Title: Quantitative analysis of lung sounds for monitoring idiopathic pulmonary fibrosis: a prospective pilot study.

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Take home message: quantitative analysis of lung sounds may represent a tool for monitoring patients with idiopathic pulmonary fibrosis.

INTRODUCTION

Accurate monitoring of disease progression in idiopathic pulmonary fibrosis (IPF) is crucial for predicting prognosis and optimizing management, including the initiation of therapies, the appropriate timing of supportive care and the prompt referral for lung transplantation. While forced vital capacity (FVC) via spirometry has been accepted as the most feasible and reliable tool to assess the deterioration in these patients in clinical practice as well as in randomized controlled trials [1][2], in recent years both visual evaluation and computer-based analysis of high-resolution computed tomography (HRCT) parenchymal patterns have been shown to correlate with disease severity based on FVC and predict outcome in several fibrotic lung diseases, including IPF [3][4][5]. Electronic stethoscopes, which permit digital recording of lung sounds, potentially represent a simple, non-invasive and reproducible tool for evaluating disease severity and progression in patients with IPF. Although computerized lung sound analysis is capable of discriminating between crackles due to pulmonary fibrosis from those due to pneumonia or heart failure [6–8], the utility of lung sounds for monitoring the course of the disease in these patients is still unknown. We have recently identified that typical, “Velcro-type” crackles are closely correlated with the extent of several HRCT features, suggesting that lung sounds might facilitate the early detection of fibrotic lung disease [9]. In this prospective pilot study, we evaluated the longitudinal change in acoustic features of lung sounds recorded from patients with IPF, and validated such features by examining correlations with several clinical, physiologic and radiologic parameters.

METHODS

Patients with a diagnosis of IPF were consecutively recruited from those attending the Interstitial Lung Disease (ILD) Clinic of the University Hospital of Southampton (UK) between March and September 2015. A group of healthy volunteers were also enrolled as controls.

Patients attended visits every two months for a total of seven study appointments over twelve months of clinical observation. At each visit, lung sounds were recorded consecutively over ten different chest locations identified according to the guidelines for computerised respiratory sounds analysis (CORSA) [10] using a digital stethoscope (Littmann 3200, 3M, USA) held manually. Other serial measurements included lung volumes via spirometry and diffusion capacity for Carbon Monoxide (DL_{CO}), dyspnea and quality of life (assessed via University of California San Diego Shortness of Breath Questionnaire - UCSD-SOB and Saint George's Respiratory Questionnaire - SGRQ), and tolerance to exercise (six-minute walk test - 6MWT). A HRCT scan was performed at baseline if not performed within 12 months prior to screening, and a follow-up chest HRCT scan was performed at the end of the study (12 months of follow up). Consecutive HRCT scans were visually scored by two expert thoracic radiologists (ARL and NS) for extent of ILD abnormalities and extent of individual radiological features. Volumes for parenchymal features and were also automatically quantified via the Computer-Aided Lung Informatics for Pathology Evaluation and Rating (CALIPER) software (Mayo Clinic, USA). Lung sound data was analysed via acoustic signals processing algorithms written in Matlab (version 2015a) [11]. For each sound file 481 variables corresponding to distinct acoustic features were generated, ranging from statistical properties to features related to the energy content of the signal and to the frequency domain.

Statistical analysis

The Intraclass Correlation Coefficient (ICC) was used to assess intra-subject reproducibility of acoustic features [12]. Multivariate analysis of variance (MANOVA) was used to compare acoustic features between IPF and control subjects. Repeated measures ANOVA was used to assess longitudinal change in the selected parameters. Estimated differences of means were calculated after adjusting for age, sex, Body Mass Index (BMI), and recording site as applicable. Multivariate linear regression was performed to investigate the correlations between acoustic features and other parameters measured at different time points throughout the study. All data was entered into the SPSS software package (version 24, IBM, USA).

RESULTS

19 patients were enrolled in the study: 3 (15.7 %) died during the observation period due to progressive disease, and 2 (10.5 %) others withdrew due to poor health conditions which prevented further clinical visits. Mean age was 70.8 (6.53 SD) and there was a male predominance (84.2%). More than two thirds of patients (68.4%) were receiving anti-fibrotic treatment at baseline. At baseline the study population had a moderate functional impairment (mean predicted FVC 73.7%) and reduced DL_{CO} (mean predicted DL_{CO} 43.5%). The study population showed a trend toward decline in % predicted FVC (-5.9%, 95% CI -4.27-16.08, p=0.862) and % predicted DL_{CO} (-5.5 %, 95% CI -2.34-13.34, p=0.35) over 12 months of clinical observation.

An intra-subject reliability analysis using 3 repeated recordings from 4 IPF subjects identified a set of 19 reproducible acoustic features (a cut-off of ICC > 0.5 was arbitrarily chosen for indicating acceptable reliability). The combination of the 19 acoustic features was shown to discriminate IPF subjects from the healthy volunteers (F=11.837, p=0.000). 6 features out of 19 underwent significant change between baseline and end of study and were therefore used for correlation analysis. Under multivariate linear regression analysis, the set of acoustic features were more associated with visual scores of total ILD extent (adjusted R^2= 0.106, p <0.005) and CALIPER-measured ILD total and peripheral volumes (adjusted R^2= 0.116 and 0.136 respectively, p<0.001) than to physiologic parameters such as FVC (adjusted R^2=0.031, p<0.001) or 6MWD (adjusted R^2=0.065 p<0.001). As to the relationships between lung sounds features and individual radiologic abnormalities, the strongest associations were found with reticulation and honeycombing, either visually assessed (R^2=0.043, p=0.04 and R^2=0.093, p=0.001, respectively) or quantified via CALIPER (R^2=0.108, p<0.001 and R^2=0.094, p=0.001, respectively). The association between lung sounds and fibrotic patterns on HRCT was further assessed against the Composite Physiologic Index (CPI), a strong predictor of morphologic severity of disease and mortality in IPF [13]. A model built combining the acoustic features and CPI performed better at discriminating extensive fibrosis on HRCT - adjudicated as sum of honeycombing and reticulation ≥ 50 % - as compared to CPI alone (AUC = 0.79, 95% CI 0.69-0.89 and AUC = 0.69, 95% CI 0.58-0.79, respectively) (Figure 1).

DISCUSSION

In this pilot study, we identified a set of acoustic features of lung sounds recorded from IPF patients showing to be reproducible, change over time and be associated with established measures of disease severity and clinical deterioration.

Chest auscultation is a simple, point-of-care, non-invasive and inexpensive assessment routinely used for monitoring the course and the response to treatment of respiratory disorders. Automated analysis of lung sounds was initially studied more than 30 years ago: however, most studies have focused on the characterization and automatic classification of diverse adventitious lung sounds rather than their longitudinal behaviour. A key preliminary finding in our study is that serial digital measurements of lung sounds using a simple electronic stethoscope provide reproducible and clinically significant acoustic measures in IPF. The analysis of longitudinal acoustic data in this study demonstrates for the first time that a set of reproducible features undergo significant change over a 12-month observation period, making them a promising surrogate of disease progression in IPF. On multivariate regression analysis, the selected acoustic features showed the strongest relationships with the extent of ILD on HRCT, either visually scored or quantitatively estimated via CALIPER. Reticulation and honeycombing were most strongly associated with acoustic features, putatively suggesting they make a major contribution to the character of “Velcro-type” crackles. The link between acoustic features and disease morphology on HRCT was corroborated by the finding that combining the CPI with acoustic features resulted in a model that was more accurate at identifying extensive fibrosis on HRCT than the CPI alone.

Our study has several strengths. It was prospective in design and used a standardised, reproducible method for lung sound recording. We collected a broad set of acoustic features and evaluated relationships between individual features and both semiquantitative (visual) and quantitative (CALIPER) measurements of disease extent. Lastly, we used commercially available electronic stethoscopes, which are inexpensive and readily available in most parts of the world. A limitation of this study is involved a small population from a single centre which limited its power to explore if change in lung sounds can actually predict disease progression or survival in these patients. Nevertheless, these pilot data provide the basis for a larger multicentre trial aimed at assessing the utility of lung sounds as a biomarker of disease behaviour in patients with IPF.

In conclusion, in this study we showed for the first time that acoustic features of lung sounds are a reproducible and valid metric of disease severity in patients with IPF. In principle, quantitative lung sounds analysis is a feasible, point-of-care, inexpensive and non-invasive novel clinical biomarker in IPF. The further exploration of lung sounds in larger longitudinal cohorts such as those of clinical trials could clarify their potential role for monitoring disease progression in these patients. Any effort in this direction should be supported by the development of novel tools providing easily interpretable read-outs for clinicians.

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FIGURES

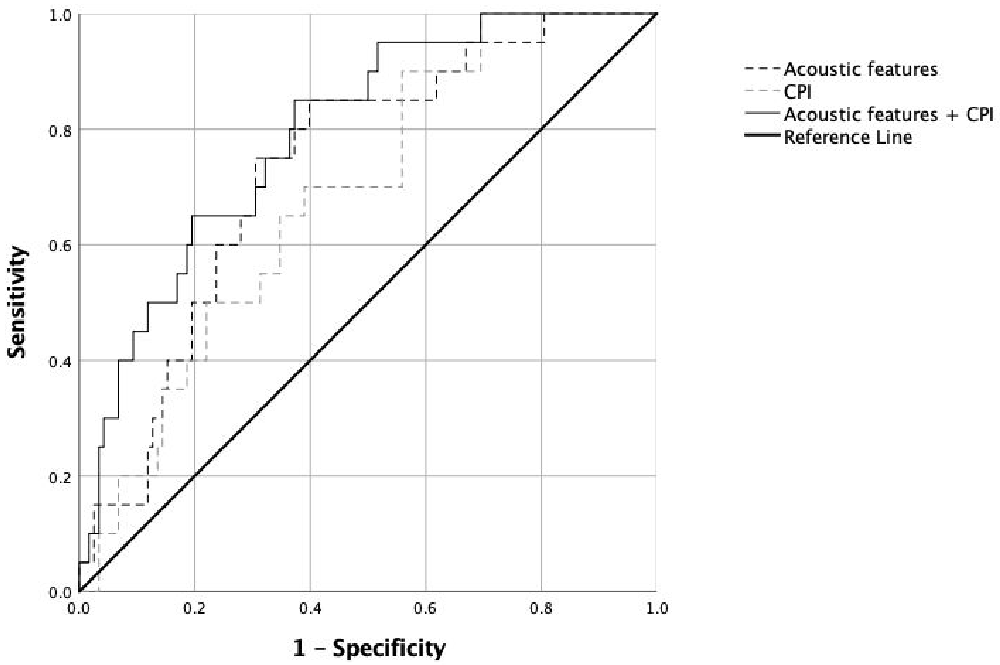

Figure 1 - ROC curves of the different models evaluated in the study for identification of extent of fibrosis ≥ 50% on High Resolution CT scan. Extent of fibrosis was calculated as sum of honeycombing + reticulation visual percentage scores. Black dotted line = acoustic features, AUC = 0.73, 95% CI 0.63-0.84. Grey dotted line = CPI (composite physiologic index), AUC = 0.69, 95% CI 0.58-0.79. Thin black line = acoustic features + CPI, AUC = 0.79, 95% CI 0.69-0.89.