Diurnal variation in forced vital capacity in patients with fibrotic interstitial lung disease using home spirometry

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INTRODUCTION

Forced vital capacity (FVC) is used as the routine physiological measure to assess disease progression in fibrotic interstitial lung diseases (f-ILDs) (1). New drugs are currently being investigated on top of "standard care" with anti-fibrotic drugs in idiopathic pulmonary fibrosis (IPF) and other f-ILD, resulting in small margins of change in FVC (2, 3). Recently, the first trial with antifibrotic medication in patients with systemic-sclerosis associated ILD has shown a numerically small but significant lower annualized rate of FVC decline (41 mL) in patients treated with nintedanib compared with placebo (3).

Data regarding a possible circadian rhythm in pulmonary function are contradictory (4-6). Diurnal variation has never been investigated in f-ILD, but could have implications for the interpretation and design of clinical trials and for monitoring in daily practice. Taking advantage of new eHealth technologies (7, 8), we aimed to assess whether there is a diurnal variation in FVC in patients with f-ILD using home spirometry. Furthermore, we evaluated whether there was a relation between FVC and activity as we hypothesized that exercise just before the measurement may affect FVC values.

METHODS

Between December 2018 and May 2019 consecutive outpatients with f-ILD were invited to participate in this prospective single center observational study for six weeks. Medical ethical committee approval was obtained and all patients provided written informed consent. Our previously developed and validated home monitoring program was used for home-based measurements (7). Patients measured FVC twice daily with a handheld spirometer (Spirobank Smart; MIR, Rome, Italy); once in the morning and once in the afternoon. FVC measurements were excluded if only one measurement was available for that day, if the morning FVC measurement was before 6 AM, or if difference from baseline FVC was >20%. In addition, steps were continuously counted using an activity tracker (Flex 2; FitBit, San Francisco, CA, USA) in blocks of 15 minutes, to assess activity during one hour before FVC measurement. At baseline and after six weeks, patients completed the King's Brief Interstitial Lung Disease questionnaire (K-BILD) online (9). In-hospital spirometry was performed at start of the study, and patients received standardized instructions about the home monitoring program. Linear mixed models were used to evaluate differences between morning and afternoon measurements. Pearson correlation coefficient was used to assess correlations between study parameters (R version 3.5.2). We estimated that between 4 and 50 patients would be needed to determine a significant difference between morning and afternoon FVC with a power of 90%, as-

suming a total variance of 0.026L and between-patient standard deviation of 0.006-0.1L, based on pilot data.

RESULTS

Of 57 invited patients, 50 patients consented to participate. Median age of patients was 68 (43-79) years and 68% were male; 50% of patients had IPF, 18% chronic hypersensitivity pneumonitis, and 12% non-specific interstitial pneumonia. Other diagnoses were combined pulmonary fibrosis and emphysema (n=4), fibrotic sarcoidosis (n=3), unclassifiable fibrosis (n=1), pleuroparenchymal fibroelastosis (n=1) and ANCA associated vasculitis with fibrosis (n=1). Median FVC was 3.0 L (range 1.5-5.2) or 76% of predicted (range 46-119), median FEV1 2.4L (range 1.4-4.0) or 82% of predicted (range 50-114), and diffusion capacity of the lung for carbon monoxide (DLCO) 50% (range 16-110). Mean±SD K-BILD total score at baseline was 57.4±11 and breathlessness and activity domain score was 45.3±18.

Home-based FVC measurements were available for 44 patients; 1 patient withdrew consent and 5 patients did not manage to perform consistent measurements due to cough or bad technique. In total, 2842 FVCs were analyzed. Activity measurements of 37 patients were analyzed; three patients did not manage to send their activity data due to technical problems. Additionally, data of patients who did not wear their activity tracker before the morning measurement were excluded.

Morning FVC was significantly higher than afternoon FVC (mean difference 36 ml, $p<0.001$). The mean difference between morning and afternoon FVC was similar for patients with IPF compared with all f-ILDs. In 33 out of 44 patients, morning FVC was numerically higher than afternoon FVC (**Figure 1a**). Mean±SD difference in FVC% predicted was 1.2±1.0%. Coefficient of variation was higher for afternoon FVC compared with morning FVC (5.1 vs. 4.6%, $p=0.018$). No diurnal variation was found for FEV1 (mean difference 7 ml, $p=0.35$). Home and hospital spirometry were highly correlated ($r=0.98$, $p<0.001$). Total variance in FVC was 0.021L and between-patient standard deviation 0.033L.

Median number of steps per day was 6290 (IQR: 3752-9439). Step count was lower before morning FVC compared with afternoon FVC (**Figure 1b**). Mean difference was 49 steps during 15 minutes before FVC measurement ($p=0.005$) and 219 steps during the hour before FVC measurement ($p<0.001$). Patients were relatively inactive during 15 minutes before spirometry; 87% of patients walked <250 steps. Daily step count correlated with

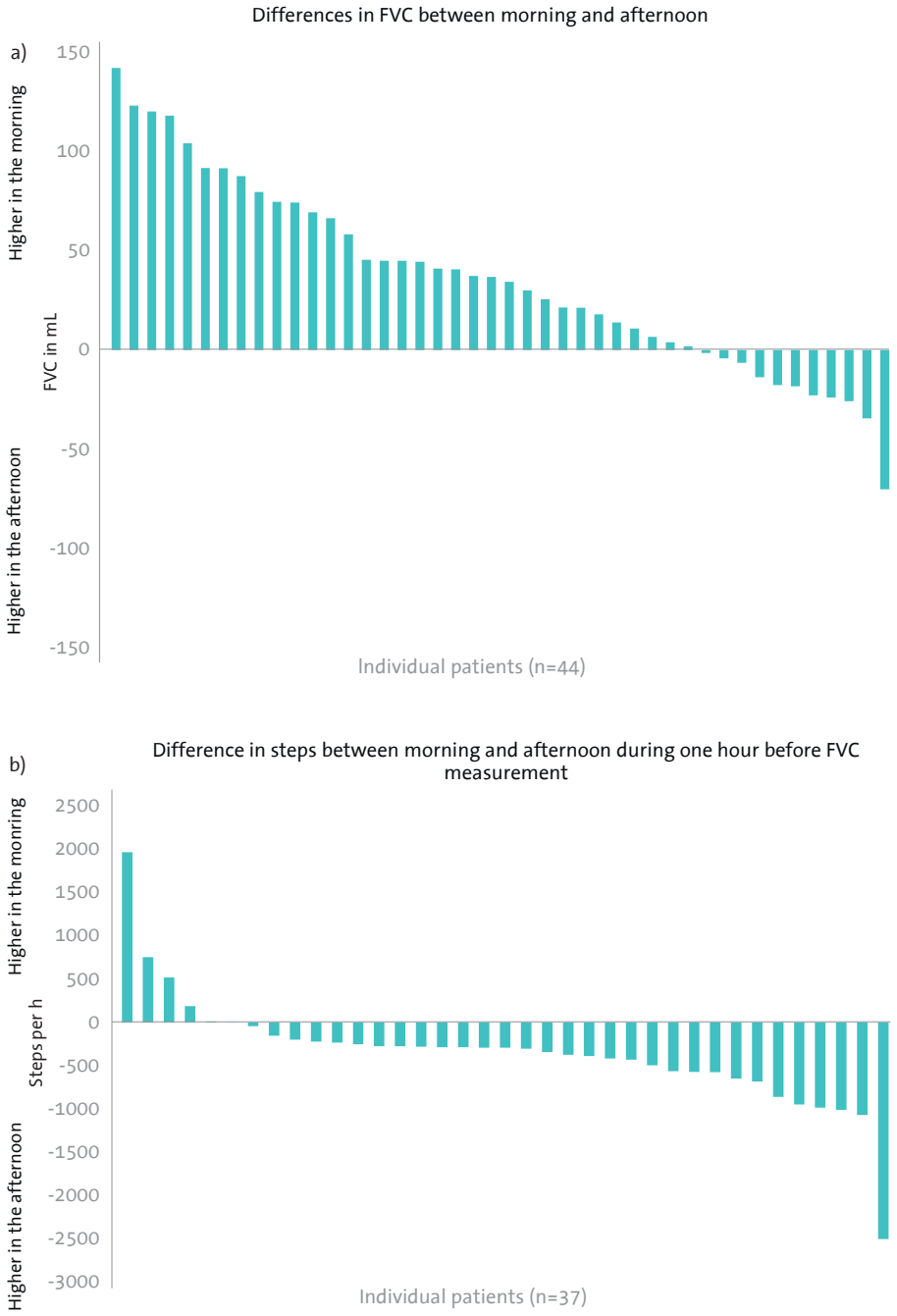

Figure 1 a) Differences in forced vital capacity (FVC) between morning and afternoon for individual patients. b) Differences in steps per hour before morning and afternoon FVC measurement.

FVC (r=0.32, p=0.028), DLCO (r=0.46, p=0.001), K-BILD total score (r=0.5, p<0.001) and K-BILD breathlessness and activities domain (r=0.6, p<0.001).

DISCUSSION

In this study, we observed a diurnal variation in FVC measured with home spirometry in patients with f-ILD, with a higher FVC in the morning than in the afternoon. In contrast, patients had a lower step count before the measurement in the morning compared to the afternoon. However, most patients were relatively inactive before both measurements, and hence activity just before measurement cannot fully explain the diurnal variation in FVC. Most patients reported that they were more tired in the afternoon and attributed differences in FVC to fatigue.

Previous studies, mainly in asthmatics or healthy subjects, suggested that diurnal variation in lung function could be due to varying airway resistance. Proposed mechanisms are a variation in plasma cortisol level, catecholamine levels, parasympathetic tone, mucociliary clearance, and activity (4-6). We did not observe a diurnal variation in FEV1 in our study, making variation in airway resistance less likely. Thus, the exact mechanism causing diurnal variation in FVC in patients with f-ILD remains to be elucidated.

Interestingly, steps per day had a stronger correlation with quality of life than with lung function, especially with the K-BILD breathlessness and activity domain. This finding suggests that activity better reflects how a patient feels and functions than pulmonary function alone. Home-based activity tracking could be a useful tool for future research, as our study showed that wearing an activity tracker for a relatively long period of time is feasible in patients with f-ILD.

A limitation of this study is that it was a single-center study, hence, these findings need validation in a larger multicenter cohort. Furthermore, some patients had technique issues leading to missing data. However, in view of the large number of recordings, we believe that the impact on study outcome is limited. Compared with a recently published study using home spirometry that reported multiple technical problems, our study had very few technical issues (10). In most previous trials with home spirometry in IPF, patients were blinded for their results. In the current study, we used an online application with direct feedback to patients and researchers, low-threshold communication with the study team and thorough instruction of patients at baseline and during the study. Hence, home-based FVC had an acceptable variability and showed reliable

results compared with hospital-based FVC. These results are encouraging for future home spirometry studies in f-ILD.

Taking into account the small margins in FVC change in current trials in IPF and other f-ILD (3), timing of spirometry should be standardized for research purposes. For daily care, we believe that differences between morning and afternoon FVC are too small to have an impact on serial changes and on treatment decisions.

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