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ORIGINAL RESEARCH

RV Contractile Function and its Coupling to Pulmonary Circulation in Heart Failure With Preserved Ejection Fraction

Stratification of Clinical Phenotypes and Outcomes

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ABSTRACT

OBJECTIVES This study sought to investigate how right ventricular (RV) contractile function and its coupling with pulmonary circulation (PC) stratify clinical phenotypes and outcome in heart failure preserved ejection fraction (HFpEF) patients.

BACKGROUND Pulmonary hypertension and RV dysfunction are key hemodynamic abnormalities in HFpEF.

METHODS Three hundred eighty seven HFpEF patients (mean age 64 ± 12 years, 59% females, left ventricular ejection fraction 59 ± 7%) underwent RV and pulmonary hemodynamic evaluation by echocardiography (entire population) and right heart catheterization (219 patients). Patients were investigated by tricuspid annular plane systolic excursion (TAPSE) to pulmonary artery systolic pressure (PASP) relationship and stratified according to TAPSE/PASP ratio tertiles (1: <0.35; 2: 0.35 to 0.57; 3: >0.57). Specifically, TAPSE/PASP ratio was taken as a noninvasive index of RV to PC coupling based on the correlation with invasively evaluated RV systolic elastance/arterial elastance ($r = 0.35$; $p < 0.0001$).

RESULTS Groups had similar prevalence of comorbidities except for a higher prevalence of atrial fibrillation and kidney dysfunction in tertile 1. Progressively increasing levels of natriuretic peptides, worse systemic and pulmonary hemodynamics, abnormal exercise aerobic capacity and ventilatory inefficiency were observed from the highest to lowest TAPSE/PASP tertile. TASPE/PASP correlated with pulmonary artery compliance ($r = 0.69$; $p < 0.0001$). Remarkably, the tertile 1 group distributed along the worse portion of the curve at lower pulmonary artery compliance and higher pulmonary vascular resistances. In addition, the TAPSE/PASP ratio emerged as an independent predictor of worse outcomes.

CONCLUSIONS A thorough assessment of RV-PC coupling and RV contractile function stratify HFpEF phenotypes at different level of risk. These observations shift the interest toward therapeutic strategies that may benefit the right heart as primary unmet need in the complex pathophysiology of the HFpEF syndrome. (J Am Coll Cardiol Img 2017;10:1211–21)

Heart failure with preserved ejection fraction (HFpEF) is a complex and heterogeneous syndrome associated with high morbidity and mortality (1,2). Despite the completion of several HFpEF trials, therapies remain elusive, which may be due to inadequate targeting of specific phenotypes (1). A primary pathophysiological abnormality is an abnormal left ventricular (LV) filling

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ABBREVIATIONS AND ACRONYMS

CpcPH = pre- and post-capillary pulmonary hypertension

HFpEF = heart failure preserved ejection fraction

IpcPH = isolated post-capillary pulmonary hypertension

PASP = pulmonary systolic pressure

PA = pulmonary artery

PAC = pulmonary artery compliance

RV = right ventricle

RV ea = pulmonary artery elastance

RV Ees = right ventricular elastance

TAPSE = tricuspid annular plane systolic excursion

due to impaired relaxation and/or increased stiffness, which combines with reduced systemic arterial compliance and ventricular-arterial uncoupling (3). Consequently, an increase in left atrial pressure yields to development of pulmonary hypertension (PH) (4). It is estimated that up to 70% to 80% of HFpEF patients develop PH (5), which can result in right ventricular (RV) dysfunction or failure (6).

Recent findings have highlighted that PH and RV dysfunction are critical players in the complex evolving framework of HFpEF syndrome (6–8). However, prior HFpEF studies have primarily focused on the RV and pulmonary circulation (PC) separately (6,9), despite the pathophysiologic importance of RV-PC coupling. A comprehensive analysis of HFpEF clinical phenotypes and outcomes based on the evaluation of RV contractile state and its coupling with the PC has not been performed yet. The sole information available is that provided by a post-hoc analysis of the RELAX (PhosphdiesteRasE-5 Inhibition to Improve CLinical Status and EXercise Capacity in Diastolic Heart Failure) trial (10) that has defined RV-PC clinical characteristics of HFpEF based on the tricuspid annular plane systolic excursion (TAPSE) to pulmonary artery systolic pressure (PASP) ratio, as previously proposed by our group (7). An extensive and improved understanding of the clinical, echocardiographic, and hemodynamic characteristics of HFpEF patients stratified across the RV to PC coupling spectrum could provide added insights into HFpEF syndrome, phenotyping who may respond more homogeneously to targeted therapies.

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Accordingly, in a broad HFpEF population, we aimed at: 1) defining the spectrum of disease severity, related clinical features and outcome, through measures of RV contractility, RV-PC coupling, and PH staging obtained by invasive hemodynamics and echocardiography; 2) testing the potential additive value of phenotyping HFpEF through the study of the right heart; and 3) validating the use of TAPSE/PASP as an indicator of RV to PC coupling against invasively recognized gold standard.

METHODS

STUDY POPULATION. This prospective study was performed in 2 centers that specialize in HFpEF: Northwestern Memorial Hospital, Chicago, Illinois, and San Paolo University Hospital, Milano, Italy. Patients were recruited from the outpatient clinics, as parts of the Chicago Northwestern University, between June 2008 and October 2012, and Milano State University (between October 2007 and April 2011) HFpEF programs. Chicago patients were enrolled in the outpatient setting after hospitalization, identified by an automated daily query of the inpatient electronic medical records. Inclusion criteria were: age ≥21 years, LV ejection fraction (EF) ≥50%, and presence of heart failure (HF) as defined by Framingham criteria (11). HF diagnosis was confirmed at the post-hospitalization, outpatient HFpEF clinic visit. All patients met the Paulus et al. (12) criteria for diagnosis of HFpEF. Exclusion criteria were moderate valvular disease, prior cardiac transplantation, history of reduced LVEF <40% (i.e., "recovered" EF), LV end-diastolic volume (EDV) >97 ml/m^2, or constrictive pericarditis. Participants gave written, informed consent, and the Institutional Review Board at Northwestern University approved the study.

Patients of the Milano cohort were part of a referral population sent because of dyspnea. They underwent echocardiography and right heart catheterization within a 48-h window between the 2, a diagnosis of HFpEF was based on Paulus et al. (12) criteria. Exclusion criteria were: severe chronic obstructive pulmonary disease; more than moderate valvular disease; acute coronary syndrome; hypertrophic cardiomyopathy; high output HF; non-Group 2 PH. The study was approved by the Ethics Board.

CLINICAL CHARACTERISTICS. The following data were collected: demographics, race/ethnicity, New York Heart Association (NYHA) functional class, comorbidities, medications, vital signs, body mass index, serum sodium, blood urea nitrogen, creatinine, hemoglobin, and brain natriuretic peptide (BNP) (Online Appendix).

ECHOCARDIOGRAPHY. Participants underwent 2-dimensional echocardiography with Doppler and tissue Doppler imaging (TDI), (Philips iE33 or 7500, Philips Medical Systems, Andover, Massachusetts; or Vivid 7, GE Healthcare, General Electric Corp., Waukesha, Wisconsin). RV was investigated with dedicated views. Cardiac structure and function were quantified as recommended by the American Society of Echocardiography (13,14). Measurements were made by experienced sonographers and cardiologists (blinded to clinical data).

LV DIASTOLIC FUNCTION. Diastolic function was assessed according to published guidelines. TDI of the mitral annulus was obtained from the apical 4-chamber view using a 1.5-mm sample volume. The systolic (s′) and the early (e′) and late (a′) diastolic peak

TDI velocities were measured. Pulsed-wave Doppler echocardiography was used to assess mitral peak E and A waves flow velocity. E/A, E deceleration time, and E/e′ were used to classify diastolic function (15,16).

RV MORPHOLOGY AND CONTRACTILE FUNCTION. RV end-diastolic and end-systolic area, basal diameter, wall thickness, and fraction area change, were obtained using 2-dimensional echocardiography; TAPSE was measured using M-mode according to the American Society of Echocardiography (14). RV wall thickness was measured at end-diastole in the subcostal view at the mid-portion of the RV free wall as reported previously (8), and as recommended by the American Society of Echocardiography (14).

PASP and right atrial pressure (RAP) were derived as previously described (7). RV contractile function was assessed through an approach recently proposed by our group (7) by plotting the relationship between TAPSE as a measure of length versus PASP as a measure of developed force.

INVASIVE HEMODYNAMICS. Right heart catheterization was performed from either the right internal jugular or right femoral vein approach using the fluoroscopy-guided Seldinger technique in a subset of patients (n = 219) (Online Appendix).

ASSESSMENT OF RV TO PC COUPLING. We evaluated RV-PC coupling by the TAPSE/PASP ratio as a potentially easy to obtain measure recently proposed by our group (7) and endorsed by others (10,17). Because the true reflection of RV to PC coupling is provided by pressure volume analysis, we validated and correlated TAPSE/PASP ratio against RV systolic elastance (Ees) /arterial elastance (Ea). Ees/Ea, was calculated as RV Ees = PASP/RV end-systolic area and RV Ea = PASP/stroke volume. Study patients were stratified by tertiles according to TAPSE/PASP as follows: 1: <0.35; 2: 0.35 to 0.57; 3: >0.57.

For the total cohort (n = 387), we used echocardiographic PASP to calculate the TAPSE/PASP ratio. In the 219 patients undergoing hemodynamic assessment, invasive TAPSE/PASP was obtained along with pulmonary arterial compliance (PAC: stroke volume/pulmonary artery [PA] pulse pressure) and pulmonary vascular resistances (PVR: difference between mean pulmonary artery pressure [mPAP] and pulmonary capillary wedge pressure [PCWP] in Wood units) calculations. The relationship between PAC and TAPSE/PASP ratio and between PAC and PVR, stratified by TAPSE/PASP tertiles, were also examined.

CARDIOPULMONARY EXERCISE TESTING. Symptom-limited cardiopulmonary exercise testing (CPET) using a 10-W bicycle protocol was performed in a subset

TABLE 1 Clinical Characteristics by TAPSE/PASP Tertile

	Tertile 1 (n = 129)	Tertile 2 (n = 129)	Tertile 3 (n = 129)	p Value
TAPSE/PASP, mm/mm Hg	*<0.35*	*0.35-0.57*	*>0.57*	
Age, yrs	68.9 ± 10.8	68.0 ± 12.2	61.5 ± 11.4	<0.001
Female	71 (55)	85 (66)	74 (57)	0.17
Race				0.007
White	92 (71)	72 (56)	77 (60)	
Black	34 (26)	40 (31)	43 (33)	
Other	3 (2)	17 (13)	9 (7)	
Comorbidities				
Coronary artery disease	67 (52)	55 (43)	60 (47)	0.32
Systemic hypertension	98 (76)	101 (78)	94 (73)	0.59
Hyperlipidemia	67 (52)	67 (52)	73 (57)	0.69
Diabetes mellitus	44 (34)	40 (31)	28 (22)	0.07
Obesity	40 (31)	59 (46)	67 (52)	0.002
Chronic kidney disease	60 (47)	42 (33)	35 (27)	0.004
Atrial fibrillation	66 (51)	38 (29)	23 (18)	<0.001
Smoker	48 (37)	42 (33)	46 (36)	0.73
COPD	48 (37)	34 (26)	40 (31)	0.17
Obstructive sleep apnea	44 (34)	42 (33)	46 (36)	0.87
Medications				
ACE inhibitor or ARB	66 (51)	80 (62)	79 (61)	0.14
Beta-blocker	97 (75)	92 (71)	75 (58)	0.009
Calcium channel blocker	33 (26)	34 (26)	32 (25)	0.96
Nitrate	23 (18)	19 (15)	10 (8)	0.05
Loop diuretic	97 (75)	72 (56)	54 (42)	<0.001
Thiazide diuretic	17 (13)	24 (19)	29 (22)	0.15
Aldosterone blocker	27 (21)	20 (16)	20 (16)	0.41
Statin	57 (44)	56 (43)	56 (43)	0.99
Aspirin	60 (47)	59 (46)	48 (37)	0.25
Warfarin	36 (28)	29 (22)	19 (15)	0.036
NYHA functional class				<0.001
I	6 (5)	13 (10)	27 (21)	
II	43 (33)	55 (43)	56 (43)	
III	79 (61)	58 (45)	43 (33)	
IV	1 (1)	3 (2)	3 (2)	
Physical exam				
Heart rate, beats/min	74.5 ± 12.2	73.5 ± 12.2	75.8 ± 13.6	0.37
Systolic BP, mm Hg	126.1 ± 18.8	129.3 ± 18.4	126.7 ± 20.4	0.36
Diastolic BP, mm Hg	68.9 ± 9.9	70.0 ± 10.8	72.2 ± 10.1	0.032
Body mass index, kg/m^2	28.9 ± 8.1	30.6 ± 7.1	32.3 ± 8.9	0.003
Laboratory data				
Sodium, mEq/l	137.1 ± 2.5	138.1 ± 2.9	138.4 ± 2.6	<0.001
Blood urea nitrogen, mg/dl	31.5 ± 18.5	25.4 ± 14.6	19.4 ± 9.9	<0.001
Creatinine, mg/dl	1.8 ± 1.3	1.6 ± 1.7	1.4 ± 1.2	0.06
eGFR, ml/min/1.73 m^2	54.4 ± 26.0	58.6 ± 23.9	67.2 ± 27.0	<0.001
Fasting glucose, mg/dl	118.2 ± 36.4	118.6 ± 55.1	108.9 ± 32.0	0.12
Hemoglobin, g/dl	11.5 ± 1.8	12.0 ± 1.7	12.1 ± 1.8	0.028
BNP, pg/ml	493 (262-875)	244 (115-482)	114 (28-314)	<0.001
NT-proBNP, pg/ml	1,400 (830-2,390)	992 (650-1,780)	546 (390-880)	<0.001

Values are mean ± SD, n (%), or median (25th to 75th percentile). *Italics* indicate the tertiles cutoff based on the TAPSE/PASP subdivision.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; BP = blood pressure; BNP = brain natriuretic peptide; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; PASP = pulmonary artery systolic pressure; TAPSE = tricuspid annular plane systolic excursion.

TABLE 2 Echocardiographic Characteristics by TAPSE/PASP Tertile

	Tertile 1 (n = 129)	Tertile 2 (n = 129)	Tertile 3 (n = 129)	p Value
TAPSE/PASP, mm/mm Hg	*<0.35*	*0.35-0.57*	*>0.57*	
LV end-diastolic volume index, ml/m^2	42.0 ± 9.2	41.4 ± 10.3	42.6 ± 11.3	0.65
LV end-systolic volume index, ml/m^2	18.7 ± 6.7	17.2 ± 5.9	17.3 ± 5.8	0.11
LV mass index, g/m^2	116.5 ± 34.0	106.6 ± 33.1	97.4 ± 26.2	<0.001
LA volume index, ml/m^2	40.6 ± 16.7	35.1 ± 10.8	31.5 ± 10.3	<0.001
LV ejection fraction, %	58.4 ± 7.2	60.2 ± 6.4	59.8 ± 6.7	0.09
Early transmitral (E) velocity, cm/s	116.7 ± 43.1	103.1 ± 35.8	91.5 ± 29.0	<0.001
Late transmitral (A) velocity, cm/s	66.4 ± 33.9	85.4 ± 29.3	81.4 ± 22.9	<0.001
E/A ratio	2.0 ± 1.0	1.3 ± 0.6	1.2 ± 0.5	<0.001
E deceleration time, ms	214.3 ± 74.1	232.7 ± 59.3	234.2 ± 58.6	0.022
S' velocity (lateral), cm/s	7.6 ± 2.4	8.5 ± 3.0	9.2 ± 2.7	<0.001
S' velocity (septal), cm/s	6.4 ± 1.7	7.3 ± 2.3	8.0 ± 2.2	<0.001
E' velocity (lateral), cm/s	8.2 ± 3.2	8.9 ± 4.1	9.9 ± 4.2	0.002
E' velocity (septal), cm/s	6.4 ± 2.0	7.0 ± 2.9	8.0 ± 3.3	<0.001
A' velocity (lateral), cm/s	7.6 ± 3.3	9.5 ± 3.9	10.5 ± 3.7	<0.001
A' velocity (septal), cm/s	6.5 ± 2.6	8.2 ± 3.2	9.5 ± 3.3	<0.001
E/e' (septal)	20.1 ± 9.6	16.6 ± 8.3	12.8 ± 5.7	<0.001
E/e' (lateral)	16.6 ± 8.9	13.8 ± 8.2	10.5 ± 4.9	<0.001
Diastolic function grade				<0.001
Normal diastolic function	3 (2)	8 (6)	25 (19)	
Grade I diastolic dysfunction	10 (8)	15 (12)	16 (12)	
Grade II diastolic dysfunction	22 (17)	57 (44)	54 (42)	
Grade III diastolic dysfunction	87 (67)	41 (32)	26 (20)	
Indeterminate diastolic function	7 (5)	8 (6)	8 (6)	
EDV_{20}	77.7 ± 24.9	79.4 ± 25.4	89.8 ± 27.6	0.002
RA pressure, mm Hg	11.8 ± 4.4	7.8 ± 4.0	6.4 ± 3.0	<0.001
PA systolic pressure, mm Hg	57.0 ± 12.1	44.9 ± 10.6	30.6 ± 6.6	<0.001
Stroke volume, ml	73.6 ± 25.2	80.3 ± 31.0	85.9 ± 26.4	0.002
Cardiac output, l/min	5.3 ± 2.1	5.9 ± 2.6	6.4 ± 2.2	<0.001
RV basal diameter, cm	4.3 ± 0.7	3.8 ± 0.7	3.9 ± 0.6	<0.001
RV end-diastolic area, cm^2	27.5 ± 9.6	25.0 ± 7.8	25.5 ± 7.2	0.032
RV end-systolic area, cm^2	17.3 ± 6.7	14.4 ± 5.2	14.0 ± 4.7	<0.001
RV wall thickness, mm	5.6 ± 1.2	5.0 ± 0.7	4.7 ± 0.7	<0.001
LV/RV diameter ratio	1.0 ± 0.2	1.1 ± 0.2	1.1 ± 0.1	<0.001
RV fractional area change, %	37.2 ± 8.8	42.5 ± 7.4	45.3 ± 6.4	<0.001
TAPSE, mm	14.2 ± 3.7	19.7 ± 4.5	23.8 ± 5.4	<0.001

Values are mean ± SD or n (%).

EDV = end diastolic volume; LV = left ventricular; PA = pulmonary arterial; RA = right atrial; RV = right ventricular; other abbreviations as in Table 1.

of 168 patients. Respiratory gases were analyzed using a calibrated metabolic cart (Sensormedics Vmax, San Diego, California). Breath-by-breath measurement of inspired oxygen and expired carbon dioxide was obtained online at rest, exercise, and recovery. CPET variables were measured and calculated based on current guidelines (18).

OUTCOMES. Participants were evaluated at least every 6 months or as clinically indicated. Intercurrent hospitalizations were documented, reviewed, and categorized as due or not to cardiovascular causes. Every 6 months, patients (or their proxies) were contacted to determine vital status (with additional verification of deaths through query of the Social Security Death Index), as it happened at San Paolo Hospital.

Last follow-up date corresponded to the date of death or last recorded visit. The primary endpoint was a combined outcome of hospitalization for any cardiovascular cause (including HF) and death for any cause. We also assessed the secondary outcome of HF hospitalization.

STATISTICAL ANALYSIS. We first stratified and compared variables by tertile of noninvasive TAPSE/PASP ratio for descriptive purposes. Categorical variables are displayed as count and percentage, and continuous data with a normal distribution as mean ± SD. Right-skewed variables are reported as median (25th to 75th percentile). Continuous variables were compared across TAPSE/PASP tertiles using one way analysis of variance (or Kruskal-Wallis statistic, when appropriate); categorical variables were compared across groups using chi-square tests (or Fisher exact test).

Multivariable Cox proportional-hazards regression was used to evaluate the relationship between TAPSE/PASP and outcomes. The proportionality assumption was tested for all models. Covariate selection was based on clinical relevance and association with TAPSE/PASP. Models were adjusted for age, sex, body mass index, systolic blood pressure, estimated glomerular filtration rate (eGFR), atrial fibrillation (AF), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), obstructive sleep apnea, and NYHA functional class. Bland and Altman analysis was performed for testing the level of concordance between estimated PASP versus measured PASP in their use for assessing RV to PC coupling by TAPSE/PASP ratio.

A 2-sided p value <0.05 was used to indicate statistical significance. Analyses were performed using Stata version 12.1 (StataCorp, College Station, Texas).

RESULTS

A total of 387 patients (299 at Chicago and 88 at Milano) were enrolled. Among the original Chicago cohort of 420 eligible patients, 120 were excluded because of unsatisfactory echo-derived PASP, and 1 patient because of inadequate imaging windows for TAPSE measurement. Among the original Milano cohort of 102 eligible patients, 12 were excluded because of unsatisfactory PASP noninvasive estimation, and 2 because of severe tricuspid regurgitation. The discrepancy of exclusion ratio between the 2 centers was most likely due to the different recruiting modalities: eligible patients previously hospitalized

for HFpEF at Northwestern University (identified systematically via daily electronic query of hospitalized patients) and referral population, generally sent for evaluation of dyspnea, at Milano University.

CLINICAL AND LABORATORY CHARACTERISTICS. Table 1 reports the clinical characteristics of the population by TAPSE/PASP tertiles. The 3 groups had similar prevalence of hypertension, coronary artery disease, hyperlipidemia, smoking, COPD, and obstructive sleep apnea. Patients in tertile 1 (TAPSE/PASP <0.35 mm/mm Hg) were older, with a higher NYHA functional class, prevalence of AF and chronic kidney disease (CKD) and a lower obesity prevalence. Use of beta-blockers and loop diuretics was more frequent in patients in tertile 1, who also had higher laboratory markers of increased risk, including BNP, N-terminal pro-brain natriuretic peptide (NT-proBNP), blood urea nitrogen, creatinine, lower sodium and eGFR.

ECHOCARDIOGRAPHIC CHARACTERISTICS. Table 2 reports the echocardiographic and Doppler characteristics stratified by TAPSE/PASP tertile 1 compared to tertiles 2 and 3. Patients in tertile 1 presented with higher LV mass, E/A and E/e′, lower cardiac and similar LV end-systolic volume and LVEF. EDV_{20} is based on noninvasive estimation of the LV end-diastolic pressure-volume relationship (19), was the lowest in tertile 1 patients, and the worst LV chamber compliance. RAP, PASP, RV diameter, RV wall thickness, and end-diastolic and end-systolic areas were higher, TAPSE and RV fractional area change lower in tertile 1. The interobserver and intraobserver variabilities of RV wall thickness were 3.5 (95% confidence interval [CI]: 0.97) and 5.1 (95% CI: 0.95), respectively, for the Northwestern database, and 3.7 (95% CI: 0.96) and 5.5 (95% CI: 0.95) for the Milano database.

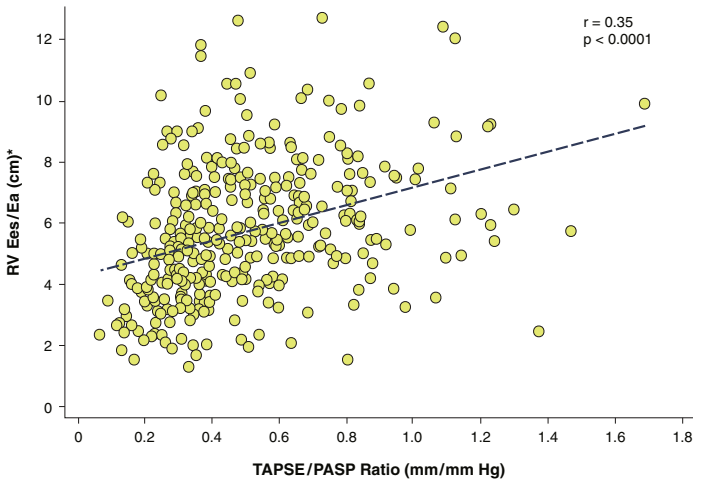
RV CONTRACTILITY, RV TO PC COUPLING, AND PULMONARY HEMODYNAMICS. The average relationship between TAPSE and PASP was similar in the 2 laboratories (Online Figure 1). The TAPSE/PASP ratio significantly correlated with RV Ees/Ea (RV-PA coupling) (Figure 1).

PCWP was similar among the tertiles, whereas significantly higher RAP, PASP, PA diastolic pressure, PVR, and transpulmonary gradient were all present in the tertile 1 group (Table 3). Patients in tertile 1 also exhibited lower cardiac output and higher systemic vascular resistance (SVR) and PVR/SVR (Table 3). Combined post- and pre-capillary PH (CpcPH), was observed in 50% of patients in tertile 1 and only in the 21% and 8% of cases in tertiles 2 and 3 (Table 4).

Figure 2A reports the correlation between TAPSE/PASP ratios obtained with measured and estimated PASPs. At Bland and Altman analysis, the TAPSE/PASP ratios with PASP obtained noninvasively were tightly related to its invasive measure (Figure 2B). Figure 3A displays the correlation between PAC and TAPSE/PASP. The exponential relationships between PVR and PAC according to TAPSE/PASP tertiles documents a more favorable distribution from the lowest through the highest tertile (Figure 3B).

Associations of TAPSE and PASP taken individually and as a ratio with other clinical descriptors are reported in Online Table 1 and described in Online Results.

FIGURE 1 Correlation Between RV Ees/Ea and TAPSE/PASP Ratio



The analysis provides an r value of 0.35 with a $p < 0.0001$. Ea = arterial elastance; Ees = cardiac elastance; PASP = pulmonary artery systolic pressure; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion.

TABLE 3 Invasive Hemodynamic Characteristics by TAPSE/PASP Tertile

	Tertile 1 (n = 83)	Tertile 2 (n = 70)	Tertile 3 (n = 66)	p Value
TAPSE/PASP, mm/mm Hg	*<0.35*	*0.35-0.57*	*>0.57*	
Right atrial pressure, mm Hg	15.7 ± 6.2	13.6 ± 6.3	12.8 ± 5.4	0.01
PA systolic pressure, mm Hg	58.6 ± 17.2	51.2 ± 14.6	45.6 ± 12.1	<0.001
PA diastolic pressure, mm Hg	27.2 ± 7.9	25.8 ± 8.2	23.5 ± 5.8	0.01
Mean PA pressure, mm Hg	37.4 ± 10.0	34.1 ± 9.8	30.8 ± 7.5	<0.001
Pulmonary capillary wedge pressure, mm Hg	23.6 ± 8.6	23.8 ± 8.0	22.5 ± 6.0	0.58
Diastolic pulmonary gradient, mm Hg	3.6 ± 4.4	2.0 ± 3.0	0.9 ± 1.5	<0.001
Transpulmonary gradient, mm Hg	13.8 ± 6.0	10.3 ± 4.4	8.3 ± 3.3	<0.001
Thermodilution cardiac output, l/min	4.9 ± 1.6	5.8 ± 2.2	6.6 ± 2.5	<0.001
Pulmonary vascular resistance, WU	3.2 ± 1.7	2.1 ± 1.3	1.5 ± 0.8	<0.001
Systemic vascular resistance, WU	19.2 ± 8.3	17.1 ± 6.5	13.4 ± 5.7	<0.001
PVR/SVR ratio	0.20 ± 0.07	0.13 ± 0.05	0.11 ± 0.05	<0.001

Values are mean ± SD.

PVR = pulmonary vascular resistance; SVR = systemic vascular resistance; WU = Wood unit; other abbreviations as in Tables 1 and 2.

TABLE 4 Invasive Hemodynamic Characteristics by TAPSE/PASP Tertile

PH Subtype	Tertile 1 (n = 83)	Tertile 2 (n = 70)	Tertile 3 (n = 66)	p Value
No PH (mPAP <25 mm Hg, PCWP >15 mm Hg)	7 (8)	9 (13)	12 (18)	0.48
Isolated post-capillary PH (Ipc PH; mPAP ≥25 mm Hg, PCWP >15 mm Hg, DPG <7 mm Hg, and PVR <3 WU)	35 (42)	45 (66)	49 (74)	0.15
Combined post- and pre-capillary PH (CpcPH; mPAP ≥25 mm Hg, PCWP >15 mm Hg, and [DPG ≥7 mm Hg or PVR ≥3 WU])	41 (50)	15 (21)	5 (8)	<0.001

Values are n (%). Overall p value <0.001.

Cpc = combined pre- and post-capillary; DPG = diastolic pulmonary gradient; Ipc = isolated post-capillary; mPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; other abbreviations as in Tables 1 and 3.

FUNCTIONAL CAPACITY. As shown in Figure 4, TAPSE/PASP values progressively reduced together with the severity of NYHA functional class. On CPET, peak VO_2 and O_2 pulse decreased, whereas VE/VCO_2 slope increased progressively from tertile 3 through 1 (Figure 5).

KIDNEY FUNCTION. Serum creatinine and estimated glomerular filtration rate (eGFR) were similar in patients without PH, with isolated post-capillary (Ipc) PH, and CpcPH (Table 5).

OUTCOMES AND RISK PREDICTION. The median follow-up duration was 13.4 months (25th to 75th percentile 5.2 to 23.7 months). During the follow-up, 86 patients (22%) had at least 1 HF hospitalization, 112 patients (29%) had at least 1 cardiovascular (CV) hospitalization, 57 patients (15%) died, and 143 patients (37%) had 1 or more clinical outcomes.

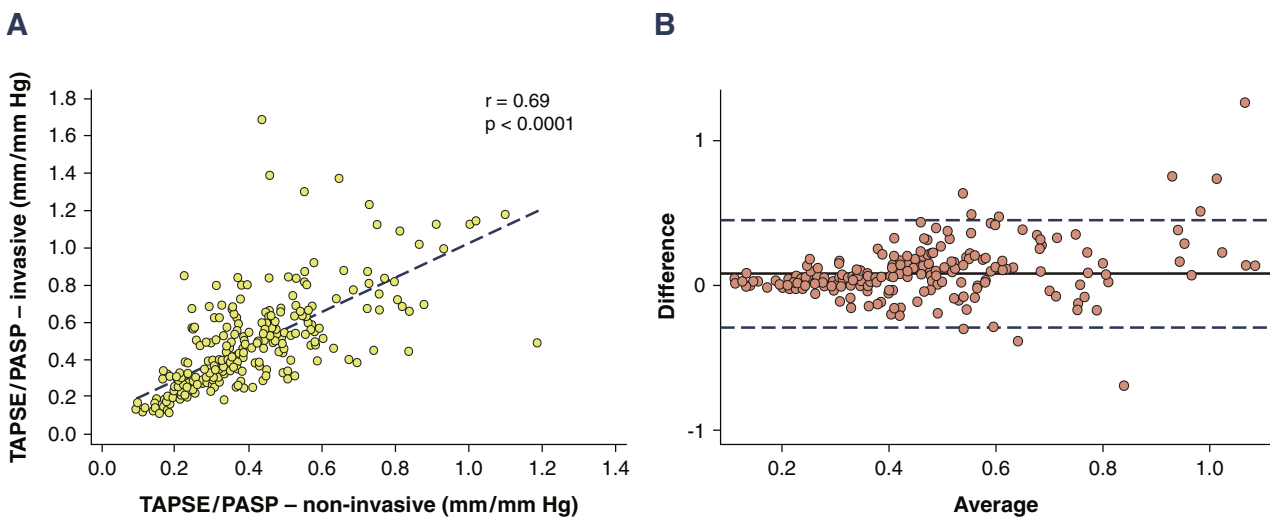
Table 6 and Figure 6 show that adverse outcomes were more common in tertile 1 compared to the others. Indeed, patients in tertile 1 had a higher hazard ratio (HR) for each of the adverse outcomes (Table 6). The association of tertile 1 with HF hospitalization and the combined CV outcome persisted after multivariable adjustment.

The strength of the association between TAPSE/PASP tertile 1 and adverse outcomes increased at lower baseline PASP values. The unadjusted HRs (95% CIs) for the association between TAPSE/PASP tertile 1 and the combined outcome in patients with baseline PASP <50 mm Hg (n = 254), <40 mm Hg (n = 168), and <30 mm Hg (n = 70) were: 2.0 (range 1.2 to 3.6), 3.2 (range 1.2 to 8.3), and 5.0 (range 1.1 to 22.2), respectively. The predictive ability of some of the most representative variables of HFpEF phenotype, such as left atrial volume indexed, E/e′, and eGFR, showed a statistical significant prediction just for eGFR (Online Table 2).

DISCUSSION

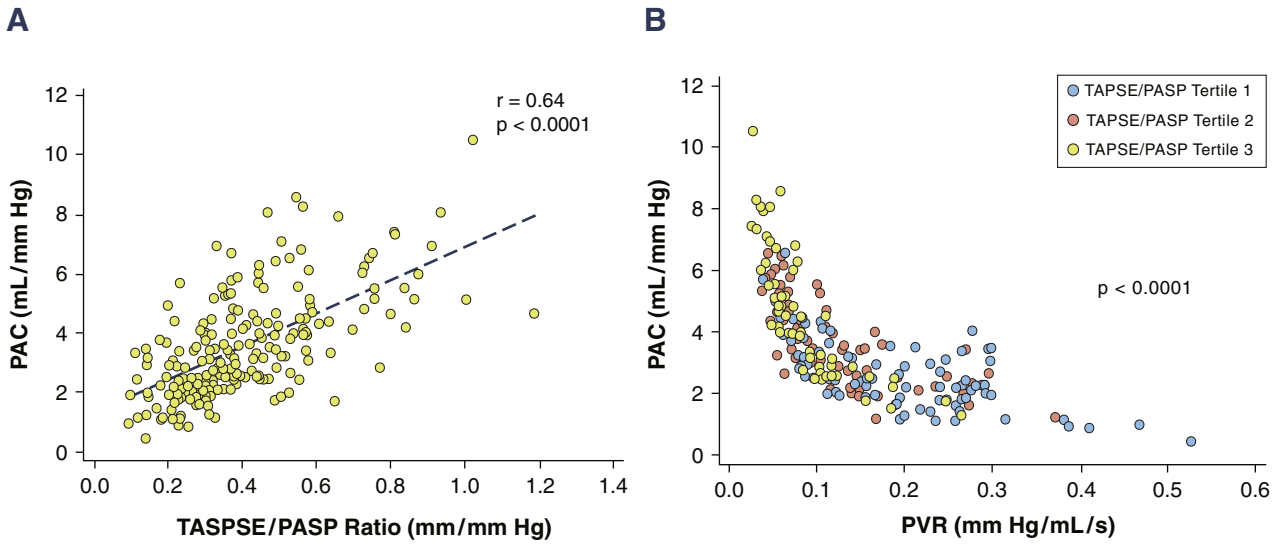
The study of RV-PC coupling performed in a large cohort of HFpEF patients adds new insights and implications into the syndrome phenotyping. Main study results show that: 1) use of the TAPSE/PASP

FIGURE 2 Correlation of TAPSE/PASP Ratio Obtained by Either Noninvasive and Invasive Measures and Their Concordance by Bland and Altman Analysis



The analyses show a high correlation of TAPSE/PASP obtained by noninvasive versus invasively measured PASP **(A)** and a high concordance by Bland and Altman analysis **(B)**. Abbreviations as in Figure 1.

FIGURE 3 Scatterplot of PAC Versus TAPSE/PASP Ratio and Scatterplot of PAC Versus PVR, Stratified by TAPSE/PASP Tertiles



A significant correlation between PAC and TAPSE/PASP ratio **(A)** was observed along with significant differences of PVR versus PAC exponential relationship by TAPSE/PASP tertiles **(B)** ($p < 0.0001$ by Kruskal-Wallis statistic of difference in PAC vs. PVR by TAPSE/PASP tertiles). PAC = pulmonary arterial compliance; PVR = pulmonary vascular resistance; other abbreviations as in Figure 1.

relationship and ratio translates into simple but effective physiology-based approaches for estimating RV contractile function and its PC coupling; and 2) because TAPSE/PASP is being increasingly endorsed by several investigators (10,17), validation against Ees/Ea provided first evidence of a quite good correlation between measures especially for lowest values TAPSE/PASP and Emax/Ea measures.

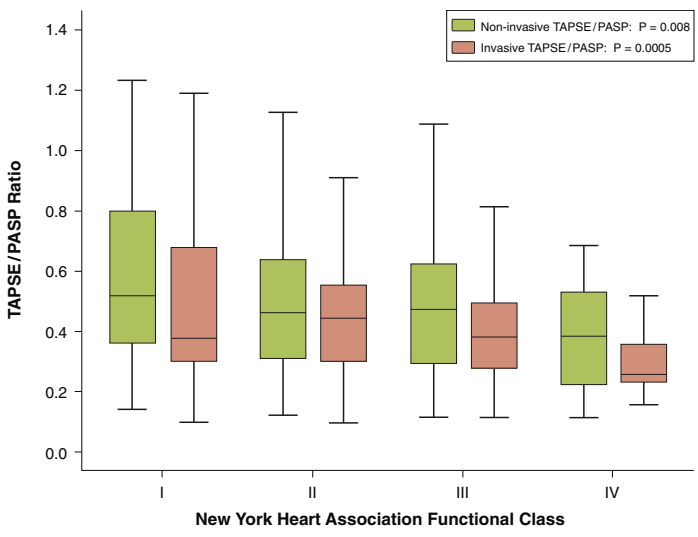
Whereas the TAPSE/PASP tertile subdivision was not sensitive for discriminating IpcPH, it clearly stratified across the CpcPH stage, with the majority of these cases distributed in the lowest TAPSE/PASP tertile. Moreover, a low TAPSE/PASP ratio was distributed in the most unfavorable portion of the PAC versus PVR exponential relationship and was related to PAC, the hemodynamic variable which most likely mirrors the effect of left atrial pulsatile loading on RV function.

Overall, as preliminarily hypothesized, we confirm that TAPSE/PASP phenotyping is an intriguing opportunity to precisely highlight peculiar clinical features and outcome in HFpEF.

TAPSE VERSUS PASP RELATIONSHIP. In most reports exploring indicators of RV function and their clinical significance in HFpEF (6,9), the assessment of RV function has been based on echocardiographic indicators of performance.

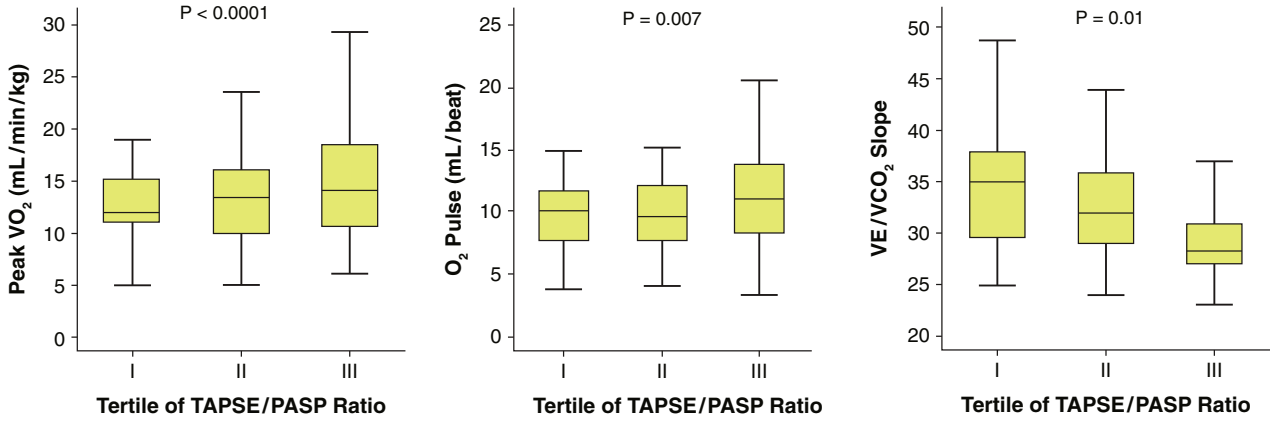
Mohammed et al. (6) reported the largest HFpEF population stratified according to TAPSE and RV visual score levels. Both techniques have some limitations. TAPSE is a load-dependent measure and

FIGURE 4 Box-and-Whisker Plots of Invasively and Noninvasively Defined TAPSE/PASP by NYHA Functional Class



An inverse relationship was observed between TAPSE/PASP and NYHA. NYHA = New York Heart Association; other abbreviations as in Figure 1.

FIGURE 5 Cardiopulmonary Exercise Testing Parameters by TAPSE/PASP Ratio



Tertile 1 typically manifests significantly lower peak VO_2, O_2 pulse, and VE/VCO_2 slope. O_2 = oxygen; VE/VCO_2 = ventilation to carbon dioxide production; VO_2 = oxygen consumption; other abbreviations as in Figure 1.

an indicator of RV longitudinal free wall motion that is susceptible to tethering effects, RV visual score is a broad qualitative indicator of RV performance; no one measures intrinsic RV contractility. We have previously proposed (7) that the relationship of TAPSE versus PASP can be taken as an index of in vivo changes in RV length (TAPSE) versus developed force (PASP), providing a noninvasive assay of RV contractile state beyond the information provided by each separate variable. Because a potential critique to this approach could be the noninvasive detection of PASP, we documented a good concordance between Doppler-derived and invasive PASP. The relationship of TAPSE versus PASP showed a similar steepness to increasing levels of pressure in both population case series.

Melenovsky et al. (20) first examined the relationship between invasively measured PASP and RV fractional area in 96 HFpEF patients with advanced HFpEF, and found a lower and steeper slope compared to controls. Our findings have the advantage of examining a broader spectrum of disease severity, ranging from cases without PH to cases with either documented IpcPH or CpcPH.

TAPSE/PASP RATIO TERTILE CLASSIFICATION. The correlation found between TAPSE/PASP and Ees/Ea confirms and expands the pathophysiological significance of TAPSE/PASP to an index of coupling of the RV with the PC. Even if the respective participation of these 2 properties is undefined, the ability of TAPSE/PASP to classify disease severity and prognosis is unequivocal. The lowest tertile of the TAPSE/PASP ratio was independently predictive of adverse outcomes. Tertile level differences supported the concept that the negative impact of PH on outcome is irrespective of the degree of LV systolic performance, but is rather related to coexistent alterations of RV to PC indexes, which truly define the severity of the disease. Low values of the TAPSE/PASP ratio (<0.35 mm/mm Hg) were increasingly predictive of outcomes in patients with lower PASP values, suggesting that the combination of a low PASP with a reduced TAPSE/PASP ratio is a marker of significant intrinsic RV dysfunction and poor outcomes in HFpEF. Patients grouped under tertile 1 had higher BNP and NT-proBNP levels and increased rates of CKD and AF. As in previous HFpEF studies (6,20), AF was common and related to right heart disease severity contributing to the RV-PA uncoupling, likely through an increased left atrial pulsatile loading and reduced cardiac output due to the irregular cardiac cycle length.

The TAPSE/PASP ratio is inversely correlated with NYHA functional class and seems helpful in unmasking early incurrence of symptoms (NYHA

TABLE 5 Kidney Function According to PH Stages

	No PH (n = 83)	IpcPH (n = 70)	CpcPH (n = 66)	p Value
Creatinine, mg/dl	1.21 ± 0.73	1.56 ± 1.48	1.65 ± 1.23	0.36
eGFR, ml/min/1.73 m^2	69 ± 30	60 ± 27	59 ± 24	0.22

Values are mean ± SD.
eGFR = estimated glomerular filtration rate; other abbreviations as in Table 4.

functional class I or II) that may already reflect an initial depression in RV functional reserve. Thus, it may be comprehensively applied to the wide variety of HFpEF patients. The association of a low body mass index is interesting in itself and helps to explain the occurrence of liver disease and cardiac cachexia in advanced right heart disease (21).

TASPE/PASP RATIO AND IMPLICATIONS FOR HEMODYNAMICS AND CPET. In HFpEF, the prevalence of CpcPH ranges between 12% (17) and 17% (22). The criteria of CpcPH, that is, PA diastolic pressure - PCWP ≥ 7 mm Hg, was met by 10% of our population, a percentage similar to the one observed by Gerges et al. (17). In our series, this class of patients was mostly distributed in TAPSE/PASP tertile 1. In the Gerges et al. (17) study, the TASPE/PASP ratio emerged as the only echocardiography-derived variable predictive of CpcPH, correlating with worse PA compliance, and a correlation coefficient similar to that observed in our study. In addition, the 2 studies identify a comparable distribution of TAPSE/PASP along the PAC versus PVR relationship with higher PVR and lower PAC for the lowest tertile.

Because the diagnosis of CpcPH requires invasive hemodynamics, the identification of noninvasive markers is highly desirable and our findings point in this direction.

The relationship between TAPSE/PASP ratio and gas exchange analysis by CPET provides additional and complementary information on the pathophysiological and clinical implications of RV-PC uncoupling. An impaired aerobic performance and ventilation efficiency reflect a greater burden of right-sided heart disease as observed in tertile I patients.

STUDY LIMITATIONS. Strengths of the study are the comprehensive assessment of a large population from 2 independent centers, with detailed clinical characteristics, echocardiography, invasive hemodynamics, and CPET data.

The analysis of underlying mechanisms and mediators of worsening RV-PC coupling are limited to the hemodynamic sequelae of increased LV filing pressure in patients with a worse TAPSE/PASP ratio. No information is provided about the role of potential additional mechanisms (myocardial ischemia, neurohumoral activation, and unfavorable RV-LV interaction). Although coronary artery and lung diseases were not consistently associated with a depressed TAPSE/PASP ratio phenotype, we cannot exclude a contribution of these factors. However, differently from patients with HF reduced EF, in HFpEF the occurrence of RV to PC uncoupling is mainly dependent on the backward unfavorable effects of an increased left atrial pressure (23). In some patients the use of TAPSE/PASP ratio is limited by the inability to estimate PASP.

Because of the cross-sectional nature of our study, the respective interaction between PH and CKD

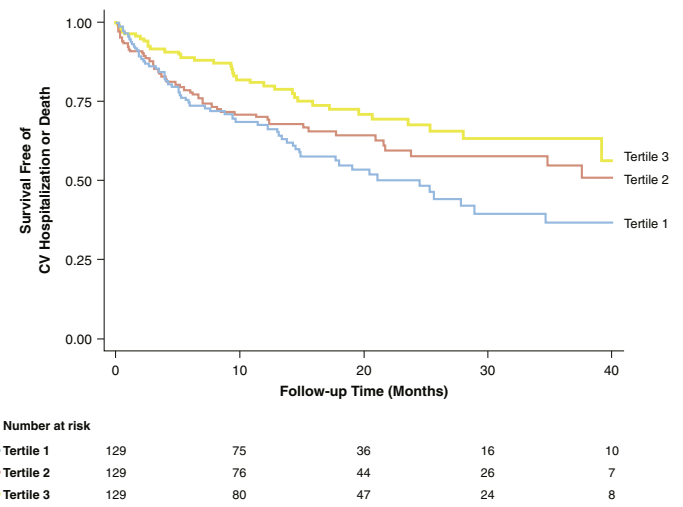
TABLE 6 Association of TAPSE/PASP Ratio Tertiles With Adverse Outcomes on Cox Proportional Hazards Analysis

	Tertile 1 (n = 129)	Tertile 2 (n = 129)	Tertile 3 (n = 129)	p Value
Outcome				
CV hospitalization	47 (36)	37 (29)	28 (22)	0.033
HF hospitalization	39 (30)	30 (23)	17 (13)	0.004
Death	27 (21)	19 (15)	11 (9)	0.019
Combined endpoint	60 (47)	48 (37)	35 (27)	0.006
Unadjusted				
CV hospitalization	1.84 (1.15–2.94)*	1.34 (0.82–2.21)	1.00 (referent)	–
HF hospitalization	2.54 (1.43–4.49)†	1.77 (0.97–3.24)	1.00	–
Death	2.44 (1.21–4.94)*	1.76 (0.84–3.71)	1.00	–
Combined endpoint	1.90 (1.25–2.88)*	1.45 (0.94–2.24)	1.00	–
Adjusted				
CV hospitalization	1.65 (0.97–2.80)	1.17 (0.69–1.99)	1.00	–
HF hospitalization	2.24 (1.19–4.22)*	1.57 (0.82–3.00)	1.00	–
Death	1.54 (0.70–3.40)	1.57 (0.70–3.53)	1.00	–
Combined endpoint	1.62 (1.01–2.59)*	1.35 (0.84–2.15)	1.00	–

Values are n (%) or HR (95% CI). *p < 0.05. †p = 0.001. Adjusted model covariates: age, sex, body mass index, systolic blood pressure, glomerular filtration rate, atrial fibrillation, smoking, diabetes mellitus, chronic obstructive pulmonary disease, obstructive sleep apnea, and New York Heart Association functional class.

CV = cardiovascular; CI = confidence interval; HF = heart failure; HR = hazard ratio; other abbreviations as in Table 1.

FIGURE 6 Kaplan-Meier Curves for Combined Endpoint of CV Hospitalization or Death, Stratified by Tertile of TAPSE/PASP Ratio



Tertile 1 displayed the worse event rate. (CV hospitalization includes HF hospitalizations.)
CV = cardiovascular; HF = heart failure; other abbreviations as in Figure 1.

remains undefined. Although a higher rate of CKD was observed in lower tertile, there were no differences between individuals without PH or IpcPH and CpcPH. Also, the implications on RV function of patients in tertile 1 receiving beta-blockers in a higher rate are undefined.

CONCLUSIONS

These results strengthen the concept that a thorough evaluation of the right heart in HFpEF is clinically meaningful and open new perspectives for positively targeting the natural history of the disease. Validation against invasive hemodynamics, better define in an easy-to-perform way the continuum of RV impairment phenotypes, clinical severity, and symptoms in HFpEF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The development of PH and RV dysfunction are key hemodynamic abnormalities in HFpEF. Despite the well-known pathophysiologic importance of developing RV- PC uncoupling, most studies have evaluated RV function and PH separately. Our study examined RV contractile function and its coupling with the PC in a broad spectrum of HFpEF patients with variable disease severity, defining the pathophysiological and prognostic implications from the non-PH condition to IpcPH and CpcPH to determine different phenotypes and levels of risk.

TRANSLATIONAL OUTLOOK: Starting from present observations, further studies are needed to determine the direct implications of developing therapies that may benefit HFpEF shifting the paradigm toward the RV and its progressive key involvement in the HFpEF syndrome.

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KEY WORDS heart failure with preserved ejection fraction, hemodynamics, pulmonary hypertension, right ventricle

APPENDIX For additional text, tables, and a figure, please see the online version of this paper.