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Cardiopulmonary Exercise Testing With Simultaneous Echocardiography After Pulmonary Embolism

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ABSTRACT

Although current guidelines recommend standard cardiopulmonary exercise testing (CPET) to evaluate symptomatic patients after pulmonary embolism (PE), CPET with simultaneous echocardiography could provide relevant information to evaluate right ventricular–pulmonary arterial coupling. The aim of this study was to investigate exercise-induced changes in echocardiographic variables of RV function or RV– arterial coupling in patients with residual thrombotic defects at 3 months after PE. This retrospective study investigated patients with residual thromboembolic disease on V/Q scintigraphy with persistent symptoms despite adequate anticoagulation after 3 months of acute PE, and resting echocardiography with a low probability of PH. At rest and during exercise, CPET and doppler echocardiography were performed following a standard protocol. Forty-five patients were included, completing a follow-up period of at least 24 months. The mean (standard deviation) age was 63 (15) years, and 24 (53%) patients were male. Four patients developed CTEPH after 2 years follow up. Correlation analyses showed that the peak TAPSE was significantly associated with peak workload ($r = 0.454$, $p = 0.003$), peak VO_2 ($r = 0.558$, $p < 0.001$), $VE/VECO_2$ (AT) ($r = -0.531$, $p < 0.001$), and oxygen pulse ($r = 0.375$, $p = 0.02$). TAPSE/PASP was only slightly associated with peak workload ($r = 0.300$, $p = 0.045$). By contrast, the change on TAPSE (from rest to peak) was significantly correlate with peak oxygen uptake ($r = 0.491$, $p = 0.01$). Also, reduced VO_2 at AT and TAPSE/PASP was seen in patients with CTEPH. CPET with synchronic echocardiography could be a useful tool in early assessment of symptomatic patients with perfusion defects on imaging after 3 months of correctly treated PE.

1 | Background

Chronic thrombo-embolic pulmonary disease (CTEPD) and Chronic thromboembolic pulmonary hypertension (CTEPH) represents a late, serious complication of acute pulmonary embolism (PE) with incomplete resolution of pulmonary thrombi and endothelial dysfunction leading to pulmonary vascular remodeling associated with loss of functional capacity, despite adequate anticoagulation therapy [1]. The incidence of CTEPH following a PE seems to be relatively low, as indicated

by various studies [2–4]. This low occurrence does not favor the implementation of adequate cost-efficient CTEPH screenings for all individuals who have experienced an acute PE episode. Recently, two approaches have emerged that aim to assist in the identification of patients at risk of developing CTEPH after PE [5–7]. Nevertheless, neither of these approaches explore the crucial aspect of early detection of the disease, which is a pivotal factor in implementing an appropriate surgical or pharmacological treatment [1]. In this context, one of the key indicators of a potential complication following PE is the presence of shortness of breath during exertion [2–6]. Despite not being routinely recommended for all patients [1], recent studies propose that cardiopulmonary exercise testing (CPET) could offer valuable insights in individuals experiencing persistent symptoms and functional limitations after PE [4, 8]. This is particularly relevant when echocardiography is inconclusive regarding the presence of pulmonary hypertension. In those studies, it was reported that a substantial group of patients encountered exercise limitations from 3 to 12 months during the follow-up period [4, 8]. However, the authors highlighted the complexity of interpreting symptoms after PE, as they demonstrated that in the majority of cases, the decline in exercise capacity is attributed to muscle deconditioning [9]. Furthermore, many patients with significant comorbidities further complicate the process of attributing specific symptoms to residual PE [4]. In fact, Farmakis et al. [8] showed that only 10% of patients had clearly poor ventilatory efficiency, a recognized surrogate of increased dead space ventilation in these patients [10]. However, this abnormality was more severe in patients that developed CTEPH during follow-up.

In light of these data, CPET has the potential to function as a robust diagnostic tool for individuals experiencing persistent symptoms or functional impairments following PE. However, CPET's efficacy in identifying patients in the early stages of CTEPD [1] who may develop CTEPH in the future is relatively limited [4–8]. Although current guidelines recommend standard CPET rather than CPET with echocardiography, the addition of echocardiogram provides insightful prognostic information [11], improves the understanding of cardiorespiratory and hemodynamic function during exercise, and is particularly useful to discover right ventricular (RV)–pulmonary arterial (PA) coupling [12]. For these reasons, as previously demonstrated in patients with pulmonary vascular diseases [11, 13], CPET with simultaneous echocardiography could be a reasonable and promising tool to explore the abnormalities in patients with residual thrombotic disease after PE.

The aim of this study was to investigate exercise-induced changes in echocardiographic variables of RV function or RV–PA coupling in patients with residual thrombotic defects after PE and persistent symptoms. We also evaluated the relationship between echocardiography variables and CPET parameters in these patients.

2 | Methods

2.1 | Study Population

This retrospective study investigated patients with the following inclusion criteria: residual thromboembolic disease on lung V/Q scintigraphy with persistent symptoms despite adequate anticoagulation after 3 months of acute PE; and rest echocardiography with a low probability of PH [1]. The patients were evaluated between February 2016 and November 2021 at the exercise laboratory unit (Pulmonary Department of Hospital del Mar, Barcelona, Spain). Patients with conditions preventing the performance of the cardiopulmonary exercise test, including neurological, musculoskeletal alterations, or uncontrolled psychiatric disorders, were excluded. Also, patients were excluded from the study if they met any of the following criteria; current or prior history of symptomatic coronary disease, known history of pulmonary hypertension, left ventricular ejection fraction $< 45\%$, significant ($\geq$ 2+ regurgitation) mitral regurgitation or aortic regurgitation valvular disease, significant (< FEV1 60% and/or < FVC 60%) respiratory disease or data of diastolic dysfunction at rest echocardiography. This study was approved by the Ethics Committee of the IMIM-Hospital del Mar.

2.2 | Cardiopulmonary Exercise Testing With Simultaneous Echocardiography

At rest and during exercise, doppler echocardiography was performed following a standard protocol [14]. Echocardiographic measurements were sampled 3 min before exercise and during the first minute of maximum workload. Pulmonary arterial systolic pressure (PASP) was estimated from peak tricuspid regurgitation jet velocity (TRV) at multiple time points, according to the simplified Bernoulli's equation: $PASP = 4(V)^2 +$ right atrial pressure, where V is the peak velocity (in m/s) of tricuspid regurgitation jet. Tricuspid annular plane systolic excursion (TAPSE) measurements were recorded with M-mode echocardiography. Echocardiographic assessment was stored in the DICOM (digital imaging and communications in medicine) format. Patients were examined on a variable-load recumbent bicycle ergometer (Ergoline Medical Graphics Corporation, St. Paul, MN, USA) as described previously [15]. Workload was increased by 10–20 W every minute up to symptoms-limited exercise. Oxygen uptake (VO_2), pulmonary carbon dioxide output (VCO_2), respiratory exchange ratio, minute ventilation (V_E), tidal volume, and respiratory rate (RR) were recorded during each respiration. Heart rate (HR) was evaluated using a twelve-lead online electrocardiogram and oxygen saturation by pulse oximetry (SpO_2).

2.3 | Follow-Up Assessment

Patients were followed over a 2-year period after the PE episode, with a standardized assessment plan according to current national guidelines [16]. Detailed demographic and clinical data, diagnostic and therapeutic procedures, and outcome variables were retrospectively recorded.

2.4 | Statistical Analysis

Continuous variables are expressed as mean $\pm$ standard deviation for normally distributed variables and median [Q1, Q3] for non-normally distributed variables. Kolmogorov-Smirnov test

was used to assess variables distribution. Normally distributed variables were compared between groups using unpaired Student's *t*-test, assuming unequal variance. Non-normally distributed variables were compared between groups using nonparametric Mann-Whitney U test or Kruskal-Wallis test. Rates and proportions were compared between interest groups using χ-square test or continuity correction test. For normally distributed continuous variables, statistical comparisons between groups were established by executing one-way ANOVA test. Analyses were performed using the SPSS/PC program (version 28.0, IBM SPSS Inc., Chicago, IL, USA) and values of $p < 0.05$ were considered statistically significant. There are no previous studies that apply this methodology to a low-prevalence disease, however the sample size was similar to previous studies with a comparable technique [17, 18].

3 | Results

In this study, we collected data from 45 patients who met the inclusion criteria and completed a follow-up period of at least 24 months. Characteristics of the study population and acute PE presentation are summarized in Table 1. The mean age was 63 [15] years, and 24 (53%) patients were male. The majority of patients had an intermediate or high-risk PE with a central and/or segmental radiological presentation. More than 70% of patients had a functional class II or III 3 months after PE. Four patients developed CTEPH after 2 years follow up. Regarding CPET parameters, patients presented a moderately decreased exercise capacity without ventilatory limitation, whereas the VE/VCO_2 (at anaerobic threshold, AT) was slightly increased (Table 2). Resting and peak exercise values of RV function or RV– arterial coupling indices are reported in Table 2. Significant correlations between echocardiographic variables (TAPSE, TAPSE/PASP, and PASP) at rest and peak exercise are illustrated in Figure 1. Correlation analyses showed that the peak TAPSE was significantly associated with peak workload ($r = 0.454$, $p = 0.003$), peak VO_2 ($r = 0.558$, $p < 0.001$), $VE/VECO_2$ at AT ($r = -0.531$, $p < 0.001$), and oxygen pulse ($r = 0.375$, $p = 0.02$) (Figure 2). Of note, TAPSE/PASP was only slightly associated with peak workload ($r = 0.300$, $p = 0.045$). By contrast, the change on TAPSE (from rest to peak) was significantly correlate with peak oxygen uptake (Figure 3A).

Detailed CPET and echocardiographic parameters for patients who developed CTEPH and those who did not need further evaluation after 2 years of follow-up are summarised in Table 3. Reduced VO_2 at AT and TAPSE/PASP was seen in patients with CTEPH.

TABLE 1 | General characteristics of the study population (*n*, 45).

Clinical characteristics, median (p25–75) or *n* (%)	
Age (years)	63 (52–75)
Male *n*, (%)	24 (53)
BMI (kg/m^2)	29 (25–31)
FEV_1 (L)	2.28 (1.5–0.3)
FEV_1 (%)	81 (61–101)
FVC (L)	3.22 (2.5–4)
FVC (%)	92 (79–100)
DLco (%)	79 (61–88)
History of thrombosis *n*, (%)	17 (31)
Functional class 3 months after PE *n*, (%)	
I	12 (27)
II	20 (44)
III	13 (29)
Hypertension *n*, (%)	24 (53)
Cancer *n*, (%)	6 (13)
Diabetes *n*, (%)	6 (13)
Dyslipidemia *n*, (%)	14 (31)
Thrombophilia *n*, (%)	9 (20)
Clinical presentation of PE *n*, (%)	
PE Risk (PESIs)	
Low	10 (22)
Intermediate	23 (51)
High	12 (27)
High probability of pulmonary hypertension by echocardiogram	28 (62)
Right ventricular dysfunction	17 (37)
BNP	1031 (213–2346)
Radiological presentation of PE *n*, (%)	
Segmental	29 (64)
Central	14 (31)
Subsegmental	10 (22)
CTEPH after 2 years follow up *n*, (%)	4 (8.8)

Abbreviations: BMI, body mass index; BNP, brain natriuretic peptid; CTEPH, chronic thromboembolic pulmonary hypertension; DLco, diffusing capacity for carbon monoxide; FEV_1, Forced expiratory volume during first second; FVC, forced vital capacity; PESIs, pulmonary embolisms severity index simplified.

4 | Discussion

The present study shows two significant findings. In patients with persistent pulmonary vascular defects and exertional symptoms after 3 months of acute PE, we observed how right ventricle function strongly correlates with exercise capacity and ventilatory efficiency. Second, it is noteworthy that abnormal exercise capacity and reduced TAPSE/PASP during exercise were observed in patients who developed CTEPH after 2-year follow-up.

Echocardiographic abnormalities during PE recovery are among the main predictors of CTEPH [19]; in fact, echocardiography is the principal CTEPH screening method, widely extended and accepted by clinical practice guidelines [1]. A resting echocardiogram that suggests a high probability of pulmonary hypertension 3 months after a correctly treated PE event is an indication to perform right heart catheterization [1].

TABLE 2 | Echo-cardiopulmonary exercises test values.

CPET, median (p25–75)	
SpO_2 basal	96 (95–97)
Work Load (watts) peak	93 (56–123)
Work Load (% predicted) peak	71 (59–86)
VO_2 mL/kg/min peak	15 (11–18)
VO_2 (% predicted) peak	72 (61–81)
RER peak	1.17 (1.02–1.33)
V'E (l/min) peak	52 (34–65)
V'E (%) peak	57.5 (46–66)
P_{ETCO2} final	35 (30–25)
HR (beat/min) peak	131 (112–147)
HR (%) peak	85 (70–92)
VO_2/HR peak	9.8 (7.2–12.7)
VO_2/HR (%) peak	87 (70–106)
SpO_2 peak	95 (93–96)
VO_2 AT (mL/min)	854 (634–1099)
VO_2 AT (% predicted)	42 (31–53)
VE/VCO_2 AT	32 (29.5–35.5)
SBP/DBP basal, mean ± sd	139 ± 15/81 ± 11
SBP/DBP peak, mean ± sd	192 ± 18/92 ± 15
SBP/DBP recovery, mean ± sd	146 ± 25/80 ± 12
Desaturation *n*, (%)	8 (17)
Dyspnoea basal	0 (0–2)
Dyspnoea final	6 (4–8)
Leg disconfort basal	0 (0–5)
Leg disconfort final	7 (4–9)
Rest echocardiography	
PASP (mmHg)	21 (11–28)
TAPSE (mm)	23 (20–25)
RV area (mm)	24 (21–27)
LA area (mm)	35 (31–39)
LVEF (%)	62 (60–66)
TAPSE/PAPs (mm/mmHg)	1.2 (0.8–1.6)
Peak exercise echocardiography	
PASP (mmHg)	39 (21–54)
TAPSE (mm)	26 (23–32)
TAPSE/PAPs (mm/mmHg)	0.7 (0.4–1.2)

Abbreviations: AT, anaerobic threshold; DBP, diastolic blood pressure; HR, heart rate; LA, left atrium; LVEF, left ventricular ejection fraction; Max, maximum; PASP, pulmonary artery systolic pressure; $PetCO_2$, end-tidal carbon dioxide tensión; RER, respiratory exchange ratio; RV, right ventricle; SBP, systolic blood pressure; SpO_2, arterial oxygen saturation measured by pulse oximetry; TAPSE, tricuspid annular plane systolic excursion; V'E, minute ventilation; VE/VCO_2, ventilatory equivalent for CO_2; VO_2, oxygen uptake; VO_2/HR, oxygen pulse.

However, the follow-up of functional limitations and new or progressive symptoms after an acute PE event, without other evident cause and without echocardiographic changes, is still poorly defined [20]. It has been suggested that different tests, including CPET, can help differentiate those who can potentially develop CTEPH [5, 21]; however, the role of CPET with synchronic echocardiography has not been established. In this regard, our study showed for the first time that the echocardiographic values at rest do not correlate with exercise capacity in this type of patients. By contrast, a peak exercise values of RV function or RV– arterial coupling could be useful to evaluate the response to exercise. TAPSE/PAPs at rest is relevant in various cardiopulmonary conditions [22], especially those related to pulmonary vascular diseases [23]. The most up-to-date PH guidelines consider this variable highly relevant during prognosis assessment [19]. Interestingly, in our study none of the patients presented data of RV-PA uncoupling at rest [23]. The TAPSE/PAPs ratio started to be used in clinical practice since its association with aerobic capacity variables was demonstrated [24]; however, although the alteration is particularly evident during exercise, previous data on its collection on exercise are lacking, probably due to execution difficulties. Our data confirm that both TAPSE/PAPs at rest and peak exercise do not represent the best outcome for patients without pulmonary hypertension. Instead peak TAPSE and change in TAPSE during exercises emerge as potential variables to explain symptoms in this patients. Furthermore, we have shown its association with ventilatory inefficiency, another relevant prognostic marker of the disease [25]. In this line, it is well know that right ventricular function at rest is a potent predictor of survival in patients with pulmonary hypertension [1]. Also, D'Alto et al. [26] demonstrated that in healthy subjects all indices of RV function at exercise were related to exercise capacity. Our results confirm this finding in patients with pulmonary vascular defects and exertional symptoms after acute PE. Moreover, a positive change in TAPSE during exercise show a good correlation with oxygen uptake indicates a potential biomarker in addition to peak TAPSE values. Until now, there was very little evidence that RV function at exercise is relevant for the evaluation of patients with post-PE syndrome [27]. However, in that work the authors included only five patients (20%) with persistent pulmonary vascular defects. In contrast, our study is focus exclusively in patients with confirm perfusion defects on V/Q scan after 3 months with adequate anticoagulation treatment. For this reason RV function during exercise could be contribute for more accurate phenotyping in these patients [27].

Despite these optimal results, our study presents a series of limitations: low number of subjects included, single-center study, and retrospective in nature. Also, TAPSE is limited as a parameter for RV systolic function i, because it is dependent on angulation, workload-dependent, evaluates only longitudinal shortening and only captures motion of the basal RV free wall. However, these weaknesses were counterbalanced by two important elements. First, all the patients included presented well-established diagnosis and thoroughly-assessed severity of the acute PE event, with an adequate follow-up period. Second, and even more importantly, the same staff which is highly-trained, carried out all tests, with reproducible methodology.

Regardless of CPET with simultaneous echocardiography is not a commonly-available test, we believe that this noninvasive tool could be implemented in PH centers with great potential to

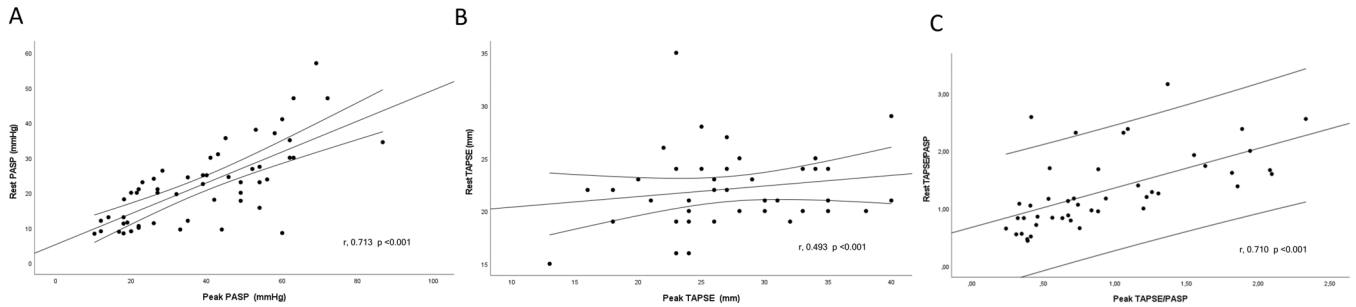

FIGURE 1 | Scatter plot representation of correlations between echocardiography parameters at rest and peak exercise. (A) Pulmonary arterial systolic pressure (PASP); (B) Tricuspid Annular Plane Systolic Excursion (TAPSE); (C) TAPSE/PASP.

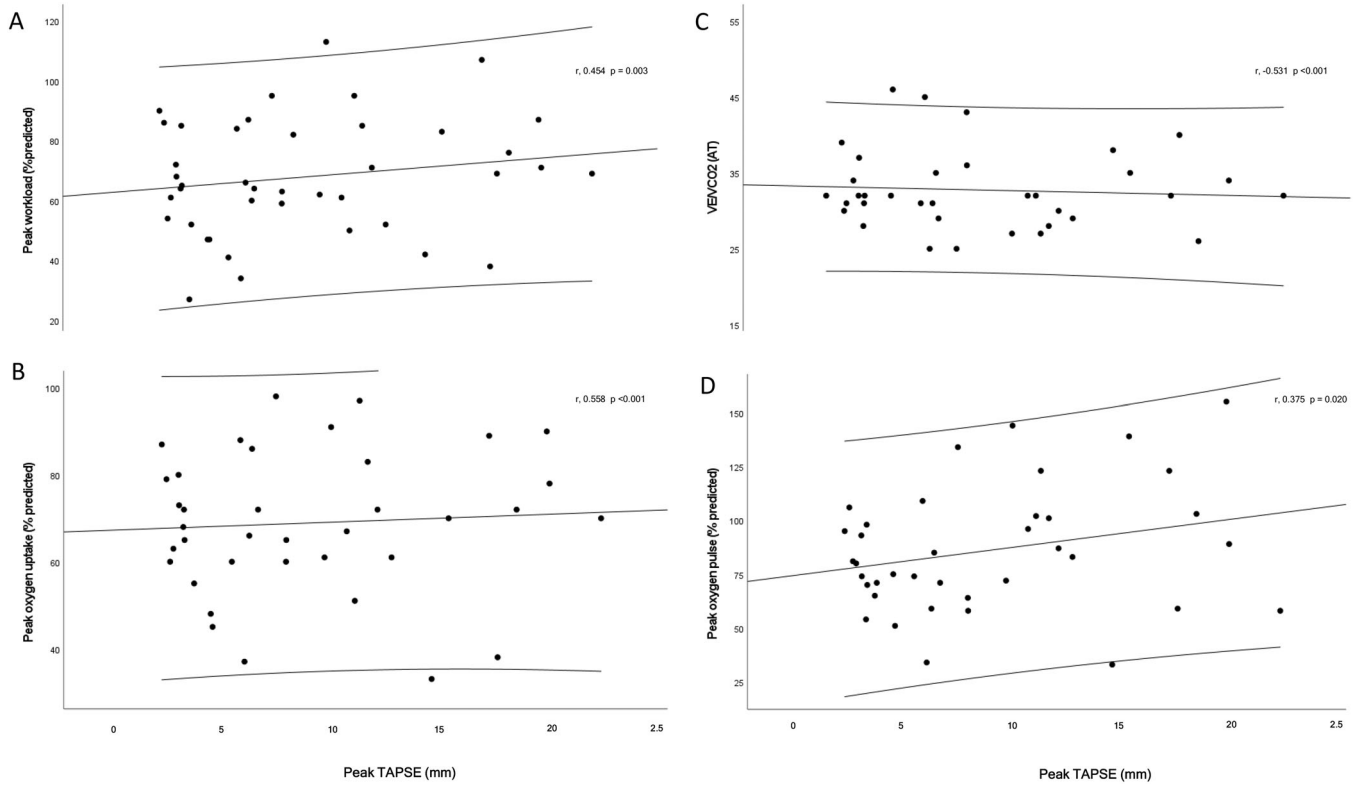

FIGURE 2 | Scatter plot representation of correlations between Tricuspid Annular Plane Systolic Excursion (TAPSE) and several parameters on cardiopulmonary exercise testing (A) peak workload, (B) peak oxygen uptake, (C) VE/VCO_2 and (D) peak oxygen pulse.

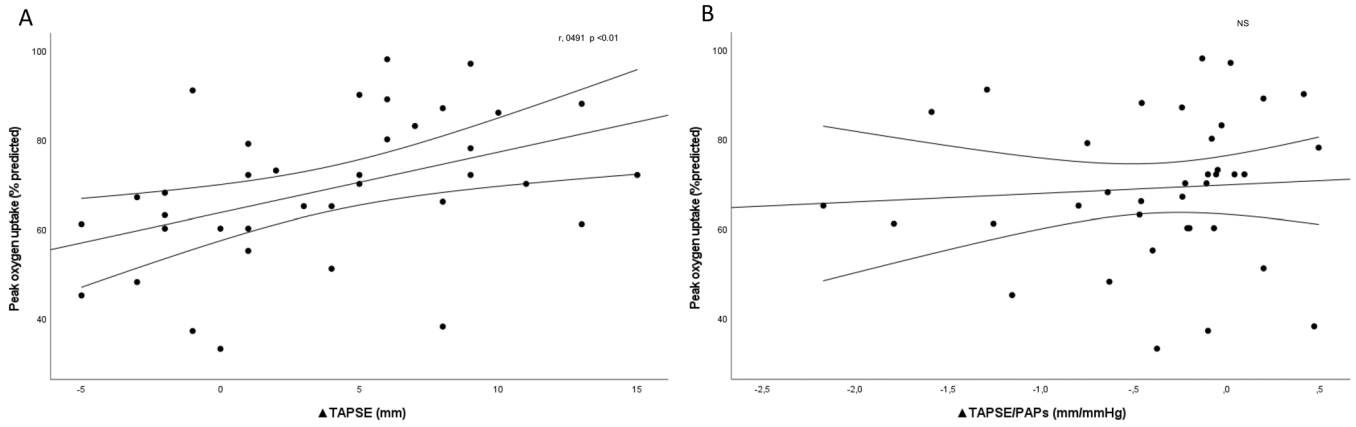

FIGURE 3 | ΔTAPSE (peak-rest) (A) and ΔTAPSE/PAPs (peak-rest) (B) as a function of peak oxygen uptake.

TABLE 3 | Cardiopulmonary exercise testing and simultaneous echocardiography values of patients with and without CTEPH after 2 years follow-up.

	CTEPH ($N = 4$)	NO CETPH ($N = 41$)	p value
Cardiopulmonary exercise testing			
Peak workload, % predicted	61 (35 to 93)	71 (59 to 86)	0.41
Peak V'O_2, % predicted	76 (65 to 80)	72 (60 to 81)	0.73
HR max, % predicted	88 (70 to 95)	85 (70 to 91)	0.73
V'O_2/HR max, % predicted	65 (58 to 65)	88 (71 to 106)	0.25
V'E max, % predicted	67 (53 to 75)	57 (53 to 75)	0.24
V'O_2 at AT, % predicted	26 (21 to 26)	44 (32 to 53)	0.02
V'E/V'CO_2 at AT	36 (35 to 36)	32 (29 to 34)	0.04
Final systemic blood pressure, mmHg	194 (186 to 199)	197 (176 to 204)	0.64
Final diastolic blood pressure, mmHg	89 (69 to 98)	89 (84 to 100)	0.50
Final dyspnea (Borg score)	7.5 (7 to 7.5)	6 (4 to 8)	0.08
Final leg discomfort (Borg score) Oxygen Desaturation, % SpO_2	6.5 (2 to 6.5)	7 (4 to 9)	0.79
	0.5 (0 to 9.2)	0 (0 to 0)	0.11
Echocardiography			
PASP (mmHg) peak	52.0 (45.0 to 61.3)	44.0 (38.0 to 49.0)	0.35
TAPSE (mm) peak	26 (23 to 27)	26 (23 to 33)	0.47
TAPSE/PASP (mm/mmHg) peak	0.59 (0.34 to 0.84)	0.75 (0.43 to 1.33)	0.05
Δ PASP (peak-rest)	20 (11 to 45)	12 (5 to25)	0.36
Δ TAPSE (peak-rest)	3.5 (0.7 to 7)	4 (−1 to 8)	0.10
Δ TAPSE/PASP (peak-rest)	−0.29 (−0.6 to −0.24)	−0.22 (−0.5 to −0.05)	0.28
PASP (% of change)	103 (51 to 146)	60 (28 to 115)	0.51
TAPSE (% of change)	16 (3 to 38)	17 (−4 to 30)	0.27
TAPSE/PASP (% of change)	−40 (−46 to −31)	−20 (−54 to −4)	0.02

Note: Data are presented as median (interquartile range) or as absolute number (percentage).
Abbreviations: AT, anaerobic threshold; HR max, maximum heart rate; PASP, Pulmonary artery systolic pressure; Peak V'O2, peak oxygen uptake; TAPSE, Tricuspid Annular Plane Systolic Excursion; V'E max, maximum minute ventilation; V'O2/HR, oxygen pulse; V'E/V'CO2, ventilatory equivalent for carbon dioxide.

increase early diagnosis and thus outcomes of prompt treatment in post PE-syndrome and beyond.

5 | Conclusions

For the first time, this study demonstrates that CPET with synchronic echocardiography could be a useful tool in the early assessment of symptomatic patients with perfusion defects on imaging after 3 months of correctly treated PE and low probability of PH at rest. These results should be confirmed in future prospective and multicenter studies.

Author Contributions

Diego A.Rodríguez Chiaradía, Lucilla Piccari and Lluis Molina conceived and designed the study and supervised the work; Karys Khilzi, Gerard Franco, Anna Rodó-Pin, Jose Gonzalez Garcia, ED and Anna Herranz performed experiments and analysed data; Isabel Blanco, Lorenzo Volpiano and Giuseppe Paciocco contributed to interpreting the results; Diego A.Rodríguez Chiaradía and Lucilla Piccari prepared figures; Karys Khilzi, Diego A.Rodríguez Chiaradía, Lucilla Piccari and Lorenzo Volpiano wrote and revised the manuscript. All authors have read and agreed to the published version of the manuscript.

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Ethics Statement

Ethics Committee of the IMIM-Hospital del Mar (ID 2022/10735).

Conflicts of Interest

The authors declare no conflicts of interest.

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