Impaired Right Ventricular–Pulmonary Arterial Coupling and Effect of Sildenafil in Heart Failure With Preserved Ejection Fraction

An Ancillary Analysis From the Phosphodiesterase-5 Inhibition to Improve Clinical Status And Exercise Capacity in Diastolic Heart Failure (RELAX) Trial

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Background—Right ventricular (RV) dysfunction (RVD) is a poor prognostic factor in heart failure with preserved ejection fraction (HFpEF). The physiological perturbations associated with RVD or RV function indexed to load (RV–pulmonary arterial [PA] coupling) in HFpEF have not been defined. HFpEF patients with marked impairment in RV–PA coupling may be uniquely sensitive to sildenafil.

Methods and Results—In a subset of HFpEF patients enrolled in the Phosphodiesteas-5 Inhibition to Improve Clinical Status And Exercise Capacity in Diastolic Heart Failure (RELAX) trial, physiological variables and therapeutic effect of sildenafil were examined relative to the severity of RVD (tricuspid annular plane systolic excursion [TAPSE]) and according to impairment in RV–PA coupling (TAPSE/pulmonary artery systolic pressure) ratio. The prevalence of atrial fibrillation and diuretic use, n-terminal probrain natriuretic peptide levels, renal dysfunction, neurohumoral activation, myocardial necrosis and fibrosis biomarkers, and the severity of diastolic dysfunction all increased with severity of RVD. Peak oxygen consumption decreased and ventilatory inefficiency (VE/VCO_2 slope) increased with increasing severity of RVD. Many but not all physiological derangements were more closely associated with the TAPSE/pulmonary artery systolic pressure ratio. Compared with placebo, at 24 weeks, TAPSE decreased, and peak oxygen consumption and VE/CO_2 slope were unchanged with sildenafil. There was no interaction between RV–PA coupling and treatment effect, and sildenafil did not improve TAPSE, peak oxygen consumption, or VE/VCO_2 in patients with pulmonary hypertension and RVD.

Conclusions—HFpEF patients with RVD and impaired RV–PA coupling have more advanced heart failure. In RELAX patients with RVD and impaired RV–PA coupling, sildenafil did not improve RV function, exercise capacity, or ventilatory efficiency.

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In patients with heart failure (HF) with reduced ejection fraction (HFrEF), right ventricular (RV) dysfunction (RVD) is associated with greater symptom burden, worse exercise capacity, greater ventilatory inefficiency, and adverse clinical outcomes.[1] RVD is common and associated with worse outcomes in HF with preserved ejection fraction (HFpEF).[2–4] Pulmonary hypertension (PH) is also common and predicts adverse outcome in both HF phenotypes.[2,5,6] The combination of RVD as evidenced by reduced tricuspid annular plane systolic excursion (TAPSE) and increased Doppler estimated pulmonary artery systolic pressure (PASP) has been shown

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to have important prognostic implications in HF, and the TAPSE/PASP ratio is proposed as a noninvasive index of RV–pulmonary arterial (PA) coupling in HF.[7] However, the

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physiological profile of RVD and perturbed RV–PA coupling as assessed by the TAPSE/PASP ratio in HFpEF has not been described. Accordingly, we performed a post hoc analysis of the Phosphodiesterase-5 Inhibition to Improve Clinical Status And Exercise Capacity in Diastolic Heart Failure (RELAX) trial of sildenafil in HFpEF, hypothesizing that RVD and incrementally, adverse RV–PA coupling are associated with more severe HF, greater activation of biomarkers reflective of neurohumoral activation, myocardial necrosis, inflammation and fibrosis, reduced exercise capacity (peak oxygen uptake, peak oxygen consumption [pVO_2]), and less efficient ventilation (steeper VE/VCO_2 slope).

The RELAX trial showed no benefit of sildenafil on exercise capacity or clinical status in patients with HFpEF.[8] It has been proposed that response to sildenafil in HFpEF may require the presence of markedly perturbed RV–PA coupling because of both PH and RVD.[9,10] Thus, in an exploratory analysis, we tested the hypothesis that sildenafil would improve RV function, exercise capacity, and ventilatory efficiency in patients with the most perturbed RV–PA coupling.

Methods

Study Subjects

The RELAX entry criteria specified New York Heart Association (NYHA) class II to IV HF symptoms, ejection fraction ≥50%, and objective evidence of HF (at least 1 of the following: HF hospitalization, documented elevation in left ventricular [LV] filling pressures at rest or with exercise at pulmonary artery catheterization, or left atrial enlargement in the setting of chronic diuretic therapy for HF).[8,11] At study entry, patients were required to have pVO_2 ≤60% of the age-/sex-predicted normal value and an elevated n-terminal probrain natriuretic peptide (NT-proBNP; ≥400 pg/mL) or brain natriuretic peptide (≥200 pg/mL) level, or previously documented elevated LV filling pressures when brain natriuretic peptide assays were not elevated. The RELAX protocol was approved by the participating centers institutional review board, and all participants provided written informed consent.

Echocardiography

Echo variables were measured by the Heart Failure Network (HFN) core echocardiography laboratory (Mayo Clinic, Rochester, MN) as previously described.[8,11] PASP was calculated using standard methods as outlined in the Methods in the Data Supplement.

The RELAX echocardiographic protocol did not include assessment of RV function. Thus, TAPSE was measured offline (blinded to treatment group) from the apical 4-chamber view by subtracting the distance between the lateral tricuspid leaflet annular insertion and sector apex in systole from the distance between the 2 in diastole. We and others have previously validated this technique,[2,12] and the normal values, clinical correlates, and prognostic implications of 2-dimensional TAPSE measured offline in 500 patients with HFpEF have been defined.[2] Intra- and Interobserver variability for 2-dimensional TAPSE and the correlation between 2-dimensional and M-mode measured TAPSE have been defined[2] (Figure I in the Data Supplement).

Although TAPSE is a simple measure of RV longitudinal function, it has shown good correlation with other techniques estimating RV global systolic function.[2,10]

Cardiopulmonary Exercise Testing

A cardiopulmonary exercise testing was performed on a cycle or treadmill using specifically designed cardiopulmonary exercise testing protocols and analyzed by the HFN core cardiopulmonary exercise testing laboratory (Massachusetts General Hospital, Boston, MA) as previously described and further described in the Methods in the Data Supplement.[8,11]

Biomarkers

Plasma biomarkers of neurohumoral activation (NT-proBNP, aldosterone, and endothelin-1), cardiac injury (troponin I), systemic inflammation (c-reactive protein), renal function (cystatin C), and fibrosis (procollagen III n-terminal peptide, galectin-3, c-telopeptide for type I collagen) were assessed at baseline by the HFN biomarker core laboratory (University of Vermont, Burlington, VT).[8,11]

Statistical Analysis

For data display, patients were grouped according to the absence or presence of RVD as assessed by TAPSE (TAPSE < or ≥17 mm)[13] and the absence or presence of PH (PASP < or ≥40 mm Hg) to define 4 subgroups (no RVD or PH; no RVD+PH; RVD without PH; and RVD+PH) with progressively more deranged RV–PA coupling as assessed by the TAPSE/PASP ratio.[7] For dichotomous variables, trends across RV–PA coupling subgroups were assessed using the Cochran Armitage trend test. Differences between patients with or without PH within each RV function subgroup were assessed with Wilcoxon rank-sum or Pearson χ^2 test. Spearman correlations were used to determine associations between RV function (TAPSE) or RV–PA coupling (TAPSE/PASP) and continuous physiological parameters. To further determine whether associations between physiological variables and the TAPSE/PASP ratio were influenced by both RV function and pulmonary pressures, we determined whether associations between PASP and variables of interest remained significant after adjusting for TAPSE using partial Spearman correlations.

General linear regression was used to test differences in baseline pVO_2 across the RV–PA coupling subgroups adjusted for pertinent variables (age, sex, body mass index, hemoglobin, and chronotropic index).[14] Similar models compared the change in TAPSE, peak Vo_2, and VE/VCO_2 from baseline to 24 weeks in patients treated with sildenafil versus placebo adjusting for baseline value, as well as RV–PA coupling group. Because RV–PA coupling group uses baseline TAPSE in the definition, baseline TAPSE was not included in the model for change in TAPSE. In addition, an interaction term for treatment allocation and RV–PA coupling subgroup was included in the aforementioned models to determine whether change with treatment varied by RV–PA coupling subgroup.

Data are presented as median (25th, 75th percentile) or frequency. All the analyses were 2-tailed, and a $P<0.05$ was considered statistically significant. Analysis was completed by the HFN data-coordinating center (Duke Clinical Research Institute, Durham, NC) using SAS statistical software (SAS Institute Inc, Cary, NC), version 9.2 or higher.

Results

Among the RELAX cohort (n=216), 138 subjects (64%) had a measurement of PASP on the core laboratory reading. Of these, TAPSE was measureable in 137 subjects. Subjects with measureable PASP and TAPSE were older, more likely male, less obese, less likely to have lung disease, and had lower hemoglobin levels than those patients without measureable PASP or TAPSE (n=79; Table I in the Data Supplement).

Fifty percent of HFpEF patients with measureable TAPSE and PASP had normal RV function (n=69), and of these, 38 (28% of study population) had no PH and 31 (23% of study population) had PH. Of patients with RVD by TAPSE criteria (n=68; 50%), 23 (17% of study population) had no PH and 45 (33% of study population) had PH (Table 1).

Median TAPSE was similar in the 2 groups with normal RV function, but the TAPSE/PASP ratio was lower in patients with normal RV function and PH when compared with normal RV function and no PH (Table 1). Median TAPSE was similar

Table 1. Baseline Characteristics According to RV Function and RV–PA Coupling

	NI RV–No PH	NI RV–PH	RVD–No PH	RVD–PH	*P* Value*
N	38	31	23	45	
Prevalence	28%	23%	18%	33%	NA
TAPSE, mm	22 (19, 25)	22 (19, 25)	13 (12, 15)	13 (11, 15)	NA
PASP, mm Hg	32.0 (28.0, 36.4)	48.4 (43.4, 56.2)†	32.0 (30.0, 35.0)	51.4 (48.4, 58.4)†	NA
TAPSE/PASP, mm/mm Hg	0.69 (0.59, 0.80)	0.44(0.39, 0.50)†	0.40 (0.35, 0.46)	0.24 (0.20, 0.30†	NA
Clinical characteristics					
Age, y	69 (63, 78)	73 (63, 77)	77 (68, 81)	71 (65, 80)	0.210
Male sex	12 (32%)	12 (39%)	15 (65%)	23 (51%)	0.032
BMI, kg/m^2	30.7 (27.9, 37.8)	33.7 (27.0, 39.9)	31.4 (27.3, 34.2)	31.0 (27.9, 34.0)	0.410
Ischemic pathogenesis	14 (37%)	8 (26%)	11 (48%)	20 (44%)	0.246
Hypertension	32 (84%)	27 (87%)	18 (78%)	37 (82%)	0.647
History of AF	12 (32%)	11 (36%)	17 (74%)	37 (82%)	<0.001
COPD	4 (11%)	4 (13%)	6 (26%)	7 (16%)	0.377
Diabetes mellitus	9 (24%)	12 (39%)	13 (57%)	16 (36%)	0.205
Functional status					
NYHA class					0.101
II	19 (50%)	19 (61%)	11 (48%)	16 (36%)	
III	19 (50%)	12 (39%)	12 (52%)	29 (64%)	
MLWHFQ score	34 (22, 49)	37 (24, 54)	49.0 (35, 67)	44 (35, 61)	0.061
Medications					
Beta-blockers	29 (76%)	24 (77%)	17 (74%)	38 (84%)	0.399
Digoxin	2 (5%)	2 (7%)	7 (30%)	7 (16%)†	0.056
Loop diuretics	19 (50%)	24 (77%)†	19 (83%)	44 (98%)†	<0.001
Laboratory values					
Creatinine, mg/dL	1.0 (0.8, 1.1)	1.1 (0.8, 1.5)	1.2 (0.9, 1.5)	1.2 (0.9, 1.5)	0.033
Cystatin C, mg/L	1.2 (1.0, 1.5)	1.4 (1.0, 1.8)	1.5 (1.2, 2.0)	1.5 (1.1, 1.8)	0.035
Hemoglobin, g/dL	13.0 (12.1, 14.1)	12.5 (11.5, 13.7)	12.5 (12.0, 13.5)	12.5 (11.8, 13.3)	0.134

AF indicates atrial fibrillation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; MLWHFQ, Minnesota Living with Heart Failure Questionnaire; NI, normal; NYHA, New York Heart Association; PA, pulmonary arterial; PH, pulmonary hypertension; RV, right ventricular; RVD, RV dysfunction; and TAPSE, tricuspid annular plane systolic excursion.

**P* represents the *P* value for the Spearman correlation between continuous variables and the TAPSE/PASP ratio or the Cochran Armitage trend test across groups for dichotomous variables.

†Wilcoxon rank-sum $P<0.05$ vs no PH within each RV function group.

in the 2 RVD groups, but the TAPSE/PASP ratio was lower in patients with RVD and PH when compared with those with RVD and no PH.

Clinical Characteristics of HFpEF Patients According to RV Function and RV–PA Coupling

Age and body size were similar across the RV–PA coupling groups (Table 1). Patients with RVD were more likely to be male. The prevalence of atrial fibrillation (past or current) was higher in patients with RVD. The prevalence of loop diuretic use was higher in patients with RVD and among patients with normal or impaired RV function; loop diuretic use was more common in patients with PH. Markers of symptom severity (NYHA functional class and Minnesota Living with HF questionnaire score) tended to be higher, and indices of renal dysfunction (cystatin C and creatinine) were higher in patients with RVD.

Biomarker Profile of HFpEF Patients According to RVD and RV–PA Coupling

The severity of neurohumoral activation (NT-proBNP, aldosterone, and endothelin-1), myocardial necrosis (troponin I), and fibrosis (procollagen III n-terminal peptide and c-telopeptide for type I collagen) increased with decreases in TAPSE or the TAPSE/PASP ratio (Table 2). Adjusting for TAPSE, PASP was still associated with NT-proBNP, endothelin, and procollagen III n-terminal peptide ($P<0.05$ for all) but not aldosterone, troponin, or c-telopeptide for type I collagen. Levels of c-reactive protein and galectin-3 were not associated with TAPSE or the TAPSE/PASP ratio.

Table 2. Biomarker Profile According to RV Function and RV–PA Coupling

	NI RV–No PH	NI RV–PH	RVD–No PH	RVD–PH	Correlation with TAPSE TAPSE/PASP	
N	38	31	23	45	*r*	*P*
NT-proBNP, pg/mL	366 (93, 835)	626 (351, 1266)	1231 (49, 2718)	1643 (963, 2548)	−0.44 −0.52	<0.001 <0.001
Aldosterone, pg/mL	164 (114, 233)	170 (105, 235)	264 (156, 383)	229 (155, 313)	−0.19 −0.21	0.007 0.013
Endothelin-1, pg/mL	2.1 (1.7, 2.4)	2.5 (2.0, 3.6)*	2.3 (2.2, 3.6)	3.0 (2.4, 4.0)	−0.23 −0.49	0.001 <0.001
Troponin I, pg/mL	6.4 (3.6, 13.3)	8.9 (4.3, 17.8)	9.9 (6.1, 21.9)	12.0 (8.4, 26.5)	−0.26	<0.001
	N=36		N=22		−0.32	<0.001
CRP, mg/L	2.4 (1.3, 7.3)	4.3 (2.5, 9.4)	7.2 (2.7, 11.7)	3.8 (1.8, 8.1)*	−0.02 −0.09	0.726 0.311
CITP, μg/L	5.1 (4.0, 7.3)	5.7 (4.1, 9.8)	6.6 (4.3, 10.2)	7.0 (5.9, 13.3)	−0.25 −0.34	<0.001 <0.001
NT-procollagen III, μg/L	6.4 (5.3, 7.8)	6.8 (6.0, 11.2)	7.0 (6.2, 10.8)	9.2 (7.8, 11.5)*	−0.21 −0.39	0.003 <0.001
Galectin-3, ng/mL	13.7 (12.3, 18.7)	13.4 (11.0, 16.8)	15.5 (12.2, 19.1)	15.1 (11.5, 23.1)	−0.10	0.144
	N=35	N=31	N=22	N=42	−0.13	0.153

In each row, the top *r* and *P* values represent the association of the variable with TAPSE and the bottom *r* and *P* values represent the association of the variable with the TAPSE/PASP ratio. Unless otherwise indicated, all variables have 1 missing value. CITP indicates c-telopeptide for type I collagen; CRP, c-reactive protein; NT-proBNP, n-terminal probrain natriuretic peptide; NT-procollagen III, n-terminal peptide of procollagen III; other abbreviations as in Table 1.

*Wilcoxon rank-sum $P<0.05$ vs no PH within each RV function group.

LV Structure and Function in HFpEF Patients According to RV Function and RV–PA Coupling

Relative wall thickness, a sex-independent measure of concentric remodeling, was associated with lower TAPSE and tended to be associated with lower TAPSE/PASP ratio, whereas neither TAPSE nor TAPSE/PASP were significantly associated the LV mass index(Table 3). Ejection fraction was lower in those with lower TAPSE and tended to be lower in those with lower TAPSE/PASP ratio. Adjusting for TAPSE, there were no associations between LV geometry or ejection fraction and PASP.

The severity of diastolic dysfunction (increased E/A ratio, E/e′ ratio, and left atrial volume index and decreased deceleration time) worsened with decreases in TAPSE or the TAPSE/PASP ratio. Adjusting for TAPSE, the E/A ratio and E/e′ ratio increased with increases in PASP. Cardiac index tended to decrease as TAPSE and TAPSE/PASP decreased. Adjusting for TAPSE, there were no associations between cardiac index and PASP.

Exercise Performance in HFpEF Patients According to RV Function and RV–PA Coupling

Body weight–indexed pVO_2 and percent-predicted pVO_2 were lower and VE/VCO_2 slope was higher in those with lower TAPSE or TAPSE/PASP ratio (Table 4). Adjusting for TAPSE, PASP was associated with lower indexed pVO_2 ($P<0.05$) but not with percent-predicted pVO_2 ($P=0.25$). Although PASP was associated with VE/VCO_2 slope ($r=0.18$; $P=0.034$), this relationship was not significant after adjusting for TAPSE ($P=0.19$). Peak exercise systolic blood pressure, peak heart rate, and the chronotropic index were lower in those with lower TAPSE and were or tended to be lower in those with lower TAPSE/PASP ratio. After adjusting for TAPSE, PASP was not associated with peak exercise systolic blood pressure or heart rate.

After adjusting for age, sex, body mass index, hemoglobin, and chronotropic index, pVO_2 still declined across the RV–PA coupling subgroups ($P=0.004$).

Effect of Sildenafil Versus Placebo on RV Function, Exercise Capacity, and Ventilatory Efficiency

Of the 137 patients with measurable TAPSE and PASP at enrollment, paired data for enrollment and 24-week TAPSE (n=116), pVO_2 (n=115), and VE/VCO_2 (n=114) were available in a subset of patients.

After adjusting for baseline values, TAPSE decreased at week 24 in the sildenafil arm (least square mean [95% confidence interval], −0.86 [−1.82 to 0.11] mm) when compared with placebo (0.73 [−0.10 to 1.55] mm; $P=0.02$) arm, indicating that sildenafil did not improve RV systolic function in HFpEF. There was no interaction between treatment allocation and RV–PA coupling groups on change in TAPSE, and sildenafil did not improve TAPSE in the subgroup with RVD and PH (Figure).

Adjusting for baseline values, change in pVO_2 was similar in sildenafil-treated (−0.11 [−0.55 to 0.33] $mL{\cdot}kg^{-1}{\cdot}min^{-1}$) and placebo-treated (−0.07 [−0.51 to 0.36] $mL{\cdot}kg^{-1}{\cdot}min^{-1}$; $P=0.90$) patients. Change in VE/VCO_2 slope was also similar in sildenafil-treated (−0.24 [−1.40 to 1.91]) and placebo-treated (−0.57 [−1.70 to 0.56]; $P=0.69$) patients. No interaction was observed between treatment allocation and RV–PA coupling groups on the change in pVO_2 or in VE/VCO_2 slope, and sildenafil did not improve these variables in the subgroup with RVD and PH (Figure).

Table 3. Echocardiographic Features According to RV Function and RV–PA Coupling

	NI RV–No PH	NI RV–PH	RVD–No PH	RVD–PH	Correlation with TAPSE TAPSE/PASP	
Group N	38	31	23	45	*r*	*P*
LV mass index, g/m^2	75.9 (59.2, 80.1)	78.5 (62.1, 96.5)	65.6 (55.4, 85.6)	79.4 (64.0, 99.5)	–0.01	0.878
	N=30	N=25	N=17	N=31	–0.14	0.168
RWT	0.38 (0.34, 0.45)	0.44 (0.36, 0.48)	0.42 (0.40, 0.47)	0.42 (0.38, 0.50)	–0.23	0.004
	N=30	N=25	N=17	N=31	–0.19	0.052
Ejection fraction, %	62 (57, 66)	60 (58, 65)	58 (54, 61)	58 (54, 65)	0.15	0.031
	N=38	N=31	N=23	N=45	0.16	0.059
E/A ratio	1.0 (0.8, 1.7)	1.6 (1.0, 2.0)	1.9 (1.1, 2.8)	3.3 (2.0, 4.0)*	–0.37	<0.001
	N=34	N=22	N=8	N=23	–0.67	<0.001
E/e′ ratio	13.3 (10.0, 17.5)	20.0 (15.7, 30.0)*	16.9 (13.3, 20.0)	22.0 (14.3, 30.0)	–0.22	0.002
	N=37	N=27	N=22	N=39	–0.38	<0.001
Deceleration time, ms	198 (177, 249)	178 (156, 211)	161 (145, 194)	164 (142, 212)	0.26	<0.001
	N=38	N=30	N=23	N=37	0.33	<0.001
LAVi, mL/m^2	40.3 (34.8, 46.6)	48.0 (40.4, 58.2)	51.4 (36.8, 62.5)	54.0 (43.0, 71.1)	–0.33	<0.001
	N=29	N=24	N=15	N=34	–0.27	0.006
Cardiac index, mL·min^{-1}·m^{-2}	2627 (2218, 3021)	2650 (2061, 2830)	2149 (1852, 2403)	2282 (2057, 2751)	0.14	0.068
	N=36	N=24	N=21	N=38	0.17	0.065

N with data for each variable is shown except where equal to the group N. In each row, the top *r* and *P* values represent the association of the variable with TAPSE and the bottom *r* and *P* values represent the association of the variable with the TAPSE/PASP ratio. LAVi indicates left atrial volume index; LV, left ventricular; and RWT, relative wall thickness; otherwise as in Table 1.

*Wicoxon rank-sum $P<0.05$ vs no PH within each RV function group.

Discussion

In this well-characterized HFpEF cohort, RVD was common and associated with more advanced HF as evidenced by higher prevalence of atrial fibrillation, greater use of loop diuretics, worse renal function, and worse diastolic dysfunction. HFpEF patients with RVD had more biomarker evidence of neurohumoral activation, myocyte necrosis and fibrosis, more impaired exercise tolerance, greater ventilatory inefficiency, and more abnormal exercise hemodynamics. Indexing RV function to RV load (TAPSE/PASP) improved the association of RV function and several biological markers of HF severity. Treatment with sildenafil for 24 weeks did not improve RV function, exercise capacity, or ventilatory efficiency, even in the subset of patients with RVD and PH, nearly all of whom had atrial fibrillation. These data further establish the high prevalence and physiological importance of RVD in HFpEF, provide insight into the mechanism for the association of RVD with poor outcomes in HFpEF, and underscore the substantial association between atrial fibrillation and RVD in HFpEF.

Prevalence and Implications of RVD in HFpEF

In this cohort with relatively advanced HFpEF, 50% of patients had evidence of RVD. This is similar to the findings in large observational HFpEF studies using 2-dimensional[2] or m-mode–derived[4] TAPSE. A catheterization laboratory-based study found that 33% of HFpEF patients had RVD (RV fractional area change <35%).[3] In contrast, in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial echocardiographic substudy, only 4% of patients had a reduced RV fractional area change.[15] As recently reviewed, in most HFpEF studies, RVD was associated with worse clinical outcomes,[10] but the physiological phenotyping of patients with RVD was limited.

Correlates of RVD in HFpEF

This study cannot establish the mechanism(s) driving RVD in HFpEF. Chronic RV pressure overload because of group 2 PH likely plays an important role and the RV may be more sensitive to load in HFpEF.[10] Here and in other observational studies assessing RV function in HFpEF,[2–4] a much higher prevalence of atrial fibrillation was observed in HFpEF patients with RVD in the setting of chronic and adequate heart rate control. Other studies have described impaired RV function in atrial fibrillation.[16] The role of coronary artery disease in contributing to RVD in HFpEF is uncertain. Ischemic heart disease was not more common in HFpEF patients with RVD here but was in another study.[3]

RVD and Exercise Performance in HFpEF

In HFrEF, the severity of RVD is associated with the severity of exercise intolerance.[1] Here, we show that RVD is also associated with the severity of impairment in exercise tolerance in HFpEF.

Table 4. Exercise Capacity in HFpEF Patients According to RV Function and RV–PA Coupling

	NI RV–No PH	NI RV–PH	RVD–No PH	RVD–PH	Correlation with TAPSE TAPSE/PASP	
Group N	38	31	23	45	*r*	*P*
Rest heart rate, bpm	63 (56, 73)	69 (61, 79)	72 (69, 79)	66 (60, 76)	–0.06 –0.12	0.389 0.168
Peak heart rate, bpm	107 (90, 130)	111 (93, 133)	108 (92, 127)	100 (85, 117)	0.16 0.13	0.020 0.129
Rest systolic BP, mm Hg	124 (110, 138)	134 (120, 140)	115 (104, 122)	120 (111, 140)	0.16 0.07	0.020 0.423
Peak systolic BP, mm Hg	162 (148, 190)	160 (142, 184)	131 (124, 164)	134 (120, 150)	0.34 0.37	< 0.001 < 0.001
Chronotropic index	0.5 (0.3, 0.7)	0.6 (0.3, 0.8)	0.5 (0.3, 0.6)	0.4 (0.2, 0.6)	0.14 0.17	0.040 0.054
RER	1.1 (1.1, 1.2)	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)	–0.05 0.24	0.449 0.784
pVO_2, mL·min^{-1}·kg^{-1}	12.5 (11.1, 14.9)	11.3 (10.8, 13.1)	11.5 (9.2, 13.5)	10.8 (8.8, 13.2)	0.26 0.37	<0.001 <0.001
% predicted pVO_2, %	76.9 (63.5, 84.6)	70.5 (64.7, 78.4)	57.5 (47.8, 67.4)	55.9 (48.8, 66.4)	0.39 0.44	<0.001 <0.001
VE/VCO_2 slope	31.3 (28.4, 37.5)	32.4 (29.6, 37.5)	34.8 (30.0, 38.3)	36.7 (34.1, 41.9)	–0.30 –0.34	<0.001 <0.001

In each row, the top *r* and *P* values represent the association of the variable with TAPSE and the bottom *r* and *P* values represent the association of the variable with the TAPSE/PASP ratio. BP indicates blood pressure; bpm, beats per minute; Chr, chronotropic; HFpEF, heart failure with preserved ejection fraction; pVO_2, peak oxygen consumption; RER, expiratory exchange ratio; TAPSE, tricuspid annular plane systolic excursion; and VE/VCO_2, expiratory to carbon dioxide volume ratio; otherwise as in Table 1.

*Wilcoxon rank-sum $P<0.05$ vs no PH within each RV function group. Peak $V0_2$ data missing in 1 patient and all the other variables in the table are missing in 2 patients.

In HFrEF patients with PH, the severity of ventilatory inefficiency is associated with the severity of resting RVD, pulmonary artery wedge pressure (PAWP), pulmonary vascular resistance, pulmonary dead space (V_D/V_T), and the degree of hyperventilation (P_{CO_2}).[17] However, peak exercise RVD, pulmonary vascular resistance, V_D/V_T, and P_{CO_2} were all much more strongly associated with the severity of ventilatory inefficiency. Importantly, peak exercise PAWP was not correlated with VE/VCO_2 slope, suggesting that in HFrEF, the association between VE/VCO_2 slope and RVD is mediated by excessive pulmonary vascular tone, which imposes a greater load on the RV while limiting pulmonary perfusion in association with excessive respiratory drive. Here, we show that in HFpEF, VE/VCO_2 slope was also inversely related to the severity of resting RVD. As pulmonary vascular resistance, (V_D/V_T), and P_{CO_2} were not assessed, we cannot fully determine the mechanism of ventilatory inefficiency in HFpEF patients but would speculate that they are similar to those described in HFrEF patients.

Impaired RV–PA Coupling as Assessed by the TAPSE/PASP Ratio

Because RV function is exquisitely load-dependent, it has been suggested that characterization of RV function may best be framed in relation to prevailing RV load.[7,10] Guazzi et al[7] demonstrated that the noninvasively assessed TAPSE/PASP ratio was associated with poor outcomes in a large (n=293) cohort of patients with HF, including 46 with HFpEF. In the current study, indexing TAPSE to PASP did significantly strengthen the association between several biological markers of HF severity and RV function, suggesting that this simple measure provides further insight into the severity of physiological derangements in HFpEF. The importance of interpreting RV function in the context of RV load is further supported by a recent study of HFpEF and control patients studied before and during acute administration of dobutamine. In controls, dobutamine enhanced RV inotropic function and produced pulmonary vasodilatation. In HFpEF, the inotropic effect of dobutamine was blunted but RV function improved, solely because of the effect of dobutamine on pulmonary vascular tone.[18]

RV–PA Coupling and Effect of Sildenafil

Here, sildenafil treatment did not improve RV function, exercise capacity, or ventilatory efficiency overall or in HFpEF patients with RVD and PH. This is consistent with a recent study of sildenafil therapy in patients with HFpEF and PH (invasively confirmed)[19] but in contrast to 3 chronic[20–22] and 2 acute[23,24] studies in HFrEF where sildenafil consistently improved pVO2 and VE/VCO_2 slope. Our findings are also in contrast to a study by Guazzi et al[25] in patients with HFpEF, where sildenafil had a favorable impact on symptoms, pulmonary vascular resistance, PAWP, TAPSE, diffusing lung capacity for carbon monoxide, and LV mass.

In the subset of RELAX HFpEF patients with RVD and PH, PASP was similar to the Guazzi HFpEF study and higher than most of the HFrEF studies (Tables II and III in the Data

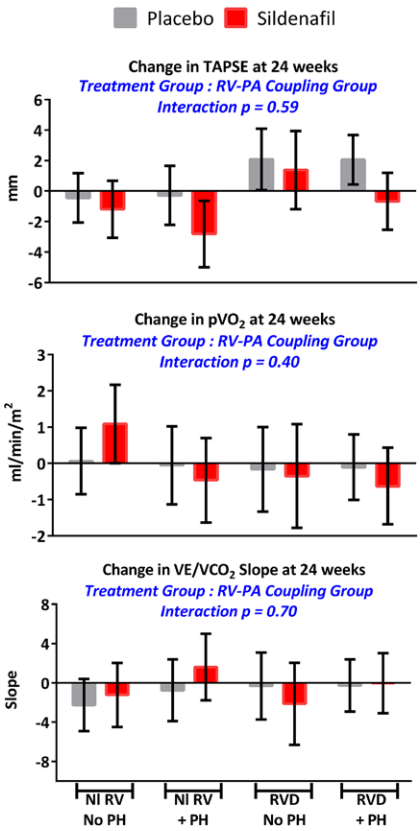

Figure. Changes in right ventricular (RV) function, exercise capacity, and ventilatory efficiency in sildenafil-treated vs placebo-treated patients according to right ventricular–pulmonary artery coupling. Bars show the least square means with 95% confidence intervals from a model that include baseline values (excluded for change in tricuspid annular plane systolic excursion [TAPSE] model), randomized treatment, RV–pulmonary arterial (PA) coupling subgroups, and the interaction between randomized treatment and RV–PA coupling subgroup. Nl indicates normal; PH, pulmonary hypertension; pVO_2, peak oxygen consumption; RVD, RV dysfunction; and VE/VCO_2, minute ventilation-carbon dioxide production relationship.

Supplement). Furthermore, cardiac index was impaired and VE/VCO_2 slope was elevated, all suggesting a component of PA hypertension in RELAX HFpEF patients with RVD and PH. Relatively selective pulmonary vasodilators can acutely increase PAWP in HF by increasing flow to a noncompliant LV.[26,27] There were adverse changes in PAWP or NT-proBNP with sildenafil in the 2 HFpEF studies where sildenafil had no benefit (Table III in the Data Supplement), but PAWP improved with sildenafil in the Guazzi study. Atrial fibrillation was an exclusion criteria in the Guazzi HFpEF study but nearly uniformly present in RELAX patients with PH and RVD. In addition, blood pressure and LV mass were higher and diabetes mellitus was less common in the Guazzi study.

Study Limitations

The limitations of post hoc analysis of clinical trial populations are well recognized, but the RELAX protocol prespecified subgroup analysis according to the presence or absence of PH.[8,11] The current study expands on this prespecified analysis by examining RV function in patients with measureable PASP. The rate at which PASP (not TAPSE) could be measured in RELAX (64%) limited our sample size but was higher than 2 other recent multicenter HFpEF trials using core laboratories where PASP was available in 48%[28] or 29%[29] of patients. Numbers in each group were small but similar to other studies of sildenafil in HFpEF.[19,25] Statistical analysis did not adjust for multiple comparisons.

Conclusions

In this cohort of patients with relatively advanced HFpEF, RVD was common and associated with a high prevalence of atrial fibrillation and more severe HF, LV diastolic dysfunction, exercise intolerance, and ventilatory inefficiency but only modest LV hypertrophy. Indexing RV function to RV load (TAPSE/PASP) improved the association of RV function and several biological markers of HF severity. Sildenafil did not improve RV function, exercise capacity, or ventilatory efficiency in HFpEF, even in patients with the most severe perturbations in RV–PA coupling.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Right ventricular (RV) dysfunction (RVD) is a poor prognostic factor in heart failure with preserved ejection fraction (HFpEF). The physiological perturbations associated with RVD or RV function indexed to load (RV–pulmonary arterial coupling) in HFpEF have not been defined. In patients with HFpEF enrolled in the Phosphodiesteas-5 Inhibition to Improve Clinical Status And Exercise Capacity in Diastolic Heart Failure (RELAX) trial of sildenafil in HFpEF, RV dysfunction (RVD) as defined by reduced tricuspid annular plane systolic excursion was common and associated with more advanced heart failure as evidenced by higher prevalence of atrial fibrillation, greater use of loop diuretics, worse renal function, and worse diastolic dysfunction. HFpEF patients with RVD had more biomarker evidence of neurohumoral activation, myocyte necrosis and fibrosis, more impaired exercise tolerance, and greater ventilatory inefficiency on cardiopulmonary exercise testing. Indexing RV function to RV load (defined by Doppler estimated pulmonary artery systolic pressure) with the use of the tricuspid annular plane systolic excursion/pulmonary artery systolic pressure ratio improved the association of RV function and several biological markers of heart failure severity. Treatment with sildenafil for 24 weeks did not improve RV function, exercise capacity, or ventilatory efficiency, even in the subset of patients with RVD and pulmonary hypertension, nearly all of whom had atrial fibrillation. These data further establish the high prevalence and physiological importance of RVD in HFpEF, provide insight into the mechanism for the association of RVD with poor outcomes in HFpEF, and underscore the substantial association between atrial fibrillation and RVD in HFpEF.

Circulation
Heart Failure

Impaired Right Ventricular–Pulmonary Arterial Coupling and Effect of Sildenafil in Heart Failure With Preserved Ejection Fraction: An Ancillary Analysis From the Phosphodiesterase-5 Inhibition to Improve Clinical Status And Exercise Capacity in Diastolic Heart Failure (RELAX) Trial

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SUPPLEMENTAL MATERIAL

Impaired Right Ventricular - Pulmonary Arterial Coupling and Effect of Sildenafil in Heart Failure with Preserved Ejection Fraction: An Ancillary Analysis From the RELAX Trial

1. Supplemental methods:

Estimation of pulmonary artery systolic pressure (PASP) and right atrial pressure (RAP) from the Heart Failure Network Core Echocardiography Manual of Operations:

PASP will be estimated from the peak tricuspid regurgitation (TR) velocity obtained with continuous wave Doppler echocardiography. It is usually obtained from the right ventricular inflow view, parasternal short-axis view or, most frequently, the apical view. After peak TR velocity is measured, systolic PA pressure is calculated as the following: *Systolic PAP = 4 x TR velocity*^{2} *+ right atrial pressure (RAP).*

RAP is estimated from the inferior vena cava (IVC) caliber response to inspiration. If the IVC dimension decreases 40% or greater with inspiration, RAP is assessed to be 5 mm Hg. If IVC caliber decreases 10-39% with inspiration, RAP is estimated to be 10 mm Hg. If the IVC dimension decreases less than 10%, RAP is assumed to be 15 mm Hg.

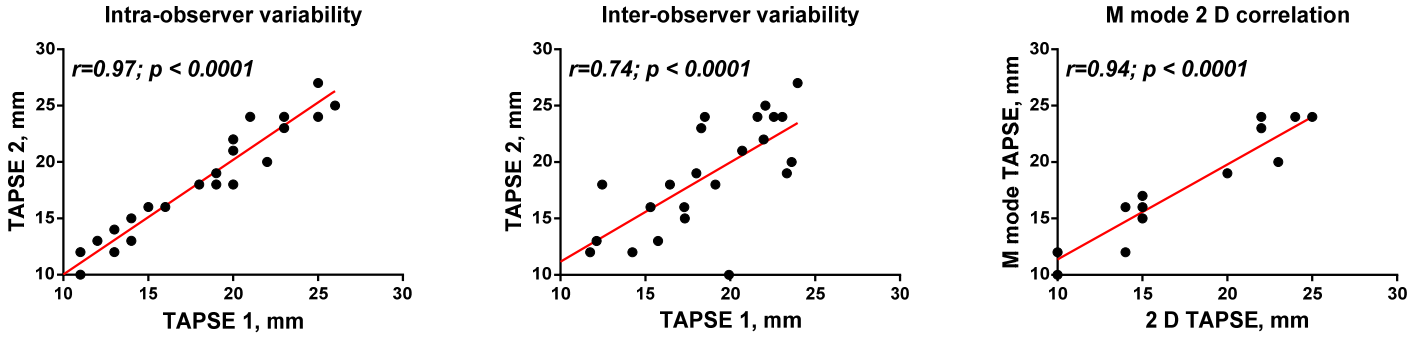
All CORE laboratory measurements in the RELAX trial were made blinded to treatment allocation.

Cardiopulmonary Exercise Testing (CPXT):

A CPXT was performed on a cycle or treadmill using specifically designed CPXT protocols and analyzed by the HFN core CPXT laboratory (Massachusetts General Hospital, Boston, MA) as previously described[1] . The VE/VCO_2 slope was determined from linear regression of VE versus VCO_2 from onset to peak exercise as measured breath by breath and averaged every 30 seconds. Age, sex, body size, and modality-predicted pVO_2 was calculated using the Wasserman equation and chronotropic index was calculated using standard formulae.

2D TAPSE

The investigator performing the offline 2D TAPSE measurements in the RELAX cohort also performed offline 2D TAPSE measurements in 500 patients (Controls and HFpEF patients) for a large observational study[2] and as part of that study assessed intra- and inter-observer variability for measures of 2D TAPSE in 25 subjects and correlation of 2D with M mode derived TAPSE for the technique in 15 subjects. Data from that analysis are shown.



Supplemental Table 1. Characteristics of RELAX patients with or without assessment of TAPSE and PASP at enrollment

	TAPSE and PASP Available	No TAPSE or No PASP	p-value
N	137	79	
Age, years	71 (65, 79)	65 (59, 71)	<0.01
Male sex	62 (45%)	50 (63%)	0.01
BMI, kg/m^2	31.5 (27.9, 36.0)	35.4 (30.8, 42.2)	<0.01
BSA, m^2	2.1 (1.9, 2.2)	2.2 (2.0, 2.5)	<0.01
Comorbidities			
Ischemic etiology	53 (39%)	31(39%)	0.94
Hypertension	114 (83%)	69 (87%)	0.42
Atrial fibrillation	77 (56%)	34 (43%)	0.06
COPD	21 (15%)	21 (27%)	0.04
Diabetes Mellitus	50 (36%)	43 (54%)	0.01
Functional status			
NYHA Class			0.79
II	65 (47%)	36 (46%)	
III	72 (53%)	43 (54%)	
MLWHFQ total score	41 (28, 57)	54 (31, 68)	0.03
Baseline Medications			
Beta Blockers	108 (79%)	56 (71%)	0.19
Digoxin	18 (13%)	4 (5%)	0.06
Calcium Blockers	43 (31%)	23 (29%)	0.73
Loop Diuretics	106 (77%)	60 (76%)	0.81
Laboratory Values			
Creatinine, mg/dl	1.1 (0.9, 1.3)	1.2 (0.8, 1.4)	0.64
Cystatin C, mg/l	1.3 (1.1, 1.8)	1.2 (1.0, 1.7)	0.16
GFR, ml/min/1.73m^2	61 (47, 77)	68 (48, 86)	0.14
Hemoglobin, g/dl	12.6 (11.9, 13.7)	13.3 (12.3, 14.3)	0.02

The p-value for dichotomous variables were derived by Pearson Chi-Square test and for continuous variables by Wilcoxon rank-sum test.

Abbreviations: Nl, normal; RV, right ventricular; RVD, RV dysfunction; PH, pulmonary hypertension; BMI, body mass index; BSA, body surface area;AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; MLWHFQ, Minnesota Living with Heart Failure Questionnaire; GFR, glomerular filtration rate

Supplemental Table 2. Entry criteria in trials of chronic sildenafil therapy in heart failure†

	HFpEF Trials			HFrEF Trials		
	RELAX[3] (n=216)	**Hoendermis[4] (n=52)**	**Guazzi[5] (n=44)**	**Guazzi 2007[6] (n=46)**	**Guazzi 2011[7] (n=45)**	**Lewis[8] (n=34)**
Effect assessed, weeks	24	12	24 & 52	12 & 24	52	12
Final Dose, mg	60 TID	60 TID	50 TID	50 BID	50 TID	75 TID
Primary Endpoint	Peak VO_2	Mean PAP	Pulmonary Function Hemodynamics, RV Function	Peak VO_2	Cardiac Structure and Function	Peak VO_2
Other Endpoints	Six Minute Walk, QOL NT-proBNP, VE/VCO_2 slope	Mean PAWP Cardiac output Peak VO_2	Lung Function LV structure Symptoms	VE/VCO_2 slope Symptoms FMD	Clinical Status Exercise Capacity	Six Minute Walk, QOL, NT-proBNP VE/VCO_2 slope
Study Setting	Multi-Center Heart Failure Clinics	Single Center Heart Failure Clinic	Two Center Hypertension Clinics	Two Center Cardiopulm Units	Two Center Cardiopulm Units	Single Center Heart Failure Clinic
Entry Criteria	HFpEF	HFpEF + Mean PAP>25 mmHg (cath)	HFpEF + PASP>40 mmHg (Echo) + Sinus Rhythm	HFrEF + Sinus Rhythm	HFrEF + E/e'>10 No Diabetes	HFrEF + Mean PAP>25 mmHg (cath)
Clinical HF diagnosis	NYHA II-IV	NYHA II-IV	Recent onset dyspnea and exercise intolerance	NYHA II-III	NYHA II-III	NYHA II-III
Ejection Fraction	≥ 50%	≥ 45%	≥ 50%	≤ 45%	<40%	<40%
Objective evidence of HF	HF Hsp in last year *or* *Invasive Hemodynamics *or* Left Atrial Enlargement + Loop Diuretic Use	Signs and Symptoms of HF	Adjudicated HF by 3 cardiologists based on Framingham criteria	Signs and Symptoms of HF	Signs and Symptoms of HF	Signs and Symptoms of HF
Screening Criteria (Must be met at Study Entry)	Peak VO_2 < 60% predicted for age and sex *and* NT-proBNP >= 400†	Mean PAP >25 mmHg *and* PAWP>15 mmHg (Cath)	PASP>40 mmHg (Echo)	None	None	Mean PAP>25 mmHg
PASP, mmHg	Overall 41 PH+RVD 51 (Echo)	52 (Cath)	53 (Cath)	33 (Echo)	37 (Echo)	NA (Mean PAP 32) (Cath)

***** At heart catheterization, elevated left ventricular end diastolic pressure (18 mmHg or greater) at rest or pulmonary artery wedge pressure at rest (15 mmHg or greater) or with exercise (25 mmHg or greater)

†Patients with an NT-proBNP(BNP) < 400(200) on screening assessment could be enrolled if they had been previously documented to have PCWP > 20 mmHG at rest or > 25 mHg with exercise within 2 weeks before/after NT-proBNP(BNP) level was < 400(200).

Abbreviations: BID, twice daily; Cath, catheterization; Cardiopulm, Cardiopulmonary; Echo, echocardiography; E/e', ratio of early trans-mitral filling velocity to early diastolic medial mitral annular tissue velocity on Doppler examination ; FMD, flow mediated vasodilatation; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; Hsp, hospitalization; NA, not available; NYHA, New York Heart Association; Peak VO2, peak oxygen consumption at cardiopulmonary exercise test; PAP, pulmonary artery pressure; PASP, pulmonary artery systolic pressure; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; QOL, quality of life; RV, right ventricular; RVD, right ventricular dysfunction; TID, three times daily

Supplemental Table 3. Baseline characteristics of patients in trials of chronic sildenafil therapy in heart failure†

	HFpEF Studies			HFrEF Studies		
	RELAX[3] (n=216)	**Hoendermis[4] (n=52)**	**Guazzi[5] (n=44)**	**Guazzi 2007[6] (n=46)**	**Guazzi 2011[7] (n=45)**	**Lewis[8] (n=34)**
Age-yr	69	74	73	63	61	58
Female sex – %	48%	71%	20%	0%	0%	85%
Body Mass Index – kg/m^2	33	29	31	23	28	NA
Functional measures						
NYHA class III	53%	79%	NA	NA	50%	38%
Peak VO_2, ml/kg/min	11.7	11.4	Not Done	15	12.8	11.2
VE/VCO_2 slope	Overall 33.6 PH+RVD 36.7	36.7	Not Done	35	35.3	43
Physical examination						
Systolic BP - mmHg	126	143	150	126	110	NA
Medical History and Medications						
History of atrial fibrillation	51%	62%	0%	0%	NA	NA
Atrial fibrillation on ECG	37%	50%	0%	0%	15%	3%
Diabetes mellitus	43%	35%	16%	NA	0%	23%
Any diuretic	86%	90%	77%	NA	NA	100%
ACE/ARB	70%	75%	95%	NA	87%/24%	83%
Beta blocker	76%	87%	82%	NA	84%	97%
Laboratory variables						
NT-proBNP – pg/ml	700	1087	NA	NA	2070	2000
Creatinine, mg/dl	1.12	1.12	NA	NA	NA	NA
Echocardiographic variables						
Ejection fraction - %	60	58	60	31	30	34
Medial E/e'	Overall 16 PH+RVD 22	13	17	Not Done	13	Not Done
LV Mass Index	77	NA	167	NA	146	Not Done
TAPSE	Overall 18 PH+RVD 13	19	11	Not Done	Not Done	RV EF =34%
Hemodynamic variables						
PA systolic Pressure, mmHg	Overall 41 PH+RVD 51 (Echo)	52 (Cath)	53 (Cath)	33 (Echo)	37 (Echo)	MEAN PAP 32 (Cath)
RA mean Pressure, mmHg	Not Done	9	23	Not Done	Not Done	7
PA mean Pressure, mmHg	Not Done	35	38	Not Done	Not Done	32
PAWP, mmHg	Not Done	20	22	Not Done	Not Done	18
Pulmonary vascular resistance (PVR) , WU	Not Done	2.6	3.6	Not Done	Not Done	4.4
Key Significant Effects	No Benefit Worse Creatinine NT-proBNP, Endothelin, uric acid	No Benefit PAWP ↓ in placebo but ↔ in sildenafil	Improved PASP, PVR, PAWP, TAPSE, DLCO	Improved pVO_2, VE/VCO_2 slope, PASP, V_D/V_T, FMD, Ergoreflex	Improved pVO_2, VE/VCO_2 slope, PASP, EF, LV mass	Improved pVO_2, VE/VCO_2 slope, PVR, Symptoms

† When data in all patients not reported, data estimated as weighted averages from values in each treatment group

Abbreviations: ACE/ARB; angiotensin converting enzyme inhibitor or angiotensin receptor antagonist; BP, blood pressure; DLCO, diffusing capacity for carbon monoxide; EF, ejection fractio; LAVI, left atrial

volume/body surface area; NA, not available; TAPSE, tricuspid annular plane systolic excursion, V_D/V_T; pulmonary dead space relative to tidal volume; Otherwise as in Supplemental table 2.

Supplemental References

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