ORIGINAL RESEARCH

Cardiopulmonary Exercise Testing in Patients Following Massive and Submassive Pulmonary Embolism

Mazen S. Albaghdadi, MD, MS;* David M. Dudzinski, MD, JD;* Nicholas Giordano, MS; Christopher Kabrhel, MD, MPH; Brian Ghoshhajra, MD, MBA; Michael R. Jaff, DO; Ido Weinberg, MD;** Aaron Baggish, MD**

***Background*—**Little data exist regarding the functional capacity of patients following acute pulmonary embolism. We sought to characterize the natural history of symptom burden, right ventricular (RV) structure and function, and exercise capacity among survivors of massive and submassive pulmonary embolism.

***Methods and Results*—**Survivors of submassive or massive pulmonary embolism (n=20, age 57±13.3 years, 8/20 female) underwent clinical evaluation, transthoracic echocardiography, and cardiopulmonary exercise testing at 1 and 6 months following hospital discharge. At 1 month, 9/20 (45%) patients had New York Heart Association II or greater symptoms, 13/20 (65%) demonstrated either persistent RV dilation or systolic dysfunction, and 14/20 (70%) had objective exercise impairment as defined by a peak oxygen consumption ($\dot{V}O_2$) of <80% of age-sex predicted maximal values (16.25 [13.4–20.98] mL/kg per minute). At 6 months, no appreciable improvements in symptom severity, RV structure or function, and peak $\dot{V}O_2$ (17.45 [14.08–22.48] mL/kg per minute, *P*=NS) were observed. No patients demonstrated an exercise limitation attributable to either RV/pulmonary vascular coupling, as defined by a VE/VCO_2 slope >33, or a pulmonary mechanical limit to exercise at either time point. Similarly, persistent RV dilation or dysfunction was not significantly related to symptom burden or peak $\dot{V}O_2$ at either time point.

***Conclusions*—**Persistent symptoms, abnormalities of RV structure and function, and objective exercise limitation are common among survivors of massive and submassive pulmonary embolism. Functional impairment appears to be attributable to general deconditioning rather than intrinsic cardiopulmonary limitation, suggesting an important role for prescribed exercise rehabilitation as a means toward improved patient outcomes and quality of life. **(*J Am Heart Assoc*.2018;7:e006841. DOI:10.1161/JAHA.117.006841.)**

Key Words: echocardiography • exercise physiology • pulmonary embolism • quality of life

Acute pulmonary embolism (PE) is a common cardiovascular emergency with an estimated incidence of 1.12 cases per 1000,[1] and is associated with ≈100 000 deaths annually in the United States.[2] For survivors of an acute PE, long-term outcomes exist along a continuum ranging from full recovery to severe permanent functional limitations with corollary right ventricular (RV) dysfunction,[3] chronic thromboembolic pulmonary hypertension, and chronic thromboembolic disease.[4–6] Objective data defining functional recovery and clinical correlates among survivors of acute PE are limited.

In patients with and without known cardiovascular disease, functional capacity as defined by measurement of peak oxygen consumption during cardiopulmonary exercise testing (CPET) is a well-established and independent predictor of long-term outcomes.[7,8] Importantly, this has been illustrated in a large study of patients recovering from acute myocardial infarction, recent coronary artery bypass grafting, or new ischemic heart disease.[8] Comparatively, few studies have comprehensively examined the cardiopulmonary physiology of recovery following acute PE.[9–11] Among acute PE survivors, cross-sectional data derived from patient questionnaires,[12–14] New York Heart Association (NYHA) functional class scoring,[15] 6-minute walk testing,[16] and objective exercise

From the Fireman Vascular Center (M.S.A., I.W.), Division of Cardiology, Corrigan Minehan Heart Center (M.S.A., D.M.D.), Department of Emergency Medicine, Center for Vascular Emergencies (N.G., C.K.), Cardiovascular Imaging, Department of Radiology (B.G.), and Cardiovascular Performance Program, Division of Cardiology (A.B.), Massachusetts General Hospital, Boston, MA; Department of Medicine, Newton-Wellesley Hospital, Newton, MA (M.R.J.).

Conflict of interest: Equity Investment, Embolitech.

Accompanying Tables S1, S2 and Figure S1 are available at http://jaha.ahajournals.org/content/7/5/e006841/DC1/embed/inline-supplementary-material-1.pdf

*Dr Albaghdadi and Dr Dudzinski are co-first authors.

**Dr Weinberg and Dr Baggish are co-senior authors.

Correspondence to: Aaron Baggish, MD or Ido Weinberg, MD, Massachusetts General Hospital, 55 Fruit St, GB852, Boston, MA 02114. E-mails: iweinberg@mgh.harvard.edu, abaggish@mgh.harvard.edu

Received June 17, 2017; accepted January 25, 2018.

Clinical Perspective

What Is New?

- Survivors of massive and submassive pulmonary embolism experience persistent exertional symptoms, objective exercise impairments, and abnormalities of right ventricular size and function.
- Overall deconditioning may account for the observed symptom burden and impaired exercise function in this high-risk population.

What Are the Clinical Implications?

- Cardiopulmonary exercise testing is a safe and effective tool to ascertain the mechanisms of persistent symptoms in patients recovering from submassive and massive pulmonary embolism.
- Cardiac rehabilitation could be a highly valuable tool to promote exercise and symptom recovery following pulmonary embolism.
- Further investigation of the impact of cardiac rehabilitation on clinical outcomes in this population is warranted.

testing[17] suggest that functional limitations are common and of variable severity, but there are sparse longitudinal data examining functional capacity following acute PE. Thus, the natural history of acute PE recovery and the mechanisms underlying persistent functional limitations throughout the post-PE recovery period remain unclear, and current venous thromboembolism guidelines are unable to provide specific guidance on participation in exercise following hospital discharge.[5,18,19]

We therefore sought to examine exercise capacity and cardiopulmonary function among survivors of massive and submassive PE. We hypothesized that acute PE survivors would demonstrate clinically significant impairments of exercise capacity with concomitant and potentially explanatory cardiopulmonary dysfunction. To address this hypothesis, we studied acute PE survivors with clinical assessment, transthoracic echocardiography, and comprehensive cardiopulmonary exercise testing at 1 and 6 months following index PE presentation.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure as this was not part of our original Institutional Review Board approval.

Study Design

We utilized a prospective, longitudinal, repeated-measures study design to examine functional capacity and clinical correlates among survivors of massive and submassive PE. This study was approved by the Partners Health Care Institutional Review Board, and all patients provided signed informed consent. The study cohort comprised patients who were treated at the Massachusetts General Hospital for acute PE as defined below. Our hospital utilizes an acute PE Response Team (PERT),[20] which is routinely activated at the time of massive and submassive PE diagnosis. The PERT is then responsible for confirmation of the PE diagnosis, initial risk stratification, and acute therapeutic management. All patients with acute PE who were cared for by the PERT during the period spanning from February 2014 to February 2015 were screened for eligibility for the present study. Inclusion criteria included survival to hospital discharge and expressed intent to receive follow-up care at our institution. Exclusion criteria were limited to an inability to perform supervised, laboratory-based exercise testing because of a preexisting orthopedic, neurologic, or other functional limitation, anticipated life expectancy of <6 months, electrocardiographic contraindications to CPET, or declined to provide consent.

Study data were obtained at 2 standardized time points that correlated with 1 and 6 months after the index PE presentation. At both time points, participants underwent clinical assessment, which included the following: ascertainment of the presence or absence of cardiovascular symptoms including the NYHA functional class and subjective exercise limitation; comprehensive resting transthoracic echocardiography (TTE); and CPET. An overview of the study design, participant recruitment, and participant attrition is shown in Figure 1.

Diagnosis and Risk Stratification of PE

At the time of PERT activation, the diagnosis of acute PE was confirmed using computed tomography. Clinical risk stratification including the completion of TTE was performed within 24 hours of PE diagnosis in accordance with current American Society of Echocardiography guidelines.[21] Submassive and massive PE were defined according to the American Heart Association definitions.[5] Submassive PE was defined as acute PE without systemic hypotension but with either RV dysfunction or myocardial necrosis. RV dysfunction was defined by the presence of 1 or more of the following: (1) RV dilatation as defined by noninvasive imaging (TTE parameters defined below); (2) RV dysfunction detected by TTE (defined below), or electrocardiography[5]; (3) elevation of N-terminal pro-brain natriuretic peptide according to age-specific cut-offs (<50 years: <450 pg/mL; 50–75 years: <900 pg/mL; >75 years: <1800 pg/mL) or troponin-T (>0.03 ng/mL). Massive PE was defined by the presence of confirmed PE coupled with cardiogenic shock as defined by a systolic blood pressure <90 mm Hg with no alternative explanation for

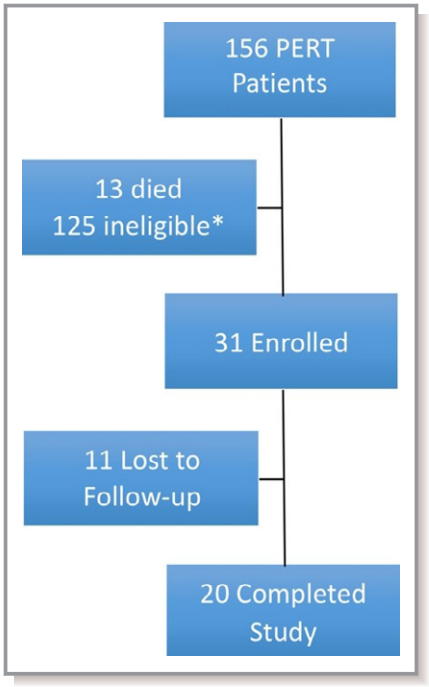


Figure 1. Study outline: All patients with acute high-risk PE who were cared for by the PERT during the time period spanning from February 2014 and February 2015 were screened for eligibility for the present study. *Patients deemed ineligible could not perform exercise because of neurologic or orthopedic issues, or declined to participate in the study. PE indicates pulmonary embolism; PERT, PE Response Team.

hemodynamic collapse.[5] Additional data obtained at the time of acute PE presentation included basic demographics, the presence or absence of comorbid medical conditions, the presence or absence of self-reported symptoms associated with acute PE, and details about PE-related treatment. PE treatment was at the discretion of the PERT and no attempt was made to alter treatment decisions based upon anticipated patient inclusion in this study.

CPET Protocol

CPET was performed at 1- and 6-month study visits using a maximal effort-limited protocol with continuous electrocardiography and measurement of metabolic gas exchange. A single exercise physiologist and supervising study physician performed all testing. Participants abstained from all exercise for 24 hours before testing. The CPET protocol consisted of a graded maximal effort test performed on an upright electronically braked cycle ergometer (Excalibur; Medgraphics, St. Paul, MN). After a 3-minute period of resting gas exchange measurement to ensure ventilatory equilibration, participants underwent a continuous ramp protocol (10–25 W/min) to volitional fatigue. Gas exchange data were measured breath-by-breath using a commercially available metabolic cart (Ultima CardiO$_2$; Medgraphics, St. Paul, MN). Peak oxygen consumption ($\dot{V}O_2$) was defined as the highest O_2 uptake, averaged over a period of 30 seconds, during the last minute of symptom-limited exercise.[22] The ventilatory threshold was determined by the modified V-slope method.[23] A pulmonary mechanical limit to exercise was defined by a breathing reserve of <10% at peak exercise or <42% of maximal voluntary ventilation.[24] Heart rate was continuously recorded during exercise using a wireless 12-lead ECG system (Mortara X12+ Transmitter; Mortara Instruments, Milwaukee, WI). Blood pressures were determined by auscultation using a manual sphygmomanometer before exercise, at 3-minute intervals during exercise, immediately after peak exercise, and at 3-minute intervals during recovery. Reference cut points defining normal cardiopulmonary exercise testing values were adopted from current guidelines, including abnormal RV/pulmonary vascular coupling defined as a VE/VCO_2 slope <33.[25]

Transthoracic Echocardiography

Cardiac structure and function were assessed using transthoracic echocardiography (ie33 and EPIQ, Philips, Amsterdam). Measurements were made off-line by a single experienced investigator (DMD) who was blinded to study time point in accordance with current guidelines.[26] The index TTE was a clinical study, while the TTEs at 1 month and 6 months were conducted according to a study protocol. All measurements were made in triplicate. Left ventricular (LV) single-dimension parameters and transmitral velocities were measured in standard fashion. LV volumes, ejection fraction, and left and right atrial volumes were calculated using modified biplane techniques.[26] LV mass was calculated using the area–length method, and LV geometry was assessed using relative wall thickness. LV and RV myocardial tissue velocities were measured using pulse-wave Doppler imaging and reported values represent the average of 3 consecutive cardiac cycles. RV end-diastolic area, end-systolic area, and fractional area change (FAC) were measured from an RV-optimized apical 4-chamber view according to American Society of Echocardiography guidelines.[21] Peak tricuspid regurgitation velocity was obtained by selecting highest velocities from among RV-inflow, parasternal short axis, apical 4-chamber, and subcostal views. Pulmonary artery acceleration time was measured according to published methods.[27] Measurements of RV function included tricuspid annular plane systolic excursion (TAPSE), RV FAC, and tissue Doppler–derived tricuspid lateral annular systolic velocity (S′). Reference cut points defining normal structure and function were adopted from published guidelines.[21,26] RV dilation was defined as a RV end-diastolic area ≥24 cm^2 in men and ≥20 cm^2 in women. RV dysfunction

was defined as the presence of a TAPSE of <1.6 cm, basal RV free wall velocity (S′) <10 cm/s, or RV FAC of <0.35.

Computed Tomography Pulmonary Angiography

Imaging was performed with 16-slice and 64-slice scanners (Siemens Healthcare, Erlangen, Germany), and all images were reconstructed at 1.0-mm slice thickness. Imaging parameters were 80 to 120 kVp and an effective milliampere of ≈200. All patients received 75 mL of iodinated contrast media (370 mg iodine per milliliter) via a power injector at a rate of 3 mL/s. Image acquisition was triggered with bolus tracking (80 HU threshold) on the main pulmonary artery. Axial 4-chamber views were used to measure the maximal diameter of the right and left ventricles, and the RV:LV ratio was calculated.[28,29]

Statistical Methods

Normality of distribution was assessed using the Shapiro–Wilk test. Continuous variables are reported as mean value±SD for normally distributed continuous variables and median with interquartile range for non-normally distributed variables. The Wilcoxon rank-sum test was used to compare variables at 1- and 6-month study visits. Mann–Whitney *U* test was used for nonparametric comparisons of unpaired data between included and excluded study subjects. Friedman's test was used for comparing multiple groups with nonparametric distribution followed by Wilcoxon rank-sum test with post hoc Bonferroni correction to compare changes in metrics of RV size and function over time. Pearson χ^2 test was used to examine the association between the composite of RV dilation and/or dysfunction (ie, RV impairment) and RV/pulmonary vascular coupling with symptom burden (NYHA class) and decreased exercise capacity (peak $\dot{V}O_2$ <80% of maximum predicted). Statistical analysis was done using IBM SPSS Statistics version 22. A *P* value of <0.05 was considered significant for all analyses.

Results

Patient Population

During the 12-month study recruitment period, there were 156 submassive and massive PE patients treated in our PERT program. Of these, 13 patients died during index hospitalization and 125 were ineligible for the present study including 14 lost to follow-up, 39 with cancer and life expectancy <6 months, 11 with electrocardiographic contraindications to CPET, and 48 patients with orthopedic or neurologic physical limitations that precluded CPET participation (Figure 1). Among the 31 patients successfully enrolled in this study, a total of 20 patients (age=57±13 years, 8/20 female) completed all aspects of the study protocol and were thus included in the final analysis.

To examine the potential bias introduced by subject attrition, baseline clinical characteristics and exercise performance between patients included in the final analysis (n=20), those enrolled but were lost to longitudinal follow-up (n=11) were compared (Tables S1 and S2). Baseline demographics were comparable between those patients who completed the study and those lost to follow-up. In addition, baseline characteristics of the studied patients (n=20) were also compared with those deemed ineligible (n=125), which revealed significant differences in presentation including the presence of dyspnea (100% versus 68.8%, *P*=0.003), RV dilation by echocardiography (55% versus 16.8%, *P*=0.001), RV dysfunction by echocardiography (85% versus 17.6%, *P*=0.001), treatment with thrombolytics (20% versus 2.4%, *P*<0.001), and catheter-directed thrombolysis (35% versus 8.8%, *P*=0.001). As such, our study population represents a relatively sick population of patients with submassive and massive PE without contraindications to aggressive therapeutic intervention.

Index Massive and Submassive PE Presentation

Patient characteristics at the time of index presentation are shown in Table 1. PE severity was classified as submassive in 17 and massive in 3 patients. Dyspnea at rest (NYHA Class IV) was reported by all participants at the time of diagnosis and was accompanied by chest pain in 8/20 (40%) and syncope in 5/20 (25%) (Figure 2). Cardiac biomarker profiling revealed elevations of cardiac troponin-T in 60% (12/20) and N-terminal pro-brain natriuretic peptide in 60% (12/20) of patients. Electrocardiographic evidence of RV dysfunction was observed in 3/20 (15%) of patients. All patients with electrocardiographic evidence of RV strain also had echocardiographic RV dysfunction. In total, 17/20 (85%) of patients showed signs of RV dysfunction as defined by either an abnormal RV FAC, S′, or TAPSE. Specifically, 15/20 (75%) patients had a reduced RV FAC (<0.35), 9/20 (45%) had a reduced S′ (<10 cm/s), and 7/20 (35%) had a reduced TAPSE (<1.6 cm/s). Echocardiographic-detected RV dilation was observed in 11/20 (55%) patients and was accompanied by impaired RV systolic function in 10/11 (91%) patients. Pulmonary artery systolic pressure estimates derived from tricuspid regurgitant velocity and pulmonary artery acceleration time and indices of RV function are shown in Figures 3 and 4. An estimated RV systolic pressure >25 mm Hg was observed in 17/20 (85%) patients (median [interquartile range]=44.4 [33.99–55.26]). RV:LV ratio >1.0 as detected by computed tomography pulmonary angiography was present in 16/20 (80%) with an average ratio of 1.5±0.29. Treatment of acute PE, administered at the discretion of the PERT, included

Table 1. Demographics, Clinical Characteristics, and Management Strategies Among Acute High-Risk PE Survivors (n=20) Who Completed All Aspects of a Serial Surveillance Protocol Post-Index Event

	Value
Demographic data	
Age, y	57 (13)
Female, n (%)	8 (40)
Preexisting comorbid conditions	
COPD or asthma, n (%)	0 (0)
CAD, n (%)	1 (5)
Prior MI, n (%)	0 (0)
CHF, n (%)	0 (0)
Prior PE, n (%)	3 (16)
Prior DVT, n (%)	4 (21)
History of tobacco abuse, n (%)	14 (70)
Clinical characteristics at the time of PE presentation	
Massive PE, n (%)	3 (15)
Submassive PE, n (%)	17 (85)
Presenting symptoms	
Shortness of breath, n (%)	20 (100)
Chest pain, n (%)	8 (40)
Syncope, n (%)	5 (25)
Heart rate, bpm	106 (21)
Systolic blood pressure, mm Hg	124 (25)
Diastolic blood pressure, mm Hg	78 (11)
Elevated troponin-T, n (%)	12 (60)
Elevated NT pro-BNP, n (%)	12 (60)
RV dilatation on TTE, n (%)	11 (55)
RV dysfunction on TTE, n (%)	17 (85)
RVSP, mm Hg	49 (15)
Management strategy at the time of PE diagnosis	
Anticoagulation, n (%)	20 (100)
Intravenous thrombolysis, n (%)	4 (20)
Catheter-directed therapy, n (%)	7 (35)
IVC filter, n (%)	3 (16)
ECMO, n (%)	0 (0)

Data are presented as mean and SD unless otherwise indicated. bpm indicates beats per minute; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; ECMO, extracorporeal membrane oxygenation; IVC, inferior vena cava; MI, myocardial infarction; NT pro-BNP, N-terminal pro-brain natriuretic peptide; PE, pulmonary embolism; RV, right ventricle; RVSP, right ventricular systolic pressure; TTE, transthoracic echocardiogram.

administration of anticoagulation (100%), catheter-directed therapy (7/20, 35%), intravenous thrombolysis (4/20, 20%), and placement of an inferior vena cava filter (3/20, 15%) (Figure S1).

One-Month Follow-up

At 1 month following the index PE, shortness of breath at rest had resolved in all patients. However, 2/20 (10%) reported persistent exertional dyspnea during activities of daily living (NYHA Class III) and 7/20 (35%) reported dyspnea during any physical activity at an intensity above that required for activities of daily living (NYHA Class II) (Figure 2). CPET data at 1 month are shown in Table 2. All patients were in normal sinus rhythm before and throughout exercise testing and aside from rare premature atrial and ventricular extrasystoles, there were no inducible arrhythmias during exercise. Median peak $\dot{V}O_2$ was 16.25 [13.4–20.98] mL/kg per minute, or 67.5% [59.75–84.75%] of age and sex peak predicted oxygen consumption with 12/20 (60%) patients demonstrating objective exercise impairment as defined by a peak $\dot{V}O_2$ of <80% of age–sex predicted maximal values (Figure 5). There was no significant association between NYHA Class II or greater symptoms (ie, those occurring during activities of daily living) and peak $\dot{V}O_2$ of <80% of age-sex predicted maximal values at 1 month (P=0.9) or 6 months (P=0.2). Among patients with an impaired peak $\dot{V}O_2$, no participants demonstrated evidence of a pulmonary mechanical limit to exercise (breathing reserve at peak exercise=43 [28–65]%). Chronotropic impairment (defined as failure to achieve >80% of maximal predicted heart rate) was observed in 6/20 (30%), impaired oxygen pulse augmentation ($\dot{V}O_2$/heart rate) was observed in 9/20 (45%), and a combination of chronotropic and oxygen pulse impairment was observed in the remaining 6/20 (30%). Echocardiographic data are shown in Table 3. Compared with index presentation, echocardiography revealed improvements in estimates of pulmonary arterial systolic pressure, including tricuspid regurgitant velocity and pulmonary artery acceleration time (Figure 3). In addition, improvements in RV size and function were observed compared with baseline as evidenced by improvement in echocardiographic measures of RV end-diastolic area and estimates of systolic function, including TAPSE, RV S′, and RV FAC (Figure 4). However, persistent RV dysfunction was evident in 7/20 (35%) and RV dilation was also present in 7/20 (35%). RV dilation was accompanied by RV dysfunction in 1/7 (14%) of patients. Among patients with a peak $\dot{V}O_2$ of <80% at 1 month, only 4 had echocardiographic evidence of RV dysfunction. There was no relationship between RV impairment (ie, the composite of RV dilation and/or dysfunction) with reduced exercise capacity defined as a peak $\dot{V}O_2$ of <80% (P=0.44) or with NYHA Class II or greater symptoms (P=0.64).

Six-Month Follow-up

Subjective functional capacity at 6 months was similar to that reported at 1-month follow-up. Specifically, all patients who reported excessive dyspnea during physical activity at an intensity above that required for activities of daily living at 1-

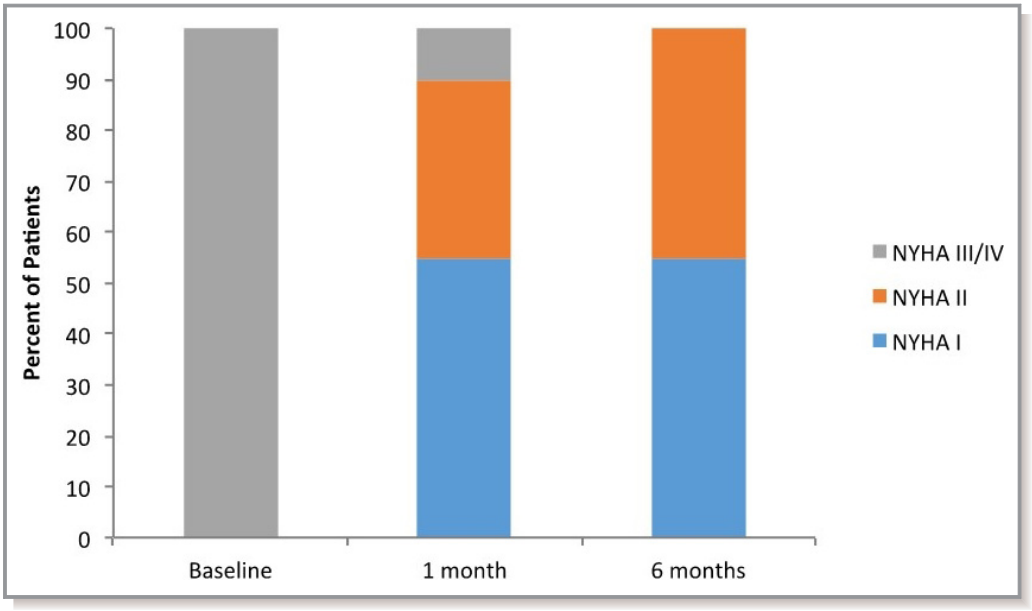


Figure 2. Change in New York Heart Association (NYHA) functional class from baseline at 1 and 6 months following acute high-risk pulmonary embolism.

month post PE remained similarly affected and the 11/20 (55%) patients who were asymptomatic at 1 month remained in this condition (Figure 2). The 2 patients who previously reported dyspnea during activities of daily living (NYHA Class III) now noted dyspnea only during physical activity at an intensity above that required for activities of daily living (NYHA Class II). CPET data at 6 months are shown in Table 2. Notably, there were no significant changes among parameters defining exercise physiology during submaximal- or maximal-effort exercise. Peak $\dot{V}O_2$ values at 1 and 6 months were tightly correlated (R=0.96) and the overall incidence of impaired exercise capacity therefore remained similar in 12/20 (60%, Figure 5). In those patients with persistent subjective limitations at 6 months, there was a numerically lower peak $\dot{V}O_2$ (19.5 versus 14.1, P=0.06). Echocardiographic data at 6 months are shown in Table 3. At 6 months, there were no significant or clinically meaningful differences in echocardiographic indices of cardiac structure and function compared with those observed at 1 month. Among patients with persistent RV dysfunction at 6 months, there was no difference in peak $\dot{V}O_2$ (20.3 versus 17.3, P=0.67) compared with those patients with normal RV function. Additionally, 10/20 (50%) of those with an elevated troponin at baseline had either RV dilation or dysfunction at the 6-month follow-up. As

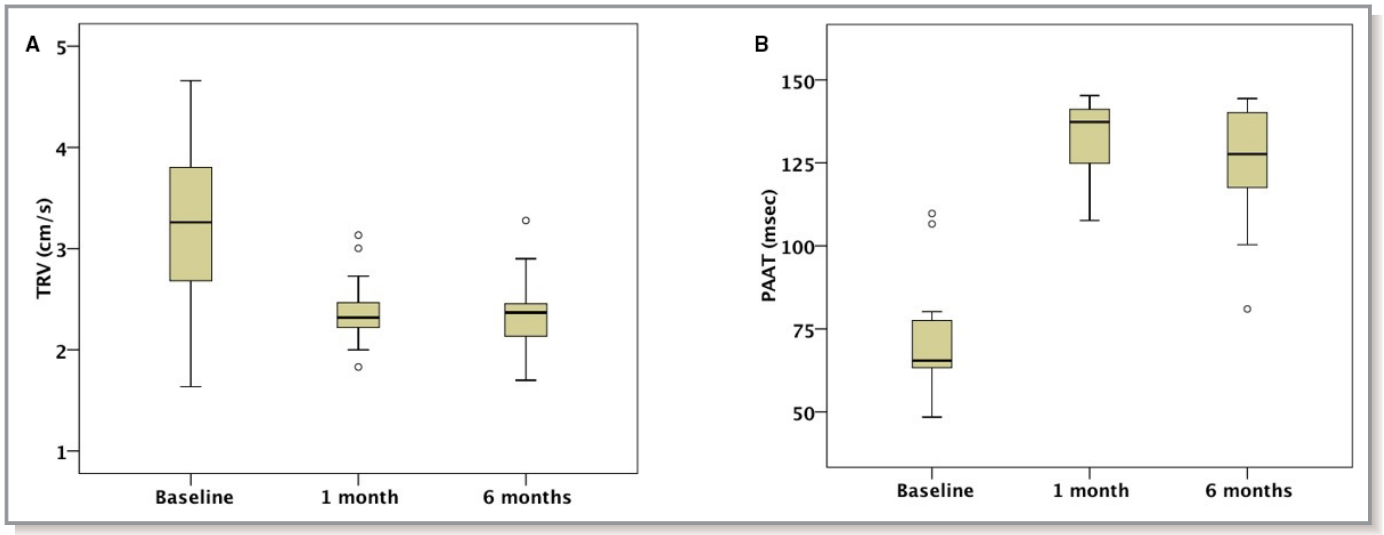


Figure 3. Changes in 2 estimates of pulmonary artery systolic pressure. A, Tricuspid regurgitant velocity (TRV) and (B) pulmonary artery acceleration time (PAAT) at 1 and 6 months following acute high-risk pulmonary embolism. *P<0.01 vs baseline. Circles represent outlier data points.

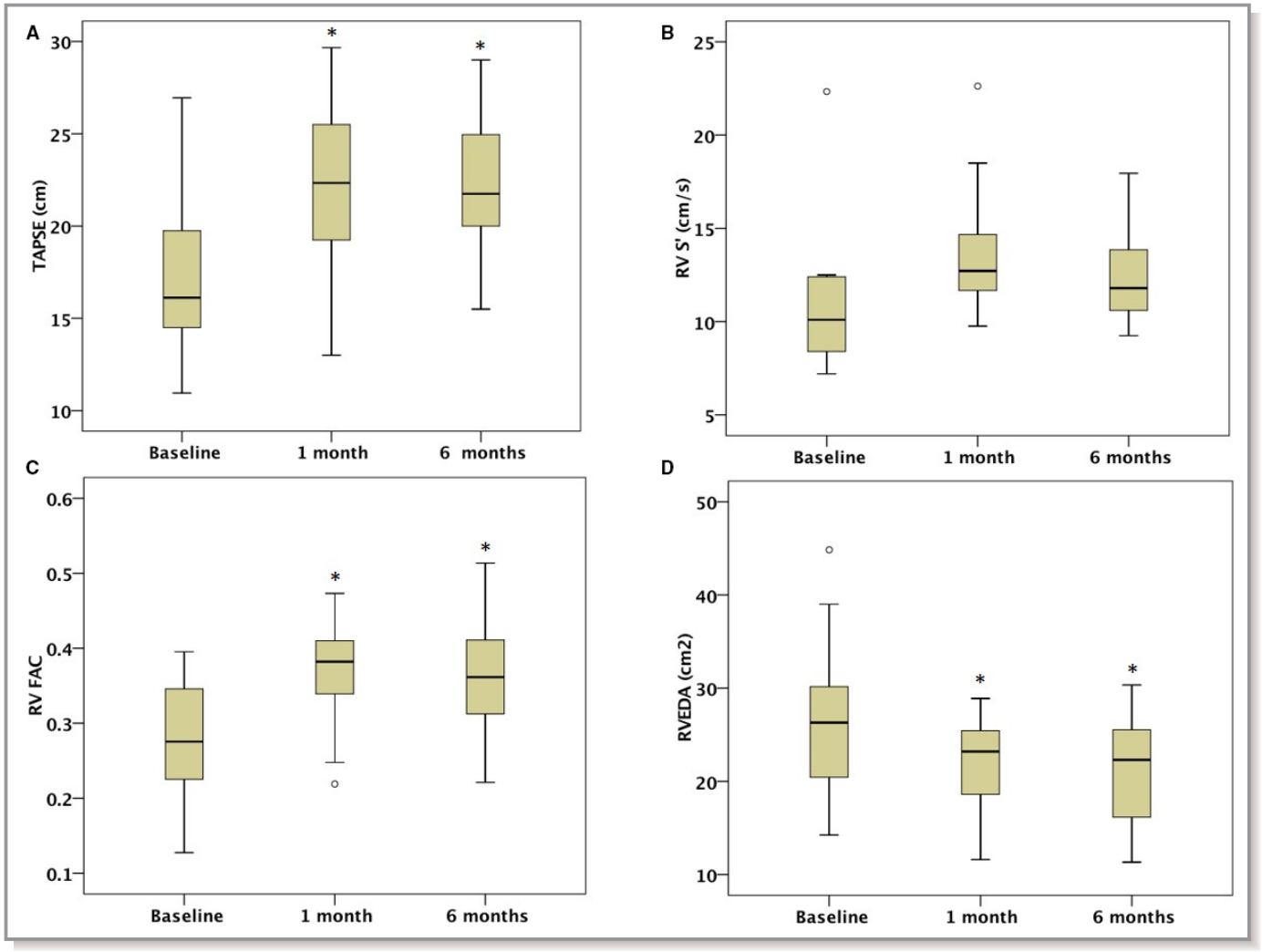


Figure 4. Changes in estimates of right ventricular RV function. A, Tricuspid annular plane systolic excursion (TAPSE), (B) RV free wall velocity (S′), (C) RV fractional area change (FAC), and (D) RV end-diastolic area (RVEDA) at 1 and 6 months following acute high-risk pulmonary embolism. *P<0.01 vs baseline. Circles represent outlier data points.

observed at the 1-month follow-up, there was no relationship between RV impairment (ie, the composite of RV dilation and/or dysfunction) with reduced exercise capacity defined as a peak $\dot{V}O_2$ of <80% (P=0.44) or with NYHA Class II or greater symptoms (P=0.89).

Discussion

A recent meta-analysis of symptomatic changes and quality of life following acute PE found that over one third of patients experience persistent, limiting symptoms (NYHA Class II-IV).[30] Persistent symptoms and functional limitations in patients with PE are thus common, but the distinct profile of recovery following submassive and massive PE is less well understood.[11] In the present study, we investigated the symptom burden, exercise physiology, and cardiac structure and function during 6 months of follow-up among survivors of massive and submassive PE with the following key findings. Most survivors of massive and submassive PE that we studied experienced persistent subjective exertional symptoms and objective impairments in peak exercise capacity up to 6 months following index PE presentation. In this cohort, RV dilation and dysfunction were common at both the 1- and 6-month follow-up time points. Importantly, we observed no meaningful relationships between RV structure, RV function, or pulmonary function during exercise and subjective symptom burden or objective exercise capacity. Hence, the high prevalence of persistent symptoms and impaired peak $\dot{V}O_2$ among massive and submassive PE survivors does not appear to be dictated by cardiopulmonary insufficiency but rather overall deconditioning.

Studies on the natural history[31,32] and treatment[33–35] of venous thromboembolism have primarily focused on clot resolution, complications related to clot progression and

Table 2. Cardiopulmonary Exercise Testing Parameters Among Acute High-Risk PE Survivors (n=20)

Parameter	1 Mo	6 Mo	*P* Value
Resting vital signs and pulmonary function data			
Heart rate, bpm	85 [69–96]	87 [71–94]	0.73
Systolic blood pressure, mm Hg	134 [126–148]	125 [115–143]	0.02
Diastolic blood pressure, mm Hg	80 [76–84]	76 [73–84]	0.19
Forced expiratory volume—1 s, L/min	2.9 [2.0–3.7]	2.8 [2.0–3.7]	0.06
Percentage of maximal predicted FEV_1, %	97.5 [80.5–105.8]	97.0 [81.3–103.8]	0.20
FVC, L	3.7 [2.6–5.1]	3.88 [2.6–4.8]	0.93
Percentage of maximal predicted FVC, %	93.5 [82.0–100.8]	93.0 [86.3–99.5]	0.81
Cardiopulmonary exercise data			
Total exercise time, min	10.3 [8.8–12.8]	11.3 [8.8–13.0]	0.07
Peak power, W	151.0 [72.8–207.3]	163.5 [78.8–202.0]	0.12
Peak $\dot{V}O_2$, L/min	1.66 [1.20–2.24]	1.77 [1.07–2.39]	0.26
Body mass index peak $\dot{V}O_2$, mL/kg per min	16.3 [13.4–21.0]	17.5 [14.1–22.5]	0.31
Percentage of predicted peak $\dot{V}O_2$, %	68 [60–85]	73 [61–90]	0.12
Peak respiratory exchange rate	1.2 [1.1–1.3]	1.3 [1.2–1.3]	0.36
Peak heart rate, bpm	150 [114–164]	151 [111–164]	0.72
Percentage of predicted peak heart rate, %	94 [74–101]	89 [70–99]	0.30
Peak systolic blood pressure, mm Hg	180 [160–194]	179 [164–196]	0.93
Peak diastolic blood pressure, mm Hg	80 [80–84]	80 [71–88]	0.38
Peak O_2 pulse, mL/beat	11 [9–16]	12 [9–16]	0.02
Percentage of predicted peak O_2 pulse, %	82 [71–91]	80 [72–100]	0.60
Breathing reserve at peak exercise, %	43 [28–65]	42 [25–63]	0.43
Overall VE/ VCO_2	27.3 [23.3–32.0]	25.9 [22.4–30.0]	0.06
$\dot{V}O_2$ at ventilatory threshold, mL/kg per min	12.2 [10.7–13.6]	12.8 [10.2–15.1]	0.19
Ventilatory threshold VO_2 as a % of peak $\dot{V}O_2$, %	71.5 [61.3–83.0]	71.5 [63.8–75.3]	0.76

All data are presented as median and interquartile range [IQR]. Wilcoxon rank sum test was used to compare medians. bpm, beats per minute; FEV_1 indicates forced expiratory volume in 1 s; FVC, forced vital capacity; PE, pulmonary embolism; VE/VCO_2, ratio of minute ventilation (VE) to carbon dioxide output (VCO_2) during exercise.

embolization, treatment-related complications, and mortality. In longitudinal studies of symptomatic recovery in patients with submassive PE, a significant proportion of patients experience continued exercise impairments and poor overall self-reported health.[14,15] In a randomized study of thrombolysis versus placebo in 1006 patients with submassive PE (PEITHO [Pulmonary Embolism Thrombolysis] trial), ≈33% of patients reported dyspnea or a subjective impairment in functional capacity at a median of >3 years of follow-up.[36] Mechanisms underlying these findings remain speculative.[9] We are aware of only 1 prior prospective study of patients with PE that utilized CPET and echocardiography in which Kahn et al examined 100 patients at 1 and 12 months following acute PE.[37] In this study, nearly half of enrolled patients had exercise limitations 1 year after PE, and persistent exercise limitation was associated with worse health-related quality-of-life metrics. Of note, this important prior work examined patients with PE of variable severity, and neither cardiac biomarker data nor echocardiographic data at index presentation were universally reported. To the best of our knowledge, this is the first prospective study to systematically characterize symptom burden, objective exercise capacity, and RV structure and function in a select population of patients with massive and submassive PE. Our use of a prospective study design, which leveraged the use of both biomarkers and echocardiography, ensured the enrollment of patients with massive and submassive PE. Importantly, it is this subset of PE patients that one would predict to have the most marked PE-related exercise limitation and long-term functional disability. Findings from the present study confirm the notion that exercise limitations are both common and persistent among massive and submassive PE survivors and now begin to shed mechanistic insights into this problem. In aggregate, our data suggest that impairments in physical

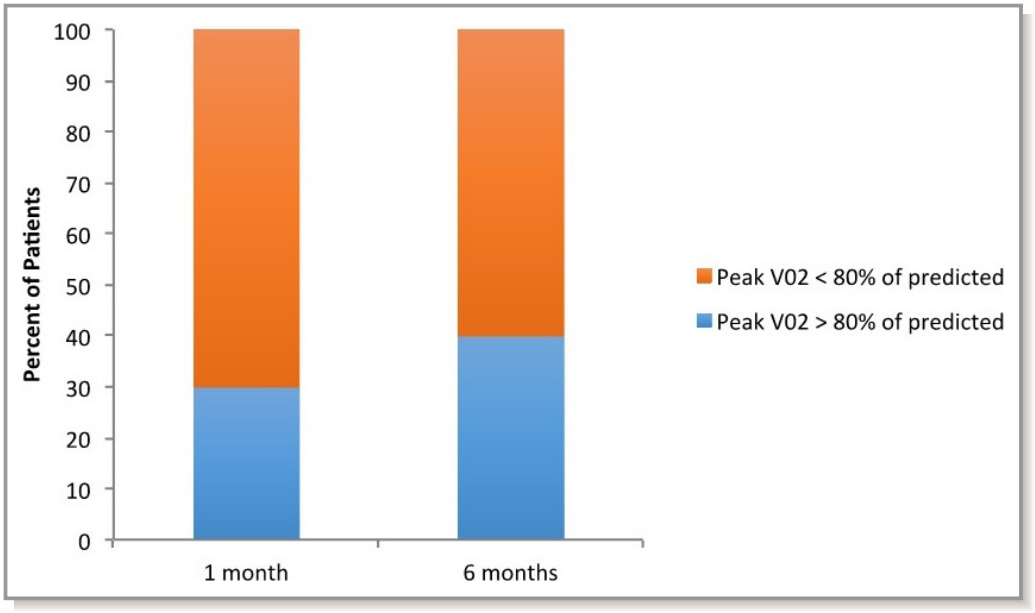


Figure 5. Patterns of cardiopulmonary exercise testing measure of peak VO_2 consumption at 1 and 6 months following acute high-risk pulmonary embolism.

function are not likely to be explained by concomitant cardiopulmonary pathology but rather by simple physical deconditioning.

In this study, we longitudinally evaluated symptomatic recovery among massive and submassive PE in conjunction with assessments of RV structure and function. RV dysfunction at the time of acute PE presentation is a well-recognized determinant of PE-related mortality.[38,39] Prior studies have typically reported a trend towards normalization of echocardiographic-detected abnormalities of RV size and function.[40–43] However, prior studies did not specifically include focus on patients with massive and submassive PE as in the current study and relied on comparatively rudimentary echocardiographic assessment of the right ventricle. In this study, we utilized a comprehensive echocardiographic assessment that included 3 guideline-recommended and relatively simple-to-use metrics of RV function that have prognostic data in a population of massive and submassive PE patients. In addition, we have incorporated RV FAC, which closely correlates with the magnetic resonance imaging reference standard for assessment of RV ejection fraction.[44] Using this approach, we demonstrated that RV dilation and dysfunction are present in more than one third of massive and submassive PE survivors at 1 and 6 months following the index event.

CPET is an attractive tool for the assessment of post-PE functional capacity, given its ability to measure a global response to exercise and to delineate between various potential sources of exercise limitation. Similarly, prior studies have documented reductions in peak $\dot{V}O_2$ among PE survivors at various single time points following the index event.[17,45] Our data extend our understanding of functional impairment after acute massive and submassive PE in several ways. First, we confirm that reductions in peak oxygen consumption are common in this patient population (Figure 5). Second and more importantly, we show that reductions in peak $\dot{V}O_2$ seen at 1 month persist up to 6 months after index presentation. Finally, our data, specifically the preservation of breathing reserve, normal ventilatory efficiency, and normal oxygen pulse values at peak exercise, indicate that impairments in peak $\dot{V}O_2$ among massive and submassive PE survivors are not attributable to underlying RV impairment, RV-pulmonary vascular coupling, or parenchymal lung disease but rather simple deconditioning.

These findings have immediate and significant clinical relevance. Quantification of exercise capacity using CPET is common and represents the standard of care for the management of patients with numerous common cardiovascular diseases including coronary artery disease, congestive heart failure,[46] and pulmonary hypertension.[47] In contrast, objective assessment of functional capacity is not routine in the management of acute PE survivors. Given the established relationship between functional impairment following PE and long-term clinical outcomes, CPET testing may represent an opportunity to both risk stratify and thus tailor therapy among massive and submassive PE survivors. Specifically, the use of dedicated exercise training, ideally in the setting of cardiac rehabilitation programs, may hold tremendous benefit for acute PE survivors in a manner similar to that which is routine among patients following acute coronary syndromes.[48] Future prospective studies defining the impact of cardiac rehabilitation among massive and submassive PE survivors will be required to clarify the role of this potentially important therapeutic option in patients recovering from acute PE.

Table 3. TTE Characteristics Among Acute Severe PE Survivors (n=20)

Parameter	First TTE	Second TTE	*P* Value
Left heart parameters			
LA volume, mm^3 (SD)	60.0 [49.3–75.7]	63.83 [54.6–79.46]	0.30
IVS, mm	9.5 [8.4–11.0]	10.5 [8.3–11.7]	0.04
PWT, mm	8.5 [7.43–10]	9.23 [7.6–10.0]	0.81
LVIDd, mm	45.5 [40.3–52.0]	44.83 [40.3–51.0]	0.84
LVIDs, mm	30.3 [27.4–37.3]	28.33 [24.8–37.8]	0.08
EDV, mL	117.8 [84.7–131.4]	117.85 [74.9–131.6]	0.95
ESV, mL	51.1 [36.6–76.1]	56.4 [37.3–75.7]	0.63
EF, %	0.50 [0.5–0.5]	0.50 [0.50–0.55]	0.72
LV mass, g	147.9 [110.7–160.1]	147.85 [124.6–176.6]	0.26
E, cm/s	65.0 [51.6–79.0]	72.94 [56.0–83.3]	0.09
A, cm/s	68.6 [55.3–93.5]	63.2 [49.6–90.7]	0.18
E′, cm/s	10.0 [7.3–13.5]	8.73 [7.4–11.9]	0.31
A′, cm/s	10.3 [9.4–11.8]	11.0 [9.57–12.5]	0.28
Right heart parameters			
RA volume, mL	53.2 [42.1–80.1]	56.62 [39.2–68.1]	0.99
RV EDA, cm^2	23.0 [18.6–25.4]	22.57 [15.7–25.8]	0.66
RV ESA, cm^2	14.7 [11.5–16.1]	13.15 [9.82–17.57]	0.59
RV FAC, %	0.4 [0.3–0.4]	0.4 [0.3–0.4]	0.94
S′, cm/s	12.5 [19.4–25.4]	12.33 [10.7–14.0]	0.45
TRV (≤2.5), m/s	2.3 [2.2–2.5]	2.3 [2.0–2.5]	0.55
PAAT (>130), ms	138.5 [114.8–144.6]	132.7 [114.7–143.3]	0.28
TAPSE, mm	22.0 [19.4–25.4]	22.25 [19.6–26.1]	0.38

All data are presented as median and interquartile range [IQR]. Wilcoxon rank sum test was used to compare paired medians. A- indicates mitral late peak diastolic flow velocity; A', maximal late mitral annular Doppler velocity; E, mitral early peak diastolic flow velocity; E′, maximal early mitral annular Doppler velocity; EDA, end diastolic area; EDV, end diastolic volume; EF, ejection fraction; ESA, end systolic area; ESV, end systolic volume; FAC, fractional area change; IVS, interventricular septum thickness; LA, left atrium; LV, left ventricle; LVIDd, left ventricular internal diameter end diastole; LVIDs, left ventricular internal diameter end systole; PAAT, pulmonary artery acceleration time; PWT, posterior wall thickness; RA, right atrium; RV, right ventricle; S′, RV free wall velocity; TAPSE, tricuspid annular plane excursion velocity; TRV, tricuspid regurgitant velocity; TTE, transthoracic echocardiogram.

Limitations

We acknowledge several limitations of this study. First, the sample size was too small to allow meaningful subgroup analyses. However, our regimented, prospective patient follow-up coupled with our detailed assessment of cardiopulmonary structure and function provide granular data in an understudied population of patients with PE. Second, we do not have echocardiographic or CPET data defining our patient population before their index PE presentation. Thus, we are unable to determine how much, if any, of the observed impairments preceded PE presentation. The possibility of premorbid deep vein thrombosis/PE and associated underlying chronic thromboembolic pulmonary hypertension may also contribute to the lack of observed improvement in functional improvement. Third, we acknowledge the potential for selection bias. While we did not observe differences between patients the patients who completed the study protocol and those who declined to participate in the 6-month study visit, it is possible that those who declined did so because they had experienced marked subjective improvement. Additionally, compared with those excluded because of loss to follow-up, the group that did complete the study protocol had a nonsignificant increased history of prior deep vein thrombosis/PE and received more therapeutic interventions, which may reflect features of a higher risk cohort. Lastly, the use of echocardiography as a tool for assessing the right ventricle is limited because of its complex 3-dimensional geometry; other imaging modalities such as magnetic resonance imaging may provide more insight in future analyses.

Conclusion

The majority of massive and submassive PE survivors have persistent subjective and objective functional limitations and abnormalities in RV structure and function through 6 months of follow-up after index PE presentation. Impairments in functional capacity appear unrelated to PE-acquired focal cardiopulmonary impairment but rather to global deconditioning. Further study is warranted to examine the optimal role of CPET following massive and submassive PE and to what degree patients with functional impairment may benefit from directed therapeutic steps including formal cardiac rehabilitation.

Disclosures

None.

References

1. Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. *Arch Intern Med*. 2011;171:831–837.
2. Horlander KT, Mannino DM, Leeper KV. Pulmonary embolism mortality in the United States, 1979–1998: an analysis using multiple-cause mortality data. *Arch Intern Med*. 2003;163:1711–1717.
3. Klok FA, Romeih S, Kroft LJ, Westenberg JJ, Huisman MV, de Roos A. Recovery of right and left ventricular function after acute pulmonary embolism. *Clin Radiol*. 2011;66:1203–1207.
4. Klok FA, van der Hulle T, den Exter PL, Lankeit M, Huisman MV, Konstantinides S. The post-PE syndrome: a new concept for chronic complications of pulmonary embolism. *Blood Rev*. 2014;28:221–226.
5. Jaff MR, McMurtry MS, Archer SL, Cushman M, Goldenberg N, Goldhaber SZ, Jenkins JS, Kline JA, Michaels AD, Thistlethwaite P, Vedantham S, White RJ, Zierler BK; American Heart Association Council on Cardiopulmonary CCP, Resuscitation, American Heart Association Council on Peripheral Vascular D, American Heart Association Council on Arteriosclerosis T and Vascular B. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation*. 2011;123:1788–1830.
6. Stewart LK, Peitz GW, Nordenholz KE, Courtney DM, Kabrhel C, Jones AE, Rondina MT, Diercks DB, Klinger JR, Kline JA. Contribution of fibrinolysis to the physical component summary of the SF-36 after acute submassive pulmonary embolism. *J Thromb Thrombolysis*. 2015;40:161–166.
7. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med*. 2002;346:793–801.
8. Kavanagh T, Mertens DJ, Hamm LF, Beyene J, Kennedy J, Corey P, Shephard RJ. Prediction of long-term prognosis in 12 169 men referred for cardiac rehabilitation. *Circulation*. 2002;106:666–671.
9. Kahn SR, Hirsch AM, Akaberi A, Hernandez P, Anderson DR, Wells PS, Rodger M, Solymoss S, Kovacs MJ, Rudski L, Shimony A, Dennie C, Rush C, Geerts WH, Aaron SD, Granton JT. Functional and exercise limitations after a first episode of pulmonary embolism: results of the ELOPE prospective cohort study. *Chest*. 2016;151:1058–1068.
10. Tavoly M, Utne KK, Jelsness-Jorgensen LP, Wik HS, Klok FA, Sandset PM, Ghanima W. Health-related quality of life after pulmonary embolism: a cross-sectional study. *BMJ Open*. 2016;6:e013086.
11. Sista AK, Miller LE, Kahn SR, Kline JA. Persistent right ventricular dysfunction, functional capacity limitation, exercise intolerance, and quality of life impairment following pulmonary embolism: systematic review with meta-analysis. *Vasc Med*. 2016;22:37–43.
12. van Es J, den Exter PL, Kaptein AA, Andela CD, Erkens PM, Klok FA, Douma RA, Mos IC, Cohn DM, Kamphuisen PW, Huisman MV, Middeldorp S. Quality of life after pulmonary embolism as assessed with SF-36 and PEmb-QoL. *Thromb Res*. 2013;132:500–505.
13. Klok FA, van Kralingen KW, van Dijk AP, Heyning FH, Vliegen HW, Kaptein AA, Huisman MV. Quality of life in long-term survivors of acute pulmonary embolism. *Chest*. 2010;138:1432–1440.
14. Kline JA, Nordenholz KE, Courtney DM, Kabrhel C, Jones AE, Rondina MT, Diercks DB, Klinger JR, Hernandez J. Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial. *J Thromb Haemost*. 2014;12:459–468.
15. Kline JA, Steuerwald MT, Marchick MR, Hernandez-Nino J, Rose GA. Prospective evaluation of right ventricular function and functional status 6 months after acute submassive pulmonary embolism: frequency of persistent or subsequent elevation in estimated pulmonary artery pressure. *Chest*. 2009;136:1202–1210.
16. Chow V, Ng AC, Seccombe L, Chung T, Thomas L, Celermajer DS, Peters M, Kritharides L. Impaired 6-min walk test, heart rate recovery and cardiac function post pulmonary embolism in long-term survivors. *Respir Med*. 2014;108:1556–1565.
17. Yan WW, Wang LM, Che L, Song HM, Jiang JF, Xu JH, Shen YQ, Zhang QP. Quantitative evaluation of cardiopulmonary functional reserve in treated patients with pulmonary embolism. *Chin Med J (Engl)*. 2012;125:465–469.
18. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, Huisman M, King CS, Morris TA, Sood N, Stevens SM, Vintch JR, Wells P, Woller SC, Moores L. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*. 2016;149:315–352.
19. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galie N, Gibbs JS, Huisman MV, Humbert M, Kucher N, Lang I, Lankeit M, Lekakis J, Maack C, Mayer E, Meneveau N, Perrier A, Pruszczyk P, Rasmussen LH, Schindler TH, Svitil P, Vonk Noordegraaf A, Zamorano JL, Zompatori M; Task Force for the D and Management of Acute Pulmonary Embolism of the European Society of C. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2014;35:3033–3069, 3069a–3069k.
20. Provias T, Dudzinski DM, Jaff MR, Rosenfield K, Channick R, Baker J, Weinberg I, Donaldson C, Narayan R, Rassi AN, Kabrhel C. The Massachusetts General Hospital Pulmonary Embolism Response Team (MGH PERT): creation of a multidisciplinary program to improve care of patients with massive and submassive pulmonary embolism. *Hosp Pract (1995)*. 2014;42:31–37.
21. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23:685–713; quiz 786–8.
22. Jones NL, Robertson DG, Kane JW. Difference between end-tidal and arterial PCO_2 in exercise. *J Appl Physiol Respir Environ Exerc Physiol*. 1979;47:954–960.
23. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol (1985)*. 1986;60:2020–2027.
24. Medoff BD, Oelberg DA, Kanarek DJ, Systrom DM. Breathing reserve at the lactate threshold to differentiate a pulmonary mechanical from cardiovascular limit to exercise. *Chest*. 1998;113:913–918.
25. American Thoracic S and American College of Chest P. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med*. 2003;167:211–277.
26. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1–39.e14.
27. Yared K, Noseworthy P, Weyman AE, McCabe E, Picard MH, Baggish AL. Pulmonary artery acceleration time provides an accurate estimate of systolic pulmonary arterial pressure during transthoracic echocardiography. *J Am Soc Echocardiogr*. 2011;24:687–692.
28. Lu MT, Cai T, Ersoy H, Whitmore AG, Levit NA, Goldhaber SZ, Rybicki FJ. Comparison of ECG-gated versus non-gated CT ventricular measurements in thirty patients with acute pulmonary embolism. *Int J Cardiovasc Imaging*. 2009;25:101–107.
29. Albrecht MH, Bickford MW, Nance JW Jr, Zhang L, De Cecco CN, Wichmann JL, Vogl TJ, Schoepf UJ. State-of-the-art pulmonary CT angiography for acute pulmonary embolism. *AJR Am J Roentgenol*. 2017;208:495–504.
30. Sista AK, Miller LE, Kahn SR, Kline JA. Persistent right ventricular dysfunction, functional capacity limitation, exercise intolerance, and quality of life impairment following pulmonary embolism: systematic review with meta-analysis. *Vasc Med*. 2017;22:37–43.
31. Kearon C. Natural history of venous thromboembolism. *Circulation*. 2003;107:I22–I30.

32. Nijkeuter M, Hovens MM, Davidson BL, Huisman MV. Resolution of thromboemboli in patients with acute pulmonary embolism: a systematic review. *Chest*. 2006;129:192–197.
33. Kucher N, Boekstegers P, Muller OJ, Kupatt C, Beyer-Westendorf J, Heitzer T, Tebbe U, Horstkotte J, Muller R, Blessing E, Greif M, Lange P, Hoffmann RT, Werth S, Barmeyer A, Hartel D, Grunwald H, Empen K, Baumgartner I. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. *Circulation*. 2014;129:479–486.
34. Meyer G, Vicaut E, Danays T, Agnelli G, Becattini C, Beyer-Westendorf J, Bluhmki E, Bouvaist H, Brenner B, Couturaud F, Dellas C, Empen K, Franca A, Galie N, Geibel A, Goldhaber SZ, Jimenez D, Kozak M, Kupatt C, Kucher N, Lang IM, Lankeit M, Meneveau N, Pacouret G, Palazzini M, Petris A, Pruszczyk P, Rugolotto M, Salvi A, Schellong S, Sebbane M, Sobkowicz B, Stefanovic BS, Thiele H, Torbicki A, Verschuren F, Konstantinides SV; Investigators P. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med*. 2014;370:1402–1411.
35. Piazza G, Hohlfelder B, Jaff MR, Ouriel K, Engelhardt TC, Sterling KM, Jones NJ, Gurley JC, Bhatheja R, Kennedy RJ, Goswami N, Natarajan K, Rundback J, Sadiq IR, Liu SK, Bhalla N, Raja ML, Weinstock BS, Cynamon J, Elmasri FF, Garcia MJ, Kumar M, Ayerdi J, Soukas P, Kuo W, Liu PY, Goldhaber SZ; Investigators SI. A prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism: the SEATTLE II Study. *JACC Cardiovasc Interv*. 2015;8:1382–1392.
36. Konstantinides SV, Vicaut E, Danays T, Becattini C, Bertoletti L, Beyer-Westendorf J, Bouvaist H, Couturaud F, Dellas C, Duerschmied D, Empen K, Ferrari E, Galie N, Jimenez D, Kostrubiec M, Kozak M, Kupatt C, Lang IM, Lankeit M, Meneveau N, Palazzini M, Pruszczyk P, Rugolotto M, Salvi A, Sanchez O, Schellong S, Sobkowicz B, Meyer G. Impact of thrombolytic therapy on the long-term outcome of intermediate-risk pulmonary embolism. *J Am Coll Cardiol*. 2017;69:1536–1544.
37. Kahn SR, Akaberi A, Granton JT, Anderson DR, Wells PS, Rodger MA, Solymoss S, Kovacs MJ, Rudski L, Shimony A, Dennie C, Rush C, Hernandez P, Aaron SD, Hirsch AM. Quality of life, dyspnea, and functional exercise capacity following a first episode of pulmonary embolism: results of the ELOPE cohort study. *Am J Med*. 2017;130:990.e9–990.e21.
38. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet*. 1999;353:1386–1389.
39. Becattini C, Casazza F, Forgione C, Porro F, Fadin BM, Stucchi A, Lignani A, Conte L, Imperadore F, Bongarzoni A, Agnelli G. Acute pulmonary embolism: external validation of an integrated risk stratification model. *Chest*. 2013;144:1539–1545.
40. Ribeiro A, Lindmarker P, Johnsson H, Juhlin-Dannfelt A, Jorfeldt L. Pulmonary embolism: one-year follow-up with echocardiography Doppler and five-year survival analysis. *Circulation*. 1999;99:1325–1330.
41. Hsiao SH, Lee CY, Chang SM, Yang SH, Lin SK, Huang WC. Pulmonary embolism and right heart function: insights from myocardial Doppler tissue imaging. *J Am Soc Echocardiogr*. 2006;19:822–828.
42. Kjaergaard J, Schaadt BK, Lund JO, Hassager C. Prognostic importance of quantitative echocardiographic evaluation in patients suspected of first non-massive pulmonary embolism. *Eur J Echocardiogr*. 2009;10:89–95.
43. Stevinson BG, Hernandez-Nino J, Rose G, Kline JA. Echocardiographic and functional cardiopulmonary problems 6 months after first-time pulmonary embolism in previously healthy patients. *Eur Heart J*. 2007;28:2517–2524.
44. Anavekar NS, Gerson D, Skali H, Kwong RY, Yucel EK, Solomon SD. Two-dimensional assessment of right ventricular function: an echocardiographic-MRI correlative study. *Echocardiography*. 2007;24:452–456.
45. Topilsky Y, Hayes CL, Khanna AD, Allison TG. Cardiopulmonary exercise test in patients with subacute pulmonary emboli. *Heart Lung*. 2012;41:125–136.
46. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136:e137–e161.
47. Mereles D, Ehlken N, Kreuscher S, Ghofrani S, Hoeper MM, Halank M, Meyer FJ, Karger G, Buss J, Juenger J, Holzapfel N, Opitz C, Winkler J, Herth FF, Wilkens H, Katus HA, Olschewski H, Grunig E. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. *Circulation*. 2006;114:1482–1489.
48. Kwan G, Balady GJ. Cardiac rehabilitation 2012: advancing the field through emerging science. *Circulation*. 2012;125:e369–e373.

Supplemental Material

Table S1. Comparison of Baseline Characteristics Between Included and Excluded Patients.

Characteristics	Included (n=20)	Excluded (n=11)	P Value
Age	57.0 (13.3)	60.2 (12.4)	0.51
Female, n (%)	8 (40)	6 (54.5)	0.44
Comorbid Conditions			
COPD or asthma, n (%)	0 (0)	2 (18)	0.05
CAD n, (%)	1 (5)	2 (22)	0.66
Prior MI n, (%)	0 (0)	2 (22)	0.10
CHF n, (%)	0 (0)	0 (0)	NA
Prior PE n, (%)	3 (16)	0 (0)	0.87
Prior DVT n, (%)	4 (21)	1 (11)	0.82
History of tobacco abuse n, (%)	14 (70)	8 (73)	0.87
PE Presenting Characteristics			
Syncope, n (%)	5 (25)	0 (0)	0.07
Shortness of breath, n (%)	20 (100)	11 (100)	NA
Chest pain, n (%)	8 (40)	6 (55)	0.44
Heart rate (beats per minute)	106 (21)	100 (13)	0.42
Systolic blood pressure (mm Hg)	124 (25)	125 (12)	0.89
Diastolic blood pressure (mm Hg)	78 (11)	76 (5.2)	0.33
Elevated Troponin T, n (%)	12 (60)	7 (63.6)	0.98
Troponin T (ng/ml)	0.2 (0.6)	0.1 (0.0)	0.81
Elevated NT pro-BNP, n (%)	12 (60)	7 (63.6)	0.53
NT pro-BNP (pg/ml)	3624.2 (2309.6)	2386.3 (1984.7)	0.72
RV:LV ratio on CT	1.5 (0.3)	1.4 (0.3)	0.44
Massive PE	3 (15)	2 (18)	0.09
Management Strategy			
Anticoagulation (%)	20 (100)	11 (100)	NA
IV thrombolysis (%)	5 (25)	0 (0)	0.07
Catheter directed therapy (%)	7 (35)	0 (0)	0.03
IVC filter (%)	3 (16)	1 (9)	0.64
ECMO (%)	0 (0)	0 (0)	NA

Values are means ± SD unless otherwise noted. Mann Whitney U test was used to compare means.

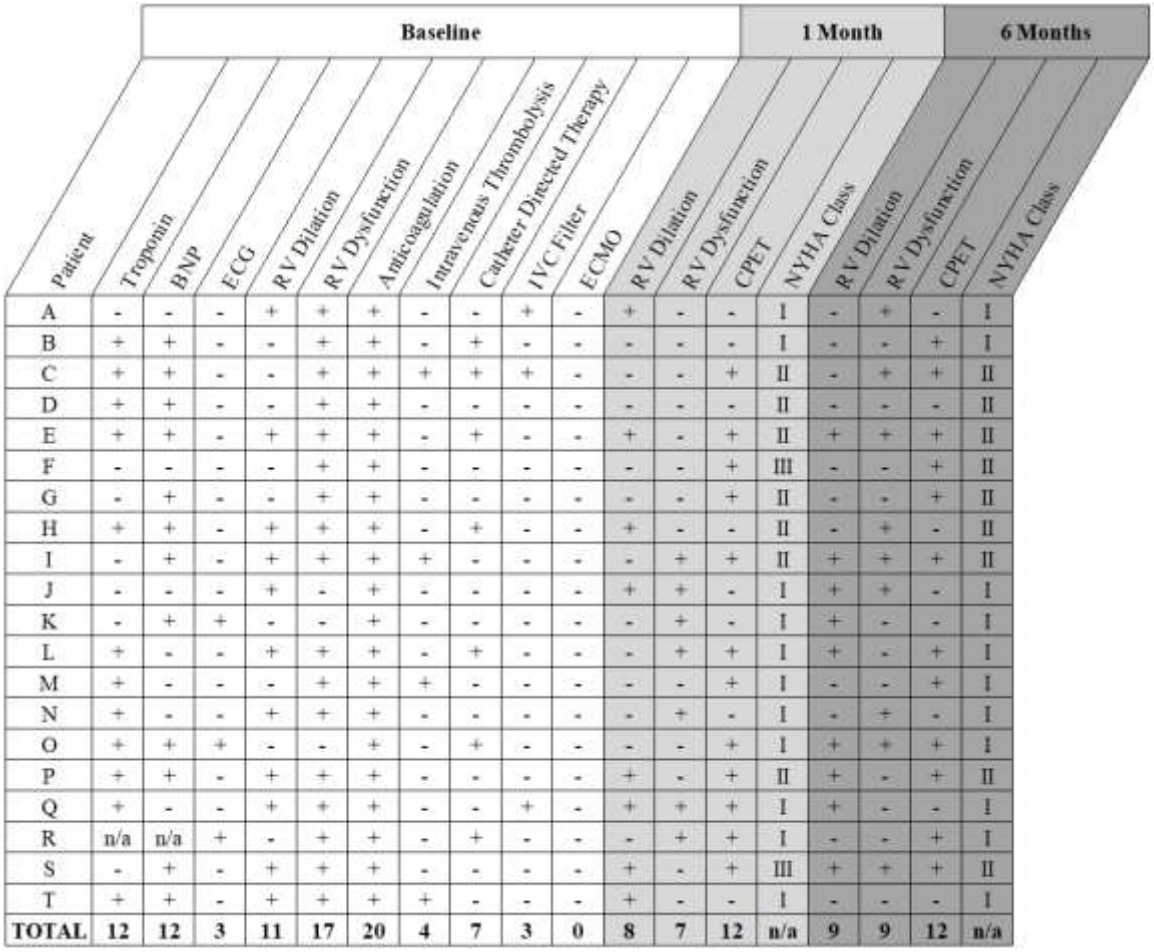
NT pro-BNP – N-terminal pro-Brain Natriuretic Peptide, CAD – Coronary Artery Disease, CHF – Congestive Heart Failure, COPD – Chronic Obstructive Pulmonary Disease, DVT – Deep Vein Thrombosis, ECMO – Extra-corporeal Membrane Oxygenation, IVC – Inferior Vena Cava, MI – Myocardial Infarction, NA – not applicable, PE – Pulmonary Embolism, RV – Right Ventricle.

Table S2. First Cardiopulmonary Exercise Testing Characteristics in Patients who had Both CPET and in those that had Only the First.

Characteristic	Included (n=20)*	Excluded (n=11)*	P Value
Total exercise time (min)	10.3 [8.8-12.8]	12.3 [9.6-14.5]	0.07
Peak power (watts)	151.0 {72.8-207.3]	149.0 [95.0-239.0]	0.42
Peak VO_2 (L/min.)	1.7 [1.2-2.2]	1.9 [1.5-2.1]	0.35
Body mass indexed peak VO_2 (mL/kg/min)	16.3 [13.4-21.0]	15.5 [12.3-22.4]	0.42
Percentage of predicted peak VO_2 (%)	67.5 [59.75-84.75]	111 [89-127]	0.08
Peak respiratory exchange rate	1.2 [1.1-1.3]	1.24 [1.2-1.3]	0.37
Peak heart rate	150 [114-164]	159 [116-193]	0.14
Percentage of predicted peak heart rate (%)	94 [74-101]	166 [151-184]	0.64
Peak systolic blood pressure (mmHg)	180 [160-194]	177 [170-194]	0.85
Peak diastolic blood pressure (mmHg)	80 [80-84]	84 [80-96]	0.63
Peak O_2 pulse (mL/beat)	11 [9-16]	13 [11-20]	0.32
Percentage of predicted peak O_2 pulse (%)	82 [70-91]	88 [82-100]	0.58
Breathing reserve (%)	43 [28-65]	34 [27-44]	0.18
Overall VE/VCO_2	27.3 [23.3-32]	27.7 [23.6-34.9]	0.99
VO_2 at ventilatory threshold (mL/kg/min)	12.2 [10.7-13.63]	12.3 [9.9-24.8]	0.25
Ventilatory threshold VO_2 as a % of Peak VO_2 (%)	71.5 [61.3-83.0]	67.0 [61.0-71.0]	0.09

*Percentages are shown out of the available data for a particular variable. Values are reported in median [IQR]. Mann-Whitney U test was used to compare medians for unpaired data.
DBP – Diastolic Blood Pressure; FVC – Forced Vital Capacity; FEV1 – Forced Expiratory Volume in 1 second; HR – Heart Rate; RER – Respiratory Exchange Ratio; SBP – Systolic Blood Pressure

Figure S1. Summary of individual subject baseline and key echocardiographic, cardiopulmonary exercise test findings, and symptoms.



	Baseline														1 Month			6 Months	
Patient	Troponin	BNP	ECG	RV Dilation	RV Dysfunction	Anticoagulation	Intravenous Thrombolysis	Catheter Directed Therapy	IVC Filter	ECMO	RV Dilation	RV Dysfunction	CPET	NYHA Class	RV Dilation	RV Dysfunction	CPET	NYHA Class
A	-	-	-	+	+	+	-	-	+	-	+	-	-	I	-	+	-	I
B	+	+	-	-	+	+	-	+	-	-	-	-	-	I	-	-	+	I
C	+	+	-	-	+	+	+	+	+	-	-	-	+	II	-	+	+	II
D	+	+	-	-	+	+	-	-	-	-	-	-	-	II	-	-	-	II
E	+	+	-	+	+	+	-	+	-	-	+	-	+	II	+	+	+	II
F	-	-	-	-	+	+	-	-	-	-	-	-	+	III	-	-	+	II
G	-	+	-	-	+	+	-	-	-	-	-	-	+	II	-	-	+	II
H	+	+	-	+	+	+	-	+	-	-	+	-	-	II	-	+	-	II
I	-	+	-	+	+	+	+	-	-	-	-	+	+	II	+	+	+	II
J	-	-	-	+	-	+	-	-	-	-	+	+	-	I	+	+	-	I
K	-	+	+	-	-	+	-	-	-	-	-	+	-	I	+	-	-	I
L	+	-	-	+	+	+	-	+	-	-	-	+	+	I	+	-	+	I
M	+	-	-	-	+	+	+	-	-	-	-	-	+	I	-	-	+	I
N	+	-	-	+	+	+	-	-	-	-	-	+	-	I	-	+	-	I
O	+	+	+	-	-	+	-	+	-	-	-	-	+	I	+	+	+	I
P	+	+	-	+	+	+	-	-	-	-	+	-	+	II	+	-	+	II
Q	+	-	-	+	+	+	-	-	+	-	+	+	+	I	+	-	-	I
R	n/a	n/a	+	-	+	+	-	+	-	-	-	+	+	I	-	-	+	I
S	-	+	-	+	+	+	-	-	-	-	+	-	+	III	+	+	+	II
T	+	+	-	+	+	+	+	-	-	-	+	-	-	I	-	-	-	I
TOTAL	**12**	**12**	**3**	**11**	**17**	**20**	**4**	**7**	**3**	**0**	**8**	**7**	**12**	**n/a**	**9**	**9**	**12**	**n/a**

NT-Brain natriuretic peptide (BNP), Electrocardiographic (ECG) evidence of right ventricular (RV) strain, RV dilation or dysfunction by TTE, Inferior vena cava (IVC), New York Heart Association (NYHA), Cardiopulmonary exercise test (CPET) refers to the presence or absence of peak $\dot{V}O_2$ <80% of max predicted. All parameters with (+) indicates either the presence of this finding or having received the treatment, and (-) indicates the absence of this finding or lack of treatment.