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RESEARCH LETTER

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Ventricular interdependent phenotype of mixed Cpc-pulmonary hypertension and HFpEF with normal left atrium: Impact on CPET metrics and clinical outcomes

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Abstract

Among 45 CpcPH/heart failure with preserved ejection fraction participants, 11 with normal left atrium (compared to 34 with abnormal left atrium, $p < 0.05$ for all) had low left ventricle (LV) transmural pressure (2.9 ± 2.4 vs. 6.2 ± 2.9 mmHg), and increased right ventricle (RV):LV ratio (2.41 ± 1.09 vs. 1.46 ± 0.66) and interventricular septal angle (149 ± 8 vs. 136 ± 10), indicating exaggerated ventricular interdependence from a dilated RV.

KEYWORDS

Cpc-PH, HFpEF, invasive exercise hemodynamics, pericardial restraint, ventricular interdependence

INTRODUCTION

Combined pre- and post-capillary pulmonary hypertension (Cpc-PH) occurs due to combination of left heart disease and pulmonary vascular disease.[1–3] In addition to these two predominant pathophysiologies, a component of pericardial restraint may lead to ventricular interdependence in CpcPH.[2–4] More specifically, this exaggerated ventricular interdependence occurs due to a dilated right ventricle (RV) compressing left ventricle (LV), which results in poor LV filling, increased LV wall stress and elevated left-heart pressures (left ventricular end-diastolic pressure [LVEDP], left atrial (LA) pressure, pulmonary artery wedge pressure [PAWP]).[3,4]

Goal of the current study is to define features of ventricular interdependent CpcPH phenotype with heart failure

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with preserved ejection fraction (HFpEF) and minimal LA dysfunction. Our hypothesis is that while the majority of CpcPH patients have left heart disease with a dysfunctional LA, a minority of patients with minimal LA dysfunction develop elevated left-sided pressures and Cpc-PH physiology due to exaggerated ventricular interdependence.[3] Compared to the abnormal LA phenotype (traditional CpcPH), these patients with normal LA (ventricular interdependence) could benefit from different treatments that may relieve RV wall stress and interdependence among the two ventricles.[5]

METHODS

In a cohort of participants ($n = 190$) undergoing invasive exercise hemodynamic study with cardiopulmonary exercise test (CPET), we identified 45 participants with CpcPH based on rest hemodynamics (per 2022 ESC/ERS guidelines[1]) and complete echocardiographic data. Cardiac magnetic resonance imaging (MRI) data was collected in a subset of 20 participants (6 normal LA, 14 abnormal LA group).[6] The participants with minimal LA dysfunction were labeled as "*normal LA group*" ($n = 11$), based on LA volume index (LAVI) <40 mL/m^2 and average E/E' (ratio of early diastolic mitral blood flow velocity to annular velocity) <10. Rest of the participants ($n = 34$) were labeled as "*abnormal LA group*," based on LAVI ≥40 mL/m^2 or average E/E' ≥10.

Physiologically, ventricular interdependence was determined with hemodynamics-based left ventricular transmural pressure[4] (LV-TMP; using right atrial pressure [RAP] as a surrogate for pericardial pressure, LV-TMP = PAWP-RAP) and cardiac imaging-based quantification of increased interventricular septal flattening (echocardiogram-based left ventricular eccentricity index in systole,[4] and cardiac MRI-based septal angle and RV:LV ratio).[7] Notably, the term "transmural pressure" (LV-TMP) in this study is related to ventricular interactions,[4] not heart-lung interactions.

Exercise hemodynamics with CPET were performed on a semi-recumbent stationary ergometer, as previously described.[6,8–10] Per guidelines, PAWP at rest was confirmed with a blood sample saturation >90%.[1,11] In obese participants with significant respirophasic changes, mean PAWP was reported at rest, averaged over 3–5 respiratory cycles (not end-expiratory) to avoid mis-diagnosis of pre-capillary PH or no PH as CpcPH/HFpEF.[1,12] Baseline characteristics were presented as mean ± *SD* for continuous variables and as frequencies and proportions (%) for categorical variables. Comparisons among groups were conducted using unpaired *t*-test for continuous variables, and χ^2 statistic or Fisher exact test for categorical data, as appropriate.

RESULTS

Baseline clinical features of abnormal ($n = 34$) versus normal ($n = 11$) LA participants were: age (years) 68 ± 13 versus 64 ± 16 ($p = 0.22$), female sex 62% versus 55% ($p = 0.34$), and BMI (Kg/m^2) 33 ± 7 versus 37 ± 9 ($p = 0.08$). Comorbidity burden was similar: hypertension (82% vs 91%, $p = 0.25$), diabetes (26% vs .36%, $p = 0.27$), atrial fibrillation (53% vs. 27%, $p = 0.07$), obstructive sleep apnea (47% vs. 27%, $p = 0.12$), chronic obstructive pulmonary disease: COPD (12% vs. 27%, $p = 0.11$), coronary artery disease (38% vs. 18%, $p = 0.11$), interstitial lung disease: ILD (3% vs. 9%, $p = 0.20$), and H_2FpEF score 6.0 ± 2.1 versus 5.0 ± 1.4 ($p = 0.07$). BNP (pg/mL) levels were 266 ± 219 versus 153 ± 198 ($p = 0.08$). Both groups had similar comorbidity burden and high H_2FpEF scores with >80% probability of HFpEF.[13]

Key metrics are shown in Figure 1. Echocardiographic features (abnormal vs normal LA groups) included metrics of ventricular interdependence: end-systolic eccentricity index 1.02 ± 0.31 versus 1.14 ± 0.39 ($p = 0.16$) and diastolic RV:LV ratio 0.90 ± 0.30 versus 0.94 ± 0.19 ($p = 0.35$). Left heart diastolic metrics included: medial E' (cm/s) 6.0 ± 1.8 versus 9.8 ± 3.8 ($p < 0.01$), lateral E' (cm/s) 7.6 ± 2.5 versus 9.8 ± 3.5 ($p = 0.02$), average E/E' 16.0 ± 6.7 versus 7.2 ± 1.7 ($p < 0.01$), E/A ratio 1.8 ± 1.3 versus 1.1 ± 0.4 ($p = 0.10$), along with atrial size metrics: LAVI (mL/m^2) 45.6 ± 16.6 versus 28.4 ± 7.8 ($p < 0.01$) and right atrial area (cm^2) 21.9 ± 9.3 versus 23.2 ± 11.4 ($p = 0.35$). Ventricular function metrics included: tricuspid annular plane systolic excursion (TAPSE, mm) 18.4 ± 5.2 versus 21.7 ± 6.8 ($p = 0.07$), TAPSE/PASP (pulmonary artery systolic pressure) ratio (mm/mmHg) 0.36 ± 0.19 versus 0.53 ± 0.34 ($p = 0.05$) and LV ejection fraction (%) 60 ± 5 versus 64 ± 5 ($p = 0.06$). There was a trend towards increased ventricular interdependence (eccentricity index) and better RV:PA coupling in the normal LA group.

Cardiac MRI features (abnormal [$n = 14$] vs. normal LA [$n = 6$] groups) included metrics of ventricular interdependence: interventricular septal angle 136 ± 10 versus 146 ± 8 ($p = 0.03$) and RV:LV ratio in systole 1.46 ± 0.66 versus 2.41 ± 1.09 ($p = 0.04$). Indexed LA volumes (mL/m^2) were 60.8 ± 24.6 versus 31.6 ± 11.3 (diastole, $p = 0.02$) and 46.2 ± 21.9 versus 21.4 ± 13.0 (systole, $p = 0.03$), LA EF (%) was 25.7 ± 14.8 versus 36.5 ± 18.7 ($p = 0.14$). LV mass index (g/m^2) 58.3 ± 14.3 versus 44.9 ± 5.7 ($p = 0.03$) and epicardial fat (g) 48.3 ± 13.0 versus 49.1 ± 16.3 ($p = 0.46$). Compared to abnormal LA group, normal LA group had higher septal angle and RV:LV ratio, indicating exaggerated ventricular interdependence.

Rest hemodynamics (abnormal vs. normal LA groups) revealed: RAP (mmHg) 14 ± 4 versus 16 ± 5 ($p = 0.10$), mean pulmonary artery pressure (mPAP, mmHg) 39 ± 7 versus 39 ± 13 ($p = 0.39$), PAWP (mmHg) 20 ± 4 versus 19 ± 3

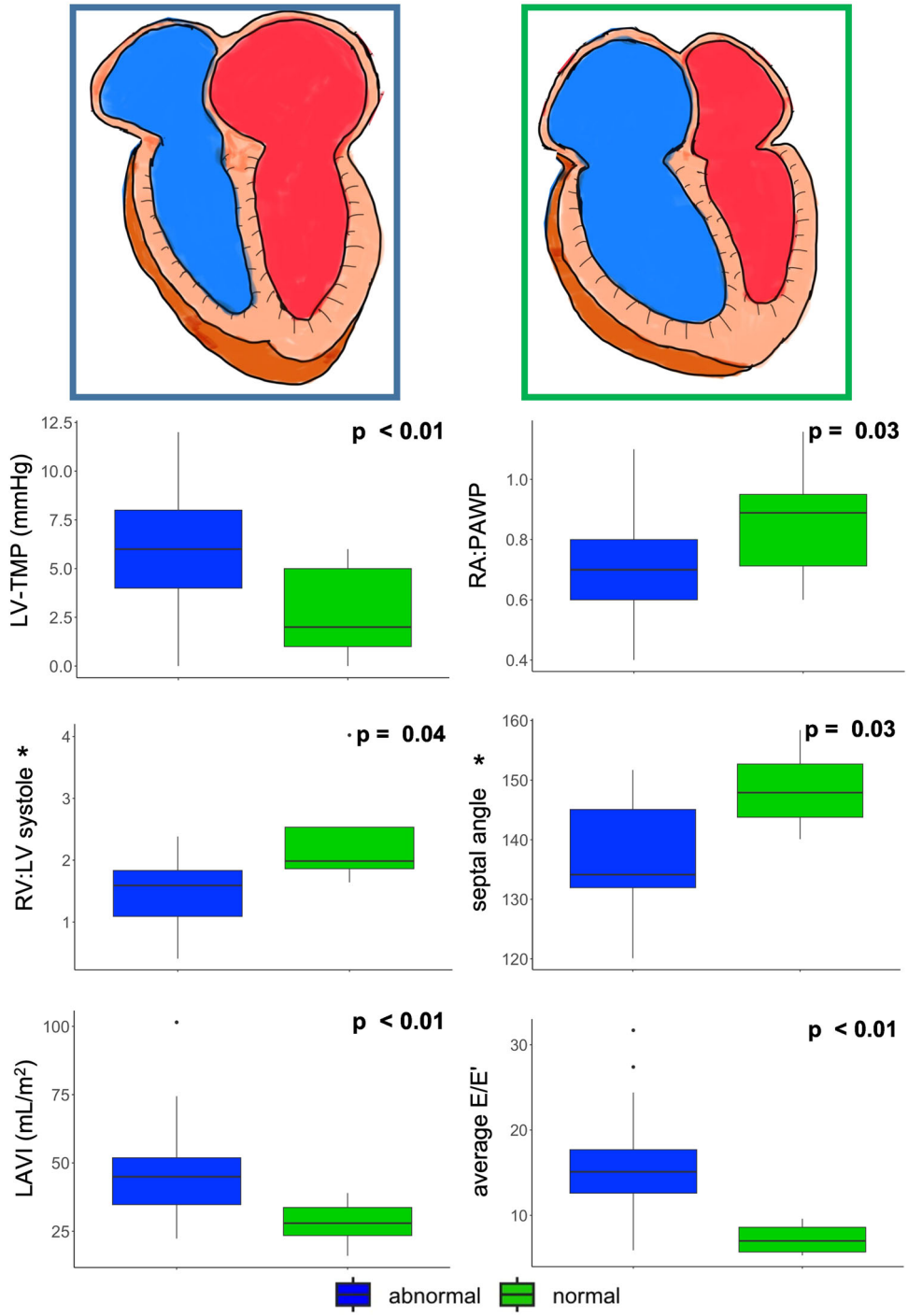

FIGURE 1 CpcPH HFpEF participants with abnormal (traditional phenotype) and normal left atrium (ventricular interdependent phenotype). *Cardiac MRI-based: $n = 14$ in abnormal LA group (blue), $n = 6$ in normal LA group (green). CpcPH, combined pre and post capillary pulmonary hypertension; E/E', ratio of mitral inflow to mitral tissue doppler early diastolic velocities; HFpEF, heart failure with preserved ejection fraction; LAVI, left atrial volume index; LV, left ventricle; LV-TMP, left ventricular transmural pressure (PAWP-RA); MRI, magnetic resonance imaging; PAWP, pulmonary artery wedge pressure; RA, right atrial pressure; RV, right ventricle.

($p = 0.04$, range: 16–24), cardiac output (CO, L/min) 4.9 ± 1.2 versus 5.3 ± 0.9 ($p = 0.17$), pulmonary vascular resistance (PVR in Woods unit: WU) 4.1 ± 2.0 versus 4.0 ± 1.9 ($p = 0.44$), LV-TMP[3,4] 6.2 ± 2.9 versus 2.9 ± 2.4 ($p < 0.01$) and RA:PAWP ratio 0.7 ± 0.2 and 0.8 ± 0.2 ($p = 0.03$). Lower LV-TMP in the normal LA group indicates an increased ventricular interdependence, which is not obviously explained by an increased epicardial fat or lung parenchymal disease (COPD or ILD).

Exercise study (abnormal vs. normal LA groups) revealed: mPAP/CO slope (mmHg/L min^{-1}) 9.0 ± 7.7 versus 7.2 ± 5.4 ($p = 0.23$), PAWP/CO slope (mmHg/

L min^{-1}) 7.8 ± 8.2 versus 4.2 ± 3.6 ($p = 0.08$), PVR (WU) 3.5 ± 2.3 versus 3.5 ± 2.2 ($p = 0.49$), peak watts 48 ± 28 versus 54 ± 44 ($p = 0.29$), peak VO_2 (%predicted, per ideal body weight) 49 ± 17 versus 56 ± 15 ($p = 0.12$), V_E/VCO_2 slope 41.9 ± 16.6 versus 40.2 ± 8.7 ($p = 0.89$), and $\Delta ETCO_2$ (mmHg) −1.8 ± 2.0 versus +1.7 ± 2.1 ($p < 0.01$). There was a trend towards better exercise capacity and gas exchange ($\Delta ETCO_2$) in the normal LA group.

On 1-year follow-up, incidence of mortality and heart failure hospitalizations (abnormal vs. normal LA groups) were: 17/34 (50%) versus 1/11 (9%), $p < 0.01$.

DISCUSSION

We report that while the majority of CpcPH patients (76%) have a traditional phenotype with left heart disease and an abnormal LA,[2,14] a minority of patients (24%) with minimal left heart disease develop CpcPH physiology due to exaggerated ventricular interdependence.[3] In these patients with near-normal left atrium, this exaggerated ventricular interdependence occurs due to compression of left heart from a dilated RV, leading to low LV transmural pressures[4] and septal flattening.[4,7] These ventricular interdependent CpcPH participants had a trend towards better RV:PA coupling, gas exchange and clinical outcomes.

In CpcPH, lack of benefit and potential harm from PH vasodilator therapies[1,2,15] is likely due to varying pathophysiologies. This includes pulmonary vein-predominant vascular remodeling (like pulmonary venoocclusive disease),[16] and exaggerated ventricular interdependence/pericardial restraint due to a dilated RV.[4] The role of pericardial restraint limiting utilization of Frank-Starling mechanism has been long described in animal studies[17] and pericardiectomy has been reported to lower LVEDPs, and increase cardiac output and peak VO_2 by nearly 30%.[18] A similar improvement in left ventricular compliance (pressure, end-diastolic volume) has been reported with pericardiotomy in humans undergoing coronary artery bypass surgery[19] and in HFpEF patients.[5] Our current findings are preliminary and do not adequately support similar recommendations in HFpEF/CpcPH. We suggest that any interventions focused on relieving RV wall stress and ventricular interdependence require more sophisticated studies, which combine multimodal methods e.g, biventricular pressure volume loops, cardiac MRI and doppler echocardiogram.[6] These future studies can also address the apparently discordant finding of low E/E' in the normal LA group in our study, which is likely due to underfilled left heart chambers. This mechanism is supported by recent cardiac MRI study by Venkateshvaran et al.[20] reporting low E/E' and underfilled LV in PH.

Regarding the imaging metrics of ventricular interdependence, our findings of higher RV volumes and RV:LV ratio in systole (compared to diastole) is consistent with Johns et al's cardiac MRI study including different PH phenotypes.[7] This study reported that as PVR increased among CpcPH and pre-capillary PH, end-diastolic RV volumes remained similar, while end-systolic RV volumes and septal angle increased, which indicate that ventricular interdependence (quantified with eccentricity index, septal angle and RV:LV ratio in CpcPH) occurs mostly in systole.[7] Lastly, with higher incidence of obesity in HFpEF, careful hemodynamics (respiratory averaged mean PAWP) and clinical context (high H_2FpEF scores) are key for appropriate PH phenotyping.[1,12,13]

Several limitations include a single center study with a small sample size, and a possible referral bias, as only less-sick patients were referred for exercise hemodynamic study. Lack of simultaneous echocardiogram and invasive hemodynamic study (median time between studies = 61 days [interquartile range: 21]) is also a limitation. Absence of exercise echocardiogram limits the ability to compare invasive exercise hemodynamics with exercise doppler metrics (E/E' and tricuspid regurgitant jet velocity), which is a major limitation as exercise doppler echocardiogram-invasive hemodynamic correlation is a key component of CpcPH/HFpEF evaluation. In summary, compared to traditional abnormal LA phenotype of HFpEF/CpcPH, the normal LA phenotype may benefit from different treatments targeted on reducing RV wall stress or relieving ventricular interdependence.

AUTHOR CONTRIBUTIONS

Study design and concept: Sofia C. Masri, James Runo, and Farhan Raza. *Data acquisition, analysis and interpretation*: Giovanna Zampierollo-Jaramillo, Anas Abed, Ahmed El Shaer, Mariana Garcia-Arango, Yimin Chen, Babak Tehrani, Wanxin Tu, Abdul Wahab Arif, Shannon Heffernan, Amir Esmaeeli, Aditya Sahai, and Farhan Raza. *Manuscript writeup and revisions*: Giovanna Zampierollo-Jaramillo, Anas Abed, Aurangzeb Baber, and Farhan Raza. *Guarantor*: Farhan Raza.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ETHICS STATEMENT

The institutional review board at UW-Madison approved this study. The study was compliant with the guidelines of the Declaration of Helsinki.

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