Reduced physical activity in lymphangioleiomyomatosis compared with COPD and healthy controls: disease-specific impact and clinical correlates

Abstract

Rationale Sporadic lymphangioleiomyomatosis (LAM) is an orphan lung disease for which daily physical activity has not been studied so far and it is unclear whether a disease-specific impact beyond airflow limitation exists. Clinical correlates indicating reduced physical activity in addition to established parameters like airflow limitation and hypoxaemia are largely undetermined.

Method We measured physical activity (steps per day, SPD; physical activity level, PAL; minutes of moderate activity, MMA) in 34 women with LAM, 32 FEV₁-matched female patients with COPD and 15 age-matched healthy women for 1 week using an accelerometer. In addition, we assessed lung function measurements, questionnaires for generic and respiratory health status (12-Item Short Form Survey, SF-12; St. George's Respiratory Questionnaire, SGRQ), dyspnoea (modified Medical Research Council dyspnoea scale, mMRC) and fatigue (Multidimensional Fatigue Inventory, MFI-20).

Results Patients with LAM (mean age 52.7 years, mean FEV₁ 62.7% predicted) showed reduced SPD, PAL and MMA ($p<0.01$) compared with healthy controls and reduced MMA ($p=0.032$) compared with female patients with COPD (mean age 65.2 years, mean FEV₁ 62.6% predicted). In multivariate regression analyses, adjusting for FEV₁ and long-term oxygen therapy, either generic health status (SF-12 physical health) or fatigue (MFI-20) were the strongest independent predictors for SPD in patients with LAM ($p=0.006$ and $p=0.004$, respectively).

Conclusions Physical activity in daily life is

substantially reduced in LAM, when compared with healthy controls and COPD - indicating a disease specific impact. The regular assessment of fatigue and generic health status may improve disease management in LAM by taking daily physical activity of patients with LAM more adequately into account.

Sporadic lymphangioleiomyomatosis (LAM) is a rare lung disease that affects almost exclusively women. It is characterised by cyst formation leading to airflow limitation, ventilatory limitations and gas exchange impairment, resulting in dyspnoea and exercise intolerance.¹ Daily physical activity is an important clinical outcome parameter in common lung diseases, such as COPD.² However, rare lung diseases such as LAM have not been studied so far and a disease-specific contribution to daily physical activity beyond airflow limitation is uncertain. In LAM, fatigue is a highly prevalent feature that has been overlooked in the past³ and that might be associated with levels of daily physical activity in this debilitating disease, just like health status and dyspnoea. Here, we hypothesised that physical activity in patients with LAM is substantially lower than in healthy controls but comparable with patients with COPD. In addition, we hypothesised that clinical variables other than airflow limitation and hypoxaemia might be associated with physical activity in patients with LAM.

We measured physical activity in 34 female patients with LAM, 32 female patients with COPD and 15 healthy women for 1 week using an activity monitor (SenseWear Armband; BodyMedia, Pittsburgh, USA) measuring steps per day (SPD), physical activity level (PAL) and minutes of at least moderate activity per day (MMA), as previously

described.² We recruited patients with LAM (mean age 52.7 years, mean FEV₁ 62.6% predicted, long-term oxygen therapy (LTOT): $n=12$ (35%)) during the annual meeting of the German LAM patient group. Patients with COPD (mean age 65.2 years, mean FEV₁ 62.7% predicted, LTOT: $n=6$ (19%)) were derived from an existing cohort⁴ and matched for FEV₁ and body mass index (BMI). Dyspnoea and health status were similar between groups. Healthy controls were recruited from our institutional database⁵ and matched for age and BMI (see online supplementary table E1 for detailed characteristics). All participants provided written informed consent (ethics approval AZ 038/12 II/AZ 185/08; German Clinical Trials Register Number DRKS00006170). Lung function parameters of patients with LAM were taken from the last available lung function report. Participants filled out questionnaires for generic and respiratory health status (12-Item Short Form Survey, SF-12; St. George's Respiratory Questionnaire, SGRQ), dyspnoea (modified Medical Research Council dyspnoea scale, mMRC) and fatigue (Multidimensional Fatigue Inventory, MFI-20⁶) at home and sent them back together with the activity monitors at the end of the measurement.

Compared with healthy controls, each of the three physical activity parameters (SPD, PAL and MMA) was significantly reduced in patients with LAM (figure 1). Unadjusted comparison between patients with LAM and COPD showed reduced MMA in LAM (figure 1), despite the significant age difference and equal dyspnoea and health status scores. Adjusted for age and LTOT as possible confounders, multivariate regression analyses showed significantly lower MMA and PAL in patients with LAM compared with COPD ($p=0.006$ and $p=0.005$, respectively),

Figure 1 Physical activity of patients with lymphangioleiomyomatosis (LAM) (bright bar) compared with patients with COPD (light grey) and healthy controls (dark grey) expressed as mean ± SE. (A) Number of steps per day (5852 ± 3327 vs 6616 ± 3351 vs 8863 ± 1884; reduction by 12% vs 34%; $p=0.360$ and $p=0.002$, respectively). (B) Daily physical activity level (1.45 ± 0.21 vs 1.54 ± 0.26 vs 1.66 ± 0.22; reduction by 24% vs 32%; $p=0.087$ and $p=0.002$, respectively). (C) Log transformed minutes of at least moderate activity per day (corresponding medians (IQR) were 61 (26–147) vs 107 (46–78) vs 153 (97–207); reduction of the median by 43% vs 60%; $p=0.032$ and $p=0.006$, respectively).

whereas SPD were not significantly lower ($p=0.152$) (online supplementary table E2). A potential explanation for this observation might be that patients with LAM walk at lower intensities compared with patients with COPD.

Airflow limitation, health status, dyspnoea and fatigue scores correlated best with SPD as outcome variable (online supplementary table E3). In multivariate regression analyses, adjusting for LTOT and FEV₁, either SF-12 physical health or MFI-20 were the strongest independent predictors for SPD in patients with LAM (total $R^2=0.476$, partial $R^2=0.178$, $p=0.006$ and total $R^2=0.449$, partial $R^2=0.207$, $p=0.004$, respectively) (online supplementary table E4).

Measures on exercise capacity (eg, 6 min walking test) and associated hypoxaemia might explain further variance in the data. The lack of these measurements is a clear limitation of our study.

We show for the first time that physical activity in daily life is substantially reduced in LAM patients, when compared with healthy controls and COPD patients with similar functional limitation, dyspnoea and health status—indicating a disease-specific impact. The underlying processes, however, are to be elucidated in further studies. Although airflow limitation and hypoxaemia—as indicated by FEV₁ and LTOT—are well-established predictors for impaired physical activity, we propose to include fatigue and generic health status into the standard clinical assessment of patients with LAM. Awareness and measurement of both features will help to

improve adequate disease management in this debilitating disease.

Thomas Bahmer,¹ Henrik Watz,² Benjamin Waschki,¹ Marco Gramm,² Helgo Magnussen,² Klaus F Rabe,¹ Hubert Wirtz,³ Detlef Kirsten,¹ Anne Kirsten²

¹LungenClinic Grosshansdorf, Airway Research Center North, Member of the German Center for Lung Research, Grosshansdorf, Germany

²Pulmonary Research Institute at LungenClinic Grosshansdorf, Airway Research Center North, Member of the German Center for Lung Research, Grosshansdorf, Germany

³Pneumology Department, Universitätsklinikum Leipzig AöR, Leipzig, Germany

Correspondence to Thomas Bahmer, LungenClinic Grosshansdorf, Woehrendamm 80, 22927 Grosshansdorf, Germany; t.bahmer@lungenclinic.de

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