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REVIEW

Mechanisms of exercise limitation and pulmonary rehabilitation in patients with cystic lung diseases

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ABSTRACT

Introduction: The main diffuse cystic lung diseases (DCLD) include lymphangioleiomyomatosis (LAM), pulmonary Langerhans cell histiocytosis (PLCH), Birt-Hogg-Dubé syndrome, and lymphocytic interstitial pneumonia. Exercise limitation is frequent and secondary to multiple mechanisms in DCLD. Some studies addressed mechanisms for exercise limitation, field tests, and pulmonary rehabilitation (PR) in DCLD.

Areas covered: This review aims to present the main mechanisms that determine exercise limitation, the responses of patients in field tests, and the details regarding the safety and efficacy of PR in DCLD, with emphasis on LAM and PLCH. A search on the issue was performed in the MEDLINE and SciELO databases between 27 November 2024 and 20 February 2025. Manuscripts were reviewed and important topics were included in this review.

Expert opinion: Reduced exercise capacity is common and multifactorial, including ventilatory, cardiocirculatory, and peripheral limitations, pulmonary hypertension (PH), and impaired gas exchange in LAM and PLCH. Variables from field tests are correlated with pulmonary function tests, and PR is safe and beneficial in LAM. Further studies are necessary to evaluate exercise in other DCLDs, the impact of other therapeutic modalities on DH, hypoxemia, and exercise-induced PH in LAM and PLCH, and the safety and benefits of PR mostly in PLCH.

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Cysts; diffuse cystic lung disease; exercise; Langerhans cell histiocytosis; lymphangioleiomyomatosis; rehabilitation; walk test

1. Introduction

Pulmonary cysts consist in low-attenuating round areas with a well-defined interface with the adjacent normal lung [1,2]. Diffuse cystic lung diseases (DCLD) are characterized by the presence of more than four cysts in the pulmonary parenchyma, usually bilateral and with a wall thickness of less than 2 mm [1,3–5].

The differential diagnosis of DCLD is challenging and broad [6–8]. The main etiologies of DCLD are lymphangioleiomyomatosis (LAM), pulmonary Langerhans cell histiocytosis (PLCH), Birt-Hogg-Dubé syndrome, lymphocytic interstitial pneumonia, and bronchiolitis [4,5,7–9]. Other diseases are included as potential etiologies for DCLD, such as hypersensitivity pneumonitis, amyloidosis, metastatic neoplasms, light-chain deposition disease, and endometriosis [1,4,5,7,8,10]. In some cases, even after a broad investigation and a multidisciplinary approach, the etiology of DCLD cannot be established [11].

Chest computed tomography (CT) is essential for the diagnostic approach of patients with DCLD. Assessment of characteristics of cysts, such as wall thickening, morphology, localization and distribution in the craniocaudal plane, the presence of additional pulmonary lesions, including nodules, ground-glass opacities, interlobular septal thickening and mosaic attenuation, and the occurrence of extrapulmonary manifestations, such as cutaneous lesions, lymphadenopathy, renal angiomyolipoma and pleural effusion, are key for diagnostic confirmation [2,3,11]. The evaluation of clinical, functional, laboratory, tomographic, and extrapulmonary features, with a multidisciplinary approach, often avoids needing a biopsy to confirm the diagnosis of DCLD [1,4,11,12].

Patients with DCLD may be asymptomatic or present with dyspnea, cough and spontaneous pneumothorax, and exercise limitation. Dyspnea and exercise limitation may have an impact on quality of life and on symptoms of anxiety and depression [1,2,7,8,12–15]. Studies that evaluated patients with DCLD during exercise focused on LAM and PLCH, and several of them demonstrated a correlation between exercise limitation and the severity of pulmonary parenchymal involvement [13–18]. Reduction in exercise capacity and in maximal oxygen uptake (VO_2) are common in LAM and PLCH, especially in patients with more severe disease, but may occur even in those with normal pulmonary function tests (PFTs) [12–18]. Multiple mechanisms, in isolation or in combination, are involved as potential causes for reduced exercise capacity in LAM and PLCH, such as ventilatory limitation, pulmonary hypertension (PH), dynamic hyperinflation (DH), impaired gas exchange, cardiocirculatory and peripheral muscle limitations [13–18].

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Article highlights

- LAM and PLCH are the DCLDs that were evaluated during exercise tests.
- Reduced exercise capacity is very prevalent in LAM and PLCH, and may occur even in patients with normal or mild impairment on PFTs.
- Multiple mechanisms are responsible for reduced exercise capacity in LAM and PLCH, including ventilatory, cardiocirculatory, and peripheral limitations, DH, PH, and impaired gas exchange.
- It is not simple to determine the contribution of each mechanism described above to exercise limitation in LAM and PLCH.
- The 6MWT and ISWT are submaximal and maximal tests to assess exercise capacity in LAM. Both tests are safe, and variables obtained, including the distance walked and DDR, are correlated with pulmonary function parameters in LAM.
- Few studies investigated patients with PLCH in field tests, all through 6MWT.
- Pulmonary rehabilitation seems to be a feasible and safe intervention in LAM, demonstrating benefits on exercise capacity , quality of life, dyspnea, and depression. However, no consistent study has evaluated PR in PLCH.

Some studies demonstrated the results of field tests, such as the six-minute walk test (6MWT) and incremental shuttle walk test (ISWT), to assess exercise capacity in DCLD, mostly in LAM, and may be considered other potential options to evaluate patients with such diseases [13,16,19–23]. Additionally, pulmonary rehabilitation (PR) is a potential option to improve exercise capacity in DCLD, although there is a concern regarding its safety in such diseases. Few studies assessed PR in DCLD, mostly in LAM [18,24,25].

This review article aims to describe the main mechanisms that determine exercise limitation in patients with DCLD, with emphasis on LAM and PLCH, and to present the main responses on 6MWT and field exercise tests and the impact and safety of exercise and PR on such diseases.

2. Methods

We assessed original manuscripts, case reports, systematic reviews/meta-analysis, and narrative reviews published in PubMed until February 2025 to perform this narrative review. We conducted a search for articles with the terms 'diffuse cystic lung diseases,' 'cystic lung diseases,' 'lymphangioleiomyomatosis,' 'pulmonary histiocytosis,' and lymphocytic interstitial pneumonia,' combined with 'exercise,' 'rehabilitation,' 'field tests,' 'physiotherapy' and 'six-minute walk test.'

The first and last authors were responsible for determining the eligibility of the manuscripts. Discrepancies between the two authors were resolved through consensus discussions. A flowchart describes the selection of articles (Figure 1). Among 220 manuscripts initially screened, we included only 57, which were published in English and involved adults. We excluded articles that involved pediatric patients, with combined diseases, LAM plus asthma, for example, and those with content outside the scope of this review.

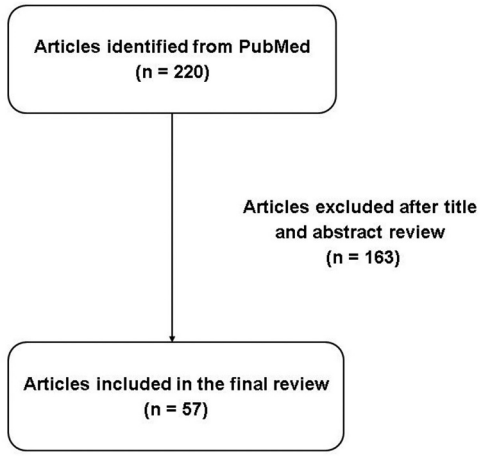

Figure 1. Flowchart with the selection of articles.

3. Lymphangioleiomyomatosis

LAM is a rare and progressive systemic neoplastic disease with metastatic potential that predominantly affects women of reproductive age [19]. LAM is associated with mutations in tuberous sclerosis complex (TSC) genes (TSC1 and TSC2) [26–28]. It is characterized by the proliferation of abnormal muscle cells (LAM cells) with cystic lung destruction, which can also occur in the presence of abdominal tumors, such as renal and hepatic angiomyolipomas and lymphangioleiomyomas, and the accumulation of chylous effusions, associated with constitutive activation of the mechanistic target of rapamycin (mTOR) pathway [26–28].

Two forms of the disease are recognized: sporadic (S-LAM) and associated with tuberous sclerosis complex (TSC-LAM). Cysts suggestive of LAM may occur in TSC in up to 80% of individuals over 40 years of age, with an underestimated prevalence [29–31]. Progressive dyspnea and spontaneous pneumothorax are the most common clinical manifestations in patients with LAM. The clinical progression of LAM is variable, ranging from asymptomatic cases, in which cysts are identified on CT scans performed for other reasons, to progressive disease that may result in death or require lung transplantation. The most common abnormalities found in PFTs in LAM are reduced diffusion capacity for carbon monoxide (DLCO), obstructive pattern, and air trapping. However, in up to 50% of cases, PFTs are normal [6,28,32]. Pulmonary involvement in TSC-LAM is generally considered less severe and has a lower progression rate than S-LAM, although this issue is not completely established [32].

The diagnosis of LAM can be established based on tomographic and clinical characteristics, including the presence of typical cysts (diffuse, regular, and thin-walled) on chest CT (Figure 2(a,b)), combined with renal angiomyolipoma and/or pelvic or abdominal lymphangioleiomyomas; chylous effusions; skin lesions compatible with TSC, such as Shagreen patches and facial angiofibromas; or neurological manifestations, such as subependymal nodules and astrocytoma. If there is no clinical manifestation to confirm the diagnosis, serum elevated vascular endothelial growth factor D (VEGF-D) may be performed. The presence of serum VEGF-D above 800 pg/mL confirms the diagnosis. In 70% of cases, a lung biopsy is not necessary. In cases where there is no clinical manifestation and serum VEGF-D is below 800 pg/mL, transbronchial or surgical pulmonary biopsy is indicated to confirm the diagnosis [26,27,30].

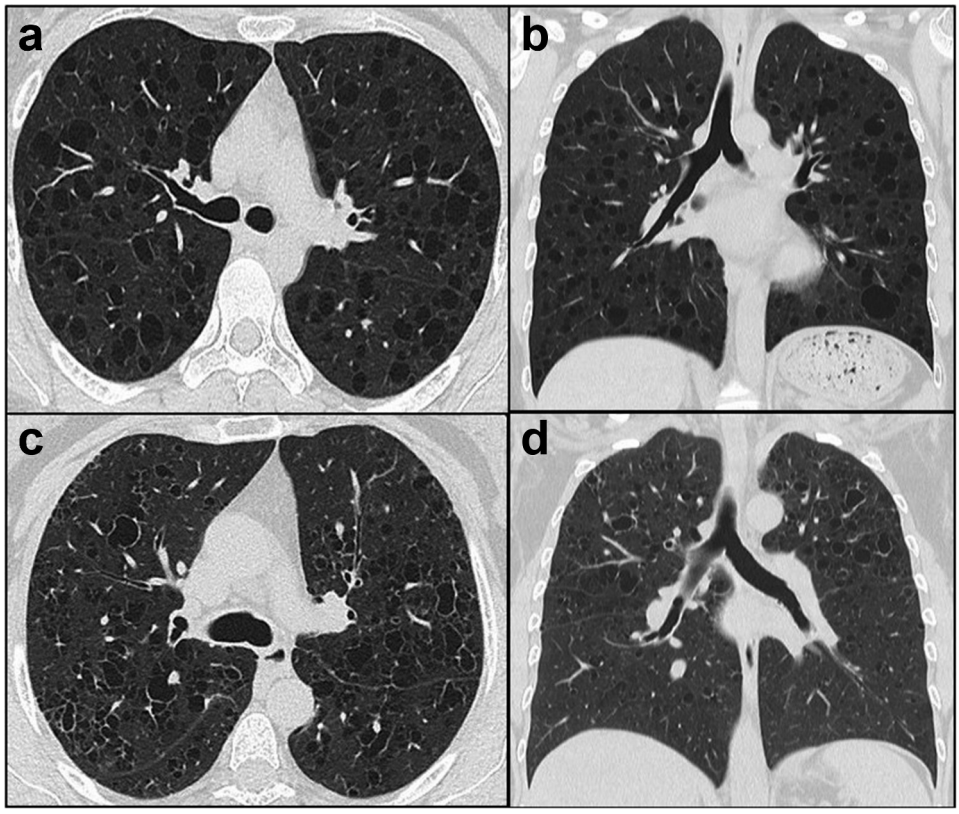

Figure 2. (a) (axial image) and (b) (coronal image): CT scans of a patient with lymphangioleiomyomatosis demontraste diffuse pulmonary cysts with regular and thin-walled walls. (c,d) CT scans of a patient with pulmonary langerhans cell histiocytosis; (c) axial image demonstrates irregular and heterogeneous pulmonary cysts; (d) coronal image shows irregular and heterogeneous pulmonary cysts predominanting in the upper lobes and sparing the lower lobes and the region of the costophrenic sinuses. Unpublished data obtained from studies approved by the institutional review board of the University of Sao Paulo Medical School. Informed consent was obtained from subject and/or parent, who gave permission for publication.

4. Mechanisms of exercise limitation in lymphangioleiomyomatosis

Patients with DCLD commonly present with respiratory symptoms, lung function abnormalities, and impaired exercise capacity. Exertional dyspnea is a prevalent and debilitating complaint, often resulting in premature exercise cessation and a significant decline in quality of life. In patients with LAM, multiple mechanisms, isolatedly or in combination, may contribute to reduced exercise capacity, including dysfunction of the airways, pulmonary parenchyma and circulation, and limitation of peripheral muscles [16,17,33–37]. CPET is an important assessment tool in patients with dyspnea and can be useful in evaluating the underlying mechanisms of exercise limitation [38]. Exercise capacity is considered reduced if the peak VO_2 is less than 85% of the predicted value. The mechanisms of exercise limitation may be defined as ventilatory limitation (ventilatory reserve lower than 15%), cardiocirculatory limitation (anaerobic threshold lower than 40% of the predicted peak VO_2 and/or oxygen pulse lower than 81% of the predicted value or with an early plateau), cardiocirculatory limitation suggestive of PH ($PETCO_2$ at anaerobic threshold lower than 40 mmHg and a VE/VCO_2 slope greater than 34) and impaired gas exchange (oxygen desaturation greater than 4%) [38]. The studies that assessed patients with LAM during exercise had variable results and are detailed below in Table 1.

In a single-center study evaluating 16 patients with LAM, Crausman et al. reported that these individuals exhibited moderate to severe obstructive patterns and reduced DLCO on PFTs [34]. Forced expiratory volume in the first second (FEV1) was decreased in 14 (87%) patients, representing 56 ± 5% of predicted. Exercise capacity was notably impaired, as evidenced by a reduced peak VO2 (57 ± 5% of predicted) and an excessive maximal ventilatory response (minute ventilation, VE, 86 ± 6%) relative to the workload achieved. Additionally, the dead space to tidal volume ratio (Vd/Vt) was abnormally elevated at rest (34 ± 3%) and during maximal exercise (38 ± 3%), representing a possible contributor to exercise limitation. Gas exchange parameters further deteriorated during exercise, suggesting the association of a pulmonary vascular component. Moreover, FEV1/forced vital capacity (FVC), FEV1/FVC, and specific airway conductance (SGaw) were significantly correlated with VO2 maximum (max) predicted, VEmax, and maximal workload achieved, reinforcing the correlation between the severity of lung involvement with reduced exercise capacity [34].

Taveira-DaSilva et al. conducted cardiopulmonary exercise testing (CPET) in 217 patients with LAM [17]. Reduced VO2 max was observed in 162 (75%) patients, among whom 28 did not reach the anaerobic threshold (AT) and 54 (33%) developed hypoxemia. Dyspnea was the primary exercise-limiting symptom (40%), and reductions were noted in VO2 max (71.5 ± 1.7% predicted), DLCO (73.5 ± 1.8% predicted) and FEV1 (75.5 ± 1.7% predicted). Among the 162 patients who achieved AT, 98 (60%) showed evidence of inefficient gas exchange, including 54 (33%) who developed hypoxemia. Additionally, 114 of the 162 patients (70%) exhibited abnormal

Table 1. Summary of the main studies that evaluated the mechanisms of exercise limitation in lymphangioleiomyomatosis.

First author, year (reference)	Subjects (n)	Details	Main results
Crausman, 1996 [26]	16	Age 37 ± 7 years FEV_1 56 ± 5% pred DLCO 55 ± 6% pred VO_2 max 57 ± 5% pred	*Ventilatory limitation and pulmonary vascular function as the primary factors for exercise limitation *Correlation between pulmonary function tests and exercise capacity
Taveira-DaSilva, 2003 [17]	217	Age 45 ± 1 years FEV_1 75 ± 2% pred DLCO 73 ± 2% pred VO_2 max 72 ± 2% pred	*Dyspnea as the major exercise-limiting symptom (40%) *75% with reduced VO_2 max *60% with inefficient gas exchange *33%with hypoxemia during exercise *70% with major cardiovascular responses *Association of pulmonary parenchymal involvement with reduced exercise capacity *Multiple mechanisms for exercise limitation: gas exchange, cardiovascular, ventilatory and muscle fatigue
Taveira-DaSilva, 2007 [29]	120	Age 46 ± 1 years FEV_1 71 ± 2% pred DLCO 64 ± 2% pred VO_2 max 70 ± 2% pred PH assessed with echocardiography	*Main reasons for exercise limitation: leg fatigue (40%), dyspnea (36%) *Prevalence of PH at rest < 10% *59% with elevations in PASP at exercise in those from mild to severe disease *64% with oxygen desaturation at exercise *PH during exercise in part associated with the development of hypoxemia
Baldi, 2012 [16]	42	Age 42 ± 11 years FEV_1 78 ± 23% pred DLCO 67 ± 24% pred VO_2 max 83 ± 21% pred	*57% with reduced exercise capacity *31% with oxygen desaturation at exercise *Dyspnea as the major reason for exercise interruption (29%) *Prevalence of DH: 55% *DH is associated with the severity of disease and may occur even in those with mild spirometric abnormalities *Ventilatory limitation, including DH, and gas exchange impairment as the major causes for exercise cessation
Queiroz, 2024 [39]	45	Median age 46 years Median FEV1 74% pred Median DLCO 66% pred Median 6MWD 510 m Median VO2 max 67% pred	*86% with reduced exercise capacity *29% with ventilatory limitation *49% with cardiovascular limitations *38% with oxygen desaturation at exercise
Zafar, 2013 [31]	9	Age 47 ± 13 years FEV_1 81 ± 25% pred DLCO 70 ± 27% pred Data assessed with echocardiography	*50% presented findings compatible with IPAVS at rest and 62% during exercise *IPAVS is a potential contributor for dyspnea and exercise limitation and was not associated with pulmonary parenchymal involvement
Sonaglioni, 2018 [30]	15	Age 47 ± 13 years FEV_1 82 ± 26% pred DLCO 51 ± 15% pred PH assessed with echocardiography	*Precapillary (increase in PVR) and postcapillary (diastolic dysfunction with increase in pulmonary capillary wedge pressure) exercise-induced PH

Legends: DH: dynamic hyperinflation; DLCO: diffusion capacity for carbon monoxide; FEV_1: forced expiratory volume in the first second; IPAVS: intrapulmonary arteriovenous shunts; PASP: pulmonary artery systolic pressure; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; VO_2 max: maximum oxygen uptake; 6MWD: six-minute walking distance.

cardiovascular responses, with 39 (24%) limited by low heart rate (HR) reserve and 24 (15%) by low breathing reserve. Even some patients with normal or mild reduced DLCO presented exercise-induced hypoxemia. Thirty-one patients were oxygen-dependent and had significantly lower VO2 max, breathing reserve, DLCO, and FEV1 than those non-oxygen-dependent. DLCO and FEV1 were identified as predictors of VO2 max. Furthermore, the decline in VO2 max was correlated with higher histologic LAM severity scores and CT scan severity grades, oxygen use, and resting PaO2 levels. The results of this study strengthen the association of pulmonary parenchymal involvement with exercise limitation [17].

Baldi et al. evaluated 42 patients with LAM to investigate dynamic responses during maximal CPET [16]. Patients with LAM exhibited lower FEV_1 (78% vs. 100% of predicted, $p < 0.05$) and DLCO (67% vs. 101% of predicted, $p < 0.05$), with a higher prevalence of FEV_1 below the lower limit of normal (40% vs. 0%, $p = 0.02$), compared to paired healthy controls. LAM was associated with reduced exercise capacity, with 57% of patients presenting work rates below the lower limit of normal. The final breathing reserve (% maximal voluntary ventilation, MVV) was reduced, and there was a trend toward a higher ventilatory response during exercise (an increased ratio of minute ventilation to carbon dioxide production, VE/VCO_2 slope; maximal minute ventilation, VE, carbon dioxide production, VCO_2) in LAM [16]. Patients with LAM exhibited greater oxygen desaturation (93% vs. 98%, $p < 0.05$), and dyspnea was the primary reason for CPET interruption (29%). DH, defined as reduction ≥ 10% in inspiratory capacity, IC, was found in 55% of patients during exercise. Patients with DH demonstrated a significantly greater ventilatory response (VE/VCO_2 slope: 37.7 vs. 31.5, $p < 0.05$), lower breathing reserve, and higher desaturation at peak exercise (91% vs. 96%, $p < 0.05$), compared with the non-DH subgroup. Forty patients with LAM performed 6MWT, with a median distance of 547 m (range: 402–690 m), 97% of the predicted (range: 66–119%). This study concluded that ventilatory limitation, including DH, and gas exchange impairment are important causes of exercise limitation in LAM, and DH may occur even in those with normal or mild spirometric abnormalities [16].

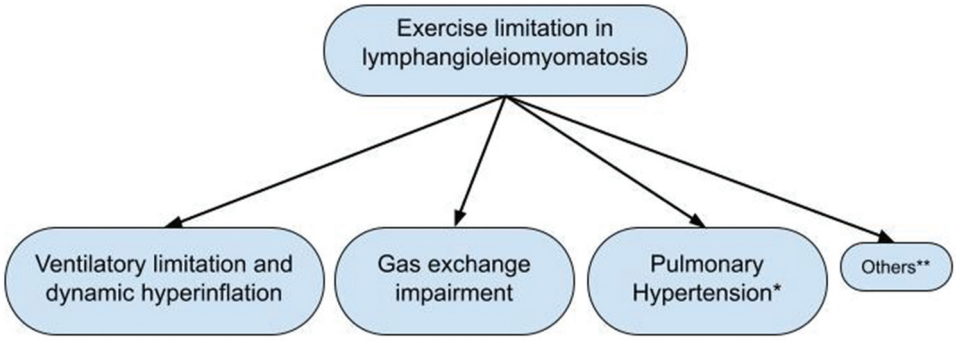

Figure 3. Mechanisms of exercise limitation in lymphangioleiomyomatosis.
*Precapillary or postcapillary pulmonary hypertension.
**Muscle fatigue, intrapulmonary arteriovenous shunts.

Queiroz et al in a single-center study assessed 45 patients with LAM, with median age, FEV_1 and DLCO of 45 years, 74% predicted and 66% predicted, respectively [39]. Patients performed CPET in a cycle ergometer, 86% had reduced exercise capacity, characterized by VO_2 max below 84%, and 29%, 49% and 38% showed ventilatory limitation, cardiovascular limitation and oxygen desaturation., respectively [39].

Pulmonary hypertension may occur in LAM and is currently classified as group III PH, typically associated with a pre-capillary pattern [35,36]. Freitas et al. assessed the prevalence and characteristics of PH in 105 patients with LAM [36]. Patients with pulmonary artery systolic pressure (PASP) >35 mmHg on transthoracic echocardiography or DLCO < 40% were further evaluated with right heart catheterization (RHC). PH was confirmed by RHC in 8 (7.6%) patients, the majority with mild PH, with 5.7% exhibiting a pre-capillary pattern and 1.9% a post-capillary profile. Patients with PH had lower FEV_1 and DLCO, reduced exercise capacity, greater oxygen desaturation, and higher dyspnea intensity during the 6MWT compared with the non-PH group [36]. Another study performed by Taveira-DaSilva et al. evaluated 95 from an initial sample of 120 patients with echocardiography and identified elevated PASP at rest in fewer than 10%, with only mild increases in PASP [37]. All patients underwent exercise testing, with a peak VO_2 of 56% of the predicted. A decline in arterial oxygen saturation (SaO_2) greater than 3% was observed in 61 (64%) patients, and 56 (59%) presented a peak PASP over 40 mmHg. This study reinforces the low prevalence and severity of PH at rest in LAM. However, PH during exercise was common and associated with hypoxemia [37].

Exercise-induced PH may occur in LAM, even in the absence of resting PH. Sonaglioni et al. assessed hemodynamic responses using echocardiography during CPET in LAM [40]. Fifteen patients without resting PH were compared with 15 control subjects. Patients with LAM demonstrated a higher mean pulmonary artery pressure (mPAP) (18.4 ± 4.4 vs. 14.3 ± 2.4 mmHg; $p = 0.001$) and pulmonary vascular resistance (PVR) (154.1 ± 25.7 vs. 121.0 ± 13.4 dyn·s·cm^{-5}; $p = 0.001$). During exercise, patients with LAM exhibited echocardiographic evidence of right ventricular overload, right ventricular systolic dysfunction, and significant increases in mPAP (14.4 ± 6.5 vs. 4.2 ± 3.1 mmHg; $p < 0.0001$), PVR ($+68.3 \pm 42.1$ vs. -0.1 ± 18.3 dyn·s·cm^{-5}; $p < 0.0001$), and pulmonary capillary wedge pressure ($+8.3 \pm 5.3$ vs. 0.5 ± 1.3 mmHg; $p < 0.0001$). These patients also exhibited reduced exercise capacity, a rapid decline in SaO_2, and increased right ventricular diastolic dimensions in CPET. These findings suggest two potential mechanisms underlying mPAP elevation: an exercise-induced rise in PVR (pre-capillary component) and an increase in PCWP (post-capillary component likely driven by diastolic dysfunction) [40]. Zafar et al. assessed nine patients with LAM with echocardiography and found that four presented results consistent with intrapulmonary arteriovenous shunts (IPAVS) at rest and during exercise, whereas 1 showed IPAVS only during recovery from exercise [41]. These pulmonary vasculopathy abnormalities also potentially contribute to dyspnea and exercise limitation in LAM [41].

In summary, studies that assessed patients with LAM during exercise demonstrated a high prevalence of decreased peak VO_2, reaching up to 75% in one of them. Although several of these studies demonstrated a correlation between reduced exercise capacity and the severity of pulmonary parenchyma involvement, it did not occur in all patients. Therefore, it is relevant to emphasize that exercise limitation may occur even in those with normal or mild abnormalities on PFTs. Multiple mechanisms, isolatedly or in combination, may determine reduced exercise capacity in LAM, such as ventilatory limitation, including DH, inefficient gas exchange, cardiovascular abnormalities, PH, and IPAVS, which is presented in Figure 3. Although PH is uncommon at rest, it may be a contributor to exercise limitation and could have a pre- and a post-capillary component. However, it is not simple to determine the contribution of each mechanism described above to the reduction of exercise capacity, which strengthens the importance of a comprehensive evaluation to guide management in LAM.

5. Pulmonary langerhans cell histiocytosis

Langerhans cell histiocytosis (LCH) is a rare multisystemic hematological disease of unknown origin, characterized by infiltration of Langerhans cells into the tissues. Pulmonary

involvement in LCH most commonly occurs as an isolated disease. Even in the manifestation called single-system pulmonary LCH (PLCH), which presents a robust epidemiological association with smoking, the clonal component is recognized and corroborated by MAPK pathway alterations and BRAF-V600E mutations [42,43].

Pathologically, cyst formation occurs by accumulation of CD1a + cells and loosely formed granulomas, with a predominant bronchiolocentric inflammation [15,43]. Up to 70% of patients present with respiratory symptoms, most commonly dyspnea, cough, and reduced exercise tolerance [13,14,42]. Pneumothorax occurs in 10–15% of cases [44].

The diagnosis of PLCH is made through the combination of symptoms in a patient with a history of smoking, which occurs in more than 90% of cases, and compatible findings on high-resolution computed tomography (HRCT) [13,44]. The typical HRCT pattern demonstrates small nodules that cavitate and form irregular cysts that vary in size and wall thickness. The abnormalities predominate in the middle and upper lung lobes and spare subpleural spaces (Figures 2C and D). In less typical cases, bronchoalveolar lavage, transbronchial or surgical lung biopsy, or even a biopsy of an extrapulmonary site, such as bone or skin, may be necessary to confirm the diagnosis [13,45].

6. Mechanisms of exercise limitation in pulmonary langerhans cell histiocytosis

Dyspnea and exercise limitation are common in patients with PLCH, more often with mild or moderate severity (modified Medical Research Council, mMRC ≤ 2), and definitely impair quality of life [13,14]. These manifestations can be partially explained by impaired PFTs, such as an obstructive pattern that occurs in 26% to 77% of patients, which depends on the severity of those included in each study. Reduced DLCO occurs in around 80% of patients, whereas a restrictive pattern is found less frequently (6–52%). Air trapping occurs in up to a third of cases in PLCH, and only 15% of patients present normal PFTs [13,15,44].

Exercise capacity is reduced in the majority of patients with PLCH. Table 2 presents the studies that assessed exercise capacity and the mechanisms of exercise limitation in PLCH. The first study that evaluated CPET in patients with PLCH was published by Crausman et al. in 1996, who found that 80% of 23 participants had reduced peak VO_2 (44 ± 3% of predicted) [15]. Rolland-Debord et al. and Heiden et al., in more recent studies, found reduced exercise capacity in 77% of 62 patients (peak VO_2 of 74 ± 18% of predicted) and 71% of 34 patients (peak VO_2 of 73 ± 19% of predicted), respectively [13,14]. Reduced exercise capacity is multifactorial in PLCH in most patients, with a prevalence above 70% of cases. Gas exchange impairment is the most prevalent mechanism of exercise limitation, according to three studies in PLCH [13–15].

The ventilatory limitation was a relevant mechanism of reduced exercise capacity in two studies [13,14]. Heiden et al. found ventilatory limitation in 88% of cases, including 68% that presented DH [13]. Rolland-Debord et al. found lower ventilatory reserve in patients with reduced VO_2 compared to those with preserved exercise capacity (25% *vs.* 37%) and a strong correlation between peak VO_2 and FEV_1 [13,14]. It is of note that the high prevalence of DH sometimes leads to early interruption of exercise due to dyspnea and may also worsen PH [13,46].

Cardiac involvement is a known cause of dyspnea in DCLDs and occurs in two-thirds of patients. It can be assessed in CPET through some variables. The oxygen pulse (VO_2/heart rate) and its curve pattern are indicators indirectly related to cardiac stroke volume behavior. An end-tidal CO_2 tension ($PETCO_2$) less than 40 mmHg at the AT may suggest underlying pulmonary vascular disease, and a higher probability of PH is greater when this variable is below 20 mmHg. The physiologic Vd/Vt and VE/VCO_2 slope reflect the ventilation efficiency, and higher values of both (VE/VCO_2 slope above 34) are predictive of pulmonary vascular dysfunction [13,47].

Crausman et al. found a peak oxygen pulse of 56 ± 3% of the predicted and a correlation of higher Vd/Vt ratio and total lung capacity (TLC) with reduced exercise capacity [15]. Heiden et al. found a VE/VCO_2 slope of 31 and $PETCO_2$ at AT of 34 mmHg in 35 patients with PLCH, but these variables were not correlated with peak VO_2, probably because they have a lower accuracy in predicting ventilatory efficiency in those with parenchymal lung disease like PLCH [13].

Table 2. Summary of the main studies that evaluated the mechanisms of exercise limitation in pulmonary langerhans cell histiocytosis.

First author, year (reference)	Subjects (n)	Details	Main results
Heiden, 2020 [13]	35	Age 47 ± 11 years FEV_1 64 ± 22% pred DLCO 56 ± 21% pred Distance (6MWT) 455 ± 101 m; 116%pred (106–135) VO_2 max 63 ± 13 % pred	*Reduced exercise capacity in 71% of patients *Exercise limitation was multifactorial in 71% of patients including ventilatory (88%) and cardiocirculatory (67%) limitations, impairment suggestive of PH (29%) and impaired gas exchange (88%) *DH occurred in 68% of patients *Exercise limitation associated with obstruction, air trapping and reduced DLCO *FEV_1 and DLCO were good predictors of exercise capacity
Rolland-Debord, 2017 [14]	62	Age 37 ± 10 years FEV_1 74 ± 25% pred DLCO 61 ± 19% pred VO_2 peak 74 ± 18% pred	*Reduced VO_2 in 71% of patients *Reduced VO_2 was associated with FEV_1, FEV_1/FVC, RV/TLC and DLCO *Reduced VO_2 was not associated with dyspnea intensity
Crausman, 1996 [15]	23	Age 37 ± 2 years FEV_1 76 ± 4% pred DLCO 59 ± 4% pred VO_2 peak 44 ± 3% pred	*Reduced VO_2 in 96% of patients *Reduced VO_2 was associated with FEV_1, FVC and DLCO. *Cardiocirculatory limitation was the predominant mechanism

Legends: DH: dynamic hyperinflation; DLCO: diffusion capacity for carbon monoxide; FEV_1: forced expiratory volume in the first second; VO_2 max: maximum oxygen uptake; 6MWT: six-minute walk test.

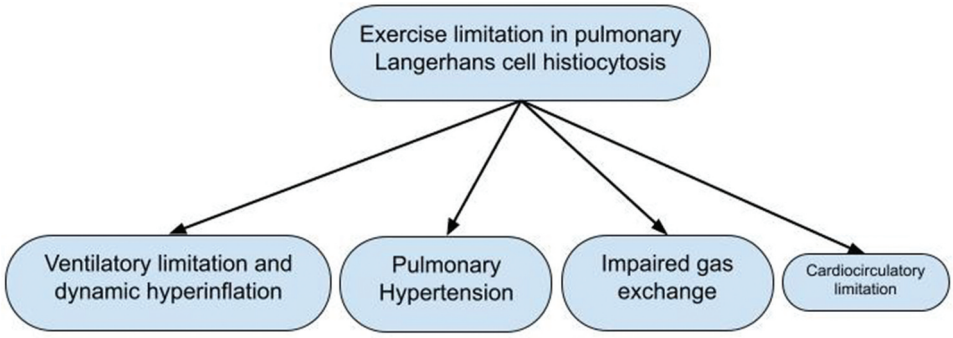

Figure 4. Mechanisms of exercise limitation in pulmonary langerhans cell histiocytosis.

Heiden et al. performed RHC in 18 patients who presented echocardiographic or functional signs suggestive of PH and found a VE/VCO_2 slope of 38 in the group with PH versus 30 in patients without PH ($p = 0.07$) [13]. The prevalence of PH was 41%, mPAP was 32 mmHg, and correlated with FEV_1 and DLCO [13]. The correlations found between cardiovascular parameters, lung volumes, and exercise capacity point to some contribution of the ventilatory component in those with PH. However, in the study of Crausman et al., the ventilatory reserve was reduced in only 21% of patients, and among those with reduced exercise capacity, the prevalence of ventilatory limitation was 23%, compared to 58% found in the study of Heiden et al [13,15]. Although Rolland-Debord et al. also found a greater ventilatory reserve than that found in the study of Heiden et al. (31% versus 13%), DH was not assessed [13,14].

Fartoukh and Dauriat performed RHC in patients with advanced PLCH (FEV_1 of 46% and pretransplantation, respectively) and found a high prevalence of PH in most cases (100% and 92%, respectively) [48,49]. All articles used the diagnostic criterion of mPAP >25 mmHg to diagnose PH, which probably underestimated the prevalence of PH according to the current criteria (mPAP >20 mmHg). PLCH is currently classified in group five of PH, which includes diseases with unclear and/or multifactorial mechanisms [50].

In summary, available data suggest that reduced exercise capacity is common and multifactorial in PLCH (Figure 4). The most prevalent mechanisms of exercise limitation are impaired gas exchange, ventilatory limitation, including DH, and cardiocirculatory limitation, including PH. Based on these findings, in addition to PFTs, echocardiography with PH assessment and CPET should be included in the evaluation of patients with PLCH who present dyspnea.

7. Field tests

Field walking tests are commonly employed to evaluate exercise capacity, prognosis, and treatment response in chronic respiratory diseases because they are simple, low-cost and valid. The 6MWT and ISWT are the most frequently used and elicit VO_2 and HR responses as high as 85–90% of the incremental exercise test [51–53]. Table 3 summarizes the main features and outcomes of field tests in LAM and PLCH.

7.1. Field tests in LAM

The 6MWT is considered a submaximal test to evaluate the functional capacity of patients with LAM, and the majority of patients reached distances above 500 meters, causing a ceiling effect [16,19,20]. Due to this effect, it cannot be used to assess maximum aerobic capacity.

Diesler et al. evaluated 62 patients with LAM (median FEV_1, DLCO, and distance walked of 83% of predicted, 58% of predicted, and 535 m/91% of predicted, respectively) [19]. The authors showed that the distance walked during the 6MWT was significantly and positively correlated with FVC, FEV_1, TLC, and DLCO (in %predicted) and negatively associated with residual volume (RV)/TLC ratio (correlation coefficients 0.43, 0.30, 0.34, 0.28 and −0.27 respectively, $p < 0.05$). Pulse oximetry desaturation during the 6MWT significantly correlated with FEV_1, DLCO, and FEV_1/FVC ratio (correlation coefficients 0.42, 0.75, and 0.49, respectively, $p < 0.05$). There was also a significant correlation between the distance-saturation product (distance walked multiplied by the lowest saturation during the 6MWT) and pulmonary function variables [19].

In the study of Yoon et al., 104 patients with LAM had FEV_1, DLCO, distance walked in the 6MWT of 77 ± 22% predicted, 63 ± 25% predicted, and 467 ± 115 m, respectively [21]. The study demonstrated that shorter distances walked during the 6MWT was an independent prognostic factor for mortality in LAM [21]. These results reinforce the association between variables of the 6MWT and of the PFTs and its relevance as a tool for evaluating the clinical status of these patients.

Although the distance walked is the primary outcome obtained in the 6MWT, other indexes incorporate desaturation during the test, such as desaturation – distance ratio (DDR) and distance-saturation product (described above). DDR is the ratio of the desaturation area to the distance walked and is associated with pulmonary function parameters and SpO_2 in patients with interstitial lung diseases (ILDs) [54]. DDR is also considered predictive of morbidity and mortality in patients with other respiratory conditions, such as chronic obstructive pulmonary disease (COPD), pulmonary arterial hypertension, idiopathic pulmonary fibrosis, LAM, and those on the waiting list for lung transplantation [20,55–57].

Queiroz et al. evaluated 40 patients with LAM (FEV_1 and DLCO of 75 ± 19% of predicted and 72 ± 21% of predicted, respectively)

Table 3. Field exercise tests in lymphangioleiomyomatosis and pulmonary Langerhans cell histiocytosis.

First author, year (reference)	Subjects (n)	Details	Main results
LAM			
Diesler, 2024 [45]	62	Age 43 (31–55) years FEV_1 83% (61–93) DLCO 59% (45–77) Distance (6MWT) 535 m (494–596)	*Distance walked (6MWT) correlated with FEV_1, RV/TLC and DLCO *Distance-saturation product correlated with FEV_1 and DLCO
Yoon, 2022 [55]	104	Age 40 ± 11 years FEV_1 77 ± 22% pred DLCO 63 ± 25% pred Distance (6MWT) 467 ± 115 m	*Distance walked (6MWT) as a prognostic factor for mortality
Queiroz, 2021 [46]	40	Age 46 ± 10 years FEV_1 75 ± 19% pred DLCO 72 ± 20% pred Distance (6MWT) 516 ± 65 m Distance (ISWT) 452 ± 139 m DDR (6MWT) 6.6 (3.8–10.9) DDR (ISWT) 8.3 (6.2–12.7)	*FEV_1, reduced DLCO and air trapping were independent predictors of DDR in the 6MWT and in the ISWT
Queiroz, 2022 [52]	45	Age 45 (38–54) years FEV_1 74 (62–88)% pred DLCO 66 (54–83)% pred Distance (6MWT) 510 m (476–564) Distance (ISWT) 429 m (330–517) VO_2 max 67 ± 15% pred	*Good correlation was observed between VO_2 peak in the ISWT and CPET *Similar results when comparing the ISWT with CPET
PLCH			
Heiden, 2020 [13]	35	Age 47 ± 11 years FEV1 64 ± 22% pred DLCO 56 ± 21% pred Distance (6MWT) 455 ± 101 m VO_2 max 63 ± 13 % pred	*VO_2 reduced in 71% of patients *Exercise limitation was multifactorial in 71% of patients including ventilatory (88%) and cardiocirculatory (67%) limitations, impairment suggestive of PH (29%) and impaired gas exchange (88%)
Le Pavec, 2012 [53]	29	PLCH with PH (83% class III/IV) Age 43 ± 9 years FEV_1 52 ± 20% pred DLCO 28 ± 8% pred Distance (6MWT) 355 ± 95 m mPAP 45 ± 14 mmHg	*No significant improvement in the distance walked after treatment of PH *Distance walked (6MWT) was not a risk factor for mortality
Paciocco, 2004 [56]	13	Age 44 ± 12 years FEV_1 89 ± 13% pred DLCO 74 ± 12% pred Distance (6MWT) 415 ± 136 m	*The extent of air trapping on HRCT was associated with the distance walked on the 6MWT

Legends:CPET: cardiopulmonary exercise test; DDR: desaturation distance ratio; DLCO: diffusion capacity for carbon monoxide; FEV1: forced expiratory volume in the first second; FVC: forced vital capacity; HR: heart rate; ISWT: incremental shuttle walking test; LAM: lymphangioleiomyomatosis; Max: maximum; mPAP: mean pulmonary artery pressure; PH: pulmonary hypertension; PLCH: Langerhans cell pulmonary histiocytosis; RER: respiratory exchange ratio; RV/TLC: residual volume/lung total capacity; TLC: total lung capacity; VO2: oxygen uptake; 6MWT: six minute walk test.

[20]. The distance walked in the 6MWT was 517 ± 64 m. The authors demonstrated that DDR obtained during the 6MWT significantly correlated with FEV_1, RV/TLC, and DLCO ($r = -0.54$, $r = 0.34$, and $r = -0.62$; respectively). Furthermore, the best multivariate association models were constructed using the variables with the best independent coefficients of determination (R^2). The derived prediction equations of DDRs during 6MWT, in a stepwise multiple linear regression model, were as follows: $18.66-(0.06\times FEV_1\%) - (0.10\times DLCO\%) + (1.54\times RV/TLC)$, R^2 adjusted = 0.43. These results demonstrate that DDR assessed in the submaximal exercise test (6MWT) is associated with pulmonary impairment, air trapping, and reduced DLCO in LAM [20].

The ISWT is a maximal exercise test conducted in an unobstructed, quiet 10-m corridor. The walking speed was determined using a standardized audio signal (beep) that started at 0.5 m/s and was progressively increased by 0.17 m/s every minute for a maximum of 20 minutes. The ISWT is terminated when the patient indicates that he cannot continue or if the operator observes that the patient cannot sustain the speed and cover the distance to the cone before the beep [58].

Two studies have evaluated ISWT in patients with LAM. In the first study, 36 (90%) patients presented oxygen desaturation during the ISWT, and the distance walked was 453 ± 139 m [20]. The DDR obtained in the ISWT had a significant correlation with FEV_1, RV/TLC, and DLCO ($r = -0.58$, $r = 0.49$, and $r = -0.62$, respectively), similar to the results obtained in the 6MWT [20]. The better multivariate association models were constructed using the variables with the best independent coefficients of determination (R^2). The derived prediction equations of DDRs during ISWT, in a stepwise multiple linear regression model, were as follows: $18.84-(0.09\times FEV_1\%)-(0.05\times DLCO\%)+(3.10\times RV/TLC)$, R^2 adjust = 0.33. These results also demonstrate that DDR assessed in the maximal exercise test (ISWT) is associated with pulmonary impairment, air trapping, and reduced DLCO in LAM [20].

Queiroz et al. evaluated 45 women with LAM (median FEV_1 and DLCO of 74% of predicted and 66% of predicted, respectively) and compared physiological responses between the CPET and ISWT, both maximal exercise tests [39]. The authors demonstrated no differences between the variables related to cardiopulmonary responses in the tests (VO_2, HR, the respiratory exchange rate, and dyspnea perception), except for a greater leg fatigue perception in the CPET. A strong linear correlation was observed between the peak VO_2 (mL/kg/min) obtained during the CPET and ISWT ($r = 0.78$). Based on the results of this study, ISWT is considered safe and determines similar responses to those of CPET in LAM [39].

7.2. Field tests in pulmonary Langerhans cell histiocytosis

Few studies used field tests to evaluate exercise capacity and desaturation during exercise in patients with PLCH, all through the 6MWT. These studies demonstrated a correlation between the distance walked with pulmonary function and CPET parameters [13,22,23]. In a cross-sectional study, Heiden et al. evaluated 35 patients with PLCH during 6MWT and CPET. FEV_1, DLCO, and distance walked in the 6MWT were 64 ± 22% predicted, 56 ± 21% predicted, and 455 ± 101 m/116% (106–135) of predicted, respectively [13]. The distance walked in the 6MWT correlated with VO_2 on the CPET ($r = 0.58$) [13].

Le Pavec et al. evaluated 29 patients with PLCH with PH, 83% of whom were World Health Organization functional class III to IV. FEV_1 and DLCO were 52 ± 20% predicted and 28 ± 8% of predicted, respectively [22]. The distance walked in the 6MWT was 355 ± 95 m, and this variable was not a risk factor for mortality. Additionally, there was no significant improvement in the distance walked after treatment of PH [22]. Paciocco et al. assessed 25 patients with DCLDs, 13 with PLCH, and showed that the extent of air-trapping on HRCT was significantly associated with the distance walked in the 6MWT ($r = -0.53$) [23].

7.3. Safety issues

The performance of PFTs and exercise testing are usually safe in patients with DCLD. A retrospective study that evaluated 691 patients with LAM between 1995 and 2015 showed that the incidence of pneumothorax during PFTs and exercise testing was low and occurred in only 0.5 percent [59]. In the studies described above that evaluated patients with DCLD, there was no description of pneumothorax during field tests [13,16,19–23,39,55].

8. Exercise and pulmonary rehabilitation

Quasi-randomized and non-randomized studies, and case reports regarding the impact and safety of exercise and PR in LAM were previously published [18,24,25,60–64]. However, to the best of our knowledge, only a case report was published about such an issue in PLCH [65]. Table 4 presents a summary of the main studies that evaluated the impact of exercise and PR in LAM and PLCH.

Exertional dyspnea is perceived as a prominent symptom in patients with LAM, and it is present with activities ranging from low-energy-demand-activities, like washing hair, to high-energy-demand-activities, like walking up inclines [66]. Because of that, patients with ILDs, including LAM, may have unique risks for adverse health events during exercise training outside of a medically supervised setting. Traditionally, patients with ILDs have been referred to supervised, center-based PR programs for the availability of supplemental oxygen, assistance with oxygen titration, and direct supervision during exercise. PR is a standard practice for patients with chronic lung diseases because it can reduce dyspnea, increase exercise capacity, and improve quality of life [67–70]. A quasi-randomized controlled clinical trial submitted 37 patients with LAM ($FEV_1 = 72 \pm 28\%$ of predicted) and examined the effects of PR [18]. The PR program was performed twice weekly for one hour of aerobic exercise (treadmill), muscle strength training, and education for 3 months. The PR group improved exercise endurance time, quality of life, six-minute walking distance (6MWD), and peak VO_2. Interestingly, this was the first intervention for LAM that induced clinically relevant changes in the Saint George Respiratory Questionnaire (SGRQ). Although the study of Araujo and coworkers did not observe a difference in anxiety symptoms, it was also the first intervention to demonstrate a trend toward a reduction in symptoms of depression in LAM [18].

However, center-based programs may not be as accessible as home-based programs and may not be preferred by all patients with LAM. In addition, LAM usually occurs in women during their productive lives, who may have difficulties to participate in PR programs and favoring a greater adherence to home-based activities. Previous studies demonstrated that home-based PR programs are feasible, safe and effective in patients with ILD, which reinforces its potential benefits in LAM [71,72]. A 12-week remote monitoring-enabled and home-based exercise program was applied in 15 patients with LAM ($FEV_1 = 67 \pm 20\%$ of predicted) who had oxygen desaturation during exercise, consisting of continuously recording SpO_2 and aerobic and strength training components [63]. The authors demonstrated improvements in 6MWD, exercise capacity, muscular endurance, and fatigue. There were no adverse events [63]. Additionally, a very recent Delphi study questioned experts in LAM about their opinion that exercise preparticipation screening steps determine whether

Table 4. Summary of the main studies and case reports that evaluated the impact of exercise and pulmonary rehabilitation in lymphangioleiomyomatosis and pulmonary Langerhans cell histiocytosis.

First author, year (reference)	Subjects (n)	Details	Main results
Araujo, 2016 [18]	37	*Aerobic exercise, muscle strength training and education for 12 weeks (*vs.* controls) *Age 43 ± 10 years *FEV_1 72 ± 28% pred *DLCO 65 ± 31% pred *6MWD 517 (445–557) *Peak VO_2 72 ± 23% pred	*Improvements in: Endurance time: 169 s (2–303) 6MWD: 59 m (13–81) Dyspnea : −2 (−4–0) SGRQ Daily physical activity Muscle strength Depression symptoms
Li, 2020 [33]	26	*Yoga for 24 weeks (*vs.* controls) *Age 40 ± 9 years *FEV_1 72 ± 22% pred *6MWD 550 ± 54 m *Peak VO_2 15.4 ± 3.3 (mL/min/kg)	*Improvements in: 6MWD: + 55 *vs* +18 m AT: 3.4 *vs* 1.6 mL/min/kg Peak work load: 11.7 *vs* 0.2 W *No differences in peak VO_2
Gloeckl, 2020 [36]	58	*Pulmonary rehabilitation in LAM *vs* COPD *Age 48 ± 10 years *FEV_1 46 ± 24 % pred *DLCO 41 ± 18 % pred *6MWD 338 ± 167 m	*Compared to COPD, LAM showed improvements in: 6MWD +49 ± 50 m Quality of life
Lowder, 2020 [37]	1	*Supervised high-intensity exercise (two weekly sessions, one year) *Age 29 years *FEV_1 2.53 L *Peak flow 3.71 L Peak VO_2 29.4 ml/kg/min	*After one year, improvements in: FEV_1 2.76 (+9.5%) Peak flow 5.45 (+47%) Peak VO_2 35.34 (+20%)
Child, 2023 [35]	15	*Home-based exercise program for 12 weeks (remote aerobic and strength training, and monitoring) *Age 49 ± 7.8 *FEV_1 67 ± 20% pred *6MWD 539 ± 65 m *Peak VO_2 92 ± 30% pred	*Improvements in: 6MWD +36 ± 34 m CPET time Muscular endurance Quality of life Fatigue
Fukuda, 2014 [39]	1	Cardiac rehabilitation and bosentan in PLHC with PH (6 months) * Age 36 years *PAPm 40 mmHg *BMI 31 kg/m^2	*Improvements in: Cardiothoracic ratio 43 → 38% (X-ray) BNP 284 → 10 pg/ml Body weight 63 → 58 kg 6MWD 214 → 275 m Quality of life

Legends: AT: anaerobic threshold; BMI: body mass index; BNP: brain natriuretic peptide; COPD: chronic obstructive pulmonary disease; CPET: cardiopulmonary exercise test; DLCO: diffusion capacity for carbon monoxide; FEV_1: forced expiratory volume in the first second; LAM: lymphangioleiomyomatosis; PAPm: mean pulmonary artery pressure; PH: pulmonary hypertension; PLCH: pulmonary Langerhans cell histiocytosis; SGRQ: Saint George Respiratory Questionnaire; VO_2 max: maximum oxygen uptake; 6MWD: six-minute walking distance.

a patient with LAM is medically appropriate to participate in a remote, unsupervised exercise program [60]. Three recommendations were suggested. First, an in-person clinical exercise test is indicated to screen for exercise-induced hypoxemia and prescribe supplemental oxygen therapy as needed before initiating a remote exercise program. Second, patients with a recent pneumothorax should wait to start an exercise program for at least four weeks after its resolution and clearance by a physician. Third, patients with high risk for cardiovascular events during exercise, severe resting PH, or risk for falls may be more appropriate for referral to exercise under supervision in a rehabilitation center. Based on that, the authors launched the 'LAMFit,' a home-based, self-monitored exercise program, which planned to incorporate target HR-guided aerobic exercise, resistance training, daily activity goal setting, reminder messaging, and LAM-specific social connection [60].

Yoga has also been considered a potential attractive alternative for PR in LAM. The current evidence suggests that yoga training may improve exercise capacity in patients with LAM [61]. Twenty-six participants were allocated to the yoga or control group ($n = 13$ each) [61]. Despite their frailty, patients diagnosed with LAM could perform yoga. The yoga intervention lasted 24 weeks, 90 minutes once a week, and there were no fewer than two at-home sessions per week (15 minutes per session). Yoga combines physical postures, breathing techniques, and meditation, and is known for its benefits in improving flexibility, muscle strength, respiratory function, and mental well-being. In the study in LAM, the yoga group exhibited improvements in the 6MWD (+55 ± 29 m vs + 18 ± 49 m, $p = 0.04$), anaerobic threshold (3.4 ± 2.4 mL/min/kg vs 1.6 ± 1.4 mL/min/kg, $p = 0.035$) and peak work load (11.7 ± 14.6 W vs 0.2 ± 9.1 W, $p = 0.027$).Moreover, the authors suggested that yoga could be a useful adjunct to the PR program in LAM; however, a larger-scale trial with extended follow-up periods should be conducted to evaluate the long-term effects of yoga training [61].

Gloeckl et al. evaluated retrospectively 58 patients with LAM ($FEV_1 = 46 ± 25\%$ of predicted) during a 4-week inpatient PR program [24]. The authors demonstrated a significant increase in the 6MWD (49 ± 50 m) and an improvement in quality of life, similar to the benefits observed in a COPD cohort [24]. A report by Lowder demonstrated favorable results on VO_2 max and pulmonary function variables after one year of supervised aerobic and resistance exercise training in a patient with TSC-LAM [25]. A systematic review reinforced the beneficial effects of physiotherapy intervention, including aerobic and

Figure 5. Proposed comprehensive pulmonary rehabilitation for patients with LAM.
Legend: HRQL: health related quality of life.

resistance training, in LAM [64]. This review demonstrated that physiotherapy intervention can improve exercise capacity and quality of life to reduce dyspnea and symptoms of depression [64]. Furthermore, patients with DCLD and exercise limitation should be monitored for signs of PH, such as lower limb edema, hypoxemia, worsening dyspnea, and tachyarrhythmias.

In summary, we consider that PR should be offered for all patients with LAM who have reduced exercise capacity, from mild to severe disease, and it is essential to have a medical indication and follow-up. Figure 5 presents a proposal for a comprehensive PR approach for patients with LAM. Despite the scant evidence, due to the lack of wide availability of PR centers, it is recommended to encourage the practice of physical activity, even outside of a formal PR, for patients who, after a comprehensive medical evaluation, do not present severe functional impairment, exercise desaturation, significant cardiovascular risk or risk of falling [26].

No consistent studies have evaluated the impact and safety of PR in patients with PLCH. To our knowledge, only one case report was published and demonstrated that rehabilitation combined with bosentan determined improvement in the 6MWD and in symptoms of depression [65].

8.1. Safety issues

Consensus recommendations were developed as guidance for exercise preparticipation screening in LAM to determine medical appropriateness to participate in a remote, unsupervised exercise program. In the experts' opinion, three features were considered the most important to be assessed: dyspnea on exertion, oxygen desaturation, and impaired health-related quality of life (HRQL). Additionally, it is essential to determine the safety of the procedure. No cases of pneumothorax or other serious events occurred during exercise, even in home-based programs [18,24,63], suggesting that PR should be employed in dyspneic patients with LAM, proving its safety. The Yoga exercise is also quite safe; no pneumothorax or other serious adverse events related to yoga exercise were reported during the study [61].

On the other hand, further studies are needed to establish the efficacy, safety, and feasibility of performing PR in patients with PLCH, especially considering the greater risk of developing significant PH during exercise.

9. Conclusion

Studies that assessed patients with DLCD during exercise focused on LAM and PLCH. Exercise limitation is very prevalent and multifactorial in LAM and PLCH and may occur even in those with normal PFTs, reinforcing the essential role of exercise tests in demonstrating abnormalities that do not appear in the exams performed at rest. The mechanisms potentially responsible for reduced exercise capacity in LAM and PLCH are ventilatory, cardiocirculatory, and peripheral limitations, DH, PH, and impaired gas exchange, which may occur isolatedly or in combination.

Field tests, such as 6MWT and ISWT, are safe and may be used and further explored to assess exercise capacity in these diseases, mainly in LAM, demonstrating correlation with PFTs and CPET parameters. Exercise and PR may be considered for patients with LAM and prescribed on a case-by-case basis.

Several issues related to the topic need to be investigated, as follows: the mechanisms of exercise limitation in other DCLD; the impact of PR in PLCH and in the long-term in LAM, including

home-based programs; and the impact of therapeutic interventions, such as oxygen supplementation, vasodilators, and bronchodilators and noninvasive positive pressure ventilation, for those with hypoxemia, exercise-induced PH and DH, respectively, to improve dyspnea and exercise tolerance.

10. Expert opinion

Several developments have been made to improve the knowledge of DCLD in the last decades, mainly in LAM and PLCH, in different issues, such as pathogenesis, genetics, diagnosis, treatment and prognosis. This review manuscript presents details regarding the exercise capacity and mechanisms responsible for exercise limitation in patients with LAM and PLCH, based on studies published in the last years. Furthermore, this article highlights details about the behavior of patients with LAM and PLCH in field tests and the benefits and safety of PR in LAM. However, evidence is partially established regarding these topics, and several questions need to be answered in LAM, PLCH, and other DCLDs.

Studies are needed to evaluate exercise capacity and mechanisms of exercise limitation in patients with other DCLDs in addition to LAM and PLCH. We speculate that the mechanisms of exercise limitation in these other DCLDs are quite similar to LAM, but studies are necessary to prove this hypothesis.

Further studies should also aim to assess RHC during exercise in LAM and PLCH to determine more precisely the occurrence of exercise-induced PH and IPAVS in those with a suspicion of PH. This investigation may impact the development of treatment modalities, such as vasodilators, for patients who present exercise-induced PH to improve exercise capacity and quality of life and reduce dyspnea. There is still a lack of interventions to attenuate DH and improve dyspnea and exercise tolerance. Then, future research should investigate the role of therapeutic modalities, such as bronchodilators and noninvasive positive pressure ventilation, on DH.

Additionally, we consider it is essential to increase the number of studies assessing the benefits and safety of PR in patients with DCLDs. Although previous robust studies regarding PR in LAM were published, future studies are needed to determine the effectiveness of this intervention in the long term. In addition, no consistent study evaluated PR in PLCH; future research is essential to assess the impact and safety of this procedure. Another potential topic regarding DCLDs, mainly LAM and PLCH, is the importance of expanding studies with home-based PR programs to assess their efficacy, feasibility, and safety.

Another potential area of study is to evaluate routinely the occurrence of hypoxemia at exercise in patients with DCLDs. In this context, additional research is encouraged to determine the benefits of oxygen supplementation on exercise capacity, dyspnea, and quality of life in those who develop hypoxemia.

Further research is warranted to assess the relevance of variables obtained in submaximal and maximal field tests, including DDR, on prognostic assessment, severity, and treatment response in LAM and PLCH.

Therefore, although progression has been obtained regarding exercise in LAM and PLCH in the last decades, many potential unexplored areas should be assessed, which will certainly contribute to a better understanding of these topics, including those related to other DCLDs, and to the management of patients.

Abbreviations

AT	anaerobic threshold
BNP	brain natriuretic peptide
COPD	chronic obstructive pulmonary disease
CPET	cardiopulmonary exercise test
CT	computed tomography
DCLD	diffuse cystic lung disease
DDR	desaturation-distance ratio
DH	dynamic hyperinflation
DLCO	diffusion capacity for carbon monoxide
FEV_1	forced expiratory volume in the first second
FVC	forced vital capacity
HR	heart rate
HRCT	high-resolution computed tomography
HRQL	health-related quality of life
IC	inspiratory capacity
ILD	interstitial lung disease
IPAVS	Intrapulmonary arteriovenous shunts
ISWT	incremental shuttle walk test
LAM	lymphangioleiomyomatosis
LCH	Langerhans cell histiocytosis
Max	maximum
mMRC	modified Medical Research Council
mPAP	mean pulmonary artery pressure
mTOR	mechanistic target of rapamycin
MVV	maximal voluntary ventilation
PASP	pulmonary artery systolic pressure
$PETCO_2$	end-tidal CO_2 tension
PFT	pulmonary function test
PH	pulmonary hypertension
PLCH	pulmonary Langerhans cell histiocytosis
PR	pulmonary rehabilitation
PVR	pulmonary vascular resistance
RHC	right heart catheterization
RV	residual volume
SaO_2	arterial oxygen saturation
SGaw	specific airway conductance
SGRQ	Saint George Respiratory Questionnaire
SpO_2	peripheral oxygen saturation
S-LAM	sporadic lymphangioleiomyomatosis
TSC	tuberous sclerosis complex
TSC-LAM	tuberous sclerosis complex-lymphangioleiomyomatosis
VCO_2	carbon dioxide production
VE max	maximal minute ventilation
VE	minute ventilation
VEGF-D	vascular endothelial growth factor D
VE	minute ventilation
VE/VCO_2	ratio of minute ventilation to carbon dioxide production
Vd/Vt	dead space to tidal volume ratio
VO_2	oxygen uptake
6MWD	six-minute walking distance
6MWT	six-minute walk test

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