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

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Abstract

Background—Right ventricular (RV) dysfunction (RVD) is a poor prognostic factor in heart failure (HF) with preserved ejection fraction (HFpEF). The physiologic 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 RELAX trial, physiologic 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 (PASP)) ratio. Prevalence of atrial fibrillation and diuretic use, NT-proBNP 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 (pVO_2) 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/PASP ratio. Compared to placebo, at 24 weeks, TAPSE decreased and pVO_2 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, pVO_2 or VE/VCO_2 in patients with PH *and* RVD.

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

Clinical Trial Registration—http://www.clinicaltrials.gov. Unique identifier: NCT00763867.

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Keywords

heart failure; hypertension; pulmonary; exercise; diastole

In patients with heart failure 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 heart failure (HF) with preserved EF (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 to have important prognostic implications in HF and the TAPSE/PASP ratio is proposed as a non-invasive index of RV-pulmonary arterial (PA) coupling in HF.[7] However, the physiologic 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 RELAX trial of sildenafil in HFpEF, hypothesizing that RVD and incrementally, adverse RV-PA coupling is associated with more severe HF, greater activation of biomarkers reflective of neurohumoral activation, myocardial necrosis, inflammation and fibrosis, reduced exercise capacity (peak oxygen uptake, 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 due to the 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–IV HF symptoms, EF ≥50% and objective evidence of HF (at least one of: 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 less than or equal to 60% of the age/sex predicted normal value *and* an elevated NT-proBNP (≥ 400 pg/mL) or BNP (≥200 pg/mL) level, or previously documented elevated LV filling pressures when BNP 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 HFN core echocardiography laboratory (Mayo Clinic, Rochester, MN) as previously described.[8, 11] PASP was calculated using standard methods as outlined in the Supplemental Methods.

The RELAX echocardiographic protocol did not include assessment of RV function. Thus, TAPSE was measured offline (blinded to treatment group) from the apical four chamber view by subtracting the distance between the lateral tricuspid leaflet annular insertion and sector apex in systole from the distance between the two in diastole. We and others have previously validated this technique[2, 12] and the normal values, clinical correlates and prognostic implications of 2-D TAPSE measured offline in 500 patients with HFpEF have been defined.[2] Intra- and Inter-observer variability for 2D TAPSE and the correlation between 2-D and M-mode measured TAPSE have been defined[2] (Supplemental Figure 1).

While 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 (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 and further described in the Supplemental Methods.[8, 11].

Biomarkers

Plasma biomarkers of neurohumoral activation (NT-proBNP, aldosterone, endothelin-1), cardiac injury (troponin I), systemic inflammation (c-reactive protein (CRP)), renal function (cystatin C), and fibrosis (procollagen III n-terminal peptide [NT-procollagen III), galectin 3, c-telopeptide for type I collagen (CITP)) 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 mmHg) to define four sub-groups (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 Cochran Armitage trend test. Differences between patients with or without PH within each RV function subgroup were assessed with Wilcoxon rank sum or Pearson chi-square test. Spearman correlations were used to determine associations between RV function (TAPSE) or RV-PA coupling (TAPSE/PASP) and continuous physiologic parameters. To further determine if associations between physiologic variables and the TAPSE/PASP ratio were influenced by both RV function and pulmonary pressures, we determined if 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 vs. placebo adjusting for baseline value as well as RV-PA coupling group. Since RV-PA coupling group uses baseline TAPSE in the definition, baseline TAPSE was not included in the model for change

in TAPSE. Additionally, an interaction term for treatment allocation and RV-PA coupling subgroup was included in the aforementioned models to determine if change with treatment varied by RV-PA coupling subgroup.

Data are presented as median (25^{th}, 75^{th} 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; Supplemental Table 1).

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 two groups with normal RV function but the TAPSE/PASP ratio was lower in patients with normal RV function and PH when compared to normal RV function and No PH (Table 1). Median TAPSE was similar in the two RVD groups but the TAPSE/PASP ratio was lower in patients with RVD and PH when compared to 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 RV dysfunction and RV-PA coupling

The severity of neurohumoral activation (NT-proBNP, aldosterone and endothelin-1), myocardial necrosis (troponin I) and fibrosis (NT-procollagen III and CITP) increased with decreases in TAPSE or the TAPSE/PASP ratio (Table 2). Adjusting for TAPSE, PASP was still associated with NT-proBNP, endothelin and NT-procollagen III ($p<0.05$ for all) but not aldosterone, troponin or CITP. Levels of CRP and galectin-3 were not associated with TAPSE or the TAPSE/PASP ratio.

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 while 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 EF 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 ($p=0.25$). While 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, BMI, hemoglobin and chronotropic index, pVO_2 still declined across the RV-PA coupling subgroups ($p=0.004$).

Effect of Sildenafil vs 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 to 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 1).

Adjusting for baseline values, change in pVO_2 was similar in sildenafil (−0.11 [−0.55 to 0.33] ml/kg/min) and placebo (−0.07 [−0.51 to 0.36] ml/kg/min; p=0.90) treated patients. Change in VE/VCO_2 slope was also similar in sildenafil (−0.24 [−1.40 to 1.91]) and placebo (−0.57 [−1.70 to 0.56]; p=0.69) treated 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 1).

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 biologic 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 physiologic 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 RV dysfunction 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 2D[2] or m-mode[4] derived TAPSE. A catheterization laboratory-based study found that 33% of HFpEF patients had RVD (RV fractional area change (FAC) <35%)[3]. In contrast, in the TOPCAT trial echocardiographic sub-study, only 4% of patients had a reduced RV FAC[15]. As recently reviewed, in most HFpEF studies, RVD was associated with worse clinical outcomes[10] but the physiologic phenotyping of patients with RVD was limited.

Correlates of RV dysfunction in HFpEF

This study cannot establish the mechanism(s) driving RVD in HFpEF. Chronic RV pressure overload due to 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]

RV dysfunction 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.

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 (pCO_2).[17] However, *peak exercise* RVD, pulmonary vascular resistance, V_D/V_T and pCO_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 pCO_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

As 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 demonstrated that the non-invasively assessed TAPSE/PASP ratio was associated with poor outcomes in a large (n=293) cohort of patients with HF, including 46 with HFpEF[7]. 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 physiologic 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 due to 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 three chronic[20–22] and two 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 in patients with HFpEF[25] where sildenafil had a favorable impact on symptoms, pulmonary vascular resistance, PAWP, TAPSE, diffusing lung capacity for carbon monoxide (DLCO) 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 (Supplemental table 2 and 3). Further, cardiac index was impaired and VE/VCO_2 slope was elevated, all suggesting a component of pulmonary arterial hypertension in RELAX HFpEF patients with RVD and PH. Relatively selective pulmonary vasodilators can acutely increase PAWP in HF by increasing flow to a non-compliant LV.[26, 27] There were adverse changes in PAWP or NT-proBNP with sildenafil in the two HFpEF studies where sildenafil had no benefit (Supplemental Table 3), 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. Additionally, blood pressure and LV mass were higher and diabetes 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 pre-specified sub-group analysis according to the presence or absence of PH.[8, 11] The current study expands upon this pre-specified 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 two 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 biologic 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Iglesias-Garriz I, Olalla-Gomez C, Garrote C, Lopez-Benito M, Martin J, Alonso D, Rodriguez MA. Contribution of right ventricular dysfunction to heart failure mortality: A meta-analysis. Rev Cardiovasc Med. 2012; 13:e62–e69. [PubMed: 23160163]
2. Mohammed SF, Hussain I, AbouEzzeddine OF, Takahama H, Kwon SH, Forfia P, Roger VL, Redfield MM. Right ventricular function in heart failure with preserved ejection fraction: A community based study. Circulation. 2014; 130:2310–2320. [PubMed: 25391518]
3. Melenovsky V, Hwang SJ, Lin G, Redfield MM, Borlaug BA. Right heart dysfunction in heart failure with preserved ejection fraction. Eur Heart J. 2014; 35:3452–3462. [PubMed: 24875795]
4. Shah SJ, Katz DH, Selvaraj S, Burke MA, Yancy CW, Gheorghiade M, Bonow RO, Huang CC, Deo RC. Phenomapping for novel classification of heart failure with preserved ejection fraction. Circulation. 2014; 131:269–279. [PubMed: 25398313]
5. Bursi F, McNallan SM, Redfield MM, Nkomo VT, Lam CS, Weston SA, Jiang R, Roger VL. Pulmonary pressures and death in heart failure: A community study. J Am Coll Cardiol. 2012; 59:222–231. [PubMed: 22240126]

6. Kjaergaard J, Akkan D, Iversen KK, Kjoller E, Kober L, Torp-Pedersen C, Hassager C. Prognostic importance of pulmonary hypertension in patients with heart failure. Am J Cardiol. 2007; 99:1146–1150. [PubMed: 17437745]
7. Guazzi M, Bandera F, Pelissero G, Castelvecchio S, Menicanti L, Ghio S, Temporelli PL, Arena R. Tricuspid annular plane systolic excursion and pulmonary arterial systolic pressure relationship in heart failure: An index of right ventricular contractile function and prognosis. Am J Physiol Heart Circ Physiol. 2013; 305:H1373–H1381. [PubMed: 23997100]
8. Redfield MM, Chen HH, Borlaug BA, Semigran MJ, Lee KL, Lewis G, LeWinter MM, Rouleau JL, Bull DA, Mann DL, Deswal A, Stevenson LW, Givertz MM, Ofili EO, O'Connor CM, Felker GM, Goldsmith SR, Bart BA, McNulty SE, Ibarra JC, Lin G, Oh JK, Patel MR, Kim RJ, Tracy RP, Velazquez EJ, Anstrom KJ, Hernandez AF, Mascette AM, Braunwald E. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: A randomized clinical trial. JAMA. 2013; 309:1268–1277. [PubMed: 23478662]
9. Forfia PR, Borlaug BA. Letter by forfia and borlaug regarding article, "pulmonary hypertension in heart failure with preserved ejection fraction: A target of phosphodiesterase-5 inhibition in a 1-year study". Circulation. 2012; 125:e408. author reply e409–410. [PubMed: 22371450]
10. Chatterjee NA, Steiner J, Lewis GD. It is time to look at heart failure with preserved ejection fraction from the right side. Circulation. 2014; 130:2272–2277. [PubMed: 25391521]
11. Redfield MM, Borlaug BA, Lewis GD, Mohammed SF, Semigran MJ, Lewinter MM, Deswal A, Hernandez AF, Lee KL, Braunwald E. Phosphdiesterase-5 inhibition to improve clinical status and exercise capacity in diastolic heart failure (relax) trial: Rationale and design. Circ Heart Fail. 2012; 5:653–659. [PubMed: 22991405]
12. Qureshi MY, Eidem BW, Reece CL, O'Leary PW. Two-dimensional measurement of tricuspid annular plane systolic excursion in children: Can it substitute for an m-mode assessment? Echocardiography. 2015; 32:528–534. [PubMed: 25048993]
13. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: A report from the american society of echocardiography endorsed by the european association of echocardiography, a registered branch of the european society of cardiology, and the canadian society of echocardiography. J Am Soc Echocardiogr. 2010; 23:685–713. [PubMed: 20620859]
14. Mohammed SF, Borlaug BA, McNulty S, Lewis GD, Lin G, Zakeri R, Semigran MJ, LeWinter M, Hernandez AF, Braunwald E, Redfield MM. Resting ventricular-vascular function and exercise capacity in heart failure with preserved ejection fraction: A relax trial ancillary study. Circ Heart Fail. 2014; 7:580–589. [PubMed: 24833648]
15. Shah AM, Claggett B, Sweitzer NK, Shah SJ, Anand IS, O'Meara E, Desai AS, Heitner JF, Li G, Fang J, Rouleau J, Zile MR, Markov V, Ryabov V, Reis G, Assmann SF, McKinlay SM, Pitt B, Pfeffer MA, Solomon SD. Cardiac structure and function and prognosis in heart failure with preserved ejection fraction: Findings from the echocardiographic study of the treatment of preserved cardiac function heart failure with an aldosterone antagonist (topcat) trial. Circ Heart Fail. 2014; 7:740–751. [PubMed: 25122186]
16. Alam M, Samad BA, Hedman A, Frick M, Nordlander R. Cardioversion of atrial fibrillation and its effect on right ventricular function as assessed by tricuspid annular motion. Am J Cardiol. 1999; 84:1256–1258. A1258. [PubMed: 10569340]
17. Lewis GD, Shah RV, Pappagianopolas PP, Systrom DM, Semigran MJ. Determinants of ventilatory efficiency in heart failure: The role of right ventricular performance and pulmonary vascular tone. Circ Heart Fail. 2008; 1:227–233. [PubMed: 19808296]
18. Andersen MJ, Hwang SJ, Kane GC, Melenovsky V, Olson TP, Fetterly K, Borlaug BA. Enhanced pulmonary vasodilator reserve and abnormal right ventricular: Pulmonary artery coupling in heart failure with preserved ejection fraction. Circ Heart Fail. 2015; 8:542–550. [PubMed: 25857307]
19. Hoendermis ES, Liu LC, Hummel YM, van der Meer P, de Boer RA, Berger RM, van Veldhuisen DJ, Voors AA. Effects of sildenafil on invasive haemodynamics and exercise capacity in heart failure patients with preserved ejection fraction and pulmonary hypertension: A randomized controlled trial. Eur Heart J. 2015; 36:2565–2573. [PubMed: 26188003]

20. Lewis GD, Shah R, Shahzad K, Camuso JM, Pappagianopoulos PP, Hung J, Tawakol A, Gerszten RE, Systrom DM, Bloch KD, Semigran MJ. Sildenafil improves exercise capacity and quality of life in patients with systolic heart failure and secondary pulmonary hypertension. Circulation. 2007; 116:1555–1562. [PubMed: 17785618]
21. Guazzi M, Samaja M, Arena R, Vicenzi M, Guazzi MD. Long-term use of sildenafil in the therapeutic management of heart failure. J Am Coll Cardiol. 2007; 50:2136–2144. [PubMed: 18036451]
22. Guazzi M, Vicenzi M, Arena R, Guazzi MD. Pde5 inhibition with sildenafil improves left ventricular diastolic function, cardiac geometry, and clinical status in patients with stable systolic heart failure: Results of a 1-year, prospective, randomized, placebo-controlled study. Circ Heart Fail. 2011; 4:8–17. [PubMed: 21036891]
23. Guazzi M, Tumminello G, Di Marco F, Fiorentini C, Guazzi MD. The effects of phosphodiesterase-5 inhibition with sildenafil on pulmonary hemodynamics and diffusion capacity, exercise ventilatory efficiency, and oxygen uptake kinetics in chronic heart failure. J Am Coll Cardiol. 2004; 44:2339–2348. [PubMed: 15607396]
24. Lewis GD, Lachmann J, Camuso J, Lepore JJ, Shin J, Martinovic ME, Systrom DM, Bloch KD, Semigran MJ. Sildenafil improves exercise hemodynamics and oxygen uptake in patients with systolic heart failure. Circulation. 2007; 115:59–66. [PubMed: 17179022]
25. Guazzi M, Vicenzi M, Arena R, Guazzi MD. Pulmonary hypertension in heart failure with preserved ejection fraction: A target of phosphodiesterase-5 inhibition in a 1-year study. Circulation. 2011; 124:164–174. [PubMed: 21709061]
26. Boilson BA, Schirger JA, Borlaug BA. Caveat medicus! Pulmonary hypertension in the elderly: A word of caution. Eur J Heart Fail. 2010; 12:89–93. [PubMed: 20023048]
27. Semigran MJ, Cockrill BA, Kacmarek R, Thompson BT, Zapol WM, Dec GW, Fifer MA. Hemodynamic effects of inhaled nitric oxide in heart failure. J Am Coll Cardiol. 1994; 24:982–988. [PubMed: 7930234]
28. Shah AM, Shah SJ, Anand IS, Sweitzer NK, O'Meara E, Heitner JF, Sopko G, Li G, Assmann SF, McKinlay SM, Pitt B, Pfeffer MA, Solomon SD. Cardiac structure and function in heart failure with preserved ejection fraction: Baseline findings from the echocardiographic study of the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial. Circ Heart Fail. 2014; 7:104–115. [PubMed: 24249049]
29. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, Shi V, Bransford T, Takeuchi M, Gong J, Lefkowitz M, Packer M, McMurray JJ. The angiotensin receptor neprilysin inhibitor lcz696 in heart failure with preserved ejection fraction: A phase 2 double-blind randomised controlled trial. Lancet. 2012; 380:1387–1395. [PubMed: 22932717]

Clinical Perspective

Right ventricular (RV) dysfunction (RVD) is a poor prognostic factor in heart failure (HF) with preserved ejection fraction (HFpEF). The physiologic perturbations associated with RVD or RV function indexed to load (RV-pulmonary arterial (PA) coupling) in HFpEF have not been defined. In patients with HFpEF enrolled in the RELAX trial of sildenafil in HFpEF, right ventricular (RV) dysfunction (RVD) as defined by reduced tricuspid annular plane systolic excursion (TAPSE) 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 and greater ventilatory inefficiency on cardiopulmonary exercise testing. Indexing RV function to RV load (defined by Doppler estimated pulmonary artery systolic pressure (PASP)) with the use of the TAPSE/PASP ratio improved the association of RV function and several biologic 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* pulmonary hypertension, nearly all of whom had atrial fibrillation. These data further establish the high prevalence and physiologic 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.

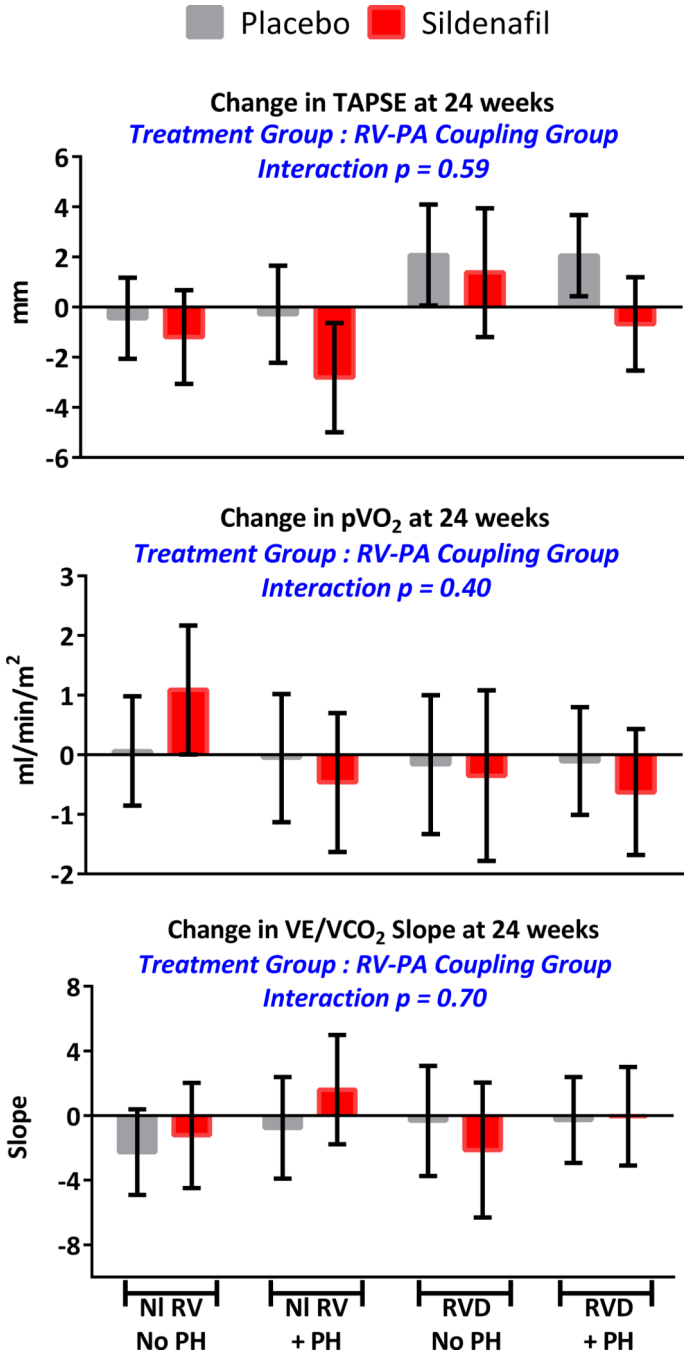

Figure 1. Changes in RV function, exercise capacity and ventilatory efficiency in Sildenafil vs placebo treated patients according to right ventricular – pulmonary artery coupling

Bars show the least square means with 95% confidence intervals from a model which include baseline values (excluded for change in TAPSE model), randomized treatment, RV-PA coupling subgroups and the interaction between randomized treatment and RV-PA coupling subgroup. Abbreviations: Nl, normal; RV, right ventricular; RVD, RV dysfunction; PH, pulmonary hypertension; TAPSE, tricuspid annular plane systolic excursion; pVO_2, peak oxygen consumption; VE/VCO_2, expiratory to carbon dioxide volume ratio

Table 1

Baseline characteristics according to RV function and RV-PA coupling

	Nl RV - No PH	Nl 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, mmHg	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/mmHg	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, years	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 etiology	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

	Nl RV - No PH	Nl RV - PH	RVD - No PH	RVD - PH	p value‡
N	**38**	**31**	**23**	**45**	
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

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

‡p represents the p value for the Spearman correlation between continuous variables and the TAPSE/PASP ratio or the Cochran Armitrage trend test across groups for dichotomous variables.

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

Table 2

Biomarker profile according to RV function and RV-PA coupling

	Nl RV - No PH	Nl 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) N=36	8.9 (4.3, 17.8)	9.9 (6.1, 21.9) N=22	12.0 (8.4, 26.5)	−0.26 −0.32	<0.001 <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) N=35	13.4 (11.0, 16.8) N=31	15.5 (12.2, 19.1) N=22	15.1 (11.5, 23.1) N=42	−0.10 −0.13	0.144 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.

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

Unless otherwise indicated, all variables have 1 missing value

Abbreviations: NT-proBNP, n-terminal pro-brain natriuretic peptide; CRP, c-reactive protein, NT-procollagen III, n-terminal peptide of procollagen III; CITP, c-telopeptide for type I collagen; otherwise as in Table 1.

Table 3

Echocardiographic features according to RV function and RV-PA coupling

	Nl RV - No PH	Nl 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) N=30	78.5 (62.1, 96.5) N=25	65.6 (55.4, 85.6) N=17	79.4 (64.0, 99.5) N=31	−0.01 −0.14	0.878 0.168
RWT	0.38 (0.34, 0.45) N=30	0.44 (0.36, 0.48) N=25	0.42 (0.40, 0.47) N=17	0.42 (0.38, 0.50) N=31	−0.23 −0.19	0.004 0.052
Ejection Fraction, %	62 (57, 66) N=38	60 (58, 65) N=31	58 (54, 61) N=23	58 (54, 65) N=45	0.15 0.16	0.031 0.059
E/A ratio	1.0 (0.8, 1.7) N=34	1.6 (1.0, 2.0) N=22	1.9 (1.1, 2.8) N=8	3.3 (2.0, 4.0) * N=23	−0.37 −0.67	<0.001 <0.001
E/e' ratio	13.3 (10.0, 17.5) N=37	20.0 (15.7, 30.0) * N=27	16.9 (13.3, 20.0) N=22	22.0 (14.3, 30.0) N=39	−0.22 −0.38	0.002 <0.001
Deceleration time, ms	198 (177, 249) N=38	178 (156, 211) N=30	161 (145, 194) N=23	164 (142, 212) N=37	0.26 0.33	<0.001 <0.001
LAVi, ml/m2	40.3 (34.8, 46.6) N=29	48.0 (40.4, 58.2) N=24	51.4 (36.8, 62.5) N=15	54.0 (43.0, 71.1) N=34	−0.33 −0.27	<0.001 0.006
Cardiac Index, ml/min/m^2	2627 (2218, 3021) N=36	2650 (2061, 2830) N=24	2149 (1852, 2403) N=21	2282 (2057, 2751) N=38	0.14 0.17	0.068 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.

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

Abbreviations: LVEDd, left ventricular end-diastolic dimension; LV, left ventricular; RWT, relative wall thickness; LAVi, left atrial volume index; ; otherwise as in Table 1.

Table 4

Exercise capacity in HFpEF patients according to RV function and RV-PA coupling

	Nl RV - No PH	Nl 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, mmHg	124 (110, 138)	134 (120, 140)	115 (104, 122)	120 (111, 140)	0.16 0.07	0.020 0.423
Peak Systolic BP, mmHg	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/kg	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.

*Wilcoxon rank-sum $p < 0.05$ vs No PH within each RV function group. Peak VO_2 data missing in one patient and all of the other variables in the table are missing in two patients.

Abbreviations: bpm, beats per minute; BP, blood pressure; Chr, chronotropic; RER, respiratory exchange ratio; pVO_2, peak oxygen consumption; RER, expiratory exchange ratio; VE/VCO_2, expiratory to carbon dioxide volume ratio