The effects of exercise training in patients with persistent dyspnea following pulmonary embolism: a randomized controlled trial

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CHEST

The Effects of Exercise Training in Patients With Persistent Dyspnea Following Pulmonary Embolism

A Randomized Controlled Trial

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BACKGROUND: Persistent dyspnea, functional limitations, and reduced quality of life (QoL) are common following pulmonary embolism (PE). Rehabilitation is a potential treatment option, but the scientific evidence is limited.

RESEARCH QUESTION: Does an exercise-based rehabilitation program improve exercise capacity in PE survivors with persistent dyspnea?

STUDY DESIGN AND METHODS: This randomized controlled trial was conducted at two hospitals. Patients with persistent dyspnea following PE diagnosed 6 to 72 months earlier, without cardiopulmonary comorbidities, were randomized 1:1 to either the rehabilitation or the control group. The rehabilitation program consisted of two weekly sessions of physical exercise for 8 weeks and one educational session. The control group received usual care. The primary end point was the difference in Incremental Shuttle Walk Test between groups at follow-up. Secondary end points included differences in the Endurance Shuttle Walk Test (ESWT), QoL (EQ-5D and Pulmonary Embolism-QoL questionnaires) and dyspnea (Shortness of Breath questionnaire).

RESULTS: A total of 211 subjects were included: 108 (51%) were randomized to the rehabilitation group and 103 (49%) to the control group. At follow-up, participants allocated to the rehabilitation group performed better on the ISWT compared with the control group (mean difference, 53.0 m; 95% CI, 17.7-88.3; $P = .0035$). The rehabilitation group reported better scores on the Pulmonary Embolism-QoL questionnaire (mean difference, –4%; 95% CI, –0.09 to 0.00; $P = .041$) at follow-up, but there were no differences in generic QoL, dyspnea scores, or the ESWT. No adverse events occurred during the intervention.

INTERPRETATION: In patients with persistent dyspnea following PE, those who underwent rehabilitation had better exercise capacity at follow-up than those who received usual care. Rehabilitation should be considered in patients with persistent dyspnea following PE. Further research is needed, however, to assess the optimal patient selection, timing, mode, and duration of rehabilitation.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov; No.: NCT03405480; URL: www.clinicaltrials.gov

CHEST 2023; 164(4):981-991

KEY WORDS: dyspnea; exercise training; pulmonary embolism; quality of life; rehabilitation

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Take-home Points

Study Question: Does an exercise-based rehabilitation program improve exercise capacity, symptoms, and quality of life in subjects who experience persistent dyspnea following pulmonary embolism?

Results: Subjects who underwent the rehabilitation program exhibited better exercise capacity and reported improved disease-specific quality of life compared with those who received usual care, although generic quality of life and dyspnea scores revealed no difference.

Interpretation: Rehabilitation following pulmonary embolism is promising and should be considered in patients with persistent dyspnea following pulmonary embolism.

Persistent dyspnea, functional limitations, and reduced quality of life (QoL) are common following pulmonary embolism (PE), with studies suggesting a prevalence of 30% to 50%.[1-4] The underlying mechanisms of post-PE impairment, apart from those with chronic thromboembolic pulmonary hypertension, are unclear and probably multifactorial. Several studies suggest that deconditioning and psychological factors are important contributors to post-PE impairment.[1,2] Current guidelines for the management of PE make little comment regarding this patient group, and optimal management is unknown.[5,6]

Rehabilitation for patients with COPD or cardiac diseases is safe and well documented in improving patients' symptoms, exercise capacity, and QoL.[7] Because deconditioning has been proposed to be a major factor in post-PE impairment, exercise-based rehabilitation stands out as a potential treatment option.[1,2] However, evidence regarding the benefits of rehabilitation in a post-PE setting is limited, and larger, randomized trials are lacking.[8-13]

The aim of the current study was to determine the effects of an 8-week exercise-based rehabilitation program on exercise capacity, dyspnea, and QoL in patients with persistent dyspnea following PE.

Study Design and Methods

Trial Design

This two-center randomized controlled trial was conducted at Østfold Hospital Trust and Akershus University Hospital in Norway.[14] The Regional Committee for Medical and Health Research Ethics in Norway approved the project (REK no. 2017/1940), and all participants provided signed informed consent. The study was reported according to Consolidated Standards of Reporting Trials (e-Appendix 3). The project is registered with ClinicalTrials.gov.[15]

Participants

We identified patients from the Venous Thrombosis Registry in Østfold Hospital (TROLL) and via International Statistical Classification of Diseases and Related Health Problems 10th revision discharge codes (ICD-10 I26.x) at Akershus University Hospital.[16,17] Inclusion criteria were: (1) PE greater than isolated subsegmental emboli diagnosed with CT pulmonary angiography 6 to 72 months prior to study inclusion; (2) age 18 to 75 years; and (3) persistent self-reported dyspnea corresponding to modified Medical Research Council (mMRC) dyspnea scale grade $\geq$ 1 with onset or exacerbation at the time of PE diagnosis.[18]

All participants underwent a comprehensive baseline evaluation, comprising a clinical examination, transthoracic echocardiography, and pulmonary function tests (spirometry, whole body plethysmography, and diffusion capacity of the lungs for carbon monoxide). Patients with significant cardiopulmonary comorbidity were excluded. A full list of exclusion criteria is provided in the published protocol.[14] Inclusion occurred between January 1, 2018, and June 1, 2022.

ABBREVIATIONS: ESWT = Endurance Shuttle Walk Test; ISWT = Incremental Shuttle Walk Test; mMRC = modified Medical Research Council; PE = pulmonary embolism; PEmb-QoL = Pulmonary Embolism Quality of Life questionnaire; QoL = quality of life; SOBQ = Shortness of Breath Questionnaire

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DOI: https://doi.org/10.1016/j.chest.2023.04.042

Randomization

After completion of the baseline evaluation, participants were randomized 1:1 to either an intervention arm or a control arm. The allocation sequence was computer generated in blocks of 10 to ensure balanced recruitment, with separate strata for the two hospitals. The allocation code was kept in sealed, opaque envelopes.

Blinding

The investigators who conducted the walking tests at follow-up were blinded to the participants' group allocation.

Intervention

The intervention group underwent a supervised outpatient exercise program for 1 h twice a week for 8 weeks. The exercise program was based on existing pulmonary rehabilitation programs and international guidelines and was individually tailored to each participant (e-Appendix 1).[7] In addition, participants were given a simple home-based exercise program to be performed once or twice weekly during the intervention period.

Minimum 80% attendance was considered as completion of the program, with no more than a 2-week break during the rehabilitation period. With higher nonattendance, the rehabilitation period was extended to ensure the completion of 16 exercise sessions.

The rehabilitation program included one 90 min educational session on the cardiopulmonary system, diagnosis and treatment of PE and its possible long-term effects, the benefits of exercise and physical activity, and the management of breathlessness. Subjects in the control arm received usual care according to guidelines.[5,6] At inclusion, all participants completed a questionnaire on their recent physical activities, and those who exercised regularly were encouraged to continue doing so irrespective of group allocation.

Primary Outcome: Incremental Shuttle Walk Test

The primary end point was the difference in Incremental Shuttle Walk Test (ISWT) performance between the groups at follow-up. The ISWT is a standardized walking test to assess exercise capacity, where participants walk between two cones 9 m apart in a tempo determined by a prerecorded audio track.[19] The test consists of 12 levels with increasing speed and has a maximum walking distance of 1,020 m. The ISWT was performed twice at baseline to account for a possible learning effect, and the best result was recorded.[20] Predicted values of ISWT at baseline was calculated by using a reference equation based on age, BMI, and sex.[21]

Secondary Outcomes

Secondary outcomes included the Endurance Shuttle Walk Test (ESWT), the EQ-5D-5L questionnaire, the Shortness of Breath Questionnaire (SOBQ), and the Pulmonary Embolism Quality of Life questionnaire (PEmb-QoL).

The ESWT is a derivative of the ISWT, where the speed is set at 85% of the maximum speed reached on the preceding ISWT. The results are reported as time in seconds, and the maximum duration of the test is 1,200 s.[22]

The EQ-5D-5L is a generic health status measure.[23] It includes five self-completed items: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each item is scored from 1 (no problem) to 5 (maximal problem/worst state). In addition, respondents score their overall health on a visual analog scale from 0 (worst imaginable health) to 100 (best imaginable health). Individual EQ-5D-5L dimension scores were transformed to EQ-5D index values using crosswalk to the UK three-level version of the EQ-5D Dolan value set.[24]

The PEmb-QoL assesses QoL following PE.[25] It contains 40 items covering six different domains. Each domain score was transformed to a 0 to 1 scale, with lower scores indicating better QoL. Scores were aggregated to a PEmb-QoL total score, using the mean score of all dimensions. Patients were excluded from the analysis if $>$ 50% of items within a dimension or $>$ 20% of the total 38 items were unanswered.

The SOBQ assesses the severity of dyspnea.[26] The questionnaire contains 24 self-completed items/activities of daily life, in which each item is scored from 0 (no breathlessness) to 5 (maximal breathlessness or unable to do because of breathlessness) and aggregated to a sum score (range, 0-120). For a valid score, $\geq$ 80% of the 24 items had to be completed.

Sample Size Calculation and Statistical Methods

Because there were no prior data concerning the ISWT in a post-PE population, we based our sample size calculation on data from studies in patients with cardiac or respiratory diseases.[14] We presumed that a mean improvement of $\geq$ 60 m compared with the control population would be a meaningful study outcome. With an SD of 140 m, a type I error risk of 5%, and power of 80%, we estimated the required sample size to be 86 participants in each study arm. Adding 10% attrition, the total sample size was estimated to be 190 participants. No interim analysis was planned. We aimed to analyze the data according to the intention-to-treat principle. Normality of the data was assessed by using the Shapiro-Wilk test and quantile-quantile plots, and descriptive statistics are reported as median (25th to 75th percentile) or number (%), as appropriate.

The primary end point (ie, between-group difference in ISWT at follow-up) was compared by using linear regression with baseline ISWT included as an independent variable. Because there may be systematic differences between the two centers, and randomization was stratified, hospital allocation was included as an independent variable. The difference in ESWT was analyzed by using the same approach.

Because a considerable ceiling effect was experienced in the primary end point, we performed prespecified supplementary analyses comprising transformation of the dependent variable and a Tobit regression analysis.[27] We supplemented with sensitivity analyses of the primary end point to account for missing values: (1) single imputation with last value carried forward (ie, corresponding to no effect of rehabilitation); (2) a linear mixed model with random intercept, with study identifier as a random effect and hospital allocation as a fixed effect; and (3) analysis using the full information maximum likelihood estimation method.[28] In addition, we conducted a supplementary per-protocol analysis. The primary end point was assessed in a prespecified subgroup analysis in which participants were dichotomized based on time since diagnosis (ie, 6-12 months and $>$ 12-72 months). In a post hoc subgroup analysis, we repeated the analysis of the primary end point in participants with more severe dyspnea, corresponding to an mMRC score $\geq$ 2. In a final supplementary analysis of the primary end point, the Pulmonary Embolism Severity Index score was included dichotomized at the 75th percentile (score $\geq$ 77, corresponding to the middle of class II [low risk]) as an independent variable.[29]

EQ-5D index values, PEmb-QoL total score, and SOBQ sum scores were compared between the groups at follow-up by using linear mixed models with random intercept, with hospital allocation as a fixed effect and study identifier as a random effect.

A statistical analysis plan was created prior to data analysis (e-Appendix 2). Stata version 17.0 (StataCorp) was used for all analyses.

Results

A total of 1,998 electronic patient records were reviewed, and 970 were excluded due to pre-existing conditions, peripheral or uncertain PE diagnosis, or patients residing outside the hospitals' catchment areas (Fig 1). We invited 1,028 people to participate in the study and scheduled primary evaluation for 337 individuals, although four individuals did not attend. Following completion of the primary evaluation, 211 individuals met the inclusion criteria and were randomized to treatment. The inclusion of participants was stopped when the pre-estimated number of primary end points was reached. Participants who were unable or unwilling to perform walking tests at follow-up were asked to complete questionnaires.

Overall, the median age of the 211 participants was 57 (49-67) years, and 56% were male (Table 1). Median time from diagnosis to inclusion was 10.3 (7.2-21.0) months. At baseline, the median walking distance for the ISWT was 695 (530-940) m, and 44 (21%) participants achieved the maximum walking distance for the test (ie, 1,020 m).

In total, 108 (51%) participants were randomized to the rehabilitation group and 103 (49%) participants to the control group (Fig 2). Those allocated to the rehabilitation group were slightly younger (median age, 55 years vs 60 years) and performed slightly worse on the ISWT at baseline (median, 680 m vs 730 m) than the control subjects. Otherwise, the groups seemed balanced regarding baseline characteristics.

Attrition was higher in the rehabilitation group (n = 14) than in the control group (n = 5) (Fig 2). In total, 14 participants did not complete the rehabilitation program: three did not respond to telephone/mail and never started the rehabilitation program, seven were unwilling to continue or did not complete the required number of exercise sessions (four reported exercise sessions conflicting with working hours as main reason, and the remaining three gave no reason), one withdrew because of pregnancy, and three withdrew because of orthopedic injury or other health issues.

A total of 94 (87%) participants from the rehabilitation group and 98 (95%) participants from the control group participated in the follow-up assessment, and the

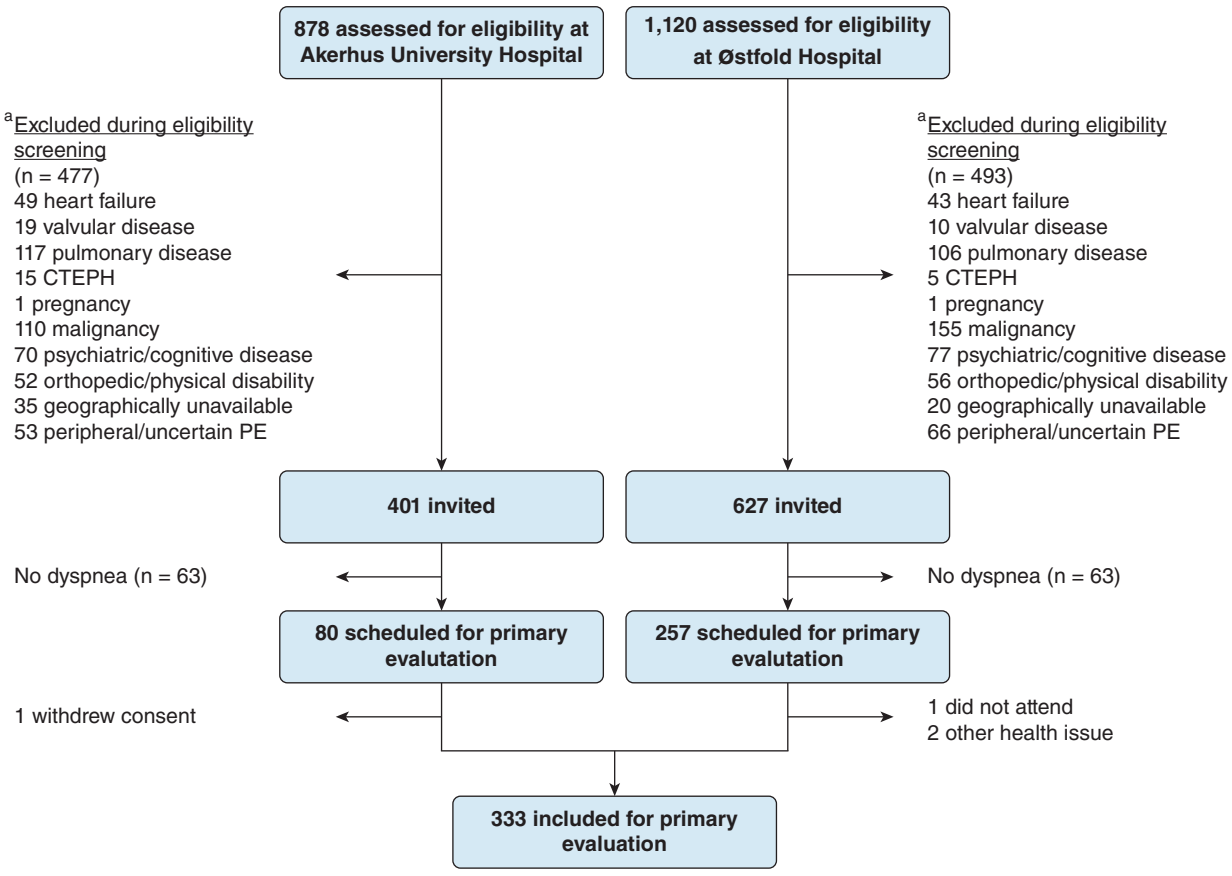

Figure 1 – *Eligibility screening. CTEPH = chronic thromboembolic pulmonary hypertension; PE = pulmonary embolism.* [a]*Some patients were excluded due to multiple reasons.*

TABLE 1] Baseline Characteristics

Characteristic	Rehabilitation Group (n = 108)	Control Group (n = 103)
Age, y	55 (48-66)	60 (52-67)
Male sex	63 (58)	54 (52)
BMI, kg/m^2	29.3 (27.1-35.3)	29.0 (26.3-32.1)
Time since diagnosis, mo	10.5 (7.1-22.4)	9.9 (7.2-19.6)
Time since diagnosis		
6-12 mo	61 (56)	59 (57)
12.1-72 mo	47 (44)	44 (43)
Anticoagulant therapy at inclusion	84 (78)	74 (72)
Duration anticoagulant therapy, mo	8.1 (6.1-17.2)	7.6 (6.2-12.7)
Unprovoked PE	63 (59)	70 (68)
Previous VTE	22 (21)	17 (17)
Pulmonary Embolism Severity Index score at diagnosis	64 (52-77)	67 (58-75)
Troponin at diagnosis, ng/L	9 (2-60)	5 (2-18)
D-dimer at diagnosis, mg/L	4.3 (2.2-9.4)	4.1 (2.1-8.2)
Comorbidities		
Hypertension	34 (32)	38 (37)
Coronary disease	5 (5)	2 (2)
Diabetes	3 (3)	7 (7)
Hypothyroidism	11 (10)	5 (5)
Chronic kidney failure (GFR < 60 mL/min/1.73 m^2)	2 (2)	2 (2)
Smoking status		
Currently smokes	7 (7)	5 (5)
Formerly smoked	60 (56)	57 (58)
Never smoked	41 (38)	37 (38)
Hospital allocation		
Akershus University Hospital	33 (31)	31 (30)
Østfold Hospital	74 (69)	73 (70)
Incremental Shuttle Walk Test, m	680 (530-905)	730 (520-950)
Incremental Shuttle Walk Test results as percentage of predicted value	87 (68-116)	103 (74-135)
Time from baseline to follow-up, wk	13.5 (11.0-17.7)	14.1 (12.5-17.2)
Performing regular exercise at inclusion	32 (34)	33 (38)
Modified Medical Research Council dyspnea scale		
1	73 (68)	75 (73)
2	31 (29)	26 (25)
3-4	4 (4)	3 (3)

Data are presented as median (25th to 75th percentile) or No. (%) unless otherwise indicated. GFR = estimated glomerular filtration rate; PE = pulmonary embolism.

primary outcome was obtained in 89 and 87 participants, respectively. Baseline characteristics for those who completed and those who dropped out are shown in e-Table 1.

One participant experienced chest pain during an exercise session and was referred to the ED for diagnostic workup, which was concluded as normal. Otherwise, no adverse events occurred during the intervention.

At follow-up, the rehabilitation group performed better on the ISWT than the control group, with a between-group mean difference of 53.0 m (95% CI, 17.7-88.3; $P = .0035$) (e-Table 2, Table 2). A Tobit regression analysis yielded similar results as the primary analysis

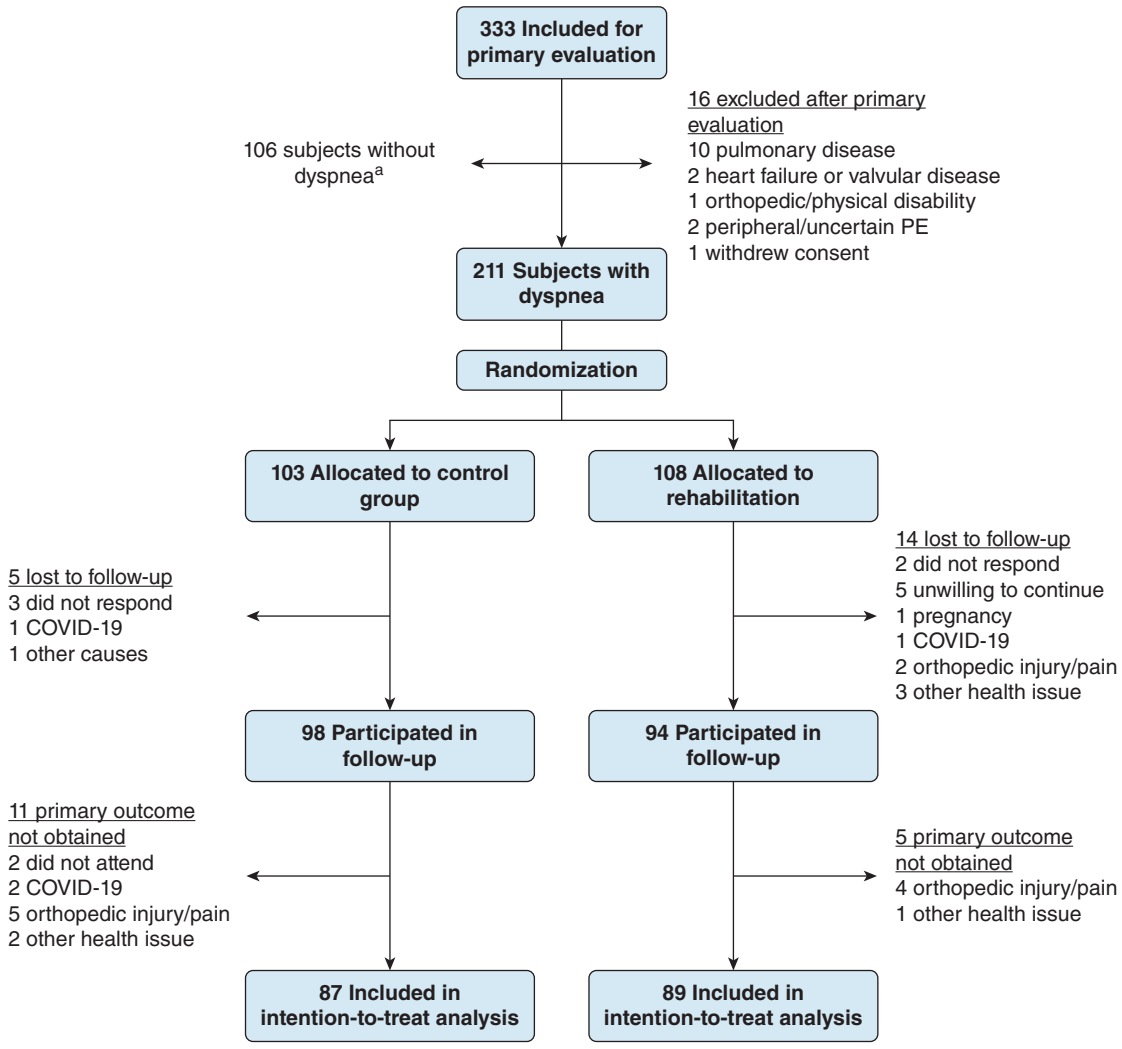

Figure 2 – *Study flow. PE = pulmonary embolism.* [a]*These participants were included from Østfold Hospital from January 1, 2018, to December 31, 2019, and are included in substudies focusing on pathophysiological changes following PE.*

(e-Table 3). Sensitivity analyses addressing missing values and per-protocol analysis did not alter the results (e-Tables 4-7).

When comparing subjects based on time from diagnosis (ie, 6-12 months and 12.1-72 months), there was a difference of 63.8 m (95% CI, 12.4-115.2; $P = .015$) and 47.4 m (95% CI, 2.0-92.9; $P = .041$), respectively, in favor of rehabilitation, but there was no difference between the two subgroups (Table 2). In further subgroup analyses of the primary end point, no difference was found between the intervention and control groups in those reporting an mMRC score ≥ 2 (e-Table 8). A higher score on the Pulmonary Embolism Severity Index (ie, score ≥ 77 compared with score < 77) was not associated with a difference in ISWT at follow-up (e-Table 9). We found no difference in ESWT performance at follow-up between the two groups (Table 3). Of note, $> 40\%$ of participants in both groups achieved the best possible result on the ESWT at baseline.

No difference was found in the EQ-5D index value or SOBQ sum score between the intervention group and the control group at follow-up (Table 4). The rehabilitation group had a better PEmb-QoL total score at follow-up compared with the control group (difference, –0.04 [–4%]; 95% CI, –0.09 to 0.00; $P = .041$). The distribution of scores within dimensions for the EQ-5D and the PEmb-QoL questionnaires are displayed in e-Figures 1 and 2, respectively.

Discussion

In this two-center randomized controlled trial, participants with persistent dyspnea following PE who

TABLE 2] Results From the Incremental Shuttle Walk Test at Baseline and Follow-up

Participants	Rehabilitation Group		Control Group		Difference[a] (95% CI)	*P* Value[a]
	Baseline	Follow-Up	Baseline	Follow-Up		
All participants	680 (530-905)	790 (540-1,020)	730 (530-950)	760 (470-1,020)	53.0 (17.7-88.3)	.0035
Time since PE diagnosis[b]						
6-12 mo (n = 103[c])	670 (530-940)	830 (620-1,020)	685 (500-950)	755 (470-1,020)	63.8 (12.4-115.2)	.015
12.1-72 mo (n = 73[c])	690 (530-860)	735 (510-970)	755 (535-980)	770 (440-1,020)	47.4 (1.98-92.9)	.041

Data are presented as meters with median (25th to 75th percentile). All participants and subgroup analyses are based on time from PE diagnosis. PE = pulmonary embolism.
[a]Between-group difference at follow-up was analyzed by using linear regression with baseline walking distance and hospital allocation included as independent variables.
[b]Difference between subgroups were calculated by using the same model with dichotomized "time since PE diagnosis" included as independent variable: 25.2 m (95% CI, −10.06 to 60.9; $P = .17$).
[c]Number of participants included in regression analysis.

underwent an 8-week outpatient rehabilitation program exhibited better exercise capacity at follow-up compared with those receiving usual care. The rehabilitation group reported better disease-specific QoL than the control group at follow-up, as assessed by the PEmb-QoL, although this difference was small. Generic QoL, dyspnea scores, and the ESWT performance revealed no difference between the groups at follow-up.

To the best of our knowledge, this is largest randomized trial to date assessing the effect of rehabilitation following PE, showing a positive effect on exercise capacity and QoL in subjects with persistent dyspnea. Several studies have reported promising results of rehabilitation following PE.[8-13] However, most of these studies have been small or have not included a control group, and there is great variation regarding time, mode, and duration of intervention. The current study adds to the growing evidence of the benefits of rehabilitation following PE.

The detected mean difference of 53 m in walking distance was lower than the presumed worthwhile improvement in our a priori sample size calculation. It can be debated whether a mean group improvement of 53 m is clinically relevant. Some previous studies have labeled mean group differences of 40 to 62 m as clinically meaningful, and our finding is well within the range suggested by these studies.[30,31] The minimal clinically important difference for the ISWT in comparable patient populations, such as patients with cardiac disease and pulmonary disease, has been estimated as 70 m and 48 m, respectively.[32,33] Minimal clinically important difference usually refers to intra-individual change (ie, the minimal difference that is perceived important by a patient), and it is not directly applicable to our analysis of the mean difference between groups.[34]

Our data from the ISWT were subject to a considerable ceiling effect, and the effect size in the current study may therefore be underestimated. Future studies may want to consider alternative tests, such as cardiopulmonary exercise test, when assessing exercise capacity in a post-PE setting. The ESWT displayed an even higher ceiling effect, and these results should be interpreted with caution. Rolving et al,[10] who assessed the effect of a home-based rehabilitation program in patients with acute PE, experienced a similar ceiling effect using the ISWT. In this study, they found a between-group mean

TABLE 3] Results From the Endurance Shuttle Walk at Baseline and 12-Week Follow-up

Participants	Rehabilitation Group		Control Group		Difference[a] (95% CI)	*P* Value[a]
	Baseline (n = 101)	Follow-Up (n = 81)	Baseline (n = 99)	Follow-Up (n = 83)		
All participants	829 (362 to 1,200)	1,200 (371 to 1,200)	885 (315 to 1,200)	1,200 (438 to 1,200)	62.0 (−41.6 to 165.7)	.24

Data are presented as seconds walked with median (25th-75th percentile).
[a]Between-group difference at follow-up was analyzed by using linear regression with baseline walking time from the Endurance Shuttle Walk Test and hospital allocation included as independent variables.

TABLE 4] EQ-5D Index Value, PEmb-QoL Total Score, and SOBQ Sum Score in the Rehabilitation and Control Group at Baseline and Follow-up

Patient Reported Outcome Measures	Rehabilitation Group		Control Group		Difference[a] 95% CI	*P* Value[a]
	Baseline	Follow-Up	Baseline	Follow-Up		
EQ-5D index value[b]	0.77 (0.69 to 0.84)	0.84 (0.73 to 0.88)	0.77 (0.69 to 0.84)	0.77 (0.70 to 0.88)	0.03 (−0.01 to 0.07)	.11
PEmb-QoL total score[c]	0.33 (0.20 to 0.48)	0.20 (0.07 to 0.38)	0.30 (0.19 to 0.45)	0.23 (0.09 to 0.44)	−0.04 (−0.09 to 0.00)	.041
SOBQ sum score[d]	19 (12 to 34)	14 (5 to 28)	19 (9 to 31)	16 (7 to 28)	−1.08 (−4.6 to 2.4)	.55

Data are presented as median (25th-75th percentile). PEmb-QoL = Pulmonary Embolism Quality of Life questionnaire; SOBQ = Shortness of Breath Questionnaire.
[a]Differences between the groups at follow-up were calculated by using linear mixed models, including study identifier as a random effect factor and hospital allocation as a fixed effect factor.
[b]EQ-5D index value was missing/not calculated in 21% in the rehabilitation group and 12% in the control group at follow-up.
[c]PEmb-QoL total score was missing/not calculated in 26% in the rehabilitation group and 19% in the control group at follow-up.
[d]SOBQ sum score was missing/not calculated in 18% in the rehabilitation group and 14% in the control group at follow-up.

difference of 25 m in favor of rehabilitation, albeit not statistically significant. Although there was no significant between-group difference, those with shorter time since PE diagnosis (6-12 months) had higher mean improvement on the ISWT compared with those with PE diagnosed > 12 months prior to inclusion.

At follow-up, the rehabilitation group reported better QoL, as assessed by using the PEmb-QoL total score, compared with the control group. However, the mean difference was small, and it can be debated whether this represents a worthwhile improvement. The EQ-5D and SOBQ scores revealed no difference. Disease-specific patient-reported outcome measures, such as the PEmb-QoL, are designed to capture elements relevant to the population of interest and may thus be more sensitive to change compared with generic questionnaires.[35] Conversely, generic patient-reported outcome measures include elements that are relevant to a wide range of patients, enabling comparison across different patient populations. Most participants reported mild symptoms and good QoL at inclusion, which may have limited the potential benefits of the rehabilitation program. It is possible that an earlier intervention, when patients would be expected to have more symptoms or larger impairment in QoL, could lead to larger effects from a rehabilitation program.

The current study included subjects with persistent dyspnea, defined as an mMRC dyspnea score of 1 ("Dyspnoea when hurrying or walking up a slight hill") or worse; this represents mild dyspnea, in contrast to rehabilitation programs provided in chronic pulmonary disease, which are usually recommended for those with more severe dyspnea.[7,36] To address this point, the inclusion criteria in the current study required the patient's sensation of dyspnea to be new onset or worsened compared with their status prior to the PE. Our subgroup analysis in participants with an mMRC dyspnea score ≥ 2 did not reveal any difference between the rehabilitation group and the control group, but this may be due to the limited number of subjects included in the analysis. The majority of previous studies in this field have not included symptoms or dyspnea as an inclusion criterion for rehabilitation,[8-11] or the degree of dyspnea has not been formally assessed.[12] However, a prospective cohort study reported improvement in training intensity, PEmb-QoL scores, and fatigue following 12 weeks of rehabilitation in 27 patients with moderate to severe dyspnea after PE, defined as modified Borg scale ≥ 3 at rest.[13]

Exercise capacity and symptoms following PE improve mostly during the first 3 to 6 months after PE.[37] In the current study, we included only subjects ≥ 6 months following the acute PE, as we considered that any spontaneous improvement beyond 6 months would be negligible and not interfere with the potential effects of rehabilitation. All participants underwent multiple tests with a medical doctor at baseline. This may reassure the participants about the safety of physical exercise and thus contribute to improved outcome at follow-up for both groups. Fear avoidance behavior is an important aspect in rehabilitation in other conditions, and studies suggest that this may play a role following PE.[38]

In the current study, there were no adverse events during rehabilitation, adding to the documentation on the safety of the physical exercise following PE.[8-13]

The attrition was higher than anticipated in this study, mainly due to health issues or unwillingness to continue to participate in the rehabilitation program. The study population was relatively young, with the majority being within the working population; this may have contributed to a higher rate of attrition, as the exercise program was mostly conducted during daytime. Compliance with a rehabilitation program may be greater if initiated closer to the time of the PE diagnosis, as shown in similar studies.[39]

Some limitations of the current study should be noted. We aimed to analyze the primary end point in an intention-to-treat analysis. Because most of the participants who did not complete the rehabilitation program did not perform the ISWT at follow-up, our analysis more closely resembles a per-protocol analysis. Furthermore, the primary end point was subject to a considerable ceiling effect, which has likely affected the results. However, the sensitivity analysis accounting for the ceiling effect and those who dropped out yielded similar results as the primary analysis, strengthening the validity of our results. The eligibility screening at Akershus Hospital was based on International Statistical Classification of Diseases and Related Health Problems 10th revision discharge codes. We cannot guarantee the completeness of these records. However, the diagnosis of PE in those included was confirmed by review of radiologic images. Due to restrictions concerning group sizes during the COVID-19 pandemic, a larger proportion than originally planned conducted the rehabilitation in small groups or alone with a physiotherapist. Therefore, many different physiotherapists contributed to the completion of the intervention, which may have caused some heterogeneity in the rehabilitation provided. The rehabilitation program in the current study consisted mainly of exercise training. It is unknown whether the addition of occupational therapy, psychology, or dietary therapy would provide additional benefits for the participants. Most participants had mild symptoms, which may have limited the potential benefits of our rehabilitation program. Patients with non-PE-related causes of dyspnea were excluded, which may limit the generalizability of our results. Finally, we included patients with a wide range in time from PE diagnosis, which may have contributed to heterogeneity in the study population.

Interpretation

This study has shown a larger improvement in exercise capacity among PE survivors with persistent dyspnea randomized to undergo an 8-week exercise-based rehabilitation program compared with participants receiving usual care. The rehabilitation group reported better QoL at follow-up as measured by the disease-specific PEmb-QoL questionnaire compared with the control group, but no differences were seen on generic QoL or dyspnea scales. Rehabilitation should be considered in patients with persistent dyspnea following PE, although further research is needed to assess the optimal patient selection, timing, mode, and duration of rehabilitation.

Funding/Support

The project was funded by Østfold Hospital Trust. The project received an unrestricted grant of 30,000 NOK from "Stiftelsen Elsa och Gustav Lindhs fond," which is a non-profit foundation, and an unrestricted grant of 100,000 NOK from the Norwegian patient organization ("The National Association for Heart and Lung Disorders-LHL") in 2019.

Financial/Nonfinancial Disclosures

The authors have reported to *CHEST* the following: F. A. K. reports grants or contracts from Bayer, Bristol Myers Squibb (BMS), Boston Scientific, Merck Sharp and Dohme (MSD), Leo Pharma, Actelion, PharmX, The Netherlands Organisation for Health Research and Development, The Dutch Thrombosis Association, The Dutch Heart Foundation, and the Horizon Europe Program, all unrelated to this work and paid to his institution. M. A. S. has obtained research grants from Netherlands Lung Foundation and Stichting Astma

Bestrijding, outside the scope of the current study; has obtained research grants from AstraZeneca, TEVA, Chiesi, and Boehringer Ingelheim outside the scope of the current study; and has obtained consultancy fees from AstraZeneca and Boehringer Ingelheim for advisory boards outside the scope of the current study. All research grants and consultancy fees were paid to Ciro. K. Stavem reports consulting fees from MSD and Union Chimique Belge (UCB) unrelated to this study. D. A. reports speaker and consultancy honoraria from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, MSD, Novartis, Novo Nordisk, Pfizer, Pharmacosmos, Philips, Roche Diagnostics, Sanofi, Takeda, and Vifor Pharma; and grant support from BMS/Pfizer, Medtronic, Bayer, and Roche Diagnostics, paid to his institution. W. G. reports fees for participation in advisory boards from Amgen, Novartis, Pfizer, Principia Biopharma Inc/a Sanofi Company, Sanofi, Swedish Orphan Biovitrum AB (SOBI), Grifols, UCB, Argenx, and Cellphire; lecture honoraria from Amgen, Novartis, Pfizer, Bristol Myers Squibb, SOBI, Grifols, Sanofi, and Bayer; and research grants from Bayer, BMS/Pfizer, and UCB. None declared (Ø. J., S. H.-P., J. G., M. T., H. H. J., R. H., A. E. A. D., P. A. S., K. Steine).

Acknowledgments

Author contributions: Ø. J. takes full responsibility for the content of the manuscript. Ø. J., S. H.-P., J. G., M. T., F. A. K., K. Steine, H. H. J., M. A. S., D. A., R. H., K. Stavem, and W. G. were responsible for the design of the study. Ø. J. included all participants and performed baseline evaluation. Ø. J. and S. H.-P. overviewed the rehabilitation process and follow-up and were responsible for data collection. Statistical analyses were performed by Ø. J. with contributions by R. H. and K. Stavem, and Ø. J. drafted the manuscript. Ø. J., S. H.-P., K. Stavem, and W. G. have directly accessed and verified the data reported in the manuscript. All authors have contributed to the interpretation of the results and revision of the text. All authors have approved the final version of the manuscript.

Role of the sponsors: The funding sources had no role in the design or execution of study, data analysis, or interpretation of the findings.

Other contributions: The authors thank all physiotherapists involved in conduction of the rehabilitation program, especially Trude Støver at Akershus University Hospital. Many thanks to all other contributors, including Hanne Fjäll Larssen, Eva Engen, Janne Katrin Gundersen, Jamal Ahmed, Camilla Tøvik Jørgensen, Rozan Albanna, Nedrin Albanna, Mats Grensemo, Amalie Berg Riise, Anna Sørlie Heranger, and the junior physiotherapists at Østfold Hospital.

Additional information: The e-Appendixes, e-Figures, and e-Tables are available online under "Supplementary Data."

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