Respiratory Medicine 218 (2023) 107397

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Original Research

A remote monitoring-enabled home exercise prescription for patients with interstitial lung disease at risk for exercise-induced desaturation☆,☆☆

Claire E. Child [a], Morgan L. Kelly [a], Haley Sizelove [a], Marissa Garvin [a], Julia Guilliams [a], Paul Kim [a], Haotian D. Cai [a], SiWei Luo [a], Kevin J. McQuade [a], Erik R. Swenson [b,c], Amanda T. Wise [a], Ylinne T. Lynch [c], Lawrence A. Ho [c], Mary Beth Brown [a,*]

[a] University of Washington, Department of Rehabilitation Medicine, Division of Physical Therapy, USA
[b] Medical Service, VA Puget Sound Health Care System, USA
[c] University of Washington, Department of Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, USA

ABSTRACT

Rationale: Alternatives to center-based pulmonary rehabilitation are needed to improve patient access to this important therapy. A critical challenge to overcome is how to maximize safety of unsupervised exercise for at-risk patients. We investigated if a novel remote monitoring-enabled mobile health (mHealth) program is safe, feasible, and effective for patients who experience exercise-induced hemoglobin desaturation.

Methods: An interstitial lung disease (ILD) commonly associated with pronounced exercise desaturation was investigated - the rare, female-predominant ILD lymphangioleiomyomatosis (LAM). Over a 12-week program, hemoglobin saturation (SpO_2) was continuously recorded during all home exercise sessions. Intervention effects were assessed with 6-min walk test (6MWT), maximal cardiopulmonary exercise test (CPET), lower extremity computerized dynamometry, pulmonary function tests, and health-related quality of life (QoL) surveys. Safety was assessed by blood biomarkers of systemic inflammation and cardiac wall stress, and incidence of adverse events.

Results: Fifteen LAM patients enrolled and 14 completed the intervention, with high adherence to aerobic (87 ± 15%) and strength (87 ± 12%) training components. An innovative characterization of exercise training SpO_2 revealed that while mild-to-moderate desaturation was common during home workouts, participants were able to self-adjust exercise intensity and supplemental oxygen levels to maintain recommended exercise parameters. Significant improvements included 6MWT distance (+36 ± 34 m, $p = 0.003$), CPET time ($p = 0.04$), muscular endurance ($p = 0.008$), QoL ($p = 0.009$ to 0.03), and fatigue ($p = 0.001$ to 0.03). Patient acceptability and satisfaction indicators were high, blood biomarkers remained stable ($p > 0.05$), and no study-related adverse events occurred.

Conclusion: A remote monitoring-enabled home exercise program is a safe, feasible, and effective approach even for patients who experience exercise desaturation.

1. Introduction

Hemoglobin desaturation during exercise is common in interstitial lung diseases (ILD) [1,2] and can be an important indication for a supervised exercise approach, such as that administered in center-based pulmonary rehabilitation (PR). However, a home-based rehabilitation or exercise training delivery model can reduce barriers to referral, attendance, and affordability, promoting more widespread use and enhancing participation [3–6]. Even before the COVID-19 pandemic, PR was grossly underused worldwide, with data from the United States and Canada showing that less than 5% of eligible patients ever undertake a PR or exercise training program [7,8].

In response to the COVID-19 pandemic, many rehabilitation centers closed or reduced their in-person capacity to minimize community viral transmission [9], exacerbating this access problem to an unprecedented scale. Many programs pivoted rapidly to telerehabilitation delivery models [10,11] that can achieve outcomes and safety standards similar to those of center-based PR, but these have been scarcely investigated in lung disease populations other than chronic obstructive pulmonary disease (COPD) [11].

An American Thoracic Society (ATS) and European Respiratory Society (ERS) policy statement (2015) on ‘Enhancing Implementation, Use and Delivery of Pulmonary Rehabilitation’ [12] called for “novel

☆ This work was funded by a Patient Benefit Grant (LAM0130PB07-18) from The LAM Foundation. Funders provided no input or contributions in the development of the research and manuscript.☆☆ This article has an online supplement, which is accessible from this issue’s table of contents online.

* Corresponding author. Health Sciences Building BB-826, Box 356490, 1607 NE Pacific St. Seattle, WA, 98195, USA.

E-mail addresses: cechild@uw.edu (C.E. Child), mlkelly@usc.edu (M.L. Kelly), h.sizelove2014@gmail.com (H. Sizelove), mgarvin27@gmail.com (M. Garvin), juliag12@uw.edu (J. Guilliams), paulkim1995@gmail.com (P. Kim), hdcai3@uw.edu (H.D. Cai), siweil@uw.edu (S. Luo), kmcquade@uw.edu (K.J. McQuade), Erik.Swenson@va.gov (E.R. Swenson), amandatwisedo@gmail.com (A.T. Wise), lynchy@uw.edu (Y.T. Lynch), laho@uw.edu (L.A. Ho), mbbrown1@uw.edu (M.B. Brown).

https://doi.org/10.1016/j.rmed.2023.107397
Received 9 May 2023; Received in revised form 11 August 2023; Accepted 24 August 2023
Available online 26 August 2023

Abbreviations list

LAM	lymphangioleiomyomatosis
TSC	tuberous sclerosis complex
ILD	interstitial lung disease
SpO_2	hemoglobin saturation
mHealth	mobile health
6MWT	six-minute walk test
RM-ANOVA	Repeated measures analysis of variance
SpO_2	hemoglobin oxygen saturation
HR	heart rate
BPM	beats per minute
BLE	Bluetooth Low Energy
F_IO_2	fraction of inspired oxygen
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
VO_2max	maximal oxygen consumption
PFTs	pulmonary function tests
VAS	visual analog scale
BP	blood pressure
BMI	body mass index
BNP	brain natriuretic peptide
VCO_2	carbon dioxide output
CRP	C-reactive protein
CPET	cardiopulmonary exercise test
%	percent
HR_{max}	highest HR achieved
VO_2max	rate of maximum oxygen consumption
SD	standard deviation
MET	metabolic equivalent
MVPA	moderate-to-vigorous physical activity
MCID	minimum clinically important difference
PR	pulmonary rehabilitation
QoL	quality of life
RPE	rating of perceived exertion
V_E	Ventilation
V_E/VCO_2	ventilatory equivalent for carbon dioxide
COPD	chronic obstructive pulmonary disorder
PAH	pulmonary arterial hypertension
DDR	desaturation distance ratio

pulmonary rehabilitation program models that will make evidence-based pulmonary rehabilitation more accessible and acceptable to patients and payers." New and alternative models of PR must provide exercise programming with sufficient fidelity to the intensity of a center-based program [13,14] to produce health benefits. However, a critical challenge to overcome in a home-based approach is how to achieve sufficient exercise stimulus and still maximize safety for patients at risk for desaturation during exertion, as is commonly observed in patients with ILD.

The purpose of this study was to investigate the safety, feasibility, and effectiveness of a prescribed exercise regimen delivered by mobile health (mHealth) technology and remote monitoring devices for patients with ILD that desaturate with exercise. Lymphangioleiomyomatosis (LAM), a rare, female-predominant cystic lung disease [15] characterized by slow annual FEV_1 decline and progressive gas exchange impairment [16], was the targeted ILD population as LAM exercise responses have been studied far less than other interstitial lung diseases. A formal 'patient benefit' needs assessment conducted in 2017 by The LAM Foundation identified the topics of 'Exercise' and 'Fatigue' as two priority areas needing research to cultivate solutions. Symptoms of generalized fatigue are common in LAM and can greatly impact quality of life (QoL) [17]. While structured exercise may help address this, little research is available to support LAM-specific exercise recommendations. A single published controlled clinical trial demonstrated benefit of center-based PR on exercise capacity and QoL in LAM [18]. However, center-based PR programs may not be as accessible as home-based programs or preferred by patients that are still heavily involved in career and family responsibilities [17]. A home-based approach may remove many of the common barriers to PR participation encountered by patients with LAM, who are generally younger than patients with other chronic lung diseases, with an average age of onset of symptoms of 38.9 ± 0.73 years [19]. Some of the results of this study have been previously reported in the form of abstracts [20,21].

2. Methods

This is a prospective interventional study with a before-after (pre-post) design without a comparator arm [22] (Fig. 1). Participants were recruited from the Center for Interstitial Lung Disease at the University of Washington (UW, Seattle, WA), the Swedish Center for Comprehensive Care – Pulmonology (Seattle, WA), and the greater LAM community of the United States and lower Canada via word-of-mouth. The UW Institutional Review Board approved the study protocol (#00007271) and all participants gave written informed consent.

Fig. 1: A prospective pilot interventional study with a before-after (pre-post) study design was conducted with n = 15 enrolled individuals with lymphangioleiomyomatosis (LAM). In pre- (Day 1, 'baseline') and post- (Day 90, 'final') intervention study visits, assessments & procedures included anthropometrics, blood draw, maximal cardiopulmonary exercise test (CPET), six-minute walk test (6MWT), lower extremity muscular strength/endurance computerized dynamometry and functional tests, pulmonary function tests, and standardized surveys for fatigue and health-related quality of life (QoL). In between the baseline and final study visits, a 12-week smartphone-guided exercise program was performed which included 4 days/week of aerobic exercise at 65-75% heart rate reserve (HRR) and 3 days/week of resistance training. Health monitoring was also performed during the intervention period for daily physical activity metrics, daily fatigue and dyspnea ratings, weekly home spirometry, and medical-grade fingertip pulse oximetry for continuous hemoglobin oxygen saturation (SpO_2) during all home exercise sessions.

Eligibility criteria are detailed in Table 1. The number of participants enrolled in this pilot study (n = 15) was calculated based on a power of 90% using the primary endpoint of 6MWT and expecting at least a 15% improvement in 6MWT distance as reported by Mereles et al. in a similar chronic lung disease patient population with known low physical activity levels, pulmonary arterial hypertension (PAH) [23].

Fig. 1. Study protocol.

Table 1
Eligibility criteria.

Inclusion Criteria	Exclusion Criteria
1) Diagnosis of LAM via biopsy or high-resolution CT scan of the chest	1) Unstable condition
2) Age 18-60 years	2) Functional class IV on the Specific Activity Scale [24]
3) Functional class I-III on the Specific Activity Scale [24]	3) Musculoskeletal or other conditions which would limit exercise participation
4) In stable condition	4) Non-compliance with medical therapies
5) No changes in medical treatment for past 3 months	5) Prior lung transplantation
6) Stable 6-min walk test (6MWT) for past 3 months (±20 m)	6) Currently pregnant

2.1. Exercise training and remote monitoring

Devices were issued to participants to permit remote monitoring during the 12-week intervention period. These included: a) a wrist-worn accelerometer (Fitbit Charge 3, Fitbit, San Francisco, CA) for heart rate (HR) monitoring, daily physical activity metrics, and exercise monitoring, b) a home spirometry device (MIR Smart One, Medical International Research, Inc) for once weekly measures of forced expiratory volume in 1 s (FEV_1) and peak expiratory flow; and c) a medical grade fingertip pulse oximeter (NoninConnect 3230 or Nonin WristOx$_2$ 3150 with fingertip sensor, Nonin Medical, Plymouth, MN) for continuous monitoring of HR and SpO_2 during exercise sessions. A daily paper logbook was provided for instructions in all tasks, weekly calendars, and self-record of: 1) changes in symptoms or perceived wellness, 2) aerobic exercise session minutes and mode, 3) daily dyspnea score, and 4) daily fatigue score on a 5-point Likert scale. Logbook entries, data from all monitoring devices, and overall program tolerance were reviewed at least weekly by investigators, who also contacted participants at least once weekly via telephone, SMS text message, or email.

Aerobic exercise was performed once/day, 4 days/week for 12 weeks at a steady state intensity 65-75% HR reserve, calculated according to Karvonen [25] using the patients' resting and peak HR observed at baseline maximal cardiopulmonary exercise testing (CPET). Participants were instructed to use the HR measurement via Fitbit for intensity pacing. Workout duration initiated at 25 min and gradually increased to 45 min by the end of week 2. Body weight-resistance exercise training occurred 3 days/week. During exercise, participants were instructed to maintain $SpO_2 \geq 85\%$, to monitor for symptoms of exercise intolerance, and to adjust exercise intensity and supplemental oxygen accordingly. Details of remote monitoring and the exercise program are provided in **e-Appendix 1**.

The study team received and reviewed raw oximetry data files from exercise sessions at least 4 times/week (Fig. 2A). For characterization of hemoglobin saturation beyond just a single nadir value, a frequency analysis was performed on each exercise session's raw data in GraphPad Prism (v9.2). SpO_2 data was grouped into five bins reflecting increasing levels of hemoglobin desaturation: none (SpO_2 >95%), mild (SpO_2 90-95%), moderate (SpO_2 84-89%), severe (SpO_2 78-83%), and very severe (SpO_2 <78%). Portion of time spent in each desaturation level was calculated for each session (example Fig. 2B), averaged for each week of the program, and for all 12 weeks together.

Fig. 2: Medical grade fingertip pulse oximeters (NoninConnect 3230 or Nonin WristOx2 3150 with fingertip sensor, Nonin Medical, Plymouth, MN) wirelessly transmitted real-time blood oxygen saturation (SpO_2, blue tracing, left axis) and heart rate (HR, red tracing, y axis) to the NoninConnect smartphone application, and enabled second-by-second data capture of every exercise session over the 12-week intervention. HR was additionally captured by wrist-worn accelerometer HR/activity monitor (Fitbit Charge 3). An example of a continuous recording of SpO_2 and HR during a participant's home exercise session is shown (A), as well as the results of a frequency analysis (GraphPad Prism v9.2) performed on that example session where the relative amount of session time spent in varying levels of hemoglobin desaturation is illustrated in a parts-of-whole bar graph (B).

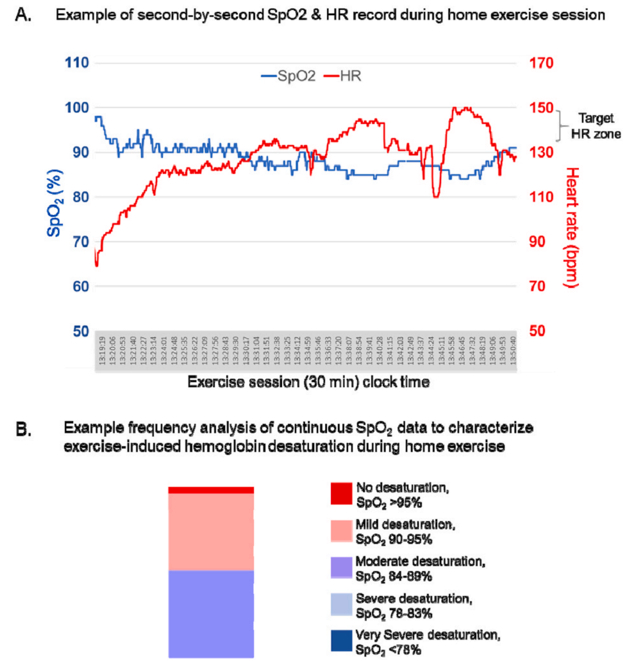

Fig. 2. Remote pulse oximetry monitoring during exercise.

2.2. Endpoints

The primary endpoint was change from baseline in six-min walk test (6MWT) distance and secondary endpoints were study visit- or self-reported variables related to physical function, lung function, and QoL. Endpoints and their methods of assessment are described in detail in **e-Appendix 1**. Briefly, the Baseline and Final study visit measurements included: 1) 6MWT to assess distance, heart rate recovery ($HR_{recovery}$), and distance desaturation ratio (DDR) [26], 2) maximal treadmill cardiopulmonary exercise test (CPET) (Balke protocol or modified Balke protocol [27,28]); 3) anthropometrics; 4) muscle performance in computerized dynamometry and functional tests; 5) fasting venous blood sampling for assay of high-sensitivity C-reactive protein as an indicator of systemic inflammation [29], brain natriuretic peptide (BNP) as an indicator of cardiac wall stress [30], and a standard metabolic panel and lipid profile; 6) A Tool to Assess Quality of Life in LAM (ATAQ-LAM) [31], the 20-item Multidimensional Fatigue Inventory (MFI-20) [32], Situational Fatigue Scale (SFS) [33], and EuroQoL Visual Analog Scale (VAS) surveys [34] to assess health-related QoL and fatigue. Feasibility included completion rate of the intervention and calculated adherence, and acceptability of a remote monitoring approach as determined in exit survey. Adverse events were defined as hospitalization, death, worsening LAM disease severity, or escalation of therapy.

2.3. Statistical analyses

Paired t-testing measured changes between Baseline and Final in all outcome variables. Repeated measures analysis of variance (RM-ANOVA) or mixed effects analysis (if any missing data) was used to detect differences over time and slope of change for variables measured daily or weekly over 12 weeks. Paired t-tests also compared simultaneous recordings of heart rate, as measured by 12-lead EKG, and pulse rate, as measured by fingertip photoplethysmography (Nonin BLE 3230), at rest (in standing) and end CPET. Pearson correlations analyzed relationships between variables. Data are presented for individual subjects, and as means with standard deviation (SD). Statistical analysis utilized GraphPad Prism version 9.3.1, and differences at α level of 0.05 were considered statistically significant.

3. Results

3.1. Enrollment and adherence

Of the 29 patients with LAM screened (Fig. 3), 15 patients with sporadic ($n = 13$) and tuberous sclerosis complex (TSC)-associated ($n = 2$) LAM were enrolled (age 48 ± 8 years, 9 ± 7 years from diagnosis). Subject baseline demographics are described in Table 2.

Fourteen of the 15 enrolled participants completed the protocol, and one drop-out (at week 4) was for reasons unrelated to the study intervention. High adherence to the aerobic (87 ± 15%) and resistance (87 ± 12%) programs was achieved. Nine patients achieved >90% adherence, four patients achieved >95% adherence, and only one patient achieved <80% adherence to the aerobic program over 12 weeks. Baseline and final assessments were performed as expected with a few exceptions due to the COVID-19 pandemic-imposed restrictions on testing center visits: 5 subjects had to delay post assessment beyond week 13 (range week 14–23), but continued training as prescribed until able to return for post assessment. Data for these individuals are demarcated graphically with different symbols and did not skew findings. One of these 5 subjects experienced symptomatic pneumothorax while participating in vigorous recreational mountain biking outside of the training plan, and at a HR intensity higher than prescribed. She was hospitalized with chest tube placement and surgical pleurodesis, and her data following pneumothorax was not included in analysis.

3.2. Intensity of home exercise

Exercise intensity was self-adjusted to stay within prescribed target HR zone and tolerance. Workload expressed as total METs*min achieved in weekly workouts increased over 12 weeks (slope = +7.6, $p < 0.0001$, e-Fig. 1a) as expected given the increase in session time from 25 to 45 min between weeks 1–4. This was reflected in a significant upward slope for daily average minutes qualifying as 'vigorous'. Average intensity of workouts expressed as average METs of weekly sessions stayed fairly constant (slope = 0.007, $p = 0.95$, e-Fig. 1b) over 12 weeks, indicating that the observed increase in weekly total workloads achieved was a consequence of increased session durations. Neither the daily reported dyspnea ($p = 0.46$) or fatigue ($p = 0.51$) VAS scores were increased over the 12 weeks of gradually lengthened aerobic exercise sessions.

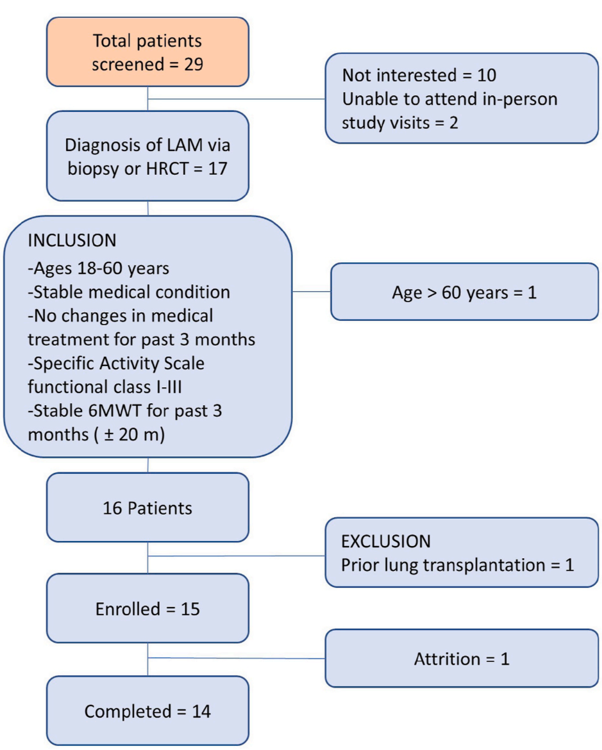

Fig. 3. Study enrollment.

Table 2
Sample demographics at baseline.

	Adults with LAM (n = 15)		
	Number (n)		%
Female	15		100
Race/Ethnicity			
White	15		100
Non-White	0		0
Etiology			
Sporadic LAM	13		87
TSC-associated LAM	2		13
Medications			
Sirolimus	8		53
Inhaled corticosteroid	1		7
Beta blocker	0		0
Short term oxygen therapy (during exertion)	2		13
Long term oxygen therapy	0		0
Menopause Status			
Premenopausal	7		47
Postmenopausal	8		53
Comorbidities			
Prior pneumothorax	9		60
Angiomyolipoma	8		53
Back pain/discitis	5		33
Hypertension	4		20
Epilepsy	2		13
Osteopenia/osteoporosis	2		13
PH-ILD	0		0
	Mean	±SD	Range
Age (years)	49.0	7.8	36.6–59.3
Clinical			
Time since diagnosis (years)	8.7	6.9	0.3–20.8
Time since initiation on sirolimus (years)	3.8	2.5	1.1–8.6
Number of prior pneumothoraces (n)	1.6	1.7	0–5
Time since last pneumothorax (years)	5.7	6.4	0.8–17.1
Anthropometrics			
Body mass index (kg/m^2)	25.1	4.5	20.4–37.0
Weight (kg)	69.0	11.0	55.5–89.8
Height (cm)	166.0	7.0	155.8–181.5
Resting pulse (bpm)	73.9	13.2	60–110
Resting SpO_2 (%)	97	1.5	94–99
Resting SBP (mmHg)	126	24	101–182
Resting DBP (mmHg)	80	14	59–107
Pulmonary Function			
FEV_1 (liter)	2.0	0.7	1.06–3.1
FEV_1 (% predicted)	66.8	20.1	39–86
FVC (liter)	3.1	0.8	2.07–4.55
FVC (% predicted)	81.6	18.5	55–109
FEV_1/FVC (% predicted)	65.4	14.1	29–79

3.3. Desaturation in home exercise

Frequency analysis performed on continuously-recorded SpO_2 during home exercise sessions revealed that participants spent the majority (55 ± 22%) of time in 'mild' hemoglobin desaturation, with only 16 ± 19%, 1.3 ± 0.9%, and 0.3 ± 0.5% of session time in 'moderate', 'severe', and 'very severe' desaturation, respectively. This distribution did not change across the intervention period ($p = 0.70$), as shown in Fig. 4 with breakdown by month. Not surprisingly, participants who spent more session time in greater than 'mild' desaturation were also observed to have lower baseline lung function ($r = -0.7$), end SpO_2 in 6MWT and CPET ($r = -0.8$, -0.7), and calculated DDR in 6MWT ($r = 0.7$).

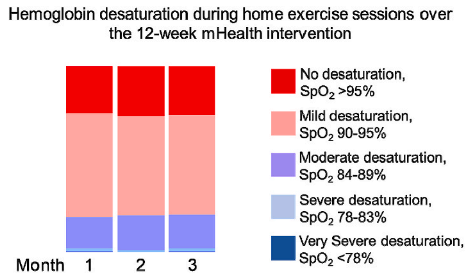

Fig. 4. Desaturation during home exercise, by month.

Participants that added or increased supplemental O_2 flow rate during exercise to keep SpO2 $\geq$85% did not report a symptomatic benefit, but did report an increased ability to achieve and maintain the prescribed HR zone.

Fig. 4: During a 12-week mobile health exercise intervention with remote monitoring for patients with lymphangioleiomyomatosis (LAM), the relative amount of home exercise session time spent by patients (n = 14-15) in varying levels of hemoglobin desaturation was unchanged over the intervention period. Data was generated by frequency analysis (GraphPad Prism v9.2) of continuously recorded exercise session hemoglobin saturation (SpO_2) values and presented as parts-of-whole bar graphs for month 1, month 2, and month 3 of the intervention.

3.4. Training effects

Distance achieved in 6MWT (Fig. 5, Table 3) increased from baseline to final, as did % predicted distance and calculated % fatigue [35] (Fig. 5, Table 3). Ability to recover HR after 6MWT also improved with training (Fig. 5, Table 3), evident as a more negative slope of HR values in recovery minutes 0-5, and as a lower percentage of end-exercise HR at 5 min recovery timepoint. Improvement observed in 6MWT correlated with improvement in lipid profile following training. Specifically, HDL increased more in those with greater increase in 6MWT distance (r = 0.65, p = 0.02).

Exercise time achieved in maximal CPET improved with training, but there was no significant change in VO_2max and other CPET parameters (Table 3). There was a tendency for METs and VO_2 at ventilatory threshold to be increased (p = 0.06) with training (Table 3), as well as indicators of effort including HR_{max} (p = 0.08) and RPE_{max} (p = 0.05). A third of the baseline CPETs were clearly respiratory-limited and this was unchanged by training. Other baseline CPETs were cardiac-limited (n = 10) and, after training, two of these patients demonstrated mixed cardiac and respiratory limitations on final CPET. At rest and end CPET, significant differences were noted between heart rate via ECG and pulse rate via fingertip photoplethysmography (rest: difference = 1.7 ± 2.2 bpm, p = 0.03; end CPET: difference = 9.3 ± 13.7 bpm, $p < 0.0001$), with the fingertip pulse oximeter reading lower than 12-lead ECG during incremental exercise.

Pulmonary function measures were unchanged with training, both for the PFTs conducted at baseline and final study visits (Table 3), and for home spirometry values of peak flow and FEV_1 collected weekly by patients over the intervention period (p = 0.178 and 0.247, respectively, Table 3).

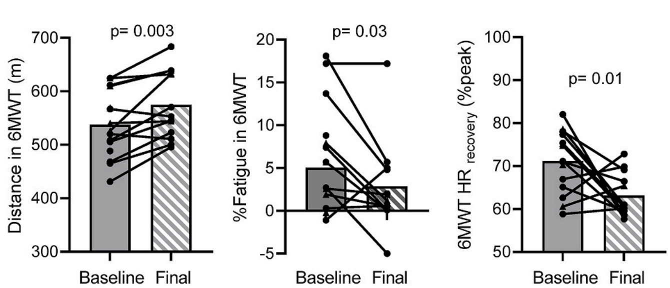

Fig. 5. Improvement in six-minute walk test (6MWT).

Table 3
Changes in exercise capacity and pulmonary function.

		Baseline	Final	Change	p
		Mean ± SD			
6MWT	Distance (m)	539 ± 65	574 ± 63	36 ± 34	**0.003**
	Distance (% predicted)	92 ± 9	99 ± 9	6 ± 4	**0.0005**
	% Fatigue	7 ± 7	3 ± 6	−4 ± 5	**0.03**
	End HR (bpm)	116 ± 14	132 ± 12	16 ± 17	**0.005**
	RPE (Borg 0-10)	4 ± 1	5 ± 2	1 ± 2	0.07
	Dyspnea (Borg 0-10)	3 ± 2	3 ± 2	0.5 ± 2	0.41
	End SpO_2 (%)	90 ± 4	88 ± 8	−2 ± 5	0.14
	DDR	6.3 ± 3	6.6 ± 4	0.5 ± 1	0.30
	$HR_{recovery}$ slope 0–5min	−6 ± 2	−9 ± 2	−3 ± 3	**0.01**
	$HR_{recovery}$ at 5 min (% of peak)	71 ± 7	63 ± 5	−8 ± 10	**0.01**
CPET	Treadmill time (min)	14 ± 4	16 ± 5	2 ± 3	**0.04**
	VO_{2max} (ml/kg/min)	25 ± 6	26 ± 6	0.6 ± 1	0.21
	VO_{2max} (% predicted)	92 ± 30	93 ± 32	1 ± 6	0.58
	$METs_{max}$	7.2 ± 2	7.4 ± 2	0.2 ± 0.5	0.25
	HR_{max} (bpm)	159 ± 18	163 ± 12	4 ± 7	0.08
	RPE_{max} (Borg 6-20)	18 ± 1	19 ± 1	0.6 ± 0.9	0.05
	End SpO_2 (%)	88 ± 6	86 ± 8	−2 ± 3	0.06
	$V_{E\ max}/VCO_{2max}$	33 ± 4	33 ± 5	0.8 ± 3	0.32
	Exercise time to VT (min)	8 ± 3	10 ± 5	1.3 ± 3.8	0.48
	METs @ VT (min)	5.5 ± 1	6.2 ± 2	0.7 ± 0.6	0.06
	VO_2 @ VT (ml/kg/min)	19 ± 5	22 ± 7	2.5 ± 2.3	0.06
PFTs	FVC (L)	3.0 ± 0.8	3.0 ± 0.7	0.04 ± 0.3	0.64
	FEV_1 (L)	1.8 ± 0.7	1.8 ± 0.8	0.01 ± 0.1	0.85
	FEV_1 (% predicted)	60 ± 19	62 ± 19	2.3 ± 9	0.45
	FEV_1/FVC (%)	61 ± 16	60 ± 17	−1.0 ± 4	0.49
	Peak expiratory flow (liter/min) in weekly home spirometry	Mo 1 avg: 330 ± 98	Mo 2 avg: 342 ± 100	Mo 3 avg: 355 ± 98	0.15
	FEV_1 (liter) in weekly home spirometry	Mo 1 avg: 1.8 ± 0.6	Mo 2 avg: 1.9 ± 0.6	Mo 3 avg: 1.9 ± 0.6	0.25

Fig. 5: A 12-week mobile health exercise intervention with remote monitoring improved submaximal exercise tolerance in patients with LAM as demonstrated by increased distance (A) in 6-min walk test (6MWT) from baseline to final study visits. B) Amount of fatigue during the 6MWT (B), calculated as percent change between the distance walked during minute 1 and during minute 6), was less after the intervention. C) Heart rate recovery ($HR_{recovery}$), as the % of end-6MWT (peak) HR at the 5 min recovery time point, was enhanced after the intervention. Mean group values (n = 14) are presented for the pre-intervention study visit 'baseline' (solid gray bar), and the post-intervention study visit 'final' (striped, gray bar), with black symbols and connecting lines representing individual patients. The patients that had extended intervention periods due to pandemic-related facility/travel restrictions are demarcated with triangles instead of circles.

A run-in period was not included in this study, so we do not report change from baseline in physical activity metrics. However, comparing Week 1 of the intervention to week 12 of the intervention, participants increased ($p < 0.05$) in average daily min of MVPA (week 1 = 27 ± 17 min, week 12 = 39 ± 15 min, change = 11 ± 17 min). Average daily Step count was also higher at the end of the intervention (week 12 = 8607 ± 2283), change of 752 ± 3183 daily steps from Week 1) than that previously reported for LAM (5852 ± 3327) [36] and close to that reported for healthy controls (8863 ± 1884) [36].

Muscular performance was improved by training in computerized dynamometry and functional testing (Table 4), specifically in measures of muscular endurance more than in peak force and power.

Fatigue, a common complaint [17] and closely related to QoL in LAM [31], was improved by training as assessed by standardized survey tools (Fig. 6, Table 5), particularly in the domains related to physical fatigue (Fig. 6 panel A & B, Table 5). QoL indicators also improved with training, as assessed by VAS rating and Total ATAQ-LAM score, an aggregation of subscales specific to physical health (Fig. 6 panel C & D, Table 5).

Fig. 6: A 12-week mobile health exercise intervention with remote monitoring improved psychometric indicators of fatigue and health-related quality of life (QoL) in patients with LAM. On the 20-item Multidimensional Fatigue Inventory (MFI-20, A) and on the Situational Fatigue Scale (SFI, B), the survey tool subdomain of 'physical fatigue' was improved from baseline to final study visit. QoL was also improved following the intervention, on EuroQoL Visual Analog Scale (VAS, C), and as represented in the Total score on the LAM-specific survey 'A Tool to Assess Quality of Life in LAM (ATAQ-LAM, D). Mean group values (n = 14) are presented for the pre-intervention study visit 'baseline' (solid gray bar), and the post-intervention study visit 'final' (striped gray bar), with black symbols and connecting lines representing individual patients. The patients that had extended intervention periods due to pandemic-related facility/travel restrictions are demarcated with triangles instead of circles.

3.5. Safety, acceptability, and feasibility

No study-related adverse events occurred. Despite the observation that participants experienced mild-to-moderate desaturation during exercise sessions, detrimental effects were not observed in blood laboratory data. BNP, as an indicator of cardiac wall stress [30], and CRP, as an indicator of systemic inflammation [37], remained stable over the 12 weeks, further suggesting safety of the intervention (Table 6).

In addition to the high adherence rates described earlier, high patient acceptability and feasibility of the remote monitoring-enabled home exercise program were revealed on exit survey (Fig. 7). Greater feasibility and acceptability were associated with lower baseline fatigue (ATAQ and SFS r = −63, p = 0.03, MFI r = −78, p = 0.004) and lower dyspnea (ATAQ r = −0.64, p = 0.03; VAS r = −0.76, p = 0.01) scores.

Fig. 7: A 12-week mobile health exercise intervention with remote monitoring for patients with lymphangioleiomyomatosis (LAM) achieved high scores in exit survey questions related to feasibility and acceptability of the home exercise program (HEP) and remote monitoring, and intention to continue the program after study completion.

4. Discussion

Feasibility of home-based exercise interventions has been demonstrated for many chronic cardiopulmonary disorders including COPD [11,38], myocardial infarction [39], heart failure [40], and PAH [41]. Our findings suggest that feasibility of a home-based approach extends

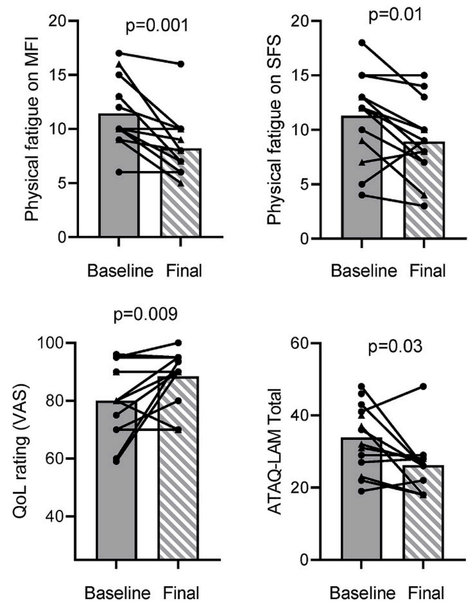

Fig. 6. Improvements in fatigue and quality of life.

Table 5
Changes in subscales of fatigue and quality of life.

		Baseline	Final	Change	*P*
		Mean ± SD			
QoL VAS (0-100) higher = ↓ impairment		80 ± 13	90 ± 8	9 ± 12	**0.009**
Fatigue VAS (0-100) lower = ↓ impairment		33 ± 28	22 ± 23	−10 ± 14	**0.03**
MFI-20 (Subscale ranges 4-20) lower = ↓ impairment	General	12 ± 3	9 ± 3	−3 ± 4	**0.01**
	Physical	11 ± 3	8 ± 3	−3 ± 2	**0.001**
	Mental	8 ± 4	8 ± 4	−0.03 ± 2	0.95
	↓ activity	8 ± 3	6 ± 1	−2 ± 3	0.08
	↓ motivation	6 ± 2	6 ± 2	−0.2 ± 2	0.80
SFS lower = ↓ impairment	Physical (0-20)	11 ± 4	9 ± 3	−2 ± 3	**0.01**
	Mental (0-40)	5 ± 5	2 ± 3	−3 ± 5	**0.04**
ATAQ-LAM (Total and subscale ranges 0-100) lower = ↓ impairment	Total	32 ± 9	26 ± 8	−6 ± 9	**0.03**
	Exertional Dyspnea	33 ± 14	26 ± 12	−5 ± 14	0.26
	Cough	31 ± 21	25 ± 15	−6 ± 15	0.18
	Energy/ Fatigue	40 ± 16	31 ± 14	−4 ± 8	0.11
	Emotional	41 ± 20	30 ± 15	−7 ± 18	0.18

Table 4
Changes in muscular performance.

			Baseline	Final	Change	*P*
			Mean ± SD			
Muscular force & power	Jump test	Peak force (N)	1208 ± 178	1246 ± 173	38 ± 72	0.09
		Peak power (W)	1806 ± 339	1842 ± 235	36 ± 226	0.59
		Peak relative power (W/kg)	26 ± 4	27 ± 3	0.5 ± 3	0.59
	Knee extension peak force (N)		300 ± 66	306 ± 65	6 ± 64	0.75
Muscular Endurance	Knee extension fatigue test (s)		34 ± 14	49 ± 25	15 ± 14	**0.008**
	Knee extension fatigue test impulse (N*s)		9018 ± 3142	12,041 ± 5311	3024 ± 3115	**0.009**
	Wall squat hold (s)		92 ± 47	158 ± 84	66 ± 63	**0.003**
	Table top hold (s)		162 ± 136	272 ± 255	110 ± 151	**0.02**

Table 6
Changes in blood laboratory data.

		Baseline	Final	Change	*p*
		Mean ± SD			
BNP (pg/ml)		32 ± 12	33 ± 9	1.6 ± 8.4	0.50
CRP (nmol/l)		2.2 ± 2.1	2.1 ± 2.1	−0.06 ± 1.6	0.90
Glucose (mg/dL)		94 ± 10	92 ± 9	−1.8 ± 9.2	0.51
Lipid profile	Total cholesterol (mg/dl)	212 ± 37	223 ± 35	11 ± 25	0.16
	Triglycerides (mg/dl)	114 ± 45	124 ± 67	10 ± 40	0.42
	HDL (mg/dl)	72 ± 14	76 ± 16	3.7 ± 7.8	0.12
	LDL (mg/dl)	117 ± 31	122 ± 29	5 ± 23	0.465
	Total cholesterol/HDL	3 ± 0.8	3 ± 0.7	0.003 ± 0.3	0.97
	LDL/HDL	3 ± 0.8	3 ± 0.7	0.003 ± 0.3	0.83
	Triglycerides/HDL	1.7 ± 0.8	1.8 ± 1.3	−0.3 ± 0.6	0.57

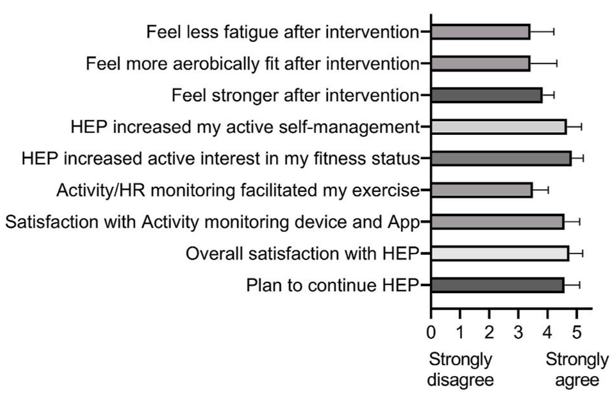

Fig. 7. High patient satisfaction for a mobile health exercise intervention.

to patients with interstitial lung disease that are at risk for hemoglobin desaturation during exercise, as we observed here for patients with lymphangioleiomyomatosis (LAM).

Newer biosensing and mHealth technologies (e.g., smartphones, wearable devices, web-based exercise tracking and coaching applications) have enabled home-based programs to be better informed by biofeedback of exercise responses and real-world physical activity behavior data, enhancing compliance, safety, and effectiveness [42,43]. The remote monitoring approach tested here has permitted this to be the first report, to our knowledge, of continuously recorded SpO_2 during home exercise, and to present it over the course of a training intervention. Other studies have reported nadir SpO_2 during 6MWT [18,44] and distance-desaturation ratio (DDR) during 6MWT and CPET in LAM [26], but no studies have characterized the entirety of hemoglobin saturation response to a home exercise regimen. Our results showed that mild-to-moderate levels of desaturation are common in LAM during home exercise sessions, and that patients can self-adjust their intensity and/or oxygen delivery appropriately based on pulse oximetry readings and symptoms. As VO_{2max} on CPET did not change significantly, but end HR on 6MWT did, it is possible that our participants learned how to exert themselves more safely and at higher intensity levels with the use of remote exercise monitoring.

While participants spent the majority (55 ± 22%) of workout time in only 'mild' desaturation (SpO_2 = 90-95%, Fig. 4), all participants spent some session time in greater levels of desaturation than this, and some substantially more. Over the intervention period, almost a quarter of group-level workout time (20 ± 20%, range 1–64%) was spent in desaturation levels <90%. Not surprisingly, participants that spent more workout time in these lower desaturation levels also exhibited more desaturation during clinical exercise testing (6MWT and CPET), which may be clinically useful for risk stratifying patients for a remote exercise program.

Exercise testing studies for patients with COPD, ILD, and PAH [45,46] have reported similar cardiorespiratory responses during the submaximal 6MWT and the maximal CPET, for example in peak HR. However, in this cohort of patients with LAM, end HR obtained in 6MWT was significantly lower than end HR obtained in CPET, which suggests that for patients with LAM, CPET adds value for quantification of exercise capacity and exercise prescription.

Improvements observed in functional and QoL outcomes following our home-based intervention were equivalent or better to those previously reported after more highly structured training interventions for this population conducted in a supervised PR setting [18,44]. Conventional PR programs commonly consist of supervised exercise training 2-3 times/week for 8-12 weeks [14]. Our program had a 93% program completion rate with high adherence (87%) to a higher frequency of aerobic exercise (4 days/week, up to 45 min per session) and strengthening (3 days/week) than is routinely prescribed during PR. By prioritizing the core components of structured aerobic and resistance training only, our program was able to achieve similar positive outcomes with lower personnel resources than more conventional, in-person PR programs that also included patient education, smoking cessation, nutritional and psychological counseling [18,44]. Other studies have shown noninferior outcomes when nutritional and psychological counseling are delivered via online or mHealth platforms, compared to in-person delivery [47–49].

Using a home-based, mHealth-enabled approach likely made adherence to a more frequent program feasible, as participants didn't need to schedule appointments at a PR center, arrange transportation, and leave their own home to participate in the intervention. Patients with LAM are also generally younger than other patients with chronic lung diseases, may be more technologically literate, and may prefer a home-based exercise program, thus increasing the feasibility of a mHealth-enabled approach.

Our study was initiated prior to the start of the COVID-19 public health emergency and continued during the early months of the pandemic with relatively little disruption. We were able to continue the trial and achieve high patient adherence despite pandemic-related restrictions that closed or reduced in-person capacities of PR centers. Some participants were affected by large wildfires causing low air quality in the Western United States in 2021, resulting in additional relative indoor confinement. The flexibility of our approach was a strength during these unexpected environmental challenges, allowing patients to pivot to different exercise settings and modalities as needed.

4.1. Safety

As noted in Results, one participant experienced symptomatic pneumothorax during a vigorous recreational activity performed outside of her prescribed exercise program. Because this participant was wearing her pulse oximeter during the pneumothorax event, she was able to provide this record to her medical care team. Spontaneous pneumothorax is a common complication of LAM, with a documented prevalence of ~55% and a high risk for recurrence [19,50]. One study showed that the incidence of pneumothorax after CPET during admissions to the National Institutes of Health Clinical Research Center was very low (0.14–0.28 of 100 patients), and likely part of the natural course of LAM [51]. Further research is needed to quantify any exercise intensity threshold that is associated with higher risk for pneumothorax.

Despite no improvement in lung function, nor in amount of exercise desaturation experienced during workouts, blood indicators of systemic inflammation and cardiac wall stress remained stable over the 12-week period, further suggesting safety of this exercise intervention. The extent to which hemoglobin saturation values dropping <90% during exercise is harmful, and if adaptations are incurred akin to that observed with high altitude [52], is unknown. It has been reported that hypoxia and oxygen desaturation promote systemic inflammation [37] and our data supports this as we observed that patients at baseline with greater desaturation during maximal exercise testing had higher blood levels of CRP ($r = 0.72$, $p = 0.003$). Curiously, this relationship was completely absolved following training and, in fact, we observed that those desaturating more during their home program (e.g., spent more exercise session time in 'severe' and 'very severe' desaturation), had *smaller* not greater baseline-to-final change in CRP ($r = 0.74$, $p = 0.006$), suggesting a possible adaptive, protective hypoxic training effect. Further investigation is needed to characterize cause-effect, particularly due to important implications on training recommendations for ILD and other chronic lung disease patients living with exercise-induced hemoglobin desaturation.

There is no current consensus on desaturation threshold for supplemental oxygen use during exercise in ILD [53]. It is unclear from our results if increasing oxygen delivery to permit exercise at a higher intensity is preferred over tempering exercise to limit peripheral oxygen desaturation. On a more practical level, desaturation to lower levels will cause the heart rate to rise, perhaps above a prescribed target, potentially limiting exercise time and intensity. Lowering exercise intensity in response to oxygen desaturation is not without risk, however, as decades of training research tell us that intensity matters, and the overload principle also applies to patients with ILD. Increasing oxygen delivery to facilitate a sufficient threshold of exercise intensity may be necessary to see substantial physiological training effects. Certainly, this is an area ripe for further investigation.

4.2. Limitations

There was no control comparative group for the exercise intervention; subjects were stable at time of enrollment and served as their own control. The presence of a selection bias toward more motivated and higher functioning patients is likely, supported by higher 6MWT distances at baseline in our sample than other published LAM study cohorts [18,44]. Our sample also did not include any patients greater than 60 years old or with advanced disease severity. An entirely home-based program as we tested may be best suited for patients with low to moderate risk(s) for exercise-related adverse events and not for patients with higher risk, such as those with unstable cardiovascular condition(s), recent pneumothorax, and/or severe exercise desaturation.

Our ancillary comparison of HR obtained in CPET by 12-lead ECG vs. by photoplethysmography at the fingertip pulse oximeter confirms that photoplethysmography tends to underreport HR during exercise testing, as previously reported by Lachant et al. in patients with PAH [54]. We utilized HR obtained by ECG, not photoplethysmography, to establish the exercise prescription. While we did not perform a comparison of HR values obtained by wrist-worn device vs. the 12-lead ECG, since wrist-worn devices also utilize photoplethysmography, it is possible that intensity pacing with wrist-worn devices during home exercise may have resulted in an underestimation of actual HR achieved in those sessions for some patients.

COVID-related community mobility and travel restrictions were incongruent among our participants who came from a variety of geographical locations across Northern America with variable local, state, and national-level public health guidelines [55,56]. Participants also had variations in availability of home exercise equipment, adding difficulty to standardization and comparison of exercise parameters. However, the use of an individualized, HR-based exercise prescription facilitated a pragmatic customization of aerobic exercise intensity to unique patient-level physiology, as well as to different home exercise equipment, community-based settings, and other contextual factors where exercise training occurred.

5. Conclusion

This entirely home-based, remote monitoring-enabled exercise regimen elicited strong adherence and gains in function and QoL on par with or greater than those reported for supervised, center-based exercise interventions. The feasibility, safety, and effectiveness demonstrated here supports the need for subsequent studies to further investigate this paradigm-changing approach to structured exercise training in chronic lung diseases, even for patients at risk for exercise desaturation.

CRediT authorship contribution statement

Claire E. Child: Writing – original draft, drafted the manuscript, Formal analysis, helped with the acquisition, analysis, and interpretation of study data. **Morgan L. Kelly:** Formal analysis, helped with the acquisition, analysis, and interpretation of study data, Writing – original draft, drafted the manuscript. **Haley Sizelove:** Formal analysis, helped with the acquisition, analysis, and interpretation of study data. **Marissa Garvin:** Formal analysis, helped with the acquisition, analysis, and interpretation of study data. **Julia Guilliams:** Formal analysis, helped with the acquisition, analysis, and interpretation of study data. **Paul Kim:** Formal analysis, helped with the acquisition, analysis, and interpretation of study data. **Haotian D. Cai:** Formal analysis, helped with the acquisition, analysis, and interpretation of study data. **SiWei Luo:** Formal analysis, helped with the acquisition, analysis, and interpretation of study data. **Kevin J. McQuade:** Formal analysis, helped with the acquisition, analysis, and interpretation of study data. **Erik R. Swenson:** Formal analysis, reviewed and revised the manuscript for important intellectual content. **Amanda T. Wise:** Formal analysis, helped with the acquisition, analysis, and interpretation of study data. **Ylinne T. Lynch:** Formal analysis, helped with the acquisition, analysis, and interpretation of study data. **Lawrence A. Ho:** Formal analysis, helped with the acquisition, analysis, and interpretation of study data. **Mary Beth Brown:** conceived and designed the study, Formal analysis, helped with the acquisition, analysis, and interpretation of study data, Writing – original draft, drafted the manuscript, provided final approval of the version to be published and agrees to be accountable for all aspects of the work.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We acknowledge Allyson Venugopal for collaboration in protocol planning and recruitment as a patient representative.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2023.107397.

References

[1] Y.H. Khor, N.S. Goh, I. Glaspole, A.E. Holland, C.F. McDonald, Exertional desaturation and prescription of ambulatory oxygen therapy in interstitial lung disease, Respir Care. Mar 64 (3) (2019) 299–306, https://doi.org/10.4187/respcare.06334.

[2] L. Dowman, C.J. Hill, A. May, A.E. Holland, Pulmonary rehabilitation for interstitial lung disease, Cochrane Database Syst. Rev. (2) (Oct 2021) CD006322, https://doi.org/10.1002/14651858.CD006322.pub4.

[3] R. Sami, K. Salehi, M. Hashemi, V. Atashi, Exploring the barriers to pulmonary rehabilitation for patients with chronic obstructive pulmonary disease: a qualitative study, BMC Health Serv Res. Aug 17 21 (1) (2021) 828, https://doi.org/10.1186/s12913-021-06814-5.

[4] H. Robinson, V. Williams, F. Curtis, C. Bridle, A.W. Jones, Facilitators and barriers to physical activity following pulmonary rehabilitation in COPD: a systematic review of qualitative studies, NPJ Prim Care Respir Med 28 (1) (Jun 4 2018) 19, https://doi.org/10.1038/s41533-018-0085-7.
[5] M. Hoffman, C. Mellerick, K. Symons, I. Glaspole, A.E. Holland, Pulmonary rehabilitation for interstitial lung disease: referral and patient experiences, Chron. Respir. Dis. 18 (Jan-Dec 2021), 14799731211046022, https://doi.org/10.1177/14799731211046022.
[6] CDC, Cardiac rehabilitation change package. Center for disease control and prevention, US dept of health and human services. https://millionhearts.hhs.gov/files/Cardiac_Rehab_Change_Pkg.pdf. (Accessed 20 April 2021).
[7] S.P. Nishi, W. Zhang, Y.F. Kuo, G. Sharma, Pulmonary rehabilitation utilization in older adults with chronic obstructive pulmonary disease, 2003 to 2012, J Cardiopulm Rehabil Prev 36 (5) (Sep-Oct 2016) 375–382, https://doi.org/10.1097/hcr.0000000000000194.
[8] P.G. Camp, P. Hernandez, J. Bourbeau, et al., Pulmonary rehabilitation in Canada: a report from the Canadian thoracic society COPD clinical assembly, Cancer Res. J. 22 (3) (May-Jun 2015) 147–152, https://doi.org/10.1155/2015/369851.
[9] L. McKowen, Cardiac rehab during COVID-19: telehealth, unpaid heroes step up to help at home, Updated April 10, 2020, https://www.tctmd.com/news/cardiac-rehab-during-covid-19-telehealth-unpaid-heroes-step-help-home. (Accessed 23 September 2020).
[10] A.L. Beatty, T.M. Brown, M. Corbett, et al., Million hearts cardiac rehabilitation think tank: accelerating new care models, Circ Cardiovasc Qual Outcomes 14 (10) (Oct 2021), e008215, https://doi.org/10.1161/circoutcomes.121.008215.
[11] N.S. Cox, S. Dal Corso, H. Hansen, et al., Telerehabilitation for chronic respiratory disease, Cochrane Database Syst Rev. Jan 29 1 (1) (2021), Cd013040, https://doi.org/10.1002/14651858.CD013040.pub2.
[12] C.L. Rochester, I. Vogiatzis, A.E. Holland, et al., An official American thoracic society/European respiratory society policy statement: enhancing implementation, use, and delivery of pulmonary rehabilitation, Am. J. Respir. Crit. Care Med. 192 (11) (Dec 1 2015) 1373–1386, https://doi.org/10.1164/rccm.201510-1966ST.
[13] J. Bondarenko, C. Babic, A.T. Burge, A.E. Holland, Home-based pulmonary rehabilitation: an implementation study using the RE-AIM framework, ERJ Open Res. Apr 7 (2) (2021), https://doi.org/10.1183/23120541.00469-2020.
[14] A.E. Holland, N.S. Cox, L. Houchen-Wolloff, et al., Defining modern pulmonary rehabilitation. An official American thoracic society workshop report, Ann Am Thorac Soc. May 18 (5) (2021) e12–e29, https://doi.org/10.1513/AnnalsATS.202102-146ST.
[15] C. McCarthy, N. Gupta, S.R. Johnson, J.J. Yu, F.X. McCormack, Lymphangioleiomyomatosis: pathogenesis, clinical features, diagnosis, and management, Lancet Respir Med. Nov 9 (11) (2021) 1313–1327, https://doi.org/10.1016/s2213-2600(21)00228-9.
[16] N. Gupta, H.S. Lee, J.H. Ryu, et al., The NHLBI LAM registry: prognostic physiologic and radiologic biomarkers emerge from a 15-year prospective longitudinal analysis, Chest. Feb 155 (2) (2019) 288–296, https://doi.org/10.1016/j.chest.2018.06.016.
[17] A. Belkin, K. Albright, K. Fier, J. Desserich, J.J. Swigris, "Getting stuck with LAM": patients perspectives on living with lymphangioleiomyomatosis, Health Qual. Life Outcome 12 (May 21 2014) 79, https://doi.org/10.1186/1477-7525-12-79.
[18] M.S. Araujo, B.G. Baldi, C.S. Freitas, et al., Pulmonary rehabilitation in lymphangioleiomyomatosis: a controlled clinical trial, Eur Respir J. May 47 (5) (2016) 1452–1460, https://doi.org/10.1183/13993003.01683-2015.
[19] J.H. Ryu, J. Moss, G.J. Beck, et al., The NHLBI lymphangioleiomyomatosis registry: characteristics of 230 patients at enrollment, Am. J. Respir. Crit. Care Med. 173 (1) (Jan 1 2006) 105–111, https://doi.org/10.1164/rccm.200409-1298OC.
[20] M.B. Brown, M.L. Kelly, C. Child, et al., Novel characterization of blood oxygen saturation during home exercise over a 12-week mobile health intervention in women with lymphangioleiomyomatosis (LAM) and relationship to training variables and outcomes, American Thoracic Society International Conference Abstracts (A4966) (2022) C108, https://doi.org/10.1164/ajrccm-conference.2022.205.1_MeetingAbstracts.A4966.
[21] M.L. Kelly, Y. Lynch, C.E. Child, et al., A mobile-health exercise intervention improves exercise tolerance, quality of life, and fatigue in lymphangioleiomyomatosis: 1232, Med. Sci. Sports Exerc. 54 (9S) (2022) 303. Sept 1, 2022.
[22] R. Aggarwal, P. Ranganathan, Study designs: Part 4 - interventional studies, Perspect Clin Res 10 (3) (Jul-Sep 2019) 137–139, https://doi.org/10.4103/picr.PICR_91_19.
[23] D. Mereles, N. Ehlken, S. Kreuscher, et al., Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension, Circulation 114 (14) (Oct 3 2006) 1482–1489, https://doi.org/10.1161/circulationaha.106.618397.
[24] L. Goldman, B. Hashimoto, E.F. Cook, A. Loscalzo, Comparative reproducibility and validity of systems for assessing cardiovascular functional class: advantages of a new specific activity scale, Circulation. Dec 64 (6) (1981) 1227–1234, https://doi.org/10.1161/01.cir.64.6.1227.
[25] J. Karvonen, T. Vuorimaa, Heart rate and exercise intensity during sports activities. Practical application, Sports Med. May 5 (5) (1988) 303–311.
[26] D.S. Queiroz, C. da Silva, A.F. Amaral, et al., Desaturation-distance ratio during submaximal and maximal exercise tests and its association with lung function parameters in patients with lymphangioleiomyomatosis, Front. Med. 8 (2021), 659416, https://doi.org/10.3389/fmed.2021.659416.
[27] American College of Sports Medicine, ACSM's Guidelines for Exercise Testing and Prescription, eleventh ed., Wolters Kluwer/Lippincott Williams & Wilkins Health, 2021.
[28] American College of Sports Medicine, ACSM's Guidelines for Exercise Testing and Prescription, ninth ed., Wolters Kluwer/Lippincott Williams & Wilkins Health, 2014.
[29] C.H. Liu, N.D. Abrams, D.M. Carrick, et al., Biomarkers of chronic inflammation in disease development and prevention: challenges and opportunities, Nat. Immunol. 11 (2017) 1175–1180.
[30] H.H. Leuchte, M. Holzapfel, R.A. Baumgartner, et al., Clinical significance of brain natriuretic peptide in primary pulmonary hypertension, J Am Coll Cardiol. Mar 3 43 (5) (2004) 764–770, https://doi.org/10.1016/j.jacc.2003.09.051.
[31] T.D. Walker, J. Desserich, K. Albright, et al., Development of ATAQ-LAM: a tool to assess quality of life in Lymphangioleiomyomatosis, Health Qual. Life Outcome 13 (Jul 30 2015) 112, https://doi.org/10.1186/s12955-015-0294-5.
[32] E.M. Smets, B. Garssen, B. Bonke, J.C. De Haes, The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue, J Psychosom Res. Apr 39 (3) (1995) 315–325, https://doi.org/10.1016/0022-3999(94)00125-o.
[33] C.M. Yang, C.H. Wu, The situational fatigue scale: a different approach to measuring fatigue, Qual Life Res. Jun 14 (5) (2005) 1357–1362, https://doi.org/10.1007/s11136-004-5680-0.
[34] EuroQol–a new facility for the measurement of health-related quality of life, Health Pol. 16 (3) (Dec 1990) 199–208, https://doi.org/10.1016/0168-8510(90)90421-9.
[35] J. Montes, M.P. McDermott, W.B. Martens, et al., Six-Minute Walk Test demonstrates motor fatigue in spinal muscular atrophy, Neurology. Mar 9 74 (10) (2010) 833–838, https://doi.org/10.1212/WNL.0b013e3181d3e308.
[36] T. Bahmer, H. Watz, B. Waschki, et al., Reduced physical activity in lymphangioleiomyomatosis compared with COPD and healthy controls: disease-specific impact and clinical correlates, Thorax. Published by the BMJ Publishing Group Limited. For permission to use (where not already granted under a licence) please go to, http://www.bmj.com/company/products-services/rights-and-licensing/; 2016:662-3. vol. 7.
[37] H.K. Eltzschig, P. Carmeliet, Hypoxia and inflammation, N Engl J Med. Feb 17 364 (7) (2011) 656–665, https://doi.org/10.1056/NEJMra0910283.
[38] J.B. Coquart, J.M. Grosbois, C. Olivier, F. Bart, I. Castres, B. Wallaert, Home-based neuromuscular electrical stimulation improves exercise tolerance and health-related quality of life in patients with COPD, Int. J. Chronic Obstr. Pulm. Dis. 11 (2016) 1189–1197, https://doi.org/10.2147/copd.s105049.
[39] B.C. Matos-Garcia, I.S. Rocco, L.D. Maiorano, et al., A home-based walking program improves respiratory endurance in patients with acute myocardial infarction: a randomized controlled trial, Can. J. Cardiol. 33 (6) (Jun 2017) 785–791, https://doi.org/10.1016/j.cjca.2016.12.004.
[40] R.J. McNamara, Z.J. McKeough, L.R. Mo, J.T. Dallimore, S.M. Dennis, Community-based exercise training for people with chronic respiratory and chronic cardiac disease: a mixed-methods evaluation, Int. J. Chronic Obstr. Pulm. Dis. 11 (2016) 2839–2850, https://doi.org/10.2147/COPD.S118724.
[41] M.B. Brown, A. Kempf, C.M. Collins, et al., A prescribed walking regimen plus arginine supplementation improves function and quality of life for patients with pulmonary arterial hypertension: a pilot study, Pulm. Circ. 8 (1) (2018 Jan-Mar 2018), 2045893217743966, https://doi.org/10.1177/2045893217743966.
[42] R.W. Brouwers, J.J. Kraal, S.C. Traa, R.F. Spee, L.M. Oostveen, H.M. Kemps, Effects of cardiac telerehabilitation in patients with coronary artery disease using a personalised patient-centred web application: protocol for the SmartCare-CAD randomised controlled trial, BMC Cardiovasc. Disord. 17 (1) (Jan 31 2017) 46, https://doi.org/10.1186/s12872-017-0477-6.
[43] J. Mattila, H. Ding, E. Mattila, A. Sarela, Mobile tools for home-based cardiac rehabilitation based on heart rate and movement activity analysis, Conf. Proc. : Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Annual Conference 2009 (2009) 6448–6452, https://doi.org/10.1109/IEMBS.2009.5333540.
[44] R. Gloeckl, C. Nell, T. Schneeberger, et al., Benefits of pulmonary rehabilitation in patients with advanced lymphangioleiomyomatosis (LAM) compared with COPD - a retrospective analysis, Orphanet J. Rare Dis. 1 (2020) 255.
[45] C. Fabre, B. Chehere, F. Bart, P. Mucci, B. Wallaert, J.M. Grosbois, Relationships between heart rate target determined in different exercise testing in COPD patients to prescribed with individualized exercise training, Int. J. Chronic Obstr. Pulm. Dis. 12 (2017) 1483–1489, https://doi.org/10.2147/copd.s129889.
[46] S.J. Singh, M.A. Puhan, V. Andrianopoulos, et al., An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease, Eur Respir J. ©Ers 6 (2014) 1447–1478, 2014.
[47] B.G. Choi, T. Dhawan, K. Metzger, et al., Image-based mobile system for dietary management in an American cardiology population: pilot randomized controlled trial to assess the efficacy of dietary coaching delivered via a smartphone app versus traditional counseling, JMIR Mhealth Uhealth 7 (4) (Apr 23 2019), e10755, https://doi.org/10.2196/10755.
[48] W.W. Mak, A.C. Tong, S.Y. Yip, et al., Efficacy and moderation of mobile app-based programs for mindfulness-based training, self-compassion training, and cognitive behavioral psychoeducation on mental health: randomized controlled noninferiority trial, JMIR Ment Health 5 (4) (Oct 11 2018), e60, https://doi.org/10.2196/mental.8597.
[49] S. Bourne, R. DeVos, M. North, et al., Online versus face-to-face pulmonary rehabilitation for patients with chronic obstructive pulmonary disease: randomised controlled trial, BMJ Open 7 (7) (Jul 17 2017), e014580, https://doi.org/10.1136/bmjopen-2016-014580.
[50] S. Harari, O. Torre, R. Cassandro, J. Moss, The changing face of a rare disease: lymphangioleiomyomatosis, Eur Respir J. Nov 46 (5) (2015) 1471–1485, https://doi.org/10.1183/13993003.00412-2015.

[51] A.M. Taveira-DaSilva, P. Julien-Williams, A.M. Jones, J. Moss, Incidence of pneumothorax in patients with lymphangioleiomyomatosis undergoing pulmonary function and exercise testing, Chest. Jul 150 (1) (2016) e5–e8, https://doi.org/10.1016/j.chest.2015.10.071.
[52] E.R. Swenson, P. Bärtsch, High Altitude: Human Adaptation to Hypoxia, 1 ed., Springer, 2014.
[53] R.K. Lim, C. Humphreys, J. Morisset, A.E. Holland, K.A. Johannson, Oxygen in patients with fibrotic interstitial lung disease: an international Delphi survey, Eur Respir J. Aug 54 (2) (2019), https://doi.org/10.1183/13993003.00421-2019.
[54] D. Lachant, E. Kennedy, B. Derenze, A. Light, M. Lachant, R.J. White, Cardiac effort to compare clinic and remote 6-minute walk testing in pulmonary arterial hypertension, Chest 162 (6) (Dec 2022) 1340–1348, https://doi.org/10.1016/j.chest.2022.06.025.
[55] M. Sulyok, M. Walker, Community movement and COVID-19: a global study using Google's Community Mobility Reports, Epidemiol. Infect. 148 (Nov 13 2020) e284, https://doi.org/10.1017/s0950268820002757.
[56] J. Sun, K. Kwek, M. Li, H. Shen, Effects of social mobility and stringency measures on the COVID-19 outcomes: evidence from the United States, Front. Public Health 9 (2021), 779501, https://doi.org/10.3389/fpubh.2021.779501.