWLS/PASP Ratio and NT-proBNP Levels



Association between measures of right ventricular (RV) function and the coupling to pulmonary circulation and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in the PARAGON-HF (Prospective Comparison of ARNI With ARB Global Outcomes in HF With Preserved Ejection Fraction) population. The **dotted blue lines** indicate the 95% CIs. PASP = pulmonary artery systolic pressure; RVFWLS = right ventricular free wall longitudinal strain.

differences were observed in NYHA functional class, NT-proBNP, or prevalence of prior HF hospitalization.

Clinical and echocardiographic characteristics of the study population stratified by tertiles of absolute RVFWLS are shown in Tables 1 and 2. Patients who showed lower values of RVFWLS were more likely to be male and had a greater burden of CV risk factors, especially AF and obesity, and a higher plasma level of NT-proBNP (Table 1). Mean absolute value of RVFWLS was 19.0% ± 6.8%, and 311 patients (58.9%) showed reduced RVFWLS defined as <20%. Prevalence of RV dysfunction by conventional measures was 22% when defined as TAPSE <17 mm and 8% when defined as FAC <35%. Overall, 388 patients (73%) had a normal TAPSE and FAC. Of these, 207 patients (53%) had evidence of RVFWLS <20%. Patients with lower values of RFWLS had more enhanced LV hypertrophy and RV dilation and more impaired biventricular systolic function (Table 2).

ASSOCIATION OF RV MEASURES WITH NT-proBNP. Both absolute RVFWLS and RVFWLS/PASP ratio were significantly associated with NT-proBNP levels in cross-sectional analysis (Figure 1, Supplemental Figure 1). These associations were linear (all *P* for nonlinearity >0.05), such that lower values of absolute RVFWLS and RVFWLS/PASP ratio were associated with higher levels of NT-proBNP. No significant effect modification was noted by sex or baseline LVEF (all *P* for interaction >0.05).

RV MEASURES AND OUTCOMES. Over a median follow-up of 2.8 years, there were 277 total HF hospitalizations and CV death.

Both absolute RVFWLS (HR per SD decrease: 1.27; 95% CI: 1.07-1.50; $P = 0.005$) and RVFWLS/PASP ratio (HR per SD decrease: 1.52; 95% CI: 1.20-1.93; $P < 0.001$) were significantly associated with recurrent HF hospitalizations and CV death (Table 3). Both measures showed a linear association with the outcome (*P* for nonlinearity >0.05) such that lower values were associated with higher incidence rates without evidence of a threshold (Central Illustration). The association was consistent after accounting for clinical confounders and measures of LV systolic and diastolic function and NT-proBNP plasma levels (Table 3). Sex and baseline LVEF did not significantly modify the association between absolute RVFWLS and RVFWLS/PASP ratio with total HF hospitalizations and CV death. The relationship of these measures with the outcome was consistent regardless of baseline TAPSE or FAC (*P* for interaction >0.05). Similar results were observed for the outcome of total HF hospitalizations alone and for time to first HF hospitalization or CV death. Although point estimates were similar for the adjusted association between RVFWLS and time to first HF hospitalization or CV death and first HF hospitalization alone, these endpoints were underpowered (Table 3). No effect modification of the treatment effect of sacubitril/valsartan was observed for the primary endpoint according to both RVFWLS and RVFWLS/PASP ratio (*P* for interaction = 0.84 and 0.27, respectively) as well as for the components (all *P* for interaction >0.05). Irrespective of treatment

TABLE 3 Association Between RV Function and the Analyzed Endpoints

	Events	Event Rate per 100 py HR (95% CI)	Unadjusted			Adjusted		
			HR (95% CI)	*P* Value	|Z|	HR (95% CI)	*P* Value	|Z|
Total (first and recurrent) HF hospitalizations and CV death	277	17.4 (14.3-21.3)						
RVFWLS, %			1.27 (1.07-1.50)	0.005	2.82	1.39 (1.05-1.83)	0.018	2.37
RVFWLS/PASP ratio			1.52 (1.20-1.93)	<0.001	3.50	1.43 (1.13-1.80)	0.002	3.06
Total (first and recurrent) HF hospitalizations	230	14.4 (11.7-18.0)						
RVFWLS, %			1.28 (1.06-1.54)	0.009	2.61	1.44 (1.07-1.94)	0.016	2.41
RVFWLS/PASP ratio			1.57 (1.22-2.01)	<0.001	3.57	1.48 (1.16-1.88)	0.002	3.17
First HF hospitalization or CV death	139	9.8 (8.33-11.6)						
RVFWLS, %			1.22 (1.03-1.44)	0.020	2.32	1.34 (0.96-1.87)	0.076	1.77
RVFWLS/PASP ratio			1.51 (1.21-1.88)	<0.001	3.68	1.46 (1.11-1.93)	0.007	2.70
First HF hospitalization	122	8.6 (7.23-10.3)						
RVFWLS, %			1.25 (1.04-1.50)	0.014	2.46	1.35 (0.96-1.90)	0.081	1.74
RVFWLS/PASP ratio			1.49 (1.18-1.88)	0.001	3.45	1.50 (1.12-2.00)	0.006	2.74
CV death	47	2.9 (2.21-3.93)						
RVFWLS, %			1.24 (0.92-1.67)	0.14	1.46	1.11 (0.60-2.04)	0.72	0.35
RVFWLS/PASP ratio			1.33 (0.91-1.94)	0.13	1.51	1.20 (0.73-1.95)	0.46	0.73

Adjusted for age, sex, region of enrollment, BMI, NYHA functional class, history of atrial fibrillation, heart rate, eGFR, GLS, E/e′, PASP (for RVFWLS), and NT-proBNP. HR are expressed per SD decrease of absolute RVFWLS (6.8%) and RVFWLS/PASP ratio (0.2 unit).

CV = cardiovascular; py = patient-years; |Z| = the absolute value of the Wald statistic; other abbreviations as in Tables 2 and 3.

assignment, tolerability and rates of adverse events did not vary significantly according to RV dysfunction, which was defined as absolute RVFWLS <20%.

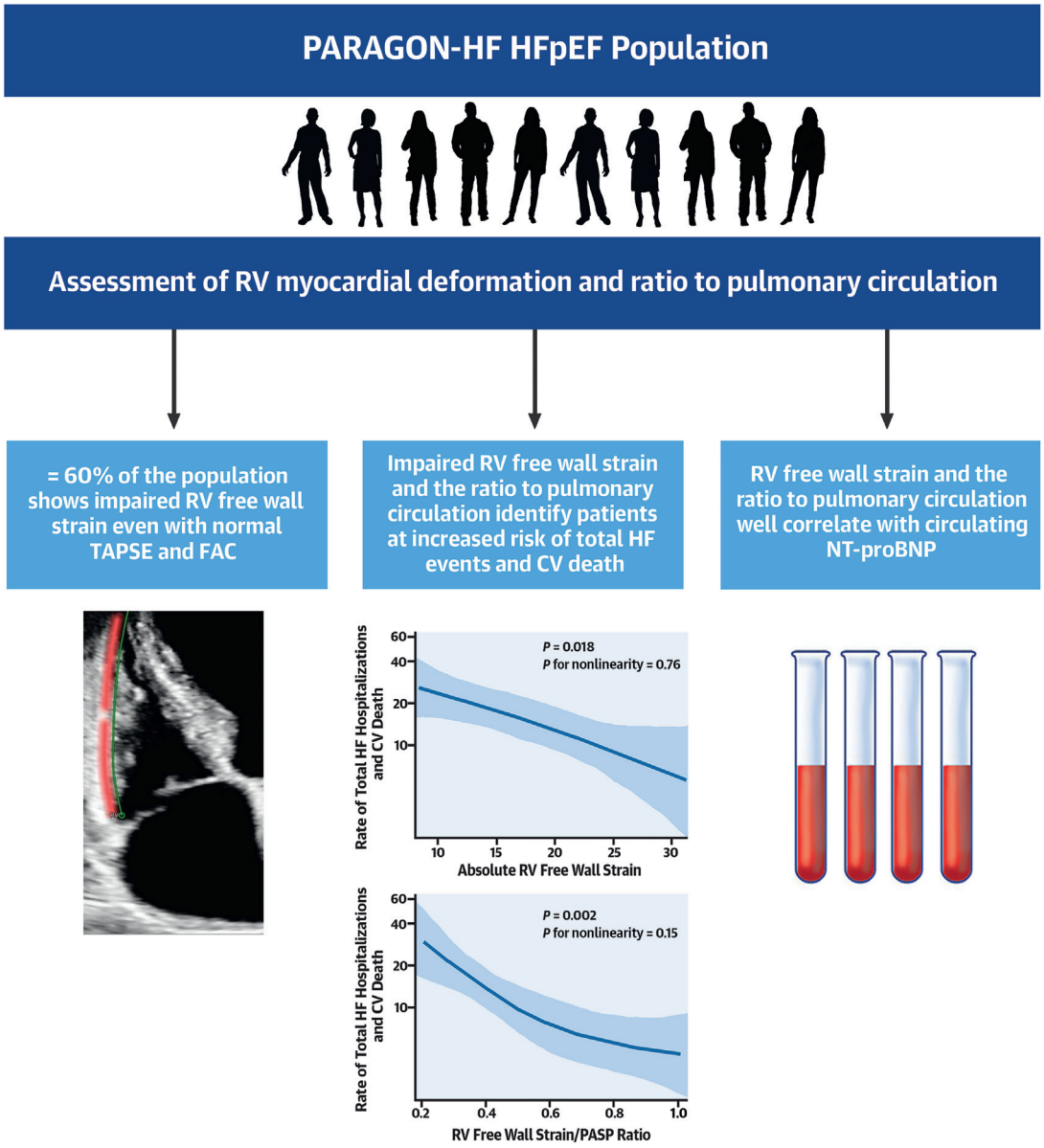
DISCUSSION

In a contemporary large HFpEF population enrolled in PARAGON-HF, we found that up to 60% of the patients had evidence of RV dysfunction assessed by myocardial deformation imaging. Reduced RV free wall strain was identified in more than one-half of patients without evidence of RV impairment as assessed by traditional echocardiographic methods. Impaired RV free wall strain and its ratio to pulmonary circulation were associated with higher circulating NT-proBNP levels and with a higher risk of total HF hospitalizations and CV death, after accounting for clinical confounders, measures of LV systolic and diastolic function, and NT-proBNP. Together, these findings suggest a high prevalence of subtle RV dysfunction, otherwise not detected by standard echocardiographic measures, and highlight a key role of RV function and its pulmonary hemodynamic consequences in the pathophysiology of HFpEF (**Central Illustration**).

Our study is among the largest to explore the role of RV function, assessed by deformation imaging echocardiography, in patients with HFpEF. It has been shown that RV dysfunction is a critical determinant of the symptomatic status and clinical outcomes among HFpEF[2,3] and is associated with a higher burden of comorbidities such as obesity and AF and right atrial remodeling.[17,18] Prevalence of RV dysfunction in HFpEF is variable because of the inclusion criteria that are applied to define HFpEF and the different imaging parameters and cutoffs used.[19] In a recent large meta-analysis,[20] the prevalence of RV dysfunction ranged from 18% to 28% by using different standard echocardiographic measures such as FAC, TAPSE, and RV S′ on tissue Doppler. Nevertheless, these data did not account for novel measures of RV myocardial function by strain imaging caused by limited available data. This is particularly relevant because current guidelines recommend the use of strain imaging for a comprehensive assessment of cardiac structure and function, including the RV.[12] Previous studies explored the clinical value of RV myocardial deformation in HFpEF, but they were mostly derived from relatively small single-center populations without focusing on the coupling with pulmonary circulation.[21] An Asian population-based cohort study assessed the clinical value of RVFWLS in patients with HFpEF, compared with those with HF with reduced EF and control subjects.[7] The prevalence of RV dysfunction among patients with HFpEF was about 32%, and both RVFWLS and its ratio to pulmonary circulation were associated with all-cause mortality and HF hospitalization, although separate analyses for patients with HFpEF alone were not

JACC VOL. 82, NO. 6, 2023
AUGUST 8, 2023:489–499

CENTRAL ILLUSTRATION **Clinical Implication of Right Ventricular Function and Coupling to Pulmonary Circulation**



Inciardi RM, et al. J Am Coll Cardiol. 2023;82(6):489–499.

Among patients with heart failure with preserved ejection fraction (HFpEF) who were enrolled in the PARAGON-HF (Prospective Comparison of ARNI With ARB Global Outcomes in HF With Preserved Ejection Fraction) trial, impairment of right ventricular (RV) free wall strain is encountered in approximately 60% of patients, even among those with normal tricuspid annular planar systolic excursion (TAPSE) and fractional area change (FAC). RV free wall strain and its ratio to pulmonary circulation identify patients at risk of recurrent HF events and cardiovascular (CV) death.

performed. The higher proportion of RV dysfunction encountered in our population (59% had a reduced RVFWLS) may be explained by the older age, the higher prevalence of advanced NYHA functional classes, and the higher use of diuretic agents underlying a potentially sicker population. Our analysis extends previous results by analyzing RV myocardial deformation and its ratio to pulmonary circulation in

a larger and international HFpEF population in relation to standard RV measures, by assessing its association with circulating NT-proBNP and the risk of total (first and recurrent) HF hospitalizations and CV death.

The pathophysiology underlying the RV involvement and impairment in HFpEF is complex.[3,22] Although the development of pulmonary hypertension is mostly related to the backward pulmonary venous transmission of elevated left-sided filling pressure, it may be questioned whether RV dysfunction is just secondary to the pulmonary afterload or actively contributes to shared underlying pathophysiologic mechanisms in HFpEF. We found that both RV dysfunction and its coupling to pulmonary hemodynamics were associated with markers of HF severity and with worse CV events regardless of LV systolic and diastolic function, suggesting that the RV and the pulmonary vasculature are not simple bystanders of the LV impairment but play a central role in the HFpEF pathophysiology as an active independent process. In addition, worsening RV function and subsequent overload interacts with the LV function, further raising left diastolic pressure and thus creating a vicious feedback loop.[3]

The best parameter to evaluate RV function is yet to be defined and accurate assessment of RV in daily practice remains challenging because of the complex shape of the chamber.[6] Although its use may be potentially limited in patients with poor acoustic window, RVFWLS has shown better correlation with cardiac magnetic resonance–derived RV ejection fraction, compared to TAPSE and FAC, with less angle and load dependency and observer variability.[23] By directly assessing the deformation of the free wall, RVFWLS has the potential to identify subtle functional impairment early without being influenced by the interventricular septum dependency. Hence, the current analysis provides potential advantages of using RVFWLS as compared to TAPSE and FAC, especially when standard measures are still in the range of normality. Because RV dysfunction is strongly associated with the presence of an elevated RV afterload in HFpEF and the RV chamber is highly sensitive to the imposed pressure, the RVFWLS/PASP ratio may act as a surrogate of the strain/stress ratio between the RV and the pulmonary circulation. In the recent past, several attempts have been made to derive a noninvasive tool able to comprehensively assess the relationship between RV contractility (strain) and afterload (stress). The ratio of RV function to pulmonary pressure has been developed and adopted in the last years to provide a more comprehensive noninvasive assay of RV-PA coupling that correlates well with the invasive gold standard end-systolic elastance/arterial elastance ratio.[22,23] It is plausible that at an early stage of the disease, the afterload increase is balanced by the preserved RV function, but as the process continues the development of subtle RV impairment in response to the pulmonary load increases the risk for HF events. Although previous interventional studies targeting pulmonary circulation have shown negative results, restoration of RV function and pulmonary hemodynamics represents a potential therapeutic goal for future studies.

STUDY LIMITATIONS. The current analysis included patients with adequate acoustic window to perform RV-dedicated analysis. Hence 48% of the original participants enrolled in the PARAGON-HF echocardiographic substudy were included in the current analysis. Nevertheless, this is in line with other RV function measures such as TAPSE and FAC that have been collected in 47% and 56%, respectively, of the population as was shown in a previous publication.[10] Compared with the overall PARAGON-HF participants, those included in the echocardiography study showed minor differences in baseline characteristics compared with those nonincluded, potentially limiting the generalizability of these findings. As for all clinical trials, PARAGON-HF had strict inclusion and exclusion criteria, and therefore these findings may not be generalizable to the community.

CONCLUSIONS

In a large HFpEF population enrolled in the PARAGON-HF trial, impairment of RV function assessed by myocardial deformation imaging was identified in approximately 60% of the population, including those with normal conventional measures of RV function. RVFWLS and its ratio to pulmonary circulation were significantly associated with elevation in NT-proBNP and total hospitalizations for HF and CV death, regardless of LV systolic and diastolic function and NT-proBNP. These data suggest that RV dysfunction may play a key pathophysiologic role in patients with HFpEF and that measures of RV dysfunction by myocardial deformation imaging might identify patients with HFpEF at increased risk for HF events that warrant more intensive care.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The PARAGON-HF trial was funded by Novartis. Dr Abanda received institutional support from National Institutes of Health (5HL9804812) through the Harvard T.H. Chan School of Public Health. Dr A. Shah has received research support from Novartis, through Brigham and Women's Hospital; and has received consulting fees from Philips Ultrasound and Bellerophon Therapeutics. Dr Cikes has received

grants, personal fees, and nonfinancial support (travel support) from Novartis, GE Healthcare, Abbott, Roche Diagnostics, Bayer, Pfizer, Boehringer Ingelheim, Berlin-Chemie Menarini, Servier, Corvia, AstraZeneca, Sanofi Genzyme, Sandoz, Amgen, Orion Pharma, and Teva Pharmaceutical Industries. Dr Vaduganathan has received research grants from American Regent, Amgen, AstraZeneca, Baxter Healthcare, Bayer AG, Boehringer Ingelheim, Chiesi, Cytokinetics, Novo Nordisk, Relypsa, Roche Diagnostics, Sanofi, and Tricog Health; and participates in clinical trial committees for studies sponsored by AstraZeneca, Occlutech, Impulse Dynamics, Galmed, Bayer AG, and Novartis. Dr S. Shah has received research grants from the National Institutes of Health (R01 HL107577, R01 HL127028, R01 HL140731, and R01 HL149423), Actelion, AstraZeneca, Corvia, and Novartis; and has served as a consultant or an Advisory Board member for Abbott, Actelion, AstraZeneca, Amgen, Bayer, Boehringer Ingelheim, Cardiora, Coridea, CVRx, Eisai, Ionis, Ironwood, Merck, MyoKardia, Novartis, Pfizer, Sanofi, Shifamed, Tenax, and United Therapeutics. Dr Zile has received grants and personal fees from Novartis, CVRx, and Medtronic; and has received personal fees from Abbott, Boston Scientific, EBR, Endotronics, Ironwood, Merck, Myokardia, and V Wave. Dr Lam has received research support from Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, and Vifor Pharma; has served as consultant or on Advisory Boards, Steering Committees, or Executive Committees for Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, Vifor Pharma, Novartis, Amgen, Merck, Janssen Research and Development, Menarini, Boehringer Ingelheim, Novo Nordisk, Abbott Diagnostics, Corvia, Stealth BioTherapeutics, JanaCare, Biofourmis, Darma, Applied Therapeutics, MyoKardia, WebMD Global, Radcliffe Group, and Corpus; and is a cofounder of eKo.ai. Dr Pfeffer has received research grant support through Brigham and Women's Hospital from Novartis; and has received consulting fees from Alnylam, AstraZeneca, Boehringer Ingelheim, Eli Lilly Alliance, Corvidia, DalCor, GlaxoSmithKline, National Heart, Lung, and Blood Institute CONNECTs (Master Protocol Committee), Novartis, Novo Nordisk, Peerbridge, and Sanofi; and has equity in DalCor. Dr McMurray has received payment paid to his employer, Glasgow University, from Novartis for his role as coprincipal investigator of PARAGON-HF; has received grants paid to his employer from AstraZeneca, Theracos, and GlaxoSmithKline during the conduct of the study; and has received grants paid to his employer from Novartis, Amgen, Bristol Myers Squibb, Bayer, Abbvie, Dal-Cor, Kidney Research UK, and Cardurion; and has received grants from the British Heart Foundation. Dr Solomon has received research grants from Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, Bristol Myers Squibb, Celladon, Cytokinetics, Eidos, Gilead, GlaxoSmithKline, Ionis, Lone Star Heart, Mesoblast, MyoKardia, National Institutes of Health/National Heart, Lung, and Blood Institute, Novartis, Sanofi Pasteur, and Theracos; and has consulted for Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Bristol Myers Squibb, Cardior, Corvia, Cytokinetics, Daiichi-Sankyo, Gilead, GlaxoSmithKline, Ironwood, Merck, Myokardia, Novartis, Roche, Takeda, Theracos, Quantum Genetics, Cardurion, AoBiome, Janssen, Cardiac Dimensions, and Tenaya. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Scott D. Solomon, Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School, 75 Francis Street, Boston, Massachusetts 02115, USA. E-mail: ssolomon@bwh.harvard.edu.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILL: In patients with HFpEF, right ventricular free wall strain detects subtle functional impairment. This parameter and the coupling to the pulmonary circulation identifies patients at high risk of hospitalization for HF and cardiovascular death.

TRANSLATIONAL OUTLOOK: Prospective studies are needed to determine whether initiation of therapeutic interventions based on early detection of RV dysfunction can improve clinical outcomes.

REFERENCES

1. Ghio S, Temporelli PL, Klersy C, et al. Prognostic relevance of a non-invasive evaluation of right ventricular function and pulmonary artery pressure in patients with chronic heart failure. *Eur J Heart Fail*. 2013;15(4):408–414.

2. Ghio S, Guazzi M, Scardovi AB, et al. Different correlates but similar prognostic implications for right ventricular dysfunction in heart failure patients with reduced or preserved ejection fraction. *Eur J Heart Fail*. 2017;19(7):873–879.

3. Guazzi M, Naeije R. Right heart phenotype in heart failure with preserved ejection fraction. *Circ Heart Fail*. 2021;14(4):e007840.

4. Gorter TM, van Veldhuisen DJ, Bauersachs J, 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(1):16–37. https://doi.org/10.1002/ejhf.1029

5. Mohammed SF, Hussain I, AbouEzzeddine OF, et al. Right ventricular function in heart failure with preserved ejection fraction: a community-based study. *Circulation*. 2014;130(25):2310–2320. erratum Circulation. 2015;131(17):e424.

6. Ghio S, Acquaro M, Agostoni P, et al. Right heart failure in left heart disease: imaging, functional, and biochemical aspects of right ventricular dysfunction. *Heart Fail Rev*. 2023;28:1009–1022. https://doi.org/10.1007/s10741-022-10276-0

7. Bosch L, Lam CSP, Gong L, et al. Right ventricular dysfunction in left-sided heart failure with preserved versus reduced ejection fraction. *Eur J Heart Fail*. 2017;19(12):1664–1671.

8. Cikes M, Solomon SD. Beyond ejection fraction: an integrative approach for assessment of cardiac structure and function in heart failure. *Eur Heart J*. 2016;37(21):1642–1650.

9. Solomon SD, McMurray JJV, Anand IS, et al, PARAGON-HF Investigators and Committees. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019;381(17):1609–1620.

10. Shah AM, Cikes M, Prasad N, et al, PARAGON-HF Investigators. Echocardiographic features of patients with heart failure and preserved left ventricular ejection fraction. *J Am Coll Cardiol*. 2019;74(23):2858–2873.

11. Solomon SD, Rizkala AR, Gong J, et al. Angiotensin receptor neprilysin inhibition in heart failure with preserved ejection fraction: rationale and design of the PARAGON-HF trial. *J Am Coll Cardiol HF*. 2017;5(7):471–482.

12. Lang RM, Badano LP, Mor-Avi V, 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. *J Am Soc Echocardiogr*. 2015;28(1):1-39.e14.

13. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29(4):277-314.

14. Shah AM, Shah SJ, Anand IS, et al, TOPCAT Investigators. Cardiac structure and function in heart failure with preserved ejection fraction: baseline findings from the echocardiographic study of the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist trial. *Circ Heart Fail*. 2014;7:104-715.

15. Minamisawa M, Inciardi RM, Claggett B, et al. Left atrial structure and function of the amyloidogenic V122I transthyretin variant in elderly African Americans. *Eur J Heart Fail*. 2021;23(8):1290-1295.

16. Lin DW, Wei LJ, Yang I, Ying Z. Semiparametric regression for the mean and rate functions of recurrent events. *J R Statist Soc B*. 2000;62:711-730.

17. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. *Circulation*. 2017;136(1):6-19.

18. Gorter TM, van Melle JP, Rienstra M, et al. Right heart dysfunction in heart failure with preserved ejection fraction: the impact of atrial fibrillation. *J Card Fail*. 2018;24(3):177-185.

19. Zakeri R, Mohammed SF. Epidemiology of right ventricular dysfunction in heart failure with preserved ejection fraction. *Curr Heart Fail Rep*. 2015;12(5):295-301.

20. Gorter TM, Hoendermis ES, van Veldhuisen DJ, et al. Right ventricular dysfunction in heart failure with preserved ejection fraction: a systematic review and meta-analysis. *Eur J Heart Fail*. 2016;18(12):1472-1487.

21. Lejeune S, Roy C, Ciocea V, et al. Right ventricular global longitudinal strain and outcomes in heart failure with preserved ejection fraction. *J Am Soc Echocardiogr*. 2020;33(8):973-984.e2.

22. Houston BA, Brittain EL, Tedford RJ. Right ventricular failure. *N Engl J Med*. 2023;388(12):1111-1125.

23. Guazzi M, Dixon D, Labate V, et al. RV contractile function and its coupling to pulmonary circulation in heart failure with preserved ejection fraction: stratification of clinical phenotypes and outcomes. *J Am Coll Cardiol Img*. 2017;10(10 Pt B):1211-1221.

KEY WORDS heart failure, pulmonary circulation, right ventricular, speckle-tracking

APPENDIX For a supplemental figure and table, please see the online version of this paper.