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RESEARCH ARTICLE

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Exercise and pulsatile pulmonary vascular loading in chronic thromboembolic pulmonary disease

Sinan Osman[1,2] | **Natasha R. Girdharry**[1,2] | **Elizabeth Karvasarski**[1,2] | **Robert F. Bentley**[3] | **Stephen P. Wright**[4] | **Nadia Sharif**[5] | **Micheal McInnis**[6] | **John T. Granton**[5] | **Marc dePerrot**[7] | **Susanna Mak**[1,2]

[1]Division of Cardiology, Mount Sinai Hospital/University Health Network, Toronto, Ontario, Canada

[2]Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada

[3]Faculty of Kinesiology and Physical Education, University of Toronto, Toronto, Ontario, Canada

[4]School of Health and Exercise Sciences, Centre for Heart, Lung and Vascular Health, University of British Columbia, Kelowna, British Columbia, Canada

[5]Department of Medicine, Division of Respirology, University Health Network, Toronto, Ontario, Canada

[6]Department of Medical Imaging, University of Toronto, Toronto, Ontario, Canada

[7]Department of Surgery, Division of Thoracic Surgery, University of Toronto, Toronto, Ontario, Canada

Correspondence
Susanna Mak, Division of Cardiology, Mount Sinai Hospital, 1603-600 University Ave, Toronto, ON M5G 1X5, Canada.
Email: Susanna.mak@sinaihealth.ca

Abstract

Chronic thromboembolic pulmonary disease (CTEPD) is characterized by organized nonresolving thrombi in pulmonary arteries (PA). In CTEPD with pulmonary hypertension (PH), chronic thromboembolic PH (CTEPH), early wave reflection results in abnormalities of pulsatile afterload and augmented PA pressures. We hypothesized that exercise during right heart catheterization (RHC) would elicit more frequent elevations of pulsatile vascular afterload than resistive elevations in patients with CTEPD without PH. The interdependent physiology of pulmonary venous and PA hemodynamics was also evaluated. Consecutive patients with CTEPD without PH (resting mean PA pressure ≤20 mmHg) undergoing an exercise RHC were identified. Latent resistive and pulsatile abnormalities of pulmonary vascular afterload were defined as an exercise mean PA pressure/cardiac output >3 WU, and PA pulse pressure to PA wedge pressure (PA PP/PAWP) ratio >2.5, respectively. Forty-five patients (29% female, 53 ± 14 years) with CTEPD without PH were analyzed. With exercise, 19 patients had no abnormalities (ExNOR), 26 patients had abnormalities (ExABN) of pulsatile (20), resistive (2), or both (4) elements of pulmonary vascular afterload. Exercise elicited elevations of pulsatile afterload (53%) more commonly than resistive afterload (13%) ($p < 0.001$). ExABN patients had lower PA compliance and higher pulmonary vascular resistance at rest and exercise and prolonged resistance-compliance time product at rest. The physiological relationship between

Abbreviations: AUC, area under curve; BMI, body mass index; BPA, balloon pulmonary angioplasty; BSA, body surface area; CO, cardiac output; CTEPD, chronic thromboembolic pulmonary disease; CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, computed tomography pulmonary angiography; ESC, European Society of Cardiology; HR, heart rate; mPAP, mean pulmonary artery pressure; MRC, Medical Research Council; PA, pulmonary artery; PAC, pulmonary arterial compliance; PADP, pulmonary artery diastolic pressure; PAPP, pulmonary artery pulse pressure; PASP, pulmonary artery systolic pressure; PAWP, pulmonary artery wedge pressure; PE, pulmonary embolism; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RA, right atrial; RC, resistance compliance; RHC, right heart catheterization; ROC, receiver operate characteristic; RV, right ventricle; SV, stroke volume; TPG, trans pulmonary gradient; TPR, total pulmonary resistance.

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changes in PA pressures relative to PAWP was disrupted in the ExABN group. In CTEPD without PH, exercise RHC revealed latent pulmonary vascular afterload elevations in 58% of patients with more frequent augmentation of pulsatile than resistive pulmonary vascular afterload.

KEYWORDS
afterload, right heart catheterization

INTRODUCTION

Chronic thromboembolic pulmonary disease (CTEPD) is a condition in which pulmonary emboli (PE) do not completely resolve[1,2] and can result in serious complications leading to an elevated mean pulmonary artery pressure (mPAP).[3] Among patients with evidence of chronic PE, assessment with right heart catheterization (RHC) in the supine resting position is necessary to differentiate between CTEPD without pulmonary hypertension (PH) where mPAP ≤20 mmHg, and CTEPD with PH where mPAP >20 mmHg termed chronic thromboembolic PH (CTEPH).[4,5]

The European Society of Cardiology (ESC) recently published updated hemodynamic definitions for both resting and exercise PH.[6] Exercise PH is present if the slope of the change in mPAP versus the increase in cardiac output (CO) between rest and exercise exceeds 3 WU.[6] The pressure-flow relationship assesses steady-state resistive afterload, however, determinants of afterload within the right ventricular-pulmonary artery circulatory unit also include a pulsatile component.[7,8] Increases in pulsatile afterload are characteristic of CTEPH, thought to be based on early pulse wave reflection off pulmonary thrombi.[9] Pulsatile afterload can be assessed at the time of RHC based on pulmonary artery pulse pressure (PAPP) relative to stroke volume (SV), known as pulmonary artery compliance (PAC). Our laboratory has previously observed that exercise during RHC can similarly reveal abnormal increases in pulsatile afterload measured as widening of the PAPP relative to increases in both SV and the pulmonary artery wedge pressure (PAWP).[10,11]

Our objective in this study was to measure the effect of exercise on indices of resistive and pulsatile afterload in a cohort of patients with CTEPD without PH undergoing RHC. We hypothesized that increases in the PAPP out of keeping with the PAWP during exercise would identify a population of patients with abnormalities of pulsatile afterload in addition to those with exercise PH as defined by the new ESC guidelines. Finally, we compared the physiology of pulmonary vascular responses in relation to the PAWP between patients with normal and abnormal exercise hemodynamic responses.

METHODS

Patients with apparent CTEPD

This retrospective study was conducted by the CTEPH program at the University Health Network/Sinai Health which provides comprehensive care including pulmonary endarterectomy (PEA) or balloon pulmonary angioplasty (BPA) for patients in the regions of Southern Ontario, western and eastern Canada. We included consecutive patients undergoing exercise RHC referred between November 2016 and April 2021 for the investigation of symptoms following PE with either low probability or no evidence of PH on transthoracic echocardiography[6] to evaluate suspected CTEPD without PH. Patients were consented prospectively to a hemodynamic and clinical registry. Patients had persistent radiologic evidence of chronic PE despite at least 6 months of therapeutic anticoagulation and typically had not undergone resting RHC previously. All patients who were referred for RHC were assessed by the multidisciplinary CTEPH team. The thoracic radiologist (M. M.) in our program confirmed the presence of chronic pulmonary embolism on a computed tomography pulmonary angiography (CTPA). The radiologic burden of disease was assessed according to our recently published approach.[12] A 32-vessel model of the pulmonary vasculature was employed to categorize thromboembolic disease based on anatomic location from proximal to distal as follows: Level 1 (main PA), Level 2 (lobar), Level 3 (segmental), and Level 4 (subsegmental). All patients were under consideration for PEA surgery or BPA and referred for exercise RHC following initial assessment by our CTEPH program. Inclusion criteria were imaging evidence of chronic PE despite anticoagulation, mPAP < 20 mmHg, and

PAWP < 15 mmHg in the supine position. Patients with documented Groups 1–3 PH were excluded. Cases were excluded if mPAP > 20 mmHg at rest, if one stage of exercise was not completed, or if exercise demonstrated evidence of left heart disease (ΔPAWP/ΔCO > 2.0 WU). At the time of RHC, written, informed consent, was obtained.

Right heart catheterization and exercise: Standard procedures

Baseline RHC was performed in the supine position. A balloon tipped fluid filled 7.5F catheter (Swan-Ganz Oximetry PacePort Thermodilution Pulmonary Artery Catheter, Edwards Lifesciences Inc.) was advanced to the PA as described previously.[11,13] Briefly, pressure transducers were zeroed at the midaxillary level and simultaneous right atrial (RA), right ventricular (RV), and PA pressures were recorded continuously, and the balloon was inflated intermittently to record the PAWP waveform. Thermodilution CO measurements were completed in triplicate within 10%. Mixed venous blood was sampled for oximetry and digital pulse oximetry was used to measure arterial saturation.

Patients were then transferred to a cycle ergometer (Ergoline Ergoselect 12) and inclined into a semiupright (45° incline) position, as reported previously.[10] In brief, sequential conditions were as follows: Rest—in the semiupright position on the cycle ergometer. Exercise—after a brief warmup of unloaded pedaling, two 6-min sequential stages of constant-work-rate cycling. The 2 work-rates were selected based on Medical Research Council (MRC) score: MRC ≥ 3–15 W/25 W, MRC < 3–25 W/40 W for women, 40 W/70 W for men based on our previously published experiences.[11,13] Thermodilution CO was determined between the second and fifth minute of each exercise work-rate.

Clinical data extraction: Standardized case report forms were populated at the time of cardiac catheterization, including demographics, and medications. Chart review was also conducted for additional clinical information including whether PEA or BPA was performed up to 1-year after RHC.

Hemodynamic data analysis and classification of exercise phenotypes

Hemodynamic analysis was performed on digitized pressure recordings as previously described.[11] Exercise was reported as the greatest single work rate completed by an individual. RA, RV, and PA pressures were analyzed over 10 beat intervals free of extrasystoles. During exercise, PAWP was reported as the automated mean. Calculated variables included SV (CO/heart rate [HR]); PA PP (systolic-diastolic PA pressure); transpulmonary gradient—TPG (mPAP-PAWP); pulmonary vascular resistance—PVR (TPG/CO); total pulmonary resistance—TPR (mPAP/CO); pulmonary artery compliance—PAC (SV/PA PP); and resistance-compliance time product—RC time (60/HRxTPG/PA PP). CO and PAC were also indexed to body surface area (BSA) and reported as cardiac index and PAC index.

Pressure-flow (ΔP/ΔCO) slopes were calculated for PAWP and mPAP. The ratios of the PAPP to PAWP (PAPP/PAWP) and mPAP (PAPP/mPAP) were also calculated as measures of pulsatile load.

Exercise hemodynamic phenotype classification

As per the ESC guideline definition, pulmonary vascular resistive afterload during exercise was considered abnormal if ΔmPAP/ΔCO > 3.0 WU.[6] Pulmonary vascular pulsatile afterload during exercise was considered abnormal if PAPP/PAWP was >2.5, based on our previous work showing that the PAPP increases proportionally to PAWP during exercise in healthy subjects.[10] We observed that the upper limit of the ratio of PAPP/PAWP (mean plus 2 standard deviations) does not exceed 2.5.[10,11] Patients were grouped according to exercise hemodynamic responses: Exercise Normal (ExNOR)—ΔmPAP/ΔCO ≤ 3 WU AND PAPP/PAWP ≤ 2.5; Exercise Abnormal (ExABN)—ΔmPAP/ΔCO > 3 WU AND/OR PAPP/PAWP > 2.5. Patients in the ExABN group were also subclassified as ExABN pulsatile (ΔmPAP/ΔCO ≤ 3 WU AND PAPP/PAWP > 2.5), ExABN resistive (ΔmPAP/ΔCO > 3 WU AND PAPP/PAWP ≤ 2.5), or ExABN both (ΔmPAP/ΔCO > 3 WU AND PAPP/PAWP > 2.5).

Statistical analysis

Normality was assessed quantitatively with a Shapiro–Wilk test. Hemodynamic, clinical, and demographic data are reported as mean ± SD or median (interquartile range (Q1–Q3)) as appropriate. Hemodynamic measures at semiupright rest (rest) and during exercise were analyzed between the ExNOR and the ExABN groups with two-way repeated measures analysis of variance with Bonferroni correction for multiple comparisons. Hemodynamic changes with exercise were also expressed as deltas (Δ); clinical and

demographic measures were compared between groups with Fisher's exact test, Mann–Whitney *U* test for nonparametric data, and Welch's corrected *t* test for normally distributed data as appropriate. The difference in proportion of patients with abnormal resistive versus abnormal pulsatile load was compared using McNemar's test. Associations between continuous variables were explored using simple linear regressions. Receiver operator characteristic (ROC) curves were generated to assess the sensitivity and specificity of resting PAC, PVR, PAPP/PAWP, and PAPP/mPAP to predict latent exercise pulmonary vascular afterload abnormalities. A two-tailed α level of 0.05 was considered significant. Statistics were completed using SPSS 28 (IBM Corp) and GraphPad Prism 9 (GraphPad Software).

RESULTS

Identification of patients with apparent CTEPD without PH

Between November 2016 and April 2021, 63 patients were referred by our CTEPH program for hemodynamic assessment. Fourteen patients had a resting supine mPAP >20 mmHg and were thus excluded from the analysis leaving 49 patients that met the hemodynamic inclusion criteria for resting CTEPD without PH. With exercise, four patients demonstrated an abnormal post-capillary response who were excluded from subsequent analysis leaving 45 patients to be analyzed (Figure 1). By design, baseline supine hemodynamics were within normal limits with a RA pressure of 4 ± 2 mmHg, mPAP of 16 ± 3 mmHg, PAWP of 8 ± 3 mmHg, cardiac index of 2.9 ± 0.6 L/min/m^2, and PVR of 1.4 ± 0.7 WU. Despite mPAP <20 mmHg, 5 patients did demonstrate a PVR > 2 WU, but none with a PVR > 3 WU.

Demographic and clinical measures as well as medications and comorbidities are included in Table 1. Eighty seven percent of patients were on warfarin or a direct anticoagulant medication. CTPA images were available for 42(93%) patients and scored as follows: Level 1—$n = 1$(2%), Level 2—$n = 25$(60%), Level 3—$n = 13$(31%), and Level 4—$n = 3$(7%). A total of 15 (33%) patients were selected to undergo interventions for treatment, 12 underwent PEA surgery, and 5 had BPA—2 of whom after initial PEA surgery. There were no significant differences in selection

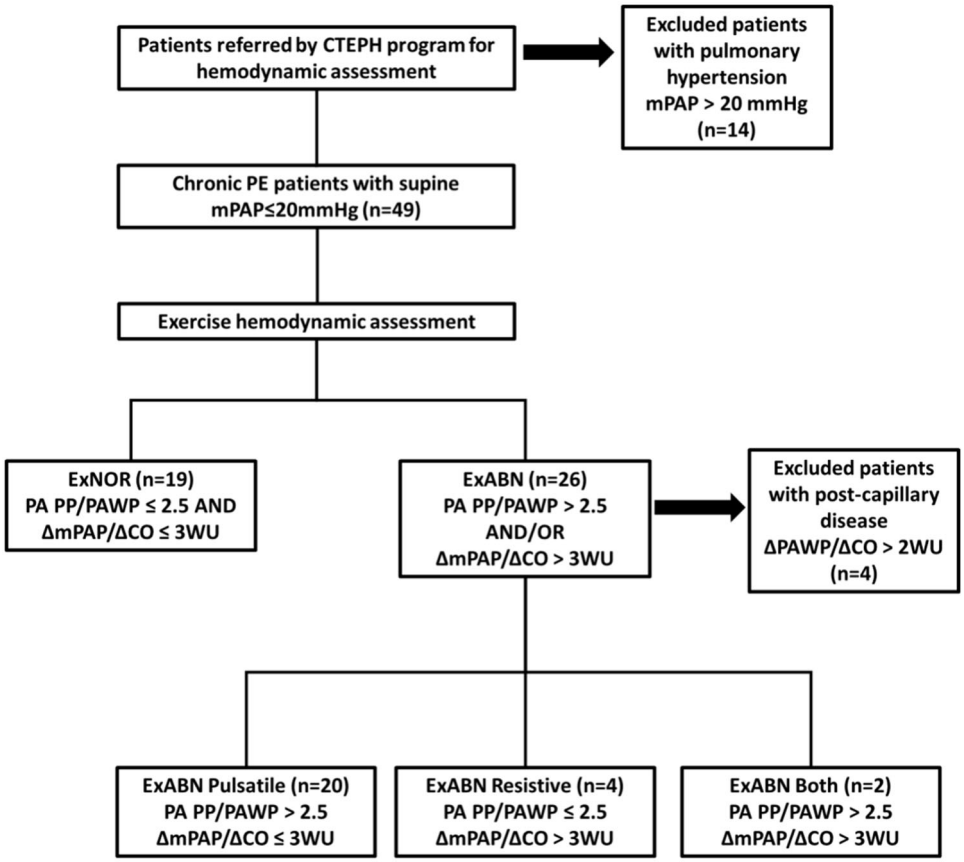

FIGURE 1 CONSORT diagram. CO, cardiac output; CTEPH, chronic thromboembolic pulmonary hypertension; ExABN, exercise abnormal group; ExNOR, exercise normal group; mPAP, mean pulmonary artery pressure; PAPP, pulmonary artery pulse pressure; PAWP, pulmonary artery wedge pressure; PE, pulmonary embolism.

TABLE 1 Clinical characteristics of all CTEPD patients and in the ExNOR and ExABN groups.

Demographic and clinical information	All CTEPD ($n = 45$)	ExNOR ($n = 19$)	ExABN ($n = 26$)	p Value
Age, *years*	53 ± 14	53 ± 15	53 ± 14	0.943
Sex, *% male/female*	71/29	84/16	62/38	0.182
Height, *cm*	175 ± 9	176 ± 8	174 ± 10	0.461
Weight, *kg*	86 (75–101)	98 (89–108)	77 (74–88)	0.010
BSA, m^2	2.1 ± 0.3	2.1 ± 0.2	2.0 ± 0.2	0.022
BMI, kg/m^2	27.5 (24.5–32.1)	31.8 (28.8–34.7)	26.2 (24.1–29.0)	0.011
Treated with PEA/ BPA, *n (%)*	15(33)	4(21)	11(42)	0.203
Comorbidities and medications				
Diabetes, *n (%)*	4(9)	2 (11)	2 (8)	0.999
Hypertension	14 (31)	7 (37)	7 (28)	0.528
COPD/asthma	7 (16)	2 (11)	5 (20)	0.681
Anticoagulation	39 (87)	15 (79)	24 (96)	0.377
Hemoglobin, *g/L*	143 ± 16	145 ± 14	142 ± 17	0.452
eGFR, *mL/min/ 1.73* m^2	83 ± 20	89 ± 21	78 ± 18	0.09
ACE/angiotensin blocker, *n (%)*	6 (13)	4 (21)	2 (8)	0.377
Beta blocker	4 (9)	1 (5)	3 (12)	0.627
Calcium channel blocker	7 (16)	2 (11)	5 (20)	0.681
Diuretics	11	16	8	0.636

Note: Data are presented as mean ± SD, median(Q1–Q3), or percentage.

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; BPA, ballon pulmonary angioplasty; BSA, body surface area; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; PEA, pulmonary endarterectomy.

for treatment interventions ($p = 0.203$) nor distribution of disease level ($p = 0.590$) between the two groups.

Exercise responses and distribution of resistive and pulsatile afterload

The distribution of resistive and pulsatile pulmonary vascular afterload measures during exercise are shown in Figure 2. As predefined, 19 patients (42%) showed no abnormalities of pulmonary vascular resistive or pulsatile afterload with exercise forming the ExNOR group. Exercise elicited an abnormal pulmonary vascular afterload response in 26 patients (58%), forming the ExABN group. Within the ExABN group, abnormalities were pulsatile in 20 patients (77%), resistive in 2 patients (8%) and both pulsatile and resistive in 4 patients (15%). Overall, the proportion of patients with pulsatile ExABN was significantly higher than the proportion with resistive ExABN ($p < 0.001$).

Clinical and hemodynamic profiles in CTEPD without PH and latent CTEPH groups

There were no significant differences regarding age, and sex between the ExNOR and ExABN groups. Weight, BSA, and body mass index (BMI) were greater in the ExNOR group compared to the ExABN group.

Resting hemodynamics from the ExNOR and ExABN groups/subgroups are presented in Table 2. Although classifications were based on exercise responses, several differences in resting hemodynamics were observed. The

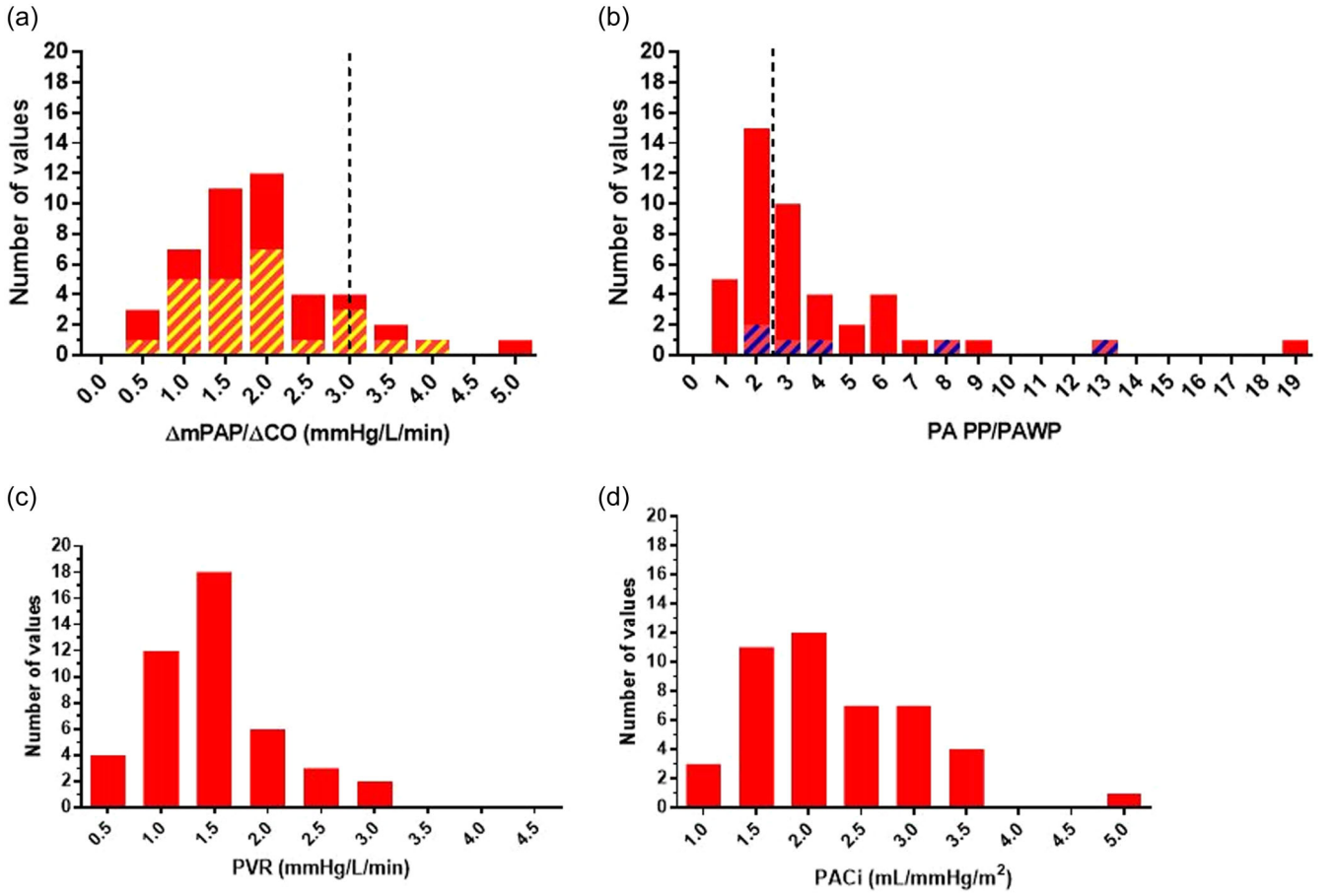

FIGURE 2 The distribution of exercise-associated resistive and pulsatile pulmonary afterload abnormalities, $n = 45$. (a) mean pulmonary artery pressure-cardiac output slope (ΔmPAP/ΔCO). The vertical line indicates the upper limit of normal for exercise ΔmPAP/ΔCO of 3 WU. Six patients or 13% of the population demonstrated a ΔmPAP/ΔCO > 3 WU. Patients with an elevated exercise Pulmonary artery pulse pressure—pulmonary artery wedge pressure ratio (PAPP/PAWP) response are indicated by the hatched portion of the bar. (b) PAPP/PAWP. The vertical line indicates the upper limit of normal for exercise PAPP/PAWP of 2.5. Twenty-four patient or 53% of the population demonstrated an exercise PAPP/PAWP > 2.5. Patients with an elevated ΔmPAP/ΔCO response are indicated by the hatched portion of the bar. Of 45 patients, 26 (58%) had abnormalities of resistive and/or pulsatile afterload during exercise. (c) pulmonary vascular resistance. (d) Pulmonary arterial compliance index.

ExABN group had lower RA and PAWP, but a higher PASP. The ExABN group also demonstrated an elevated PVR, PAPP/mPAP, and a lower PAC index. Increases in PVR were associated with higher TPG in the ExABN group and not differences in CO between the two groups. Lower PAC index was also associated with broader PA PP in the ExABN group and not differences in SV between the two groups.

Exercise hemodynamics from the ExNOR and ExABN groups/subgroups are presented in Table 3. There was no difference in work rate achieved between the two groups. With exercise, the ABN group had lower RA pressure and PAWP, but a higher PASP. In response to exercise, the ExABN group also demonstrated an elevated PVR, PAPP/mPAP, and a lower PAC index. Increases in PVR were associated with higher TPG in the ExABN group and not differences in CO between the two groups. Lower PAC index was also associated with a broader PA PP in the ExABN group and not differences in SV between the two groups.

The relationships between PAC, PVR, and PAWP at rest and during exercise

The PAC-PVR relationships at rest and with exercise in the ExNOR and ExABN groups are illustrated in Figure 3a,b. The ExABN group was shifted toward the horizontal limb of PAC-PVR relationship based on both higher PVR and lower PAC. The calculated RC time product was significantly prolonged in the ExABN compared to the ExNOR group at rest.

TABLE 2 Resting hemodynamics in ExNOR and ExABN groups, and ExABN subgroups.

Hemodynamics	ExNOR ($n = 19$)	ExABN ($n = 26$)	ANOVA	ExABN pulsatile ($n = 20$)	ExABN resistive ($n = 2$)	ExABN both ($n = 4$)
HR, *bpm*	69 ± 15	70 ± 13	0.875	71 ± 15	66 ± 4	66 ± 6
SBP, *mmHg*	127 ± 12	122 ± 13	0.115	122 ± 14	116 ± 2	123 ± 12
DBP	82 ± 10	81 ± 10	0.429	82 ± 9	69 ± 17	78 ± 12
TDCI, $L/min/m^2$	2.6 ± 0.6	2.7 ± 0.6	0.979	2.8 ± 0.6	2.4 ± 0.6	2.6 ± 0.4
SVi, mL/m^2	39 ± 9	40 ± 9	0.836	40 ± 9	38 ± 11	40 ± 8
SaO_2, *%*	96 ± 2	98 ± 2[a]	0.031	98 ± 2	97 ± 1	95 ± 3
SvO_2	67 ± 6	70 ± 5	0.261	70 ± 5	71 ± 5	69 ± 6
RAP, *mmHg*	4 ± 3	2 ± 2[a]	0.027	1 ± 2	4 ± 0	2 ± 3
PASP	23 ± 4	26 ± 5[a]	0.039	25 ± 5	29 ± 8	29 ± 7
PADP	9 ± 3	7 ± 3	0.281	7 ± 3	8 ± 3	6 ± 2
mPAP	15 ± 3	16 ± 3	0.443	15 ± 4	17 ± 1	16 ± 4
PAPP	15 ± 3	19 ± 5[a]	0.003	18 ± 4	21 ± 11	23 ± 8
PAWP	9 ± 3	6 ± 3[a]	0.007	6 ± 3	8 ± 4	5 ± 3
TPG	7 ± 3	10 ± 3[a]	<0.001	10 ± 2	9 ± 6	11 ± 3
PVR, *mmHg/L/min*	1.2 ± 0.6	1.9 ± 0.7[a]	<0.001	1.9 ± 0.7	1.8 ± 0.3	2.2 ± 1.0
TPR	2.9 ± 1.0	3.0 ± 1.0	0.088	2.9 ± 1.0	3.8 ± 1.5	3.1 ± 0.9
PACi, $mL/mmHg/m^2$	2.8 ± 0.7	2.2 ± 0.5[a]	<0.001	2.3 ± 0.5	2.4 ± 0.2	1.8 ± 0.3
RC time, *s*	0.4 ± 0.12	0.48 ± 0.11[a]	0.008	0.49 ± 0.10	0.39 ± 0.07	0.46 ± 0.15
PAPP/PAWP	1.9 ± 0.8	4.6 ± 3.7[a]	0.004	4.2 ± 2.7	3.4 ± 3.1	7.7 ± 7.0
PAPP/mPAP	1.0 ± 0.2	1.2 ± 0.3[a]	0.002	1.2 ± 0.2	1.2 ± 0.5	1.5 ± 0.3

Note: Data are presented as mean ± SD.

Abbreviations: ABN, abnormal; CTEPD, chronic thromboembolic pulmonary disease; DBP, diastolic blood pressure; HR, heart rate; NOR, normal; PACi, pulmonary artery compliance index; PADP, pulmonary artery diastolic pressure; PAPP, pulmonary artery pulse pressure; PAPP/mPAP, pulmonary artery pulse pressure—mean pulmonary artery pressure ratio; PAPP/PAWP, pulmonary artery pulse pressure—pulmonary artery wedge pressure ratio; PASP, pulmonary artery systolic pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RC time; resistance-compliance time product; SaO2, arterial oxygen saturation; SBP, systolic blood pressure; Svi, stroke volume index; SvO2, mixed venous oxygen saturation; TDCI, thermodilution cardiac index; TPG, trans-pulmonary gradient; TPR, total pulmonary resistance.

[a]Significant vs. ExNOR, $p < 0.05$.

The effect of exercise on the RC time product was also different (Figure 3c), declining significantly in the ExABN group (−0.12 ± 0.02 s) with no significant change observed in the ExNOR group (−0.04 ± 0.02 s).

We examined the relationships between the PAWP and the PA pressures (Figure 4). As noted, the ExABN group demonstrated lower PAWP at both rest and exercise. Despite smaller PAWP increases compared to the ExNOR group, exercise in the ExABN group was associated with larger increases in PA PP (Δ13 ± 7 mmHg vs. Δ 7 ± 4 mmHg, $p = 0.003$) and larger PASP responses to exercise (Δ19 ± 8 mmHg vs. Δ14 ± 6 mmHg, $p = 0.025$) (Figure 4a,b). Analysis of individual data demonstrated that relationships between PAWP and PA pressures (Figure 4c,d) during exercise also differed between the ExNOR and ExABN groups. In the ExNOR group, linear relationships between the PAWP and PA pressures were preserved with exercise. In the ExABN group during exercise, a linear relationship between PAWP and PASP, was not observed.

Sensitivity and specificity of resting measures in predicting ExABN

ROC curves were created to examine the sensitivity and specificity of resting measures of PAC, PVR, PAPP/mPAP, and PAPP/PAWP in predicting latent abnormalities of pulmonary afterload as illustrated in Figure 5. Only PAPP/PAWP and PAPP/mPAP ratios demonstrated

TABLE 3 Exercise hemodynamics in ExNOR and ExABN groups, and ExABN subgroups.

Hemodynamics	ExNOR ($n = 19$)	ExABN ($n = 26$)	ANOVA	ExABN pulsatile ($n = 20$)	ExABN resistive ($n = 2$)	ExABN both ($n = 4$)
Work rate, *W*	57 ± 21	48 ± 17	0.124	50 ± 15	28 ± 18	44 ± 19
HR, *bpm*	105 ± 21	107 ± 19	0.995	110 ± 19	98 ± 29	100 ± 16
SBP, *mmHg*	157 ± 21	155 ± 22	0.309	156 ± 22	156	152 ± 24
DBP	80 ± 9	81 ± 14	0.826	82 ± 14	83	78 ± 12
TDCI, $L/min/m^2$	5.6 ± 1.4	5.9 ± 1.2	0.819	6.3 ± 1.1	4.2 ± 0.7	4.8 ± 0.1
SVi, mL/m^2	55 ± 14	56 ± 13	0.849	59 ±± 14	44 ± 6	49 ± 7
SaO_2, *%*	97 ± 2	96 ± 3	0.758	97 ± 2	99 ±± 1	94 ± 2
SvO_2	45 ± 7	46 ± 8	0.727	45 ± 7	55 ± 20	46 ± 4
RAP, *mmHg*	5 ± 3	3 ±± 3[a]	0.007	3 ± 2	6 ± 4	3 ± 2
PASP	38 ± 7	45 ± 12[a]	0.031	44 ± 13	42 ± 4	52 ± 4
PADP	16 ± 4	14 ± 4	0.074	14 ± 5	17 ± 2	13 ± 2
mPAP	26 ± 4	27 ± 7	0.365	27 ± 7	30 ± 4	31 ± 3
PAPP	22 ± 5	32 ± 10[a]	<0.001	31 ± 10	26 ± 2	39 ± 5
PAWP	13 ± 4	8 ± 3[a]	<0.001	8 ± 3	14 ± 4	8 ± 4
TPG	13 ± 3	20 ± 5[a]	<0.001	19 ± 6	16 ± 0	23 ± 4
PVR, *mmHg/L/min*	1.2 ± 0.5	1.7 ± 0.6[a]	<0.001	1.6 ± 0.5	2.0 ± 0.1	2.4 ± 0.5
TPR	2.3 ± 0.7	2.5 ± 0.8	0.104	2.2 ± 0.7	3.7 ± 0.7	3.2 ± 0.6
PACi, $mL/mmHg/m^2$	2.7 ± 0.8	1.9 ± 0.6[a]	0.001	2.0 ± 0.6	1.7 ± 0.4	1.3 ± 0.1
RC time, *s*	0.36 ± 0.10	0.36 ± 0.09	0.303	0.36 ± 0.09	0.41 ± 0.15	0.36 ± 0.07
PAPP/PAWP	1.7 ± 0.5	5.1 ± 3.7[a]	<0.001	5.1 ± 3.7	1.9 ± 0.3	6.7 ± 4.6
PAPP/mPAP	0.8 ± 0.2	1.2 ± 0.2[a]	<0.001	1.2 ± 0.2	0.9 ± 0.1	1.3 ± 0.1

Note: Data are presented as mean ± SD.

Abbreviations: ABN, abnormal; CTEPD, chronic thromboembolic pulmonary disease; DBP, diastolic blood pressure; HR, heart rate; NOR, normal; PACi, pulmonary artery compliance index; PADP, pulmonary artery diastolic pressure; PAPP, pulmonary artery pulse pressure; PAPP/mPAP, pulmonary artery pulse pressure—mean pulmonary artery pressure ratio; PAPP/PAWP, pulmonary artery pulse pressure—pulmonary artery wedge pressure ratio; PASP, pulmonary artery systolic pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RC time; resistance-compliance time product; SaO2, arterial oxygen saturation; SBP, systolic blood pressure; Svi, stroke volume index; SvO2, mixed venous oxygen saturation; TDCI, thermodilution cardiac index; TPG, trans-pulmonary gradient; TPR, total pulmonary resistance.

[a]Significant vs. ExNOR, $p < 0.05$. Within group differences are not shown.

an acceptable area under the curve (AUC) of 0.82 and 0.81, respectively. Despite the high AUC a PAPP/mPAP > 1 had a sensitivity of 96% but a specificity of 50%. PAPP/PAWP of 2.5 had a sensitivity of 85% and a specificity of 39%, while a ratio >4.8 had a specificity of 100%.

DISCUSSION

As hypothesized, among CTEPD patients with mPAP ≤20 mmHg, and without left heart disease, abnormalities of pulsatile afterload were commonly elicited by exercise, more so than abnormalities of resistive afterload. Several observations were consistent with the notion that the ExABN group had deranged pulmonary vascular physiology despite normal resting hemodynamics, including the position of this group toward the horizontal limb of the RC time curve. Further, relationships between PA pressures and PAWP typically observed in healthy subjects with exercise,[11] were not present in the ExABN group. We did not find a greater level of disease or a higher probability to be selected for treatment interventions in the ExABN group compared to the ExNOR group. The addition of exercise revealed over 50% of our study population to have latent abnormalities of pulmonary vascular afterload despite normal resting hemodynamics.

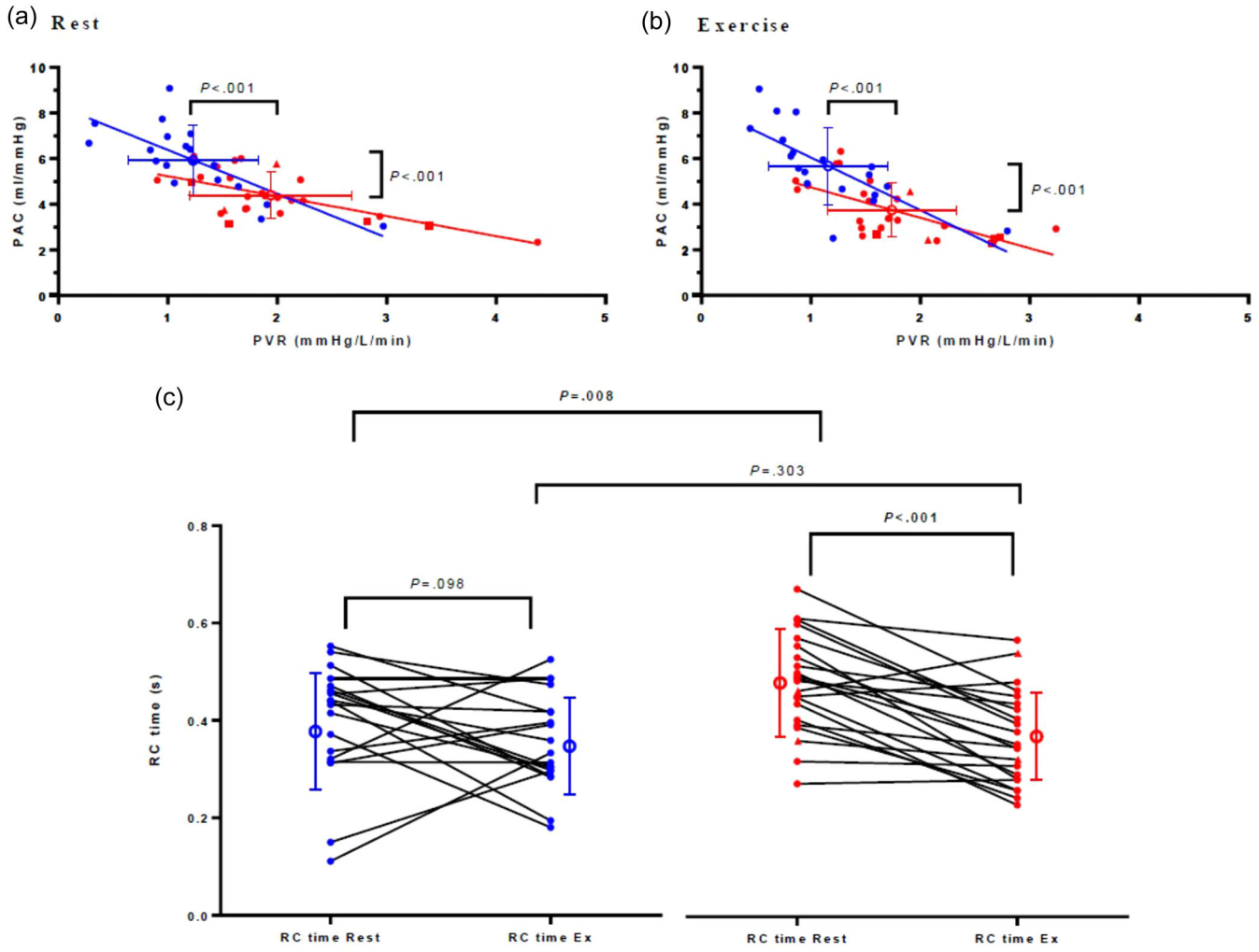

FIGURE 3 Relationship between PVR and PAC, and RC-time at rest and exercise in ExNOR and ExABN groups. PVR-PAC relationship at rest (a) and exercise (b) and change in RC time product with exercise (c) in the ExNOR group (blue symbols) and ExABN group (red symbols, red circles—latent pulsatile, red triangles—latent resistive, red squares—latent both). Open symbols indicate group means. Ex, exercise; PAC, pulmonary artery compliance; PVR, pulmonary vascular resistance; RC time, resistance-compliance time product.

Our study extends previous work[14-17] by considering abnormal increases of pulsatile pulmonary vascular afterload in addition to the latest ESC guideline definition of exercise PH based on resistive abnormalities. Previous studies included patients with mPAP up to 25 mmHg, and who had been selected for PEA surgery. We employed more restrictive hemodynamic criteria (mPAP ≤ 20 mmHg) to exclude patients with PH as per both the ESC guidelines and the most recent World Symposium definition.[5] This may explain why, compared to these previous studies, we observed a lower prevalence of $\Delta mPAP/\Delta CO > 3$ WU,[14,17] approximately one-fifth of our sample. When comparing the hemodynamic responses observed in this study to other studies examining patients with CTEPD without PH, differences in exercise work rate may explain discrepant results. Our program employed pragmatic, fixed workrates based on self-reported exertional symptoms as measured by the MRC score, compared with previous studies that employed either a similar fixed work rate,[17] 40% of maximum work rate[16] or a peak symptom-limited protocol.[14,15]

The current study is consistent with the investigations that have shown relatively greater impairment of resting PAC relative to PVR[9,18] among patients with established CTEPH. The anatomic distribution of organized thrombotic material may contrast significantly to the diffuse, angioproliferative remodeling of pulmonary arterioles in Group 1 pulmonary arterial hypertension.[19] It has been demonstrated that more proximal disease burden assessed radiographically in CTEPH patients is associated with higher pulsatile afterload due to summation of early pulse wave reflection.[9] In addition, the distribution of disease can be asymmetric, and lung

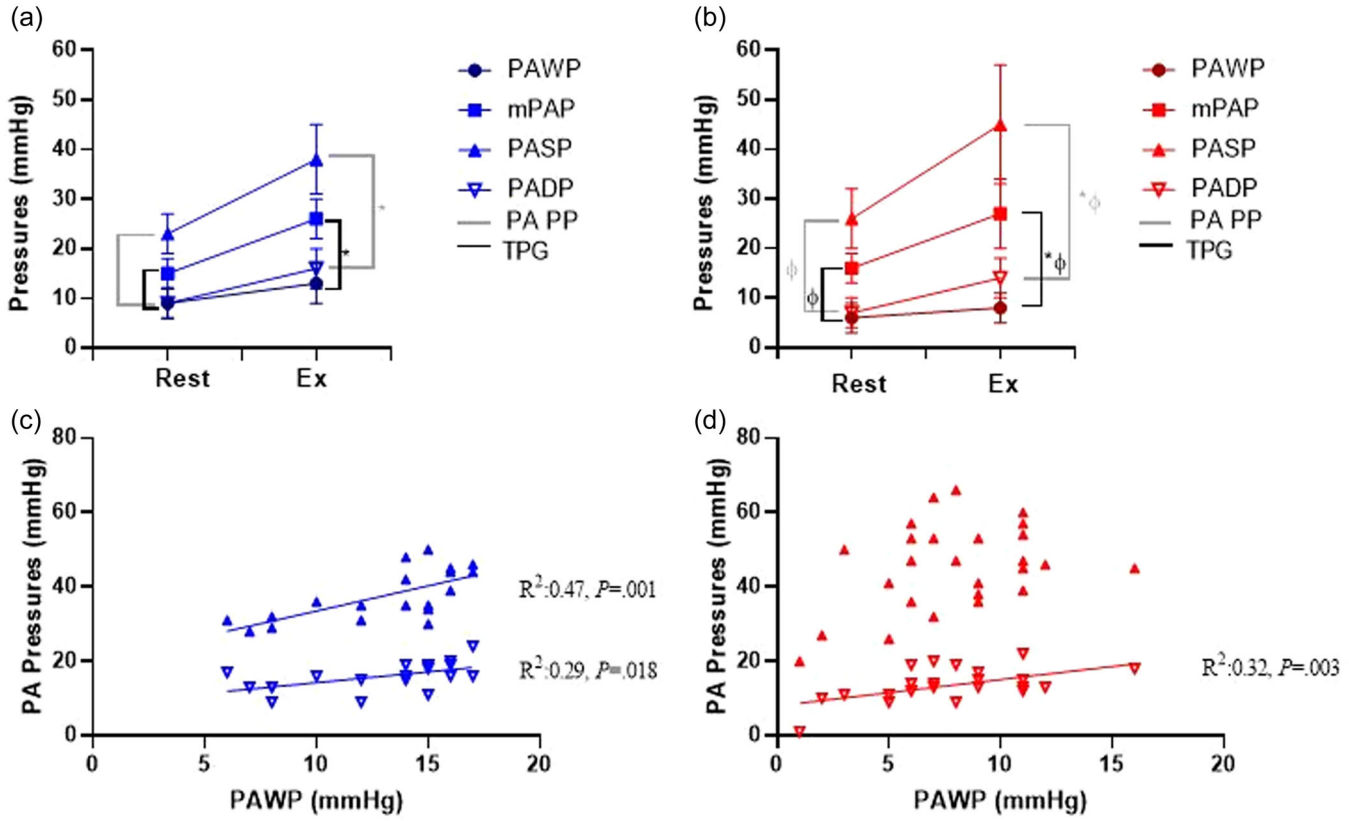

FIGURE 4 PA pressures and PAWP correlations at rest and exercise. ExNOR (left panels, blue symbols) and ExABN (right panels, red symbols) groups. (a, b) Relationship of PA pressures and PAWP at rest and exercise; (c, d) individual data relationships between PAWP and PASP or PADP at exercise. Linear correlations shown were significant. mPAP, mean pulmonary artery pressure; PA, pulmonary artery; PADP, pulmonary artery diastolic pressure; PASP, pulmonary artery systolic pressure; PAWP, pulmonary artery wedge pressure. * = significant versus rest, $p < 0.05$. Φ = significant versus ExNOR, $p < 0.05$.

segments with relatively normal perfusion may preserve lower resistance. Whether the same findings also apply to patients with CTEPD without PH is not known, as they do not demonstrate hemodynamic abnormalities at rest, thus requiring exercise RHC to reveal any latent abnormalities of RV afterload. In this study we briefly describe the distribution of disease level in all the CTEPD patients but found no differences between the ExNOR and ExABN groups. Future work should examine disease burden in CTEPD patients without PH that demonstrate altered pulsatile and/or resistive afterload with exercise in more detail to determine the potential implications of anatomic distribution and locus of chronic thrombi on RV afterload.

In this study, we employed the relatively simple measurement of PAPP to approximate the amplitude of pulsatile stress,[8] incorporated in calculations such as PAC, PAPP/mPAP, and PAPP/PAWP. PAPP/mPAP has been referred to as normalized PAPP or pulmonary fractional PP, with a ratio of about 1 at rest in health.[20] Even at rest PAPP/mPAP demonstrates mixed results in chronic PE patients and appears to be a function of mPAP rather than an indication of pulsatile load abnormalities.[9,21] While PAC may be a more widely used measure of pulsatile pulmonary vascular load it is also not without limitations. Calculation of PAC from variables measured during RHC demonstrates a broad range among both, healthy individuals and patient populations.[22-25] As such, there is no consensus on physiologic ranges for PA compliance or a single threshold value denoting abnormal compliance. In health, exercise associated increases of PAWP are closely related to both declines in PAC as well as predictable linearly-related increases in the PAPP.[11] As a direct corollary, the ratio of PAPP to PAWP during exercise maintains a relatively narrow range in health.[10] We have previously shown that PAPP/PAWP > 2.5 appears to identify abnormal pulsatile afterload during exercise,[10] even as resistive load is normal. Using this approach, the resultant ExABN group identified in the current study demonstrated several pathophysiological characteristics. The ExABN group demonstrated lower PAC index and higher PVR despite lower PAWP even at rest. During exercise, the physiological relationships described above

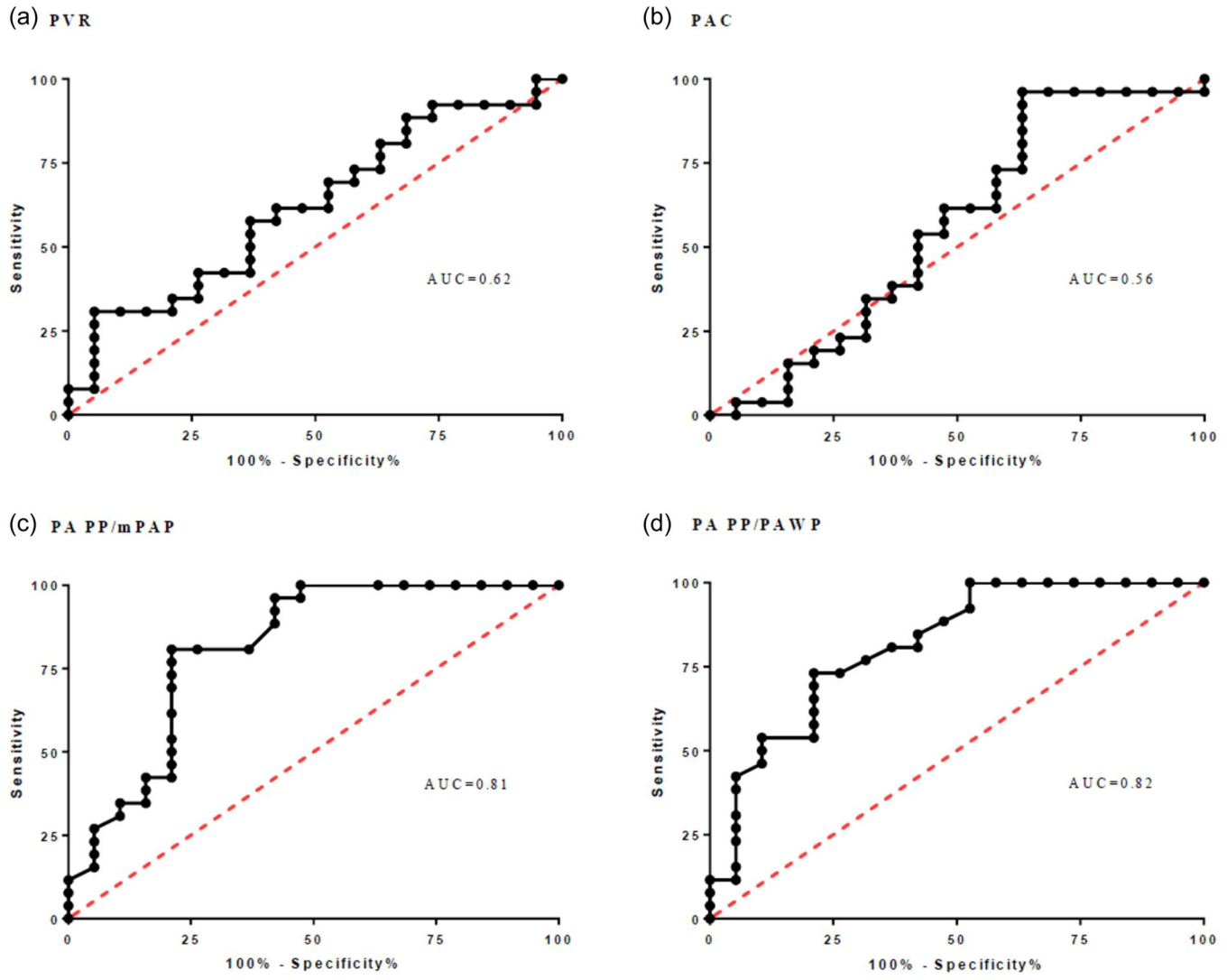

FIGURE 5 Receiver operator characteristic curves for baseline supine measures of pulmonary vascular afterload. Red dotted line is the line of identity. (a) pulmonary vascular resistance; (b) pulmonary arterial compliance, (c) pulmonary artery pulse pressure to mean pulmonary artery pressure ratio, (d) pulmonary artery pulse pressure to pulmonary artery wedge pressure ratio. AUC, area under the curve.

between increases in PAWP, and the PAPP were not discernible in the ExABN group.

Among ExABN patients, we also observed altered interrelationships between PAC, PVR and the RC time product, another manifestation of the higher pulsatile relative to resistive afterload. Across populations, PAC is demonstrated to be related to PVR in a characteristic hyperbolic relationship known as RC time. Previous work has also shown that exercise-increases in PAWP lowers RC time[11] based on lower PAC relative to PVR.[11,24] The ExABN group in the current study demonstrated marked declines in PAC and RC time with exercise, despite lower PAWP. The ExABN group was also positioned toward the horizontal limb of the RC time relationship at rest and exercise.

The clinical implications of this study are unclear. Patients in the ExNOR group were more likely to be obese. The lack of differences in level of disease between the two groups of patients highlights the notion that exercise limitation after pulmonary embolism is complex, and may relate to gas exchange abnormalities or deconditioning and other factors unrelated to the pulmonary vascular physiology.[26,27] Our findings suggest that exercise hemodynamic evaluation of CTEPD patients considering measures of pulsatile afterload may be more sensitive than ΔmPAP/ΔCO alone to identify abnormal hemodynamic afterload responses. Resting measurements of PAC, PAPP/PAWP also did not demonstrate great utility to predict latent abnormalities in CTEPD without PH. There is currently no consensus on the role of exercise hemodynamic information to

guide treatment decisions in CTEPD without PH. Whether patients with latent abnormalities of pulsatile pulmonary vascular afterload may benefit from interventions would require further study. Of note, a recent study demonstrated in a small group of CTEPH patients with mPAP < 25 mmHg, abnormal increases in ΔmPAP/ΔCO with exercise, were reduced after PEA surgery.[14]

Limitations of our study include the cross-sectional, single center design. We acknowledge that the surrogate measurements of both PAC and PAPP/PAWP are limited and do not illuminate the mechanism of increased pulsatile loads at rest in CTEPH or during exercise in CTEPD without PH. The study is also limited based on a lack of measures of gas exchange or ventilation. Gas exchange measurements would more clearly document actual limitations to aerobic capacity, help to differentiate causes of dyspnea in a complicated disease model, and provide a metric of relative exercise intensity. While this study is limited without examinations of a correlation between anatomical disease burden and hemodynamic abnormalities a future direction to provide further proof of concept would be to evaluate whether more proximal anatomic distribution of thromboembolic disease is associated with more latent pulsatile afterload abnormalities.

CONCLUSION

In our experience, 58% of patients with CTEPD, defined by resting mPAP ≤ 20 mmHg, demonstrate abnormal pulmonary vascular afterload responses to exercise. Pulsatile abnormalities of pulmonary vascular afterload were elicited more frequently than resistive abnormalities.

AUTHOR CONTRIBUTIONS

Sinan Osman, Natasha R. Girdharry, Elizabeth Karvasarski, Robert F. Bentley, Stephen P. Wright, and Susanna Mak contributed substantially to the study design, data analysis, data acquisition, interpretation, and the writing of the manuscript. Nadia Sharif and Micheal McInnis both contributed substantially to data acquisition and interpretation. John T. Granton, and Marc dePerrot contributed substantially to the revision of the work and final approval of the version to be published. Susanna Mak had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

The prospective registry was approved by the Mount Sinai research ethics board (REB no. 16-0217-E) and additional retrospective analysis was also approved by Mount Sinai and University Health Network research ethics boards (REB no. 19-0272-C and no. 19-6077).

ORCID

Sinan Osman http://orcid.org/0000-0002-6708-2763
Nadia Sharif http://orcid.org/0000-0001-9961-515X
Susanna Mak http://orcid.org/0000-0003-2193-602X

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