Dynamic right ventricular function response to incremental exercise in pulmonary hypertension

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Abstract
Pulmonary hypertension is a progressive disease whose survival is linked to adequate right ventricle adaptation to its afterload. In the current study, we performed an in-depth characterization of right ventricle function during maximum incremental exercise in patients with pulmonary hypertension and how it relates to exercise capacity. A total of 377 pulmonary hypertension patients who completed a maximum symptom-limited invasive cardiopulmonary exercise testing were evaluated to identify 45 patients with heart failure with preserved ejection fraction, 48 with exercise pulmonary hypertension, and 47 with established pulmonary arterial hypertension. These patients were compared to 17 age- and gender-matched normal controls. Load-adjusted right ventricle function was quantified as the ratio of right ventricle stroke work index to pulmonary arterial elastance. All patients with pulmonary hypertension had reduced peak VO2 %predicted compared to controls. Right ventricle function deteriorated for all pulmonary hypertension groups by 50% of peak VO2. Worsening of right ventricle function during freewheeling exercise was associated with greater reduction in peak VO2 compared to those whose right ventricle function deteriorated at later exercise stages (i.e. min 1, 2, and 3). On multivariate analysis, reduced ratio of right ventricle stroke work index to arterial elastance was an independent predictor of peak VO2 %predicted (β-Coefficient –5.46, 95% CI: –9.47 to –1.47, p = 0.01). Right ventricle function deteriorates early during incremental exercise in pulmonary hypertension, occurring by 50% of peak oxygen uptake. The current study demonstrates that right ventricle dysfunction is an early phenomenon during incremental exercise in pulmonary hypertension, occurring by 50% of peak oxygen uptake. The threshold at which right ventricle function is compromised during incremental exercise in pulmonary hypertension influences aerobic capacity and may help guide exercise strategies to mitigate dynamic worsening of right ventricle function during exercise training.

Keywords
cardiopulmonary physiology and pathophysiology, exercise, heart failure, pulmonary heart disease

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Introduction
Pulmonary hypertension (PH) is a progressive and ultimately fatal disease in which survival is closely linked to how effectively right ventricle (RV) contractility adapts to the increased afterload imposed by pulmonary arterial (PA) vasoconstriction and remodeling.1 In PH, RV function is compromised following maximum2–4 and sub-maximum exercise.5,6 However, end-exercise pulmonary hemodynamics may not be germane to the activities of daily living, which are generally accomplished at lower exercise intensities.

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Amongst healthy individuals, the hemodynamic load on the RV is more substantial than that of the left ventricle. This disproportionate load is even greater in PH. There is growing literature to support strenuous and prolonged exercise can promote myocardial injury which disproportionately affects the RV.\textsuperscript{4} In this context, the extent of RV dysfunction is dependent on the exercise intensity and duration\textsuperscript{9} and this might have important implications especially for PH patients undergoing exercise training regimens. Nonetheless, the dynamic response of the RV to changing RV afterload during different stages of incremental exercise has not been completely described in patients with PH.

In the current study, we sought to perform in-depth characterization of RV function throughout incremental exercise in patients with exercise PH, heart failure with preserved ejection fraction (HFpEF), and pulmonary arterial hypertension (PAH) using invasive cardiopulmonary exercise testing (iCPET). We sought to determine (1) when during incremental exercise, RV function deteriorates relative to its afterload; and (2) how the timing of decreased RV function relates to exercise hemodynamics and maximum exercise capacity.

**Methods**

**Study population and design**

We retrospectively identified patients between March 2011 and September 2018 who had undergone resting supine right heart catheterization (RHC) followed by symptom-limited upright iCPET as part of their clinically indicated evaluation for unexplained exercise intolerance.\textsuperscript{11} The study protocol was approved by Partners Healthcare Human Research Committee (2011P000272).

Included patients had normal left ventricular ejection fraction defined as >0.55 with no significant valvular abnormalities by resting echocardiography. Based upon resting and maximum exercise pulmonary gas exchange and hemodynamics, we identified five discrete phenotypes\textsuperscript{2,3,12,13}: (i) HFpEF defined by peak pulmonary arterial wedge pressure (PAWP) >17 mmHg for ages >50 years or peak PAWP >19 for ages ≤50 years; (ii) HFpEF with associated abnormal increases in pulmonary vascular resistance (PVR) (HFpEF+PVR), defined additionally by a peak PVR >1.34 Wood units (WU) for ages ≤50 years or a peak PVR >2.10 WU for ages >50 years; (iii) exercise PH, defined by normal supine resting RHC hemodynamics, but peak mean pulmonary arterial pressure (mPAP) >30 mmHg and peak PVR >1.34 WU for patients aged ≤50 years or a peak mPAP >33 mmHg and peak PVR >2.10 WU for patients aged >50 years; (iv) resting established PAH, defined by resting supine RHC mPAP of >20 mmHg and PAWP ≤15 mmHg along with PVR ≥3 WU\textsuperscript{14}; and (v) control subjects who exhibited a normal physiological limit to exercise defined by a peak oxygen uptake (peak VO\textsubscript{2}) and peak cardiac output (CO) of ≥80% predicted. Controls were matched for age and gender to the other groups.

Exclusion criteria included: (1) acute coronary syndrome defined by ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, or unstable angina during exercise testing; (2) patient with only rest and peak exercise hemodynamic values (i.e. no intermediate hemodynamic values between rest and peak exercise) and those with ≥3 missing individual pulmonary hemodynamic data points during incremental exercise testing; and (3) submaximal cardiopulmonary exercise testing defined by peak respiratory exchange ratio <1.05, a peak heart rate <85% predicted, and a peak mixed-venous partial pressure of oxygen >27 mmHg.

**Invasive cardiopulmonary exercise testing**

Our RHC and iCPET techniques have been described previously\textsuperscript{11,15,16} and are detailed in the supplementary material. Briefly, RHC was performed in the supine position with a five-port pacing PA catheter (Edwards LifeSciences, Irvine, CA, USA) inserted percutaneously under fluoroscopic and ultrasound guidance into the internal jugular vein and a radial artery catheter concurrently placed in the radial artery. Patients underwent a symptom-limited incremental CPET using an upright cycle ergometer with a breath-by-breath assessment of gas exchange (ULTIMA CPX; Medical Graphics Corporation, St Paul, MN, USA). Pulmonary and systemic hemodynamics were continuously and simultaneously monitored during exercise (Xper Cardio Physiomentoring System; Phillips, Melbourne, FL, USA). An electronic average of pulmonary pressures over three respiratory cycles was used.\textsuperscript{17} Arterial and mixed venous blood gases and pH were collected during each minute of exercise, and the arterial–mixed venous oxygen content difference (Ca – vO\textsubscript{2}) was calculated. Systemic oxygen extraction was calculated as CaO\textsubscript{2} – CvO\textsubscript{2} divided by CaO\textsubscript{2}. Fick CO was determined every minute. Systemic oxygen delivery was calculated by multiplying CO by the arterial oxygen content (CaO\textsubscript{2}).

**Measurements**

**RV function assessment.** Because RV pressure waveforms were not available for all patients for conventional single beat analysis, a load-adjusted RV function, an alternative method based upon stroke work index (SWI) and PA elastance, \(E_a\) was developed based upon experimental pressure/volume data used in a previous study.\textsuperscript{18} Briefly, archived measurements of RV pressure and RV volume, provided by a 5 Fr conductance/micromanometer catheter, and mPAP were used to define the relationship between SWI/\(E_a\) and RV–PA coupling (\(E_e/\(E_a\)) derived from both single beat and multi-beat methods.\textsuperscript{18} Data had been acquired from 12 anesthetized swine (~55 kg) under IACUC-approved protocols and in
accordance with the NIH Guide for the Care and Use of Laboratory Animals. Input signals were sampled at 200 Hz with data recorded before and during interventions to alter RV afterload alone or in combination with inotropic depression or augmentation. Using standard linear regression, there was significant correlation between RV SWI/Ea (RV SWI / Ea × 10⁻³). RV SWI was calculated as¹⁹: (1.25 × mean PA pressure – right atrial pressure (RAP)) × SV index (SVI) and expressed as mmHg.mL/m². Ea was calculated as: RV-end systolic pressure (RVESP)/SVI and expressed as mmHg/ mL/m². The RVESP was estimated as²⁰: (1.65 × mPAP) – 7.79. Data were collected at the following intervals during incremental exercise testing: rest, 50% of peak VO₂ (in ml/min/kg) attained, 75% of peak VO₂ (in ml/min/kg) attained, and peak exercise (in ml/min/kg). The RVESP was estimated as²⁰: (1.65 × mPAP) – 7.79. The RV work reserve was determined by the difference between rest and peak exercise RV stroke work index.

Table 1. Baseline characteristics and resting hemodynamics.

| Characteristics                  | Controls (n = 17) | ePH (n = 48) | HfPEF (n = 24) | HfPEF + PVR (n = 21) | PAH (n = 47) |
|---------------------------------|------------------|--------------|----------------|----------------------|--------------|
| **Age, years**                  | 61 ± 10          | 67 ± 9       | 62 ± 15       | 70 ± 10              | 70 ± 10      |
| **Female (n %)**                | 10 (58)          | 25 (52)      | 12 (50)       | 7 (34)               | 26 (55)      |
| **BMI (kg/m²)**                 | 30 ± 5           | 30 ± 7       | 35 ± 8<sup>d</sup> | 31 ± 8              | 28 ± 7       |
| **Hemoglobin (g/dL)**           | 13.6 ± 2.2       | 13.5 ± 2.0   | 13.0 ± 1.7    | 13.6 ± 1.9           | 13.9 ± 1.9   |
| **Co-morbidities (n %)**        |                  |              |                |                      |              |
| **Systemic hypertension**       | 9 (53)           | 28 (58)      | 14 (58)       | 14 (66)              | 30 (64)      |
| **Hyperlipidemia**              | 5 (29)           | 24 (50)      | 12 (50)       | 14 (66)              | 22 (46)      |
| **Diabetes**                    | 1 (6)            | 11 (23)      | 5 (21)        | 4 (19)               | 6 (13)       |
| **Medications (n %)**           |                  |              |                |                      |              |
| **Beta adrenergic receptor blocker** | 1 (6)          | 15 (31)<sup>a</sup> | 17 (71)<sup>b</sup><sup,e</sup> | 14 (67)<sup>b</sup><sup,e</sup> | 13 (27)      |
| **Calcium channel receptor blocker** | 0 (0)          | 9 (18)<sup>a</sup> | 2 (8)         | 8 (38)<sup>c</sup>   | 9 (15)<sup>a</sup> |
| **ACE inhibitor or ARB**        | 4 (23)           | 11 (23)      | 9 (37)        | 4 (19)               | 11 (23)      |
| **Diuretics**                   | 2 (12)           | 16 (33)      | 17 (70)<sup>b</sup> | 15 (71)<sup>b</sup> | 22 (47)<sup>a</sup> |
| **Pulmonary function testing**  |                  |              |                |                      |              |
| **FEV<sub>1</sub> (% predicted)** | 93 ± 12<sup>a</sup> | 72 ± 18<sup>a</sup> | 61 ± 21<sup>a</sup> | 59 ± 20<sup>a</sup> | 70 ± 23<sup>a</sup> |
| **FVC (% predicted)**           | 93 ± 12          | 74 ± 19<sup>a</sup> | 60 ± 18<sup>b</sup><sup,e</sup> | 63 ± 16<sup>a</sup> | 69 ± 20<sup>a</sup> |
| **FEV<sub>1</sub>/FVC (%predicted)** | 97 ± 8          | 97 ± 12      | 94 ± 13       | 93 ± 16              | 102 ± 13     |
| **Resting right heart catheterization** |           |              |                |                      |              |
| **Heart rate (bpm)**            | 74 ± 22          | 75 ± 12      | 74 ± 14       | 76 ± 15              | 79 ± 16      |
| **SaO<sub>2</sub> (%)**         | 97 ± 1<sup>a</sup> | 97 ± 2<sup>a</sup> | 97 ± 2<sup>a</sup> | 96 ± 3              | 95 ± 3       |
| **RAP (mmHg)**                  | 3 ± 2            | 4 ± 4        | 10 ± 4<sup>b</sup><sup,e</sup> | 10 ± 4<sup>b</sup><sup,e</sup> | 4 ± 4       |
| **SVI (mL/m²)**                 | 34.1 ± 12.4      | 38.1 ± 11.6  | 38.5 ± 10.4  | 36.8 ± 11.9          | 33.6 ± 11.2  |
| **Cl (L/min/m²)**               | 2.4 ± 0.4        | 2.8 ± 0.8    | 2.7 ± 0.7    | 2.7 ± 0.6            | 2.6 ± 0.9    |
| **RV stroke work index (mmHg/mL/m²)** | 516 ± 282    | 835 ± 364   | 915 ± 312    | 1115 ± 538<sup>a</sup> | 1244 ± 640<sup>b</sup> |
| **mPAP (mmHg)**                 | 15 ± 3           | 21 ± 5       | 28 ± 5<sup>b</sup> | 32 ± 7<sup>a</sup><sup,b</sup> | 32 ± 11<sup>a</sup><sup,b</sup> |
| **PAWP (mmHg)**                 | 6 ± 2            | 9 ± 3        | 19 ± 3<sup>b</sup><sup,e</sup> | 20 ± 4<sup>a</sup><sup,b</sup> | 8 ± 3       |
| **PVR (WU)**                    | 1.8 ± 0.6        | 2.3 ± 0.4    | 1.5 ± 0.5    | 2.0 ± 0.6            | 5.5 ± 3.2<sup>d</sup><sup</sup> |
| **TPR (WU)**                    | 2.9 ± 0.9        | 3.9 ± 0.9    | 5.0 ± 1.4<sup>b</sup> | 6.3 ± 1.7<sup>a</sup> | 6.4 ± 1.9<sup>c</sup> |
| **PA compliance (mL/mmHg)**     | 7.3 ± 3.7        | 4.6 ± 1.4<sup>a</sup> | 4.6 ± 1.8<sup>a</sup> | 3.2 ± 1.3<sup>a</sup> | 2.4 ± 0.9<sup>c</sup> |
| **Ea (mmHg/mL/m²)**             | 0.54 ± 0.27      | 0.75 ± 0.27  | 1.05 ± 0.37  | 1.28 ± 0.40<sup>b</sup> | 1.54 ± 1.02<sup>c</sup> |

<sup>a</sup>: p < 0.05 vs. controls; <sup>b</sup>: p < 0.05 vs. ePH; <sup>c</sup>: p < 0.05 vs. HfPEF; <sup>d</sup>: p < 0.05 vs. HfPEF+PVR; <sup>e</sup>: p < 0.05 vs. PAH; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; ePH: exercise pulmonary hypertension; HfPEF: heart failure with preserved ejection fraction; PVR: pulmonary vascular resistance; PAH: pulmonary arterial hypertension; RAP: right atrial pressure; SVI: stroke volume index; Cl: cardiac index; RV: right ventricle; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; TPR: total pulmonary resistance; WU: Wood units; PA: pulmonary arterial; Ea: arterial elastance; FEV<sub>1</sub>: forced expiratory volume during the first second; FVC: forced vital capacity; SaO<sub>2</sub>: Oxygen saturation in arterial blood.
Statistical analysis

Unless otherwise stated, values are presented as mean and standard deviation. Comparisons of baseline characteristics, resting hemodynamics, and CPET parameters among the five study groups were performed using one-way ANOVA with Bonferroni post hoc correction. Comparisons among the different hemodynamic interval (i.e. rest, 50% peak VO₂ attained, 75% peak VO₂ attained, and peak exercise VO₂) among the groups were performed using two-way repeated measures analysis of variance with Bonferroni post hoc correction. The relationships between RV SWI/Ea and peak VO₂ (ml/min/kg) was examined using linear regression. Univariate analysis was performed to determine the predictors of peak RV function (as measured by RV SWI/Ea) and peak VO₂ (%predicted) for HFpEF, exercise pulmonary hypertension, and PAH groups. Non-collinear variables (i.e. Pearson correlation r < 0.6) with a significant p value (p < 0.05) on univariate analysis were incorporated into multivariate models to identify independent predictors of peak VO₂ (%predicted). Comparison between patients receiving and not receiving B-adrenergic receptor blocker therapy were performed using independent student’s t-test. A probability value of <0.05 was considered significant. Statistical analyses were performed using GraphPad Prism 7 (GraphPad Software, LLC, La Jolla, CA, USA) and SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Demographic and clinical characteristics

A total of 1515 consecutive iCPET reports were analyzed to identify 377 patients with PH, of whom 45 had HFpEF (21 with abnormal PVR response during exercise, HFpEF + PVR), 48 had exercise pulmonary hypertension (ePH), and 47 had PAH, based on the aforementioned inclusion and exclusion criteria; 17 age- and gender-matched control subjects were additionally selected for the data analysis. Therefore, the study sample consisted of 157 subjects (Figure S2).

There was no statistical difference in the age, resting mean hemoglobin concentration, and number of females

| Table 2. Maximum cardiopulmonary exercise data and peak exercise hemodynamics. |
|---------------------------------------------|
| **Maximum CPET data**                      |
| Controls (n = 17)                          |
| ePH (n = 48)                               |
| HFpEF (n = 24)                             |
| HFpEF + PVR (n = 21)                       |
| PAH (n = 47)                               |
| Peak VO₂ (% predicted)                     | 107 ± 20 | 69 ± 15 | 60 ± 20 | 59 ± 17 | 56 ± 17 |
| Peak VO₂ (mL/kg/min)                       | 22.9 ± 9.7 | 13.1 ± 3.5 | 10.9 ± 2.9 | 11.1 ± 3.1 | 11.1 ± 3.4 |
| Peak heart rate (% predicted)              | 82 ± 16 | 78 ± 14 | 68 ± 15 | 72 ± 16 | 78 ± 14 |
| Peak SaO₂ (%)                              | 97 ± 2 | 94 ± 4 | 96 ± 5 | 93 ± 5 | 89 ± 7 |
| V̇E/V̇CO₂ slope                             | 30 ± 5 | 36 ± 8 | 33 ± 7 | 39 ± 8 | 46 ± 13 |
| Peak end-tidal CO₂ (mmHg)                  | 36 ± 4 | 34 ± 8 | 35 ± 5 | 33 ± 7 | 30 ± 7 |
| Peak P₂A−O₂ (mmHg)                         | 22 ± 12 | 40 ± 18 | 23 ± 15 | 41 ± 17 | 54 ± 19 |
| Peak DO₂ (mL/kg/min)                       | 29 ± 12 | 21 ± 6 | 17 ± 4 | 15 ± 3 | 17 ± 6 |
| Peak systemic O₂ extraction (Ca – vO₂/CaO₂) | 0.77 ± 0.04 | 0.65 ± 0.09 | 0.66 ± 0.11 | 0.72 ± 0.09 | 0.65 ± 0.10 |

Peak exercise hemodynamics

| CO (% predicted)                           | 111 ± 16 | 86 ± 19 | 75 ± 21 | 67 ± 13 | 73 ± 26 |
| CI (L/min/m²)                              | 6.5 ± 1.8 | 4.9 ± 1.0 | 4.5 ± 0.9 | 3.8 ± 0.6 | 4.2 ± 1.3 |
| SVI (mL/m²)                                | 50.5 ± 10.6 | 42.1 ± 7.1 | 43.3 ± 6.6 | 37.1 ± 6.9 | 35.1 ± 9.6 |
| RA pressure (mmHg)                         | 8 ± 1 | 7 ± 4 | 17 ± 6 | 19 ± 6 | 8 ± 6 |
| RV stroke work index (mmHg.mL/m²)          | 1511 ± 485 | 1884 ± 661 | 1574 ± 465 | 1564 ± 499 | 1967 ± 694 |
| mPAP (mmHg)                                | 23 ± 12 | 42 ± 8 | 44 ± 7 | 48 ± 8 | 52 ± 15 |
| PAWP (mmHg)                                | 12 ± 3 | 12 ± 4 | 32 ± 5 | 25 ± 6 | 12 ± 4 |
| PVR (WU)                                   | 1.3 ± 0.4 | 2.9 ± 0.6 | 1.2 ± 0.5 | 2.9 ± 0.5 | 5.4 ± 3.5 |
| TPR (WU)                                   | 2.4 ± 0.5 | 4.3 ± 1.1 | 4.7 ± 1.0 | 6.2 ± 0.8 | 6.9 ± 3.4 |
| PA compliance (mL/mmHg)                    | 3.1 ± 0.9 | 2.1 ± 0.5 | 2.5 ± 0.6 | 1.7 ± 0.4 | 1.4 ± 0.7 |
| Ea (mmHg/mL/m²)                            | 0.86 ± 0.23 | 1.48 ± 0.34 | 1.52 ± 0.38 | 1.96 ± 0.44 | 2.44 ± 1.45 |

a: p < 0.05 vs. controls; b: p < 0.05 vs. ePH; c: p < 0.05 vs. HFpEF; d: p < 0.05 vs. HFpEF+PVR; e: p < 0.05 vs. PAH; ePH: exercise pulmonary hypertension; HFpEF: heart failure with preserved ejection fraction; PVR: pulmonary vascular resistance; PAH: pulmonary arterial hypertension; CPET: cardiopulmonary exercise testing; VO₂: oxygen consumption; DO₂: oxygen delivery; CO: cardiac output; CI: cardiac index; SVI: stroke volume index; RA: right atrial; RV: right ventricle; mPAP: mean pulmonary artery pressure; PAWP: pulmonary arterial wedge pressure; TPR: total pulmonary resistance; WU: Wood units; PA: pulmonary arterial; Ea: arterial elastance.
between the groups. HFpEF had higher body mass index compared to ePH and PAH patients. The baseline characteristics and co-morbidities are summarized in Table 1.

**Resting RHC data**

Resting RHC data are presented in Table 1. There was no difference between the resting values of cardiac index (CI) and SVI among the five groups. The resting mean RAP was greater in both HFpEF groups compared to controls, ePH, and PAH but there was no difference in the mean RAP between the HFpEF groups. The resting PAWP was greatest in the HFpEF groups while resting PVR was greatest in PAH. Resting Ea was greater in PAH compared to controls, ePH, and HFpEF but was not different compared to HFpEF + PVR. The resting mean PA compliance was reduced in PAH compared to controls, ePH, and HFpEF but not different compared to HFpEF + PVR.

**Invasive cardiopulmonary exercise test**

Maximum invasive CPET and peak exercise hemodynamic data are summarized in Table 2. PAH demonstrated greater arterial oxygen desaturation at peak exercise that was associated with a widened alveolar–arterial gradient compared to controls, ePH, and HFpEF. PAH also demonstrated more ventilatory inefficiency as indicated by a markedly abnormal Ve/VCO₂ slope compared to controls, ePH, and HFpEF. Systemic oxygen extraction was reduced in HFpEF and PAH groups compared to controls.

By study design, peak PAWP was higher in the HFpEF groups and peak PVR was greatest in PAH. The peak RAP was greatest in the HFpEF groups. All PH patients had mean peak TPR that was >3 WU. The peak PA compliance and Ea were similarly decreased in PAH and HFpEF + PVR compared to controls, HFpEF, and ePH.

**Effect of incremental exercise on RV function**

Patients were evaluated at rest, 50%, 75%, and 100% of attained peak VO₂. At rest, RV stroke work index was increased in PAH compared to controls and ePH. Resting Ea was greater in PAH compared to controls, ePH, and HFpEF but was not different from HFpEF + PVR. By 50% peak VO₂, ePH and HFpEF groups realized a significant increase in RV afterload (Ea) and RV stroke work index (Fig. 1). There was no difference in resting RV function among groups; however, RV SWI/Ea was reduced for all PH groups by 50% of peak VO₂ (Fig. 2), given the disproportional increase in Ea in relation to RV SWI. PAH and HFpEF + PVR showed impaired eXertional RV work reserve (Fig. 2).

**Correlates of peak VO₂**

The univariate analysis for predicting peak VO₂ (% predicted) are presented in Table S1. On multivariate analysis, RV SWI/Ea at peak exercise, RV work reserve, peak CI, and peak Ea, emerged as independent correlates of peak VO₂ (% predicted) (Table 3). Patients who experience reduction in the RV SWI/Ea during freewheeling phase of exercise tended to have more significant reduction in peak exercise VO₂ (mL/min/kg) compared to those who experience reduced RV function at later stages of exercise (i.e. min 1, 2, and 3) (Table S2).

**Discussion**

This is the first study to directly demonstrate reduced RV function as assessed by RV SWI/Ea, occurs even during unloaded and low-level exercise in different forms of PH. Another novel finding of this study is that earlier deterioration in RV function during incremental exercise is associated with greater reduction in peak exercise aerobic capacity.
The initial response of the RV to increasing afterload is to augment its work reserve.\(^2,3\) This homeometric adaptation (or Anrep effect) triggered by various autocrine/paracrine factors allows for preservation of RV contraction relative to its afterload and therefore RV function.\(^1,2,1\) When the RV is no longer able to augment its work force in the face of increasing afterload, RV function deteriorates.\(^2,3,5,6\) In the current study, in ePH, HfPEF, and PAH, RV decompensation occurs by 50% of peak VO\(_2\) and is seen in some cases even during unloaded exercise.

In a previous study of resting PAH and ePH patients, a plateau of mPAP versus VO\(_2\) was observed at the
ventilatory anaerobic threshold (VAT), suggesting but not proving that dynamic RV decompensation had occurred. In the current study, VO\textsubscript{2} at VAT across all groups approximated that at 50% peak VO\textsubscript{2} (data not shown) supporting the aforementioned study finding of dynamic RV decompensation at VAT.

Another important finding of the present work is that dynamic exercise RV decompensation is associated with impaired peak exercise capacity (peak VO\textsubscript{2}). Peak VO\textsubscript{2} is an important prognostic indicator in patients with heart failure\textsuperscript{2,24} and PAH.\textsuperscript{25} Along with this decrease in peak exercise aerobic capacity, there is a commensurate decrease in SVI across all PH groups throughout incremental exercise testing. Additionally, we showed that patients who experienced reduced RV SWI/Ea earlier during incremental exercise testing were more likely to have more significantly depressed peak exercise aerobic capacity.

Regular exercise training benefits the majority of patients with PH.\textsuperscript{26} However, during exercise in patients with PH, the RV is forced to increase its output against a high resistance circuit. This along with the inability to further recruit and later distend the pulmonary vasculature results in RV–PA uncoupling with deterioration in SVI augmentation and aerobic exercise capacity.\textsuperscript{2,3} An advantage of examining the entire domain of incremental exercise is that one might be able to discriminate those patients with preserved dynamic RV function during exercise who may benefit from a more intensive exercise regimen. In this context, the ideal exercise training protocol for patients with pulmonary vascular disease will likely require identifying approaches that provide sufficient stimulus for favorable adaptations without presenting excessive RV load and wall stress. While mild elevation in cardiac wall stress occurs normally during exercise due to increases in ventricular afterload, the response is greater in animal models of severe PH,\textsuperscript{27} and may be greater in patients who experience deterioration in RV function at lower workloads. In heart failure, even a transient elevation in wall stress is known to prompt detrimental proinflammatory response in the myocardium.\textsuperscript{28} Additionally, in a monocrotaline rat model of PAH, intermittent exercise protocol was shown to be superior to more customary continuous training protocol in improving PA hemodynamics and maladaptive RV hypertrophy.\textsuperscript{29} Similar findings have been reported in patients with heart failure\textsuperscript{30} in response to intermittent exercise training protocol.

**Limitations**

The controls subjects were referred for iCPET evaluation at a tertiary referral center for unexplained exertional intolerance and, therefore, control subjects may not be representative of a completely healthy population. However, they were selected based on normal physiologic response to exercise (peak VO\textsubscript{2} and peak CO \(\geq 80\%\) predicted) and may therefore be regarded as “symptomatic normal” subjects. The upper limit of normal for exercise mPAP, PVR, and PAWP has been the subject of controversy and we are aware of several definitions of an abnormal response.\textsuperscript{31,32} In the current study, we used age-related mPAP, PAWP, and PVR thresholds,\textsuperscript{15} which has been previously used\textsuperscript{2,3,12,13,25} and was shown to have over 90% concordance for ePH with definitions based on a mPAP-CO slope and TPR > 3 WU.\textsuperscript{25} It is important to note that all of the ePH patients also satisfy peak TPR criteria of > 3 WU.\textsuperscript{32}

Our prior studies examined RV function response during incremental exercise testing using conventional single beat estimation of RV-PA coupling.\textsuperscript{2,3,13} RV–PA coupling (Ees/Ea) reflects the matching of RV contractile function and its afterload. The single beat method is complex and requires RV pressure waveform that is interpretable and of good quality. In the current study, we opted to use RV SWI/Ea as a measure of RV function because it is a simple measure that can be derived from conventional right heart hemodynamic values. Additionally, using post hoc analysis of a prior publication,\textsuperscript{18} we showed a significant correlation between RV SWI/Ea and Ees/Ea using both single beat analysis of RV pressure waveform and multi-beat analysis using conductance catheter (Figure S1).

**Conclusions**

In conclusion, the current study demonstrates that RV function is reduced at early stages during incremental exercise in PH, occurring before 50% of peak oxygen uptake. Furthermore, the threshold at which RV function deteriorates during incremental exercise in PH influences the peak aerobic capacity. Future studies are necessary to help understand the significance of the current study findings to guide exercise prescriptions and inform long-term outcomes in PH patients.

**Author’s contribution**

I.S., R.K.F.O., M.B.B., M.F.-U., D.M.S., and A.B.W. contributed to conception and design of the work, interpretation of the data, and writing. I.S., M.F.-U., and R.K.F.O. contributed to data acquisition and analysis. I.S., R.K.F.O., and D.M.S. together conceived the original study design, performed the primary data analysis and interpretation, and writing of the manuscript. P.H., M.B.B., M.F.-U., and A.B.W. contributed substantially to the study design, data analysis and interpretation, and writing of the manuscript. A.B.W., P.H., and M.B.B. contributed to study design and critically reviewed the manuscript. D.M.S. and I.S. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version of the manuscript and are accountable for all aspects of the work.

**Conflict of interest**

The author(s) declare that there is no conflict of interest.

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Supplemental material
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