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Right Ventricular Contractile Reserve and Pulmonary Circulation Uncoupling During Exercise Challenge in Heart Failure

Pathophysiology and Clinical Phenotypes

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ABSTRACT

OBJECTIVES Right ventricular (RV) exercise contractile reserve (RVECR), its phenotypes, and its functional correlates are among the unresolved issues with regard to the role of the right ventricle in heart failure (HF) syndrome, and understanding these issues constitutes the objective of this study.

BACKGROUND Although the role of the right ventricle in HF syndrome might be fundamental, the pathophysiology of the failing right ventricle has not been extensively investigated.

METHODS Ninety-seven patients with HF (mean age 64 years, 70% men, mean left ventricular ejection fraction 33 ± 10%) underwent maximal exercise stress echocardiographic and cardiopulmonary exercise testing. RVECR and RV-to-pulmonary circulation (PC) coupling were assessed using the length-force relationship (tricuspid annular plane systolic excursion [TAPSE] vs. pulmonary artery systolic pressure) and the slope of mean pulmonary artery pressure versus cardiac output. On the basis of TAPSE, patients were categorized into 3 groups: those with TAPSE at rest ≥16 mm (group A, n = 60) and those with TAPSE at rest <16 mm, who were divided according to median TAPSE at peak exercise (15.5 mm) into 2 subgroups (group B, ≥15.5 mm, n = 19; group C, <15.5 mm, n = 18).

RESULTS Although they had similar left ventricular ejection fractions and rest RV impairment, compared with patients in group C, those in group B showed some degree of RVECR (upward shift of the length-force relationship), better RV-to-PC coupling (lower mean pulmonary artery pressure vs. cardiac output slope), and greater ventilatory efficiency (lower slope of minute ventilation to carbon dioxide output). Rest mitral regurgitation and net changes in pulmonary artery systolic pressure were the variables retained in the best regression model as correlates of RVECR.

CONCLUSIONS In patients with HF, RVECR unmasks different phenotypes. Impaired RV function at rest might not invariably lead to unfavorable RVECR and exercise RV-to-PC coupling. Testing these variables appears useful even in more advanced stages of HF to define various clinical conditions and, most likely, to define different levels of risk. (J Am Coll Cardiol HF 2016;4:625-35) © 2016 by the American College of Cardiology Foundation.

In heart failure (HF), the development of right ventricular (RV) dysfunction and failure is a turning point in the natural history of the syndrome that signals a worsening outcome (1).

Multiple factors underpin a deterioration in RV function and RV-to-pulmonary circulation (PC) uncoupling with a sustained backward transmission of increased left ventricular (LV) filling pressure as a main trigger of pulmonary arterial remodeling and RV pressure overload (2). Other mechanisms are primary RV involvement, the occurrence of ischemia, and unfavorable ventricular interdependence (2).

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ABBREVIATIONS AND ACRONYMS

CO = cardiac output

CPET = cardiopulmonary exercise testing

CSA_{LVOT} = cross-sectional area of the left ventricular outflow tract

ECR = exercise contractile reserve

EF = ejection fraction

ERO = effective regurgitant orifice

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

LV = left ventricular

mPAP = mean pulmonary artery pressure

MR = mitral regurgitation

PASP = pulmonary artery systolic pressure

PC = pulmonary circulation

PVR = pulmonary vascular resistance

RV = right ventricular

RVECR = right ventricular exercise contractile reserve

RVOT = right ventricle outflow tract

SV = stroke volume

TAPSE = tricuspid annular plane systolic excursion

VCO_2 = carbon dioxide output

VE = minute ventilation

VTI_{LVOT} = velocity-time integral of pulsatile Doppler obtained at the level of the left ventricular outflow tract

Measuring RV functional reserve during pharmacological (3) or physical (4) stress is more challenging and informative than assessing RV systolic performance at rest; however, significant issues, such as the relationship between baseline and stress-induced contractile function and the exercise correlates of contractile reserve, remain unresolved.

Although right heart catheterization and pressure-volume analysis provide the best precision (5), Doppler echocardiographic analysis is a suitable, reliable, and safe method that is seemingly underused for this purpose. Accordingly, Grunig et al. (6) recently proposed the change in pulmonary artery systolic pressure (PASP) from rest to peak exercise as measure of RV contractility and prognosis.

A meaningful addition in the study of different RV functional responses to exercise is an analysis by gas exchange with cardiopulmonary exercise testing (CPET) (7,8).

The main objective of our study was to define RV exercise contractile reserve (RVECR) and the corresponding RV-to-PC coupling in patients with HF with reduced ejection fraction (HFrEF) with various degrees of RV dysfunction at rest.

The specific aims of the study were to define how, and if, the severely failing right ventricle at rest might still improve function during maximal exercise and to identify the hemodynamic and cardiac correlates of RVECR. Our final aim was to identify the CPET phenotype typical of preserved or impaired RVECR.

METHODS

STUDY POPULATION. Ninety-seven of 105 eligible patients with HFrEF referred for functional assessment were enrolled in the study between September 2012 and June 2015. Eight patients were excluded because of inadequate echocardiographic windows (Figure 1).

The inclusion criteria were as follows: 1) signs and symptoms of HF with LV dilation (indexed end-diastolic volume >80 ml/m^2) and reduced LV ejection fraction (≤40%, on echocardiography using the Simpson rule); 2) N-terminal pro-B-type natriuretic peptide level ≥400 pg/ml; 3) capable of performing maximal exercise; and 4) adequate acoustic windows.

The exclusion criteria were as follows: 1) recent myocardial infarction (<3 months) or unstable angina; 2) aortic stenosis; 3) peripheral artery disease; 4) significant anemia (hemoglobin <10 g/dl); 5) chronic obstructive lung disease of moderate or severe degree (forced expiratory volume at the first second <70%); and 6) previous cardiac surgery. We enrolled 97 patients (70% men; 60% with ischemic etiology; 30% in New York Heart Association functional class I, 30% in class II, 33% in class III, and 7% in class IV). No patient was undergoing physical training or taking phosphodiesterase 5 inhibitors or other pulmonary vasodilators.

STUDY DESIGN. The study design is depicted in Figure 1. The population was divided into 3 groups on the basis of tricuspid annular plane systolic excursion (TAPSE) at rest (cutoff 16 mm). Sixty patients (group A) had TAPSE ≥16 mm at rest, and 37 patients had TAPSE <16 mm at rest. Among this latter group, 2 phenotypes were identified according to RVECR, defined as median exercise-induced TAPSE increase (15.5 mm). Nineteen patients had preserved RVECR (group B), and 18 had impaired RVECR (group C).

All patients signed 2 informed consent forms, which were approved by the local ethics committee.

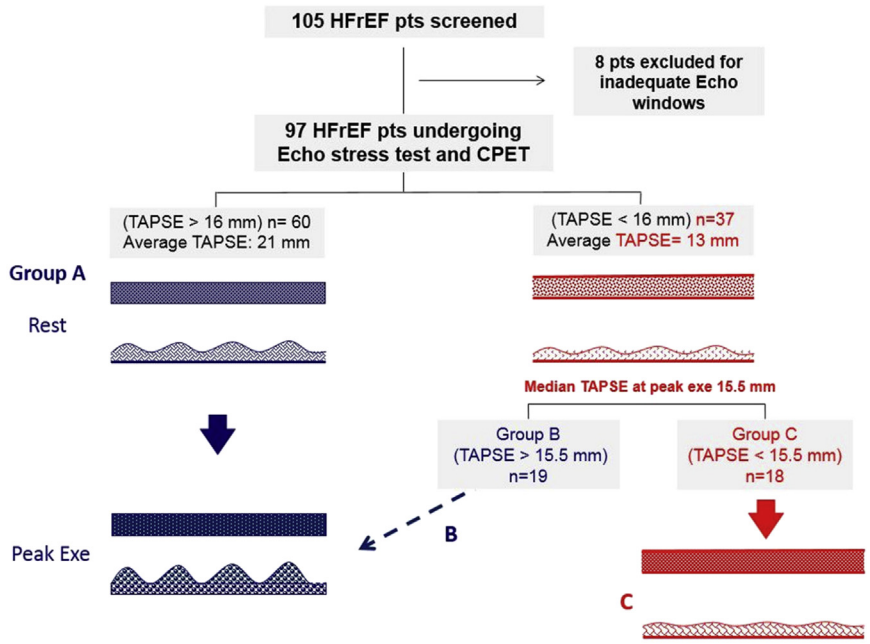
ECHOCARDIOGRAPHY AT REST AND DURING EXERCISE. Echocardiography (iE33, Philips Medical Systems, Andover, Massachusetts) was performed at rest and during exercise (every 2 min using a tiltable, electronically braked cycle ergometer) to assess systolic, diastolic, and valvular function. Exercise loop registration was extended to at least 5 s. An experienced cardiologist performed all tests. Stored images were analyzed offline by the same cardiologist. Measurements were averaged over 3 beats (sinus rhythm) or over 5 beats (atrial fibrillation).

Left heart dimensions and systolic function. Indexed LV end-diastolic volume and LV mass were measured at rest. Relative wall thickness, left atrial volume, and LV ejection fraction were measured (using Simpson's rule) at rest and during exercise.

LV diastolic function. Doppler echocardiography was used to assess the early mitral peak (E) and late wave (A) flow velocities. Tissue Doppler imaging of mitral annular movement was obtained from the apical 4-chamber view. The sample volume was placed sequentially at the lateral and septal annular sites, and the derived variables were averaged. The analysis was performed for early (e′) and late (a′) diastolic peak velocities.

The ratio of early transmitral flow velocity to annular velocity (E/e′) was considered an index of LV

FIGURE 1 Study Flowchart From the Enrollment Process to Group Subdivision



The final population was divided into 3 groups: patients with tricuspid annular plane systolic excursion (TAPSE) at rest ≥16 mm (group A, n = 60) and those with TAPSE at rest <16 mm, who were divided according to median TAPSE at peak exercise (15.5 mm) into 2 subgroups (group B, ≥15.5 mm, n = 19; group C, <15.5 mm, n = 18). CPET = cardiopulmonary exercise testing; Echo = echocardiographic; Exe = exercise; HFrEF = heart failure with reduced ejection fraction; pts = patients.

filling pressure. Adequate mitral and tissue Doppler imaging signals were obtained in all patients.

Systemic hemodynamic status. Stroke volume (SV) was calculated by applying the equation: SV = $VTI_{LVOT} \times CSA_{LVOT}$, where VTI_{LVOT} is the velocity-time integral of pulsatile Doppler obtained at the level of the LV outflow tract, and CSA_{LVOT} is the cross-sectional area of the LV outflow tract, determined using the circumference area formula. Cardiac output (CO) (SV × heart rate) was obtained both at rest and at peak exercise.

Cardiac power output was calculated as the product of mean blood pressure, LV SV, and heart rate (cardiac power output = mean blood pressure × [SV/60] × HR) both at rest and at peak exercise.

The degree of mitral regurgitation (MR) was evaluated by means of a visual scale (1 = mild, 2 = mild to moderate, 3 = moderate to severe, and 4 = severe). The quantification was performed by measuring the vena contracta, effective regurgitant orifice (ERO), and regurgitant volume, according to guidelines (9). MR severity during exercise was assessed by optimizing visualization of the regurgitant jet and continuous Doppler signal over several beats to overcome loss of signal due to breathing and thoracic movement. An ERO cutoff of 20 mm^2 was used to identify severe MR, both at rest and during exercise.

RV dimensions, systolic function, and pulmonary hemodynamic status. RV dimensions were assessed using RV end-diastolic area. RV systolic function was evaluated using RV fractional area, tricuspid s′ velocity on tissue Doppler imaging, and TAPSE according to current indications (10). RV functional contractile reserve was assessed through an approach recently described by our group (11) by plotting the relationship between TAPSE as a measure of length and PASP as a measure of developed force.

PASP was estimated from the transtricuspid peak velocity of continuous Doppler and calculating the gradient as: $4 \times Vmax^2$. Right atrial pressure was added to the transtricuspid gradient, measuring variations in the inferior vena cava dimensions during breathing, as previously reported (12). Pulmonary vascular resistance (PVR) was calculated using the following formula: PVR = (V_{TR}/RV outflow tract velocity-time integral) × 10) + 0.16) (13). Exercise RV-to-PC coupling was assessed by the slope of the relationship between mean pulmonary artery pressure (mPAP) and CO and TAPSE together with their ratio at rest and peak exercise. mPAP was calculated using the formula:

0.6 × systolic pulmonary artery pressure + 2, as proposed by Chemla et al. (14).

CPET. Symptom-limited CPET (Vmax; Sensormedics, Yorba Linda, California) was performed using individualized ramp protocols. To facilitate simultaneous echocardiographic assessment, the ramp steepness was limited to a maximum of 15 W/min. Twelve-lead electrocardiograms and the blood pressure were continuously recorded.

Minute ventilation (VE), oxygen uptake, and carbon dioxide output (VCO_2) were acquired breath by breath and averaged over 10 s. The V-slope method was used to determine the first ventilatory threshold.

VE and VCO_2 values, from the start of exercise to peak, were input into spreadsheet software (Excel; Microsoft, Redmond, Washington) to calculate the VE/VCO_2 slope using least squares linear regression ($y = mx + b$, where m is the slope).

Exercise oscillatory ventilation was defined according to guideline criteria (15). Circulatory power was calculated as the product of peak oxygen uptake and peak systolic blood pressure (16) and ventilatory power, calculated as peak systolic blood pressure divided by VE/VCO_2 slope (17).

TAPSE, mPAP, PASP, AND ERO COEFFICIENTS OF VARIATION AT REST AND PEAK EXERCISE. The intraobserver coefficients of variation for TAPSE, mPAP, PASP, and ERO measurements at rest were 2%, 4%, 3%, and 4.2%, respectively. The interobserver coefficients of variation were 3.2% for TAPSE, 4.1% for mPAP, 4.5% for PASP, and 3.4% for ERO at rest. For measures obtained at peak exercise, the intraobserver coefficients of variation were 4%, 3%, 3.4%, and 4% for TAPSE, mPAP, PASP, and ERO, respectively. The interobserver coefficients of variation were 3% for TAPSE, 4.2% for mPAP, 4.5% for PASP, and 3.8% for ERO.

FOLLOW-UP FOR MAJOR CLINICAL EVENTS. The subjects were followed for major cardiac-related events (hospitalization and mortality) every 6 months after enrollment via hospital and outpatient medical chart review.

STATISTICAL METHODS. Qualitative variables are summarized as percentages and quantitative variables as mean ± SD. Variations in quantitative variables were tested using 1-way analysis of variance or the analogous nonparametric method (Kruskal-Wallis). In cases of significance, contrasts between groups A and B and between groups B and C were evaluated. Because the contrasts were not orthogonal, Bonferroni correction for multiple comparisons was tested, and the level of significance was ≤0.025. For qualitative variables, the chi-square test or Fisher exact test was used. A contrast analysis was performed in cases of significance. Although tracking the event rate was not a primary goal, event differences among the groups were tested using the Fisher exact test. The relationships between echocardiographic variables and RVECR were investigated by multiple linear regression. The echocardiographic variables (covariates) included in the initial model were selected on the basis of their clinical relevance. The covariates analyzed were as follows: LV mass index, E/e′ ratio at rest, LV end-diastolic volume index at rest, severe MR at peak exercise, and net changes of PASP and CO. The variables included in the bivariate model were statistically significant.

Because of a limited number of patients, net changes of the clinical parameters at peak exercise were introduced among explicative variables to ensure a relevant goodness of fit model. Comparison-wise error alpha equal to 0.05 was applied for any multiple test, as proposed by Bender and Lange (18).

The analyses were performed using Stata version 12 (StataCorp LP, College Station, Texas).

RESULTS

PATIENT POPULATION. The groups were similar with regard to age, sex, and cardiovascular risk factors (Table 1). Group C showed a more severe degree of dyspnea (New York Heart Association functional class). Treatment was similar among groups except for higher use of potassium-sparing diuretic agents in group C.

CPET FUNCTIONAL PHENOTYPES. CPET variables are listed in Table 2. All patients performed maximal aerobic exercise, reaching a peak exercise respiratory exchange ratio >1.1. Group C patients had worse exercise tolerance compared with those in group B (lower maximal work load, peak oxygen uptake, and peak oxygen pulse). Patients in group C had severely impaired ventilatory efficiency (steeper VE/VCO_2 slope and lower peak end-tidal carbon dioxide) and lower ventilatory power. No differences among the groups were observed in the exercise oscillatory ventilation rate, although a higher trend was observed in group C. Group C patients exhibited lower peak systolic, diastolic, and pulse pressure.

ECHOCARDIOGRAPHIC CHARACTERISTICS. Echocardiographic variables are listed in Table 3. Patients in group C showed significantly worse remodeling, with increased left atrium and LV mass index. No group differences were observed in LV ejection fraction at rest and at peak exercise. Patients in group C had a higher rate of grade III diastolic dysfunction and increased pulmonary vein S/D and E/e′ ratios. Those in groups B and C had significantly reduced TAPSE, RV fractional area, and s′.

Significantly higher PVR and mPAP at rest and tricuspid regurgitation, PASP, TAPSE/PASP, mPAP/CO, and mPAP/TAPSE at rest and peak exercise were observed in group C patients.

Figure 2 shows the distribution of TAPSE versus PASP at rest and at peak exercise in the 3 groups. Patients in group A showed the highest TAPSE-versus-PASP relationship, whereas those in groups B and C exhibited a similarly downward-shifted regression line at rest. Group B exhibited some upward shift in the relationship during exercise, implying a different adaptation of the RV chamber to the imposed load. A higher rate of severe MR ERO at rest and during exercise was observed in group C. Greater MR severity described a progressively lower TAPSE/PASP ratio (**Figure 3**).

Figure 4 depicts a case of preserved RVECR and no MR (group B) compared with a patient with no RVECR and MR (group C). The rest and peak indexed LV SV, CO, and cardiac power output were significantly reduced in group C. The slopes of mPAP versus CO and mPAP versus TAPSE were progressively steeper from group A to group C, reflecting higher RV-to-PC uncoupling (**Figure 5**).

CARDIAC PARAMETERS ASSOCIATED WITH RVECR. Variables retained in the best regression model as determinants of RVECR are listed in **Table 4**. In the multiple regression analysis, the net change of peak PASP from rest and severe MR at rest emerged as the strongest cardiac correlates of RVECR in the overall HFrEF population.

MORTALITY AND HOSPITALIZATION. Hospitalization and cardiac-related mortality at a median follow-up period of 16 months did not reach statistical significance in the 3 groups, although the mortality rate was higher in group C (**Table 5**).

DISCUSSION

The present results provide new insights into the significance of RV contractile reserve in patients with HF with pathophysiological and clinical implications. The major findings are as follows: 1) HF with similar impairment in LV function is associated with multiple RV contractile reserve phenotypes; 2) depressed RV function at rest does not necessarily imply a worse adaptive response during physical challenge; 3) a lack of RVECR is associated with worse aerobic and ventilation efficiency; and 4) correlates of worse RV-to-PC coupling during exercise are the net change in PASP increase and severe functional MR at rest.

RV DYSFUNCTION AND RVECR. For many years, it has been assumed that a failing right heart is a

TABLE 1 Baseline Characteristics and Therapy Distribution

	HF (n = 97)	Group A (n = 60)	Group B (n = 19)	Group C (n = 18)	p Value
Age, yrs	64 ± 11	64 ± 13	62 ± 10	65 ± 8	0.73
Body mass index, kg/m^2	27 ± 4	27 ± 4	26 ± 4	26 ± 4	0.22
Female	30	35	16	28	0.27
Smokers or ex-smokers	42	39	53	44	0.25*
Hypertension	62	64	68	50	0.45
Diabetes	36	34	37	44	0.71
Hypercholesterolemia	62	61	63	67	0.90
Dyspnea	74	72	56	93	0.10*
NYHA functional class					
I	30	34	50	8	0.013*
II	30	37	13	21	
III	33	24	37	57	
IV	7	5	0	14	
NT-proBNP, pg/ml	2,780 ± 1,606	2,140 ± 1,430	2,270 ± 1,706	2,890 ± 1,509	0.032*
Therapy					
Beta-adrenergic receptor blockers	87	85	94	88	0.61
Ca^{2+} antagonists	10	10	6	12	0.90*
ACE inhibitors	57	64	34	53	0.15
ARBs	24	24	38	12	0.23*
Aldosterone antagonists	52	46	44	82	0.022
Diuretic agents	78	74	75	94	0.19*
Nitrates	9	7	6	12	0.87*
Statins	63	60	56	77	0.40*

Values are mean ± SD or %. *Fisher exact test.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; HF = heart failure; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

TABLE 2 Cardiopulmonary Exercise Testing Variables According to Groups

	HF (n = 97)	Group A (n = 60)	Group B (n = 19)	Group C (n = 18)	p Value
Maximal work, W	65 ± 25	69 ± 26	68 ± 21	46 ± 18‡	0.0029
Peak VO_2, ml/kg/min	13.0 ± 3.7	13.5 ± 3.5	14.1 ± 4.2	10.2 ± 2.3‡	0.008†
Predicted peak VO_2, %	53 ± 15	55 ± 14	55 ± 14	43 ± 13‡	0.0082†
Peak RER	1.17 ± 0.12	1.17 ± 0.14	1.17 ± 0.14	1.19 ± 0.12	0.88
Peak O_2 pulse, ml/beat	9.0 ± 2.7	9.3 ± 2.8	10.0 ± 2.7	7.4 ± 2.0‡	0.0068
VE/VCO_2 slope	34 ± 10	31 ± 7	35 ± 10	42 ± 12‡	0.0001†
End-tidal CO_2, mm Hg	33 ± 6	35 ± 5	33 ± 6	28 ± 4‡	0.0001
EOV	44	40	42	61	0.28*
Circulatory power, mm Hg · ml O_2 · kg^{-1} · min^{-1}	1,886 ± 672	2,144 ± 627	1,734 ± 508	1,182 ± 366	0.0001†
Ventilatory power, mm Hg	4.8 ± 1.5	5.3 ± 1.3	4.7 ± 1.6	3.5 ± 1.2‡	<0.0001
Rest heart rate, beats/min	71 ± 13	71 ± 12	65 ± 10	76 ± 17	0.07†
Peak heart rate, beats/min	110 ± 19	113 ± 19	107 ± 14	104 ± 22	0.16
Rest systolic BP, mm Hg	122 ± 16	123 ± 15	119 ± 15	118 ± 20	0.38
Peak systolic BP, mm Hg	153 ± 25	158 ± 24	150 ± 25	138 ± 25	0.013
Rest diastolic BP, mm Hg	76 ± 8	77 ± 7	75 ± 10	72 ± 9	0.24†
Peak diastolic BP, mm Hg	81 ± 9	82 ± 8	81 ± 10	76 ± 9	0.003

Values are mean ± SD or %. *Chi-square test. †Kruskal-Wallis test. ‡$p < 0.025$, group B versus group C.

BP = blood pressure; EOV = exercise oscillatory ventilation; HF = heart failure; RER = respiratory exchange ratio; VCO_2 = carbon dioxide output; VE = minute ventilation; VO_2 = oxygen uptake.

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TABLE 3 Echocardiographic Parameters at Rest and at Peak Exercise

	HF (n = 97)	Group A (n = 60)	Group B (n = 19)	Group C (n = 18)	p Value
Rest LV end-diastolic volume index, ml/m^2	95 ± 31	90 ± 23	95 ± 28	113 ± 47	0.21‖
Rest LV mass index, g/m^2	130 ± 32	126 ± 30	121 ± 22	154 ± 37‡	0.0017
Rest LVEF, %	33 ± 9	33 ± 8	34 ± 9	32 ± 11	0.88
Peak LVEF, %	37 ± 11	37 ± 10	37 ± 14	35 ± 10	0.66
Rest E/A ratio	1.6 ± 1.2	1.4 ± 0.9	1.6 ± 1.4	2.9 ± 1.5‡	0.0018‖
Rest S/D ratio	0.93 ± 0.48	1.0 ± 0.5	0.82 ± 0.5	0.72 ± 0.4	0.12
Rest E-wave deceleration time, ms	176 ± 69	178 ± 64	195 ± 86	150 ± 62	0.13
Rest E/e′ ratio	25 ± 14	22 ± 11	25 ± 16	38 ± 13‡	0.0001‖
Rest left atrial volume index, ml/m^2	54 ± 26	47 ± 18	52 ± 24	80 ± 35‡	0.0005‖
Rest MR ERO, mm^2	19 ± 10	17 ± 8	17 ± 8	26 ± 12	0.012
Peak MR ERO, mm^2	30 ± 13	26 ± 11	32 ± 8	38 ± 15	0.018
Rest MR regurgitant volume, ml	31 ± 15	26 ± 12	32 ± 17	39 ± 17	0.038
Peak MR regurgitant volume, ml	45 ± 20	40 ± 18	52 ± 15	51 ± 23	0.14
Rest severe MR (ERO ≥20 mm^2)	23	13	21	56	0.001†
Peak severe MR (ERO ≥20 mm^2)	38	32	33	70	0.013*
Rest RV end-diastolic area, cm^2	17 ± 5	17 ± 4	18 ± 5	20 ± 8	0.39‖
Rest RV fractional area, %	40 ± 12	43 ± 11	37 ± 12	30 ± 11	0.0005
Peak RV fractional area, %	40 ± 12	42 ± 12	42 ± 12	31 ± 11‡	0.0084‖
Rest TAPSE, mm	18 ± 4	21 ± 3	14 ± 2§	13 ± 3	<0.0001
Peak TAPSE, mm	20 ± 5	23 ± 4	18 ± 2	13 ± 2	<0.0001‖
Rest tricuspid s′, cm/s	10.2 ± 3.0	11.4 ± 2.7	8.7 ± 1.9§	6.8 ± 1.6	0.0001
Peak tricuspid s′, cm/s	11.9 ± 3.7	13.4 ± 3.1	11.3 ± 0.35	7.2 ± 1.0	0.026‖
Rest tricuspid regurgitation velocity, m/s	2.7 ± 0.6	2.6 ± 0.5	2.6 ± 0.6	3.0 ± 0.7	0.018
Peak tricuspid regurgitation velocity, m/s	3.5 ± 0.6	3.5 ± 0.5	3.5 ± 0.7	3.7 ± 0.6	0.42
Rest PASP, mm Hg	37 ± 16	34 ± 13	36 ± 16	48 ± 21	0.027‖
Peak PASP, mm Hg	59 ± 18	57 ± 16	59 ± 22	65 ± 19	0.33
Rest mPAP, mm Hg	22.0 ± 8.3	22.7 ± 7.7	23.8 ± 9.3	30.8 ± 12.7‡	0.026‖
Peak mPAP, mm Hg	34 ± 10.3	35.7 ± 10.4	37.3 ± 13.0	40.8 ± 11.4	0.26
Rest TAPSE/PASP, mm/mm Hg	0.55 ± 0.24	0.67 ± 0.22	0.44 ± 0.17§	0.31 ± 0.13	0.0001‖
Peak TAPSE/PASP, mm/mm Hg	0.36 ± 0.15	0.42 ± 0.14	0.34 ± 0.11	0.21 ± 0.08	0.0001
Rest mPAP/TAPSE, mm Hg/mm	1.23 ± 0.81	0.94 ± 0.37	1.74 ± 0.73	2.57 ± 1.27	0.0001
Peak mPAP/TAPSE, mm Hg/mm	1.67 ± 0.95	1.33 ± 0.52	2.07 ± 0.68	3.39 ± 1.27	0.0001
mPAP/TAPSE slope	3.28 ± 6.62	4.6 ± 5.1	4.07 ± 3.40	10.06 ± 8.66	0.001
Rest pulmonary resistance, WU	2.6 ± 1.3	2.2 ± 0.9	2.8 ± 1.2	3.5 ± 1.7	0.0016‖
Rest LV SV index, ml/m^2	29 ± 9	31 ± 9	27 ± 8	21 ± 6‡	0.0001
Peak LV SV index, ml/m^2	32 ± 11	34 ± 10	32 ± 9	23 ± 8‡	0.0002
Rest LV CO, l/min	3.7 ± 1.2	4.0 ± 1.2	3.3 ± 0.8§	2.9 ± 1.0	0.0004
Peak LV CO, l/min	6.6 ± 2.6	7.2 ± 2.6	6.5 ± 1.8	4.4 ± 1.9‡	0.0002
Rest cardiac power output, W	0.74 ± 0.25	0.82 ± 0.24	0.66 ± 0.2§	0.51 ± 0.20	<0.0001
Peak cardiac power output, W	1.55 ± 0.70	1.7 ± 0.7	1.52 ± 0.60	0.88 ± 0.40‡	0.0001
Rest PASP/CO, mm Hg/l/min	11.3 ± 6.9	9.4 ± 5.0	11.6 ± 6.0	17.6 ± 9.0	0.0004‖
Peak PASP/CO, mm Hg/l/min	11.1 ± 7.3	9.6 ± 6.0	10 ± 5	17.3 ± 10.0	0.0027‖
mPAP/CO slope	6.54 ± 9.47	6.56 ± 6.41	5.17 ± 3.29	8.4 ± 15.9	0.001

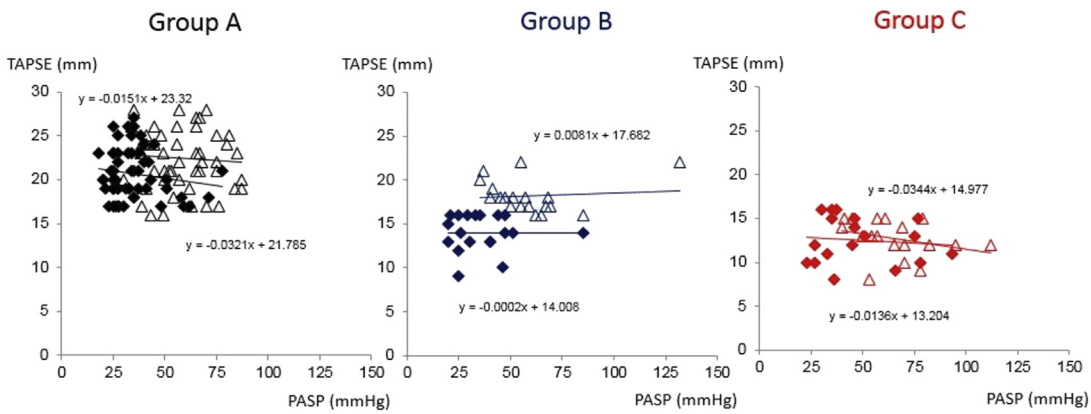
Values are mean ± SD or %. The p values for Mann-Whitney *U* test at rest and peak exercise are also reported. *Chi-square test. †Fisher exact test. ‡p < 0.025, group B versus group C. §p < 0.025, group A versus group B. ‖Kruskal-Wallis test.

A = late diastolic transmitral velocity; CO = cardiac output; e′ = early diastolic septal velocity; E = early diastolic transmitral velocity; ERO = effective regurgitant orifice; HF = heart failure; LV = left ventricular; LVEF = left ventricular ejection fraction; mPAP = mean pulmonary artery pressure; MR = mitral regurgitation; PASP = pulmonary artery systolic pressure; RV = right ventricular; SV = stroke volume; TAPSE = tricuspid annular plane systolic excursion.

turning point in the evolving nature of HF syndrome (1,11,19). Major pathophysiological consequences of RV failure and increased central venous pressure result in resistance in pulmonary lymphatic drainage and a decline in renal function, leading to cardiorenal syndrome and systemic congestion (20). This evidence points to a crucial role of an accurate evaluation of RV function and its coupling with the PC in the assessment of HF.

At variance with the left ventricle, however, the study of the failing right heart in vivo has only recently been put in the perspective of its adaptation and functional reserve during different stimuli, such as dobutamine stress echocardiography (3) and

FIGURE 2 Relationship of Tricuspid Annular Plane Systolic Excursion and Pulmonary Artery Systolic Pressure at Rest and at Peak Exercise in the 3 Groups

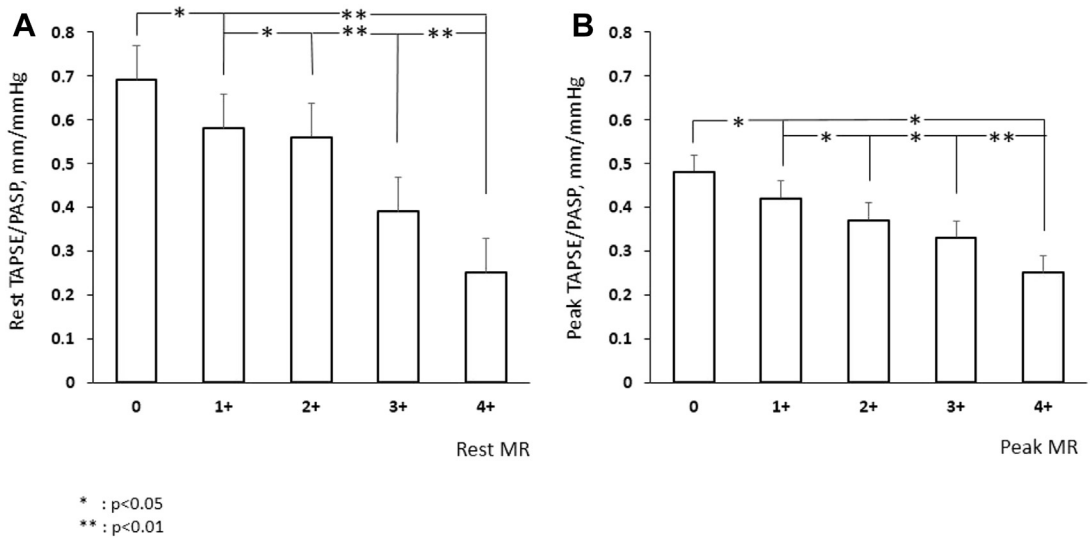


Group A had the highest tricuspid annular plane systolic excursion (TAPSE) for similar systolic load. Group B and C patients exhibited a similarly downward-shifted regression line. Group B maintained some ability of upward shift in the relationship, suggesting better right ventricular adaptation to the imposed work. Solid symbols denote rest; empty symbols denote peak exercise. PASP = pulmonary artery systolic pressure.

exercise (4); no data have been provided on RVECR in HF focusing on the adaptive RV contractile response to a physiological challenge such as maximal exercise. Our findings have possibly shifted the paradigm from isolated RV systolic performance assessment to RV contractile functional reserve analysis, thus making it possible to phenotype different RV adaptive patterns that are unpredictable at rest. Specifically, the identification of those RV chambers that, despite depressed function at rest, are still responsive to inotropic stimuli might provide best insights on clinical decision making, such as indications for valve surgery, LV assist device implantation, and transplantation.

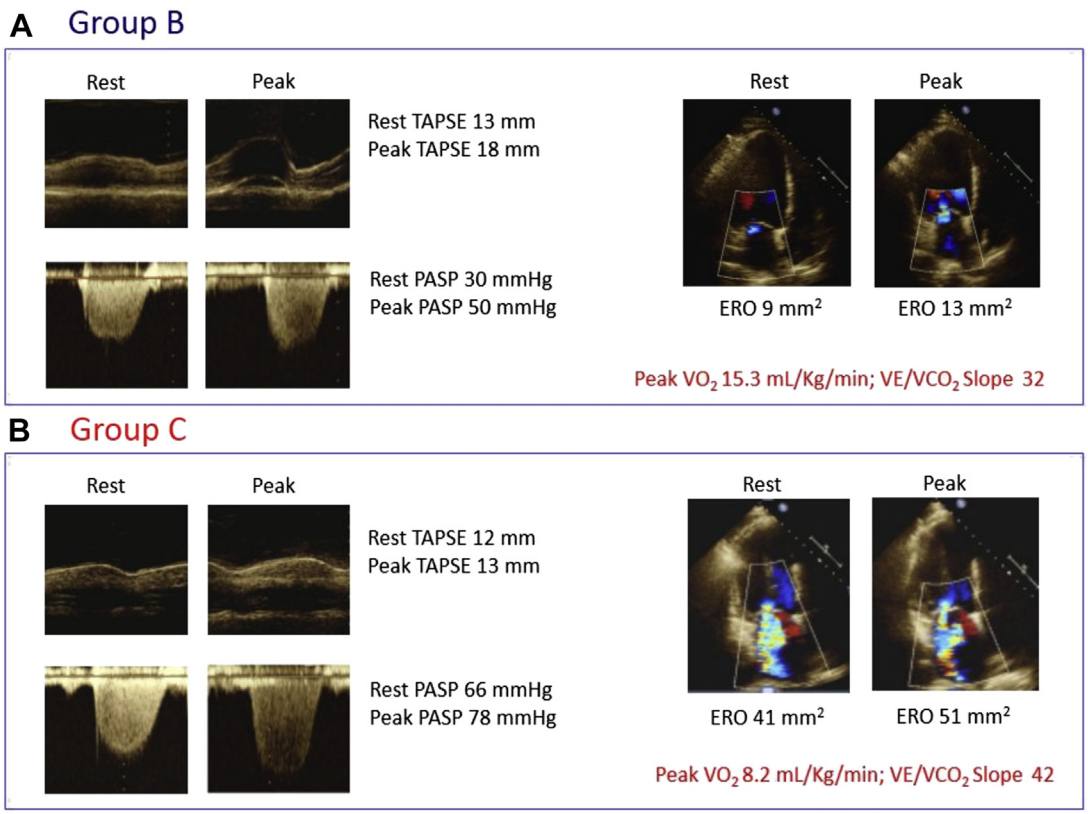
As for the left ventricle, the optimal measure of RV contractility is on the basis of pressure-volume

FIGURE 3 Ratio of Tricuspid Annular Plane Systolic Excursion to Pulmonary Artery Systolic Pressure at Rest and at Peak Exercise According to the Severity of Mitral Regurgitation



(A) At rest; **(B)** at peak exercise. MR = mitral regurgitation; PASP = pulmonary artery systolic pressure; TAPSE = tricuspid annular plane systolic excursion.

FIGURE 4 Example of a Patient With Right Ventricular Contractile Reserve Recovery During Exercise (Group B) and a Patient Without Right Ventricular Contractile Reserve (Group C)

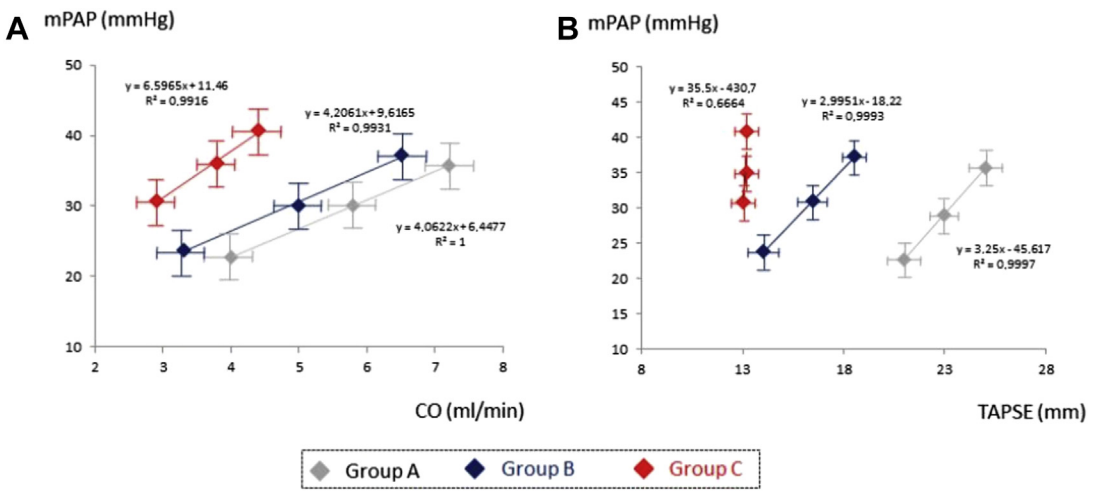


(A) Group B; **(B)** Group C. ERO = effective regurgitant orifice; PASP = pulmonary artery systolic pressure; TAPSE = tricuspid annular plane systolic excursion; VCO_2 = carbon dioxide output; VE = minute ventilation; VO_2 = oxygen uptake.

analysis (1,5) and measurements of maximal elastance. This method is the gold standard, although it is unpractical and cumbersome, especially during exercise. To make this method easier, Grunig et al. (6) recently proposed the exercise-induced extent of PASP increase as a surrogate measure of RV functional reserve. Although prognostic, isolated PASP analysis is flawed in cases in which the right ventricle works in the flat portion of the Frank-Starling curve and is still able to develop some pressure without any improvement in the functional response. In a previous study, we proposed that the relationship of TAPSE to PASP, taken as an index of in vivo RV length (TAPSE) versus developed force (PASP), provides a noninvasive assay of RV contractile state (11). This approach to RV contractile performance separated different relationships across mortality rate (survivors vs. nonsurvivors) and broadly applied to cardiac failure of both systolic and diastolic origin. Furthermore, the combination of both variables in a ratio emerged as a strong and independent predictive variable (hazard ratio: 10.3) among those retained in the multivariate regression model, especially in combination with CPET (7). The TAPSE/PASP ratio has been recently validated against pulmonary hemodynamic status in a broad population of patients with HF, emerging as an independent predictor of combined pre- and post-capillary pulmonary hypertension and correlating with pulmonary compliance (21).

We adopted the relationship between TAPSE and PASP at rest versus peak exercise as a tool to detect changes in RV contractile reserve, clearly defining 3 different patterns, with group B patients who, in contrast to group C, were still able to display an upward shift in this relationship, despite similarly depressed RV function at rest, and with group C showing no changes in this relationship. As a reflection of changes in vascular afterload and a determinant of RV function, MR at rest and the net change in PASP from rest to peak exercise were retained in the

FIGURE 5 Mean Pulmonary Artery Pressure Versus Cardiac Output and Mean Pulmonary Artery Pressure Versus Tricuspid Annular Plane Systolic Excursion Relationship in the 3 Groups



(A) Cardiac output; **(B)** tricuspid annular plane systolic excursion. **Gray symbols** denote group A; **blue symbols** denote group B; **red symbols** denote group C. CO = cardiac output; mPAP = mean pulmonary artery pressure; TAPSE = tricuspid annular plane systolic excursion.

multiple regression analyses as independent correlates of RV functional reserve.

RV-TO-PC COUPLING AT REST AND DURING EXERCISE. After assessing RV contractility and its reserve to incremental exercise, we focused on what has been repeatedly stressed in recent years: the need to recognize PC and the right ventricle as an integrated functional unit. In previous studies performed with stress echocardiography, a multipoint measure of mPAP versus CO has been validated as a valuable assessment of RV-to-PC coupling (22).

Because the CO response is dependent on heart rate, we deemed it correct to also evaluate the relationship between mPAP and TAPSE changes during exercise to directly relate the increase in flow to an index of systolic RV functional efficiency. Stepwise worsening in RV-to-PC coupling was observed with an increase in the mPAP versus CO slope and the mPAP versus TAPSE slope from group A to C. Although group C showed a clear mismatch, the better RV-to-PC coupling observed in group B would suggest underlying intrinsic RV disease as a reason for the observed uncoupling.

Overall, it is remarkable that the impairment in RV contractile reserve and uncoupling were associated with a more severe degree of functional MR, a well-defined determinant of exercise induced pulmonary hypertension and prognosis (23). Despite the limited number of cardiac-related events and a nonsignificant difference among groups, a higher cardiac related event rate was observed in group C.

FUNCTIONAL CORRELATES AND CPET PHENOTYPES. Most previous studies, except one (24) looking at RV function in combination with CPET data, have been limited to the analysis of RV systolic function indicators at rest, showing a strict link between abnormalities in exercise ventilation efficiency and impaired RV performance (7). In a cohort of patients

TABLE 4 Variables Retained in the Best Regression Model as Determinants of Right Ventricular Exercise Contractile Reserve

	Regression Coefficient	95% Confidence Interval	Test	p Value
Rest LV mass index	−0.009	−0.030 to 0.011	−0.87	0.385
Rest severe MR (ERO)	−1.296	−2.766 to 0.174	−1.76	0.043
Net change in PASP	0.056	0.001 to 0.112	2.04	0.045
Change in LV CO	0.161	−0.203 to 0.524	0.88	0.382

Abbreviations as in Table 3.

TABLE 5 Cardiac-Related Mortality and Hospitalization in at Least 6 Months of Follow-Up (Median Time 16 months) in the 3 Groups

	Group A (n = 60)	Group B (n = 19)	Group C (n = 18)	p Value*
Cardiac-related mortality	2	0	6	0.151
Hospitalization	8	2	6	>0.900
Overall severe clinical events	10	2	7	0.114

*Fisher exact test.

with HFrEF assessed by simultaneous exercise gas exchange analysis and hemodynamic monitoring, Lewis et al. (8) demonstrated that the pulmonary vasomotor response and RV function during exercise have a critical role in determining ventilatory efficiency, as shown by the steepness of the VE/VCO_2 slope. Our findings exactly reproduce these observations and add potentially new insights into the cause-effect relationship between RV-to-PC coupling and impaired gas exchange efficiency during exercise. We observed that together with a severely compromised VE/VCO_2 slope, patients in group C exhibited an impressively high rate (60%) of exercise oscillatory ventilation, an ominous sign of an unfavorable prognosis and severely compromised circulatory power, which is a comprehensive indicator of poor hemodynamic response to exercise challenge (15).

STUDY LIMITATIONS. The results of this study are affected by the obvious limitations related to the noninvasive assessment of RV contractility and RV-to-PC coupling. Measuring CO at the LV outflow tract level might not take into account significant valvular disease and might not be the same as measuring RV outflow tract-derived CO through right heart catheterization. However, invasive hemodynamic monitoring during incremental exercise is technically difficult to perform and is not routinely incorporated into clinical exercise testing evaluation. In daily clinical practice, RV function is assessed by echocardiography, and the possibility of detecting noninvasively accurate and predictive measures of RV contractility (11) and RV-to-PC coupling (22) could provide a step forward in the follow-up of these patients.

Exercise stresses PC through an increase in CO and left atrial pressure, each of which results in an increase in mPAP. The relationship between these variables is defined by the PVR equation. PVR was estimated by the Abbas formula, which although not validated in a large population of patients with HF remains a reference Doppler method in cardiac patients (23). We were able to record increased PVR and left atrial pressure only at rest. Measurements during physical challenge would obviously have helped properly define the respective contribution of these variables in the hemodynamic response. An increase in the transpulmonary gradient and PVR typically characterize the pulmonary hemodynamic response of HFrEF (8), and a major contribution to the increase in left atrial pulsatile load and pulmonary pressure during exercise is promoted by exercise-induced MR (23). Our findings of a net change in PASP and severe MR (ERO) at rest as determinants of exercise-induced RV response to exercise clearly point in this direction, suggesting a primary pathophysiological role of an abnormal increase of the vascular and pulsatile load. No information is available regarding potential ischemic RV disease and its relative contribution in RVECR and RV-to-PC uncoupling.

CONCLUSIONS

In patients with HF, impaired RV function at rest might not invariably lead to an unfavorable RV contractile adaptive response to exercise. Testing the degree of RVECR and RV-to-PC coupling during exercise could be useful, even in the more advanced stages of disease, to unmask various clinical phenotypes and different levels of risk.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In HF, the development of RV dysfunction and failure is a turning point that signals clinical deterioration and worsening outcomes. The pathophysiology of RV-to-PC uncoupling in HF is not well defined, and the information available is limited primarily to RV function at rest. In HF, exercise stresses the PC and the right ventricle through an increase in CO at the expense of increased LV filling pressure, each of which might precipitate RV-to-PC uncoupling. A thorough evaluation of the right heart and pulmonary system during exercise might improve the pathophysiological and clinical characterization of patients with HF who present with depressed RV function at rest and might still have a favorable adaptive response in terms of RV contractility and RV-to-PC coupling. Our study highlights the significant role of studying the right heart during exercise in patients with HF syndrome to determine different phenotypes and levels of risk with direct implications on therapeutic targets.

TRANSLATIONAL OUTLOOK: On the basis of the present observations, further studies are needed to determine the utility of unmasking exercise-induced RV-to-PC adaptive response in patients with evidence of severely compromised RV function at rest. Although no specific pharmacological therapies for the right ventricle and PC have been identified, the findings appear helpful to pave the way to a more detailed characterization of right heart disease and its reversibility in HF syndrome.

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