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Computerized respiratory sounds: novel outcomes for pulmonary rehabilitation in COPD

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Running head: Respiratory sounds as outcomes for PR

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Abstract

Introduction: Computerized respiratory sounds (CRS) are a simple and non-invasive measure to assess lung function. Nevertheless, their potential to detect changes after pulmonary rehabilitation (PR) is unknown and needs clarification if respiratory acoustics are to be used in clinical practice. Thus, this study investigated the short- and mid-term effects of PR on CRS in subjects with COPD.

Methods: 41 subjects with COPD completed a 12-week PR program and a 3-month follow-up. Secondary outcome measures included dyspnea, self-reported sputum, FEV_1, exercise tolerance, self-reported physical activity, health-related quality of life and peripheral muscle strength. CRS, the primary outcomes, were recorded at right/left posterior chest using two stethoscopes. Airflow was recorded with a pneumotachograph. Normal respiratory sounds, crackles and wheezes were analyzed with validated algorithms.

Results: There was a significant effect over time in all secondary outcomes, with the exception of FEV_1 and of the impact domain of the St. George's Respiratory Questionnaire. Inspiratory and expiratory median frequency of normal respiratory sounds in the 100-300Hz band were significantly lower immediately (MD=-2.3Hz, 95%CI -4→-0.7 and MD=-1.9Hz, 95%CI -3.3→-0.5) and at 3-months (MD=-2.1Hz, 95%CI -3.6→-0.7 and MD=-2Hz, 95%CI -3.6→-0.5) post-PR. Mean number of expiratory crackles (MD=-0.8, 95%CI -1.3→-0.3) and inspiratory wheeze occupation rate (median 5.9 vs 0) were significantly lower immediately post-PR.

Conclusions: CRS are sensitive to short- and mid-term effects of PR in subjects with COPD. These findings are encouraging for the clinical use of respiratory acoustics. Future research is needed to strengthen these findings and explore the potential of CRS to assess the effectiveness of other clinical interventions in COPD.

Keywords: chronic lung disease; rehabilitation; computerized respiratory sounds

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) affects 210 million people worldwide,[1] placing a substantial burden on healthcare systems.[2] According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), COPD is characterized by a persistent and progressive airflow limitation, but also by its systemic consequences, mainly exacerbations and comorbidities.[3] Clinical manifestations are thus highly variable and no single outcome is able to assess the effectiveness of therapeutic interventions.[4] In line with this evidence, the latest American Thoracic Society/European Respiratory Society research statement in COPD recognizes that the effectiveness of interventions in COPD should be established using both patient-centered and surrogate outcomes.[5]

Pulmonary rehabilitation (PR) is one of the core components of the management of subjects with COPD.[6] Patient-centered outcomes, namely health-related quality of life, exercise capacity and dyspnea, have been identified as the most important outcomes of PR.[7] Surrogate outcomes, such as the forced expiratory volume in 1 second (FEV_1), have also been used.[8, 9] However, unlike the other outcomes, FEV_1 has not been found to be responsive to PR.[8, 9] Based on this evidence, and in the absence of other globally accepted surrogate outcome for lung function, it has been generally established that PR does not improve lung function in COPD.[6] Nevertheless, FEV_1 mainly reflects structural changes in the large airways[10] and it is well-recognized that COPD primarily targets small airways.[3] Hence, there is a need to explore new surrogate outcomes to assess the effects of PR on lung function.

Computerized respiratory sounds are a simple, objective and non-invasive surrogate measure to assess the function of the respiratory system.[11] Computerized respiratory sounds can be divided in two main types, normal and adventitious sounds.[12] Normal respiratory sounds are generated by the airflow in the respiratory tract and characterized by broad spectrum noise.[12] Adventitious respiratory sounds are additional sounds, which can be continuous (wheezes) or discontinuous (crackles).[12] Both normal and adventitious respiratory sounds are directly related to movement of air, changes within lung morphology and presence of secretions.[11, 13] In subjects with COPD, it has been shown that the number of detected wheezes, as well as their frequency, during forced expiratory maneuvers decreased after inhalation of terbutaline.[14] It has also been demonstrated that it is possible to characterize the course of acute exacerbations of

COPD in two different respiratory sound patterns based on the variation of spectral parameters.[15] From the limited evidence, it can be hypothesized that computerized respiratory sounds have potential to detect changes in lung function after PR. However, this is unknown as this measure has never been used to assess this intervention.

Thus, this study primarily aimed to investigate the short- and mid-term effects of PR on computerized respiratory sounds in subjects with COPD. The secondary aim was to explore correlations between computerized respiratory sounds and patient-centered outcomes.

METHODS

Design and Subjects

This was a one-arm longitudinal study investigating the effects of PR on computerized respiratory sounds in subjects with COPD. Subjects with COPD were recruited from two primary care centers. Inclusion criteria were i) diagnosis of COPD according to the GOLD,[3] ii) age ≥40 years old and iii) clinical stability for 1 month prior to the study (i.e., no hospital admissions or exacerbations as defined by the GOLD or changes in medication for the respiratory system).[3] Subjects were excluded if they presented severe psychiatric, neurologic or musculoskeletal conditions[16] and/or unstable cardiovascular disease that could interfere with their performance during the exercise training sessions. The study was approved by the Center Health Regional Administration (2013-05-02) and from the National Data Protection Committee (3292/2013). Eligible subjects, identified via clinicians, were contacted by the researchers, who explained the purpose of the study and asked about their willingness to participate. When subjects agreed to participate, an appointment with the researchers was scheduled. Written informed consent was obtained prior to data collection.

Intervention

The PR program was held for 12 weeks and was composed of 3 weekly sessions of exercise training and 1 weekly session of psychoeducation. A detailed description of the program is provided elsewhere.[17]

Data Collection

Data were collected before and immediately after PR and then at 3-months post-PR. Two baseline computerized respiratory sound recordings with a 1-week interval before the intervention (hereafter referred to as baselines 1 and 2) were collected to confirm the stability of subjects' respiratory acoustics.[18, 19] At baseline 1, socio-demographic, anthropometric (height and weight) and clinical (smoking habits, exacerbations in the previous year) data were first obtained. Dyspnea was assessed with the Modified British Medical Research Council (mMRC) questionnaire.[3] Then, computerized respiratory sounds were recorded.

Dyspnea at rest, self-reported sputum, computerized respiratory sounds, lung function, exercise tolerance, self-reported physical activity, health related quality of life and peripheral muscle strength were assessed at baseline 2 (immediately pre-PR), immediately post-PR and at 3-months post-PR. Subjects' were classified using both the GOLD spirometric classification (mild, moderate, severe-to-very severe) and the GOLD combined assessment (A, B, C and D).[3] All assessments were performed by two physiotherapists and the order was standardized.

Outcome Measures

Secondary outcomes

Dyspnea. Dyspnea at rest was assessed with the modified Borg scale.[20] Subjects were asked to rate their dyspnea from 0 to 10.

Self-reported sputum. Self-reported sputum was assessed using a numerical rating scale from 0 to 10 anchored at either end with a statement ('no sputum at all'=0; 'the worst sputum imaginable'=10). Subjects were asked to select the number that best represented their subjective perception.[21]

Lung function. A spirometric test, using a portable spirometer (MicroLab 3500, CareFusion, Kent, UK), was performed according to standardized guidelines.[22]

Exercise tolerance. Exercise tolerance was measured using the 6-minute walk test (6MWT). Two tests were performed according to the protocol described by the American Thoracic Society[23] and the best performance was considered.

Peripheral muscle strength. The knee extensors muscle strength of the dominant limb was determined by 1 repetition maximum (Multigym Plus G112X, Vitoria-Gasteiz, ES).[24]

Self-reported physical activity. The brief physical activity assessment tool, which consists of two questions assessing the frequency/duration of vigorous and moderate physical activity undertaken in a ''usual'' week, was used.[25] A score higher or equal to 4 indicates that the subject is sufficiently active.[25]

Health-related quality of life. The St. George's Respiratory Questionnaire (SGRQ), with its three domains (symptoms, activities and impact), was used.[26] Scores range from 0 (no impairment) to 100 (maximum impairment).

Primary outcomes

Computerized respiratory sounds. After 5-min of quiet sitting, airflow and respiratory sounds were acquired simultaneously during 20 seconds.[27] Subjects were in a seated-upright position, wearing a nose clip and breathing through a mouthpiece connected to a heated pneumotachograph (3830, Hans Rudolph, Inc., Shawnee, KS, USA). A peak airflow of 0.4–0.6 l/s was selected as computerized respiratory sounds have been shown to be reliable at this airflow range in subjects with COPD.[28] Subjects had visual biofeedback of the flow signal (RSS 100R Research Pneumotach System, Hans Rudolph, Shawnee, KS, USA) and were instructed to maintain the flow between two horizontal lines. Recording was preceded by a training phase of at least 3 breathing cycles.

Recordings were performed simultaneously at right and left posterior chest (5 cm laterally from the paravertebral line and 7 cm below the scapular angle)[29] using the LungSounds@UA interface.[30] Two chest pieces (Classic II S.E., Littmann®, 3M, St. Paul, MN, USA), with a microphone (frequency response between 20Hz and 19kHz - TOM-1545P-R, Projects Unlimited, Inc.®, Dayton, OH, USA) and preamplifier circuit (Intelligent Sensing Anywhere®, Coimbra, PT) in the main tube, were attached to the subject's skin with adhesive tape (Soft Cloth Surgical Tape, 3M, St. Paul, MN, USA). The analogue sound signals were further amplified and converted to digital by an audio interface (M-Audio® ProFire 2626, Irwindale, CA, USA). The signal was converted with a 24-bit resolution at a sampling rate of 44.1kHz and recorded in .wav format.

All generated files were processed using algorithms written in Matlab®R2009a (Mathworks, Natick, MA, USA). Breathing phases were automatically detected using the positive and negative airflow signals. Mean inspiratory and expiratory time were then calculated. The mean airflows and tidal volumes were calculated per breathing phase using flow and volume raw signals. The flow was timed synchronized with the sound to combine the detected breathing phases with sound signals.

Crackles were detected using a multi-algorithm technique based on established algorithms.[31] This multi-algorithm technique showed a 7% performance improvement over the best individual algorithm.[31] Wheezes were detected using an algorithm based on time-frequency analysis.[32] The mean number of crackles and the wheeze occupation rate (proportion of the breathing phase occupied by wheezes) during inspiration and expiration were extracted per chest location (right and left posterior chest).

Normal respiratory sounds were analyzed based on the methodology proposed by Pasterkamp,[33] after excluding adventitious respiratory sounds. The median frequency (F50) and the mean intensity were determined for the two most commonly analyzed frequency bands, i.e., 100 to 300Hz and 300 to 600Hz and extracted per breathing phase and per chest location.[33, 34]

Statistical Analysis

A power calculation was not performed since there is no published data using computerized respiratory sounds to assess the effects of PR in subjects with COPD. Descriptive statistics were used to describe the sample and to examine the outcome measures. Differences between subjects who completed the study and dropouts were tested using independent t-tests for continuous normally distributed data, Mann-Whitney U tests for continuous non-normally distributed data and chi-square tests for categorical data.

Computerized respiratory sounds were explored between right and left posterior chest, however, no significant differences were found. Hence, data from both locations were pooled to simplify the interpretability of the findings.

Computerized respiratory sounds and breathing pattern (inspiratory/expiratory airflow, volume and time) parameters were compared between baseline 1 and baseline 2 with paired t-tests for normally distributed data or Wilcoxon signed-rank test for non-normally distributed data. After confirming that there were no significant differences, baseline 2, hereafter referred as baseline, was used for further analysis.

Subjects were considered to have crackles or wheezes if they had at least a mean of one crackle/wheeze at baseline. To investigate differences in the number of subjects with crackles/wheezes across time points the Cochran Q test was used and the Kendall’s coefficient of concordance (Kendall’s W) was reported as estimate of effect size.[35] This coefficient was interpreted as follows: very weak (0-.20), weak (.20-.40), moderate (.40-.60), strong (.60-.80) and very strong (.80-1.00) effect.[35] If the effect of time was significant, pairwise comparisons were performed using Bonferroni correction.

Normality was verified for all outcome measures. When data were normally distributed, one-way analysis of variance (ANOVA) with repeated measures was used to establish the effects of time. The effect size was computed via Partial eta-squared as it is the index more commonly reported in the analysis of variance.[36] Partial eta-squared (η^2) was interpreted as a small (≥.01), medium (≥.06) or large (≥.14) effect.[36] When the effect of time was significant, post hoc analyzes were conducted with pairwise comparisons using the Bonferroni correction to assess differences across the three time points (baseline, post-PR and 3-months post-PR).

When data were not normally distributed, the Friedman test was used, together with the effect size estimate Kendall's W.[35] If the effect of time was significant, post hoc analyzes were conducted with Wilcoxon signed-rank tests using Bonferroni correction.

As relationships between computerized respiratory sounds (F50, mean intensity, mean number of crackles and wheeze occupation rate) and secondary outcome measures are yet little understood, correlations with Pearson's coefficient (r) or Spearman's rho (r_s) were explored.

Differences on breathing parameters across time were also explored with ANOVAs for repeated measures, as the breathing pattern can play a role in the genesis of normal[37] and adventitious respiratory sounds.[38, 39]

Statistical analyzes were performed using IBM SPSS Statistics version 20.0 (IBM Corporation, Armonk, NY, USA) and plots were created using GraphPad Prism version 5.01 (GraphPad Software, Inc., La Jolla, CA, USA). The level of significance was set at .05.

RESULTS

Subjects

A total of 51 subjects were enrolled, however the final sample comprised 41 subjects (Figure 1).

(insert Figure 1)

Subjects were mostly male (85%), had a mean age of 67±9 years old and a mean FEV_1 of 69±22% of the predicted (Table 1). There were no significant differences between completers and dropouts with regard to any of the baseline characteristics (p>.05).

(insert table 1)

Secondary outcome measures

There was a significant effect over time in all secondary outcomes ($p<.007$; η^2 from .12 to .61), with the exception of FEV_1 ($p=.16$) and SGRQ impact ($p=.35$) (Table 2).

(insert table 2)

Primary outcome measures

Normal respiratory sounds

The inspiratory and expiratory F50 of normal respiratory sounds changed only in the 100 to 300Hz band ($p=.006$, $\eta^2=.06$ and $p=.01$, $\eta^2=.05$) (Figure 3). Inspiratory F50 was significantly lower immediately after PR and at 3-months post-PR compared to baseline (MD=-2.3(95%CI -4→-0.7)Hz, $p=.006$ and MD=-2.1(95%CI -3.6→-0.7)Hz, $p=.005$). Similar changes were observed in expiratory F50 compared to baseline (MD=-1.9(95%CI -3.3→-0.5)Hz, $p=.01$ and MD=-2(95%CI -3.6→-0.5)Hz, $p=.009$).

No significant differences were seen in the 300 to 600Hz band (inspiration $p=.42$ and expiration $p=.57$) (Figure 2). Also no significant differences in the mean intensity of normal respiratory sounds ($p>.05$) were found (Figure 2).

(insert figure 2)

Immediately post-PR, there were weak-to-moderate relationships between inspiratory F50 (300 to 600Hz band) and SGRQ symptoms ($r=.57$; $p<.001$), SGRQ total ($r=.52$; $p=.001$), rest dyspnea ($r=.41$; $p=.008$) and self-reported sputum ($r=.33$; $p=.04$).

Crackles

All subjects had inspiratory crackles across the different time points, however the frequency of subjects with expiratory crackles decreased across time ($p=.005$; Kendall's $W=.13$). Expiratory crackles were present in all subjects before the intervention whereas after PR expiratory crackles were found in 34 (82.9%; $p=.004$) subjects and at 3-months post-PR in 37 (90.2%; $p=.19$) subjects. Also no significant difference was found in the frequency of subjects with expiratory crackles between post-PR and 3-months post-PR ($p=.49$).

The mean number of inspiratory crackles did not change significantly across time ($p=.51$) (Figure 3). Expiratory crackles, however, changed across the three time points ($p=.01$; $\eta^2=.07$). Their mean number was significantly lower immediately after PR, compared to baseline (MD=-0.8(95%CI -1.3→-0.3), $p=.003$) (Figure 3).

(insert figure 3)

After PR, weak-to-moderate positive relationships were found between the mean number of inspiratory (r=.4; p=.01) and expiratory (r=.33; p=.04) crackles and rest dyspnea. No other relationships were found.

Wheezes

The frequencies of subjects with inspiratory (p=.006, Kendall's W=.08) and expiratory (p=.002; Kendall's W=.09) wheezes were different across time points. Twelve (29.3%) subjects presented inspiratory and 17 (41.5%) expiratory wheezes before the intervention, whereas immediately after PR they were only 6 (14.6%; p=.06) and 9 (22%; p=.01) and at 3-months post-PR, 4 (9.8%; p=.006) and 8 (19.5%; p=.004), respectively. No significant differences were observed in the frequency of subjects with inspiratory/expiratory wheezes between post-PR and 3-months post-PR (p=1).

Figure 5 shows the behavior of wheeze occupation rate over time of subjects with wheezes at baseline. Inspiratory wheeze occupation rate changed across the three time points ($p<0.001$; Kendall's W=.51). Post hoc analysis was conducted with a Bonferroni correction. Inspiratory wheeze occupation rate was significantly lower after PR (median 0) compared to the baseline (median 5.9, p=.001). Expiratory wheeze occupation rate changed significantly across time ($p<0.003$; Kendall's W=.31), however, during post-hoc tests no significant results were found. Only a tendency for lower expiratory wheeze occupation rate after PR (median 0.8) compared to baseline (median 8.9) (p=.04) was observed (Figure 4).

(insert figure 4)

In subjects with no inspiratory (n=29; 70.7%) or expiratory (n=24; 58.5%) wheezes at baseline, no significant differences in the behavior of inspiratory (medians of 0 at baseline, post-PR and 3-months post-PR; p=.77) or expiratory (medians of 0 at baseline and 3-months post-PR and median of 2 post-PR; p=.54) wheeze occupation rates were found across the three time points.

A moderate correlation between expiratory wheeze occupation rate and FEV_1 was verified (r_s=-.35; p=.03) before the intervention. No other relationships were found.

Breathing pattern

No significant differences over time were observed on inspiratory/expiratory flow (p=.06 and p=.12), volume (p=.14 and p=.18) or time (p=.48 and p=.58) during the recordings of respiratory sounds (Figure 5).

(figure 5)

DISCUSSION

To the best of authors' knowledge, this was the first study investigating the effects of PR on computerized respiratory sounds in subjects with COPD. The main findings indicated that F50 of normal respiratory sounds, number of crackles and wheeze occupation rate were able to detect significant differences in lung function immediately post-PR and that most of these effects were not maintained at 3 months.

The mean frequency of normal respiratory sounds was sensitive to PR, while intensity remained unchanged. Similar observations were reported by Malmberg et al. which found respiratory sounds intensity at standardized airflows to be less informative than the F50 as an indicator of flow obstruction in adults with asthma and healthy subjects.[40] Sánchez-Morillo et al. also found that F50 was one of the respiratory sounds parameters to better distinguish between two groups of subjects with acute exacerbation of COPD.[15] Inspiratory and expiratory F50 were significantly lower immediately and at 3-months post-PR. To the authors' knowledge, no published studies have tested the change in normal respiratory sounds after PR. Previous studies have demonstrated that higher F50 are related with pathologic events, such as bronchoconstriction and presence of pneumonia[15, 40] and therefore, the decrease in F50 found in this study may reflect an improvement of lung function after PR. This decrease was only significant in the 100 to 300Hz band, possibly because this frequency band is where, in stable conditions, most of the acoustic energy resides.[11, 41] Nevertheless, as bronchoconstriction and sputum generate flow-turbulent noise, and flow turbulence produce sounds in high frequency ranges,[42] the frequency band of 300-600Hz is also of clinical importance. Positive relationships between inspiratory F50 and subjects' symptoms (SQRQ symptoms, rest dyspnea, self-reported sputum) and health-related quality of life (SGRQ total) were only found at this high frequency band (300-600Hz). Future studies assessing the effects of PR on normal respiratory sounds of subjects with acute exacerbation of COPD should therefore consider both low and high frequency bands.

The mean number of inspiratory crackles did not change across time, but it is well-known that COPD is characterized by inspiratory crackles.[43, 44] Moreover the mean number of inspiratory crackles at the three time points was within the range of previously reported results.[45-47] The mean number of expiratory crackles, however, was significantly lower immediately after PR. No studies have investigated the change in number of crackles in subjects with COPD after PR. Nevertheless, a slight decrease in the number of expiratory crackles (from 0.8±0.8 to 0.7±0.1) after standard medical treatment has been previously reported in 11 subjects with pneumonia.[47] After PR the slight, but consistent, reduction in the number of expiratory crackles may be due to a combination of a number of factors. First, the active airway clearance techniques practiced during the PR program may have enhanced sputum evacuation.[48, 49] A systematic review about the use of airway clearance techniques in subjects with COPD found that active airway clearance techniques were effective removing secretions.[49] Second, the participation in the PR program may have optimized the use of maintenance bronchodilator therapy[6] and it is known that bronchodilators act on airway smooth muscle, reducing air trapping and hyperinflation.[50, 51] Although not yet well understood, these airway changes might have been responsible for decreasing the genesis of crackles. Despite the possible explanatory reasons, the lower mean number of expiratory crackles after PR, seem to point out to an improvement of subjects' lung function. A recent study showed that expiratory crackles are significantly more frequent during periods of increased disease severity (acute exacerbations of COPD) than stable periods (median 3.17 vs. 0.83).[45] Additionally, a positive correlation was found between crackles and rest dyspnea. To date, there are no references in the literature about this correlation. It is believed; however, that hyperinflation may explain this relationship, as it is fundamental to the origin of dyspnea[52] and may contribute to crackles' genesis.

Inspiratory wheeze occupation rate was significantly lower after PR compared to the baseline. A significant decrease in inspiratory wheeze occupation rate (from 9.2±14.1% to 0.4±1.9%) has been previously reported in 9 patients with lower respiratory tract infection after 3 weeks of pharmacotherapy plus respiratory physical therapy.[53] Inspiratory wheezes have also been associated with more severe airway obstruction in patients with asthma[54] and characteristic of acute exacerbations of COPD.[45] Based on this evidence, it is possible that the significant decrease in inspiratory wheeze occupation rate observed in this study reflects an improvement on subjects' airway obstruction after PR. Wheeze occupation rate during expiration did not change with PR. Expiratory wheezes, in contrast with inspiratory wheezes, are a common sign in subjects with COPD[14, 46] and baseline values were in line with earlier studies.[46] It was also verified that severity of airflow limitation was correlated with expiratory wheeze occupation rate, with lower values of FEV_1 producing higher wheeze occupation rate, as previously shown by Fiz et al.

No short- or mid-term improvement in FEV_1 was observed after PR, which is in agreement with previous studies.[55, 56] In light of this research, it has been established that PR does not improve lung function in COPD.[6] However, FEV_1 is only one possible parameter to measure lung function, inspiratory capacity, diffusing capacity and respiratory sound parameters are examples of other possible surrogate outcomes.[4] In this study, the potential of computerized respiratory sounds for assessing the short-term effect of PR on lung function has been shown. This noteworthy finding demonstrates that respiratory sounds are a more sensitive indicator on the status of lung function, than FEV_1, which is in line with the study from Gavriely et al.[57] In this study, half of subjects with a history compatible with COPD had normal spirometry and abnormal respiratory sounds, revealing that airway abnormalities not detectable by standard spirometry generate abnormal acoustic signals.[57] Our results also demonstrate that, in the absence of a maintenance strategy, the significant effects of PR on respiratory sound parameters are no longer present at 3 months post-PR, whilst in the secondary outcomes the decline will probably only be noted later.[58] This finding therefore points out to the importance of keeping subjects motivated in changing behaviors after the program to maintain the benefits.

Strengths and limitations

Recordings of respiratory sounds were made in the sitting position on two standardized chest locations, in line with the CORSA guidelines.[59] This will facilitate the comparison of these results with other studies. It could be argued that changes observed in normal and adventitious respiratory sounds after PR could be due to subjects' breathing pattern changes. However, to account for this bias, airflow was standardized during all respiratory sound recordings. Moreover, an analysis of the breathing pattern parameters showed that no changes over time were observed. In addition, respiratory sounds were recorded at an airflow of 0.4–0.6 l/s, which has already been shown to be reliable in subjects with COPD.[28] Nonetheless, the interpretation of the results from this study should be tempered considering the following limitations. Computerized respiratory sounds have high inter-subject variability among subjects with COPD.[28] To minimize the bias, each subjects served as his/her own control, but a control group was not included. Future research examining changes in respiratory acoustics could use cross-over designs to overcome the high inter-subject variability of computerized respiratory sounds.[28] In these studies, any component that is related to the differences between subjects can be removed from comparisons.[60] To confirm the stability of subjects' respiratory acoustics, two baseline computerized respiratory sound recordings were collected with only 1-week interval. An additional recording (e.g., one month before the intervention) could have been performed, as symptoms in subjects with COPD are characterized by weekly variability[61]. However, as no research has been conducted on this topic, these limitations do not appear to remove the validity and importance of the results found and will inform further study designs. The sample included mainly subjects with early COPD (mild and moderate), and thus it was not possible to explore how the disease severity related to the sensitivity to change of respiratory sound parameters. Future studies should use a more balanced sample of COPD grades to clarify these findings. This study only assessed the short- and mid-term effects of PR on computerized respiratory sounds, thus, the long-term effects of PR could not be established. Future studies with long-term follow-ups are therefore needed. The complex set up used to record respiratory sounds and airflow can also be seen as a limitation of the study and restricts the application of computerized respiratory sounds in day-to-day clinical practice. As computerized RS shows promise, research should focus in developing technological solutions to acquire RS and airflow with minimal setup.

CONCLUSIONS

Median frequency of normal respiratory sounds, mean number of crackles and wheeze occupation rate are sensitive outcomes to measure the short- and mid-term effects of PR in subjects with COPD. Future research is needed to strengthen these findings and to extend these observations to other clinical interventions and respiratory diseases.

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Figure captions:

Figure 1 - Flow of subjects throughout the study.

Figure 2 – Median frequency (F50 – A and B) and mean intensity (Imean – C and D) of normal respiratory sounds at two frequency bands (100-300Hz and 300-600Hz) across time (n=41). Data are presented as mean ± 95% confidence intervals. Significant different from baseline (*). PR, pulmonary rehabilitation; 3M, 3-months.

Figure 3 – Mean number of inspiratory (A) and expiratory (B) crackles across time. Data are presented as mean±95% confidence intervals (n=41). Significant different from baseline (*). PR, pulmonary rehabilitation; 3M, 3-months.

Figure 4 – Wheeze occupation rate during inspiration (A, n=12) and expiration (B, n=17) across time. Data are presented as box and whisker plots with median, interquartile ranges and 5-95% percentiles. Significant different from baseline (*). PR, pulmonary rehabilitation; 3M, 3-months.

Figure 5 – Inspiratory and expiratory flow (A), volume (B) and time (C) across the three time points (n=41). Data are presented as mean ± 95% confidence intervals. PR, pulmonary rehabilitation; 3M, 3-months.

Quick Look

Current knowledge

Based on FEV_1, it has been generally established that pulmonary rehabilitation does not improve lung function in COPD. Nevertheless, FEV_1 mainly reflects structural changes in the large airways and it is well-recognized that COPD primarily targets small airways. Computerized respiratory sounds are a non-invasive measure to assess lung function, but their potential to detect changes in lung function after pulmonary rehabilitation is unknown.

What this paper contributes to our knowledge

Computerized respiratory sounds parameters, namely median frequency of normal respiratory sounds, mean number of crackles and wheeze occupation rate, can be used to measure the short- and mid-term effects of pulmonary rehabilitation in subjects with COPD.

Computerized respiratory sounds: novel outcomes for pulmonary rehabilitation in COPD

Running head: Respiratory sounds as outcomes for PR

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Abstract

Introduction: Computerized respiratory sounds (CRS) are a simple and non-invasive measure to assess lung function. Nevertheless, their potential to detect changes after pulmonary rehabilitation (PR) is unknown and needs clarification if respiratory acoustics are to be used in clinical practice. Thus, this study investigated the short- and mid-term effects of PR on CRS in subjects with COPD.

Methods: 41 subjects with COPD completed a 12-week PR program and a 3-month follow-up. Secondary outcome measures included dyspnea, self-reported sputum, FEV_1, exercise tolerance, self-reported physical activity, health-related quality of life and peripheral muscle strength. CRS, the primary outcomes, were recorded at right/left posterior chest using two stethoscopes. Airflow was recorded with a pneumotachograph. Normal respiratory sounds, crackles and wheezes were analyzed with validated algorithms.

Results: There was a significant effect over time in all secondary outcomes, with the exception of FEV_1 and of the impact domain of the St. George's Respiratory Questionnaire. Inspiratory and expiratory median frequency of normal respiratory sounds in the 100-300Hz band were significantly lower immediately (MD=-2.3Hz, 95%CI -4→-0.7 and MD=-1.9Hz, 95%CI -3.3→-0.5) and at 3-months (MD=-2.1Hz, 95%CI -3.6→-0.7 and MD=-2Hz, 95%CI -3.6→-0.5) post-PR. Mean number of expiratory crackles (MD=-0.8, 95%CI -1.3→-0.3) and inspiratory wheeze occupation rate (median 5.9 vs 0) were significantly lower immediately post-PR.

Conclusions: CRS are sensitive to short- and mid-term effects of PR in subjects with COPD. These findings are encouraging for the clinical use of respiratory acoustics. Future research is needed to strengthen these findings and explore the potential of CRS to assess the effectiveness of other clinical interventions in COPD.

Keywords: chronic lung disease; rehabilitation; computerized respiratory sounds

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) affects 210 million people worldwide,[1] placing a substantial burden on healthcare systems.[2] According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), COPD is characterized by a persistent and progressive airflow limitation, but also by its systemic consequences, mainly exacerbations and comorbidities.[3] Clinical manifestations are thus highly variable and no single outcome is able to assess the effectiveness of therapeutic interventions.[4] In line with this evidence, the latest American Thoracic Society/European Respiratory Society research statement in COPD recognizes that the effectiveness of interventions in COPD should be established using both patient-centered and surrogate outcomes.[5]

Pulmonary rehabilitation (PR) is one of the core components of the management of subjects with COPD.[6] Patient-centered outcomes, namely health-related quality of life, exercise capacity and dyspnea, have been identified as the most important outcomes of PR.[7] Surrogate outcomes, such as the forced expiratory volume in 1 second (FEV_1), have also been used.[8, 9] However, unlike the other outcomes, FEV_1 has not been found to be responsive to PR.[8, 9] Based on this evidence, and in the absence of other globally accepted surrogate outcome for lung function, it has been generally established that PR does not improve lung function in COPD.[6] Nevertheless, FEV_1 mainly reflects structural changes in the large airways[10] and it is well-recognized that COPD primarily targets small airways.[3] Hence, there is a need to explore new surrogate outcomes to assess the effects of PR on lung function.

Computerized respiratory sounds are a simple, objective and non-invasive surrogate measure to assess the function of the respiratory system.[11] Computerized respiratory sounds can be divided in two main types, normal and adventitious sounds.[12] Normal respiratory sounds are generated by the airflow in the respiratory tract and characterized by broad spectrum noise.[12] Adventitious respiratory sounds are additional sounds, which can be continuous (wheezes) or discontinuous (crackles).[12] Both normal and adventitious respiratory sounds are directly related to movement of air, changes within lung morphology and presence of secretions.[11, 13] In subjects with COPD, it has been shown that the number of detected wheezes, as well as their frequency, during forced expiratory maneuvers decreased after inhalation of terbutaline.[14] It has also been demonstrated that it is possible to characterize the course of acute exacerbations of

COPD in two different respiratory sound patterns based on the variation of spectral parameters.[15] From the limited evidence, it can be hypothesized that computerized respiratory sounds have potential to detect changes in lung function after PR. However, this is unknown as this measure has never been used to assess this intervention.

Thus, this study primarily aimed to investigate the short- and mid-term effects of PR on computerized respiratory sounds in subjects with COPD. The secondary aim was to explore correlations between computerized respiratory sounds and patient-centered outcomes.

METHODS

Design and Subjects

This was a one-arm longitudinal study investigating the effects of PR on computerized respiratory sounds in subjects with COPD. Subjects with COPD were recruited from two primary care centers. Inclusion criteria were i) diagnosis of COPD according to the GOLD,[3] ii) age ≥40 years old and iii) clinical stability for 1 month prior to the study (i.e., no hospital admissions or exacerbations as defined by the GOLD or changes in medication for the respiratory system).[3] Subjects were excluded if they presented severe psychiatric, neurologic or musculoskeletal conditions[16] and/or unstable cardiovascular disease that could interfere with their performance during the exercise training sessions. The study was approved by the Center Health Regional Administration (2013-05-02) and from the National Data Protection Committee (3292/2013). Eligible subjects, identified via clinicians, were contacted by the researchers, who explained the purpose of the study and asked about their willingness to participate. When subjects agreed to participate, an appointment with the researchers was scheduled. Written informed consent was obtained prior to data collection.

Intervention

The PR program was held for 12 weeks and was composed of 3 weekly sessions of exercise training and 1 weekly session of psychoeducation. A detailed description of the program is provided elsewhere.[17]

Data Collection

Data were collected before and immediately after PR and then at 3-months post-PR. Two baseline computerized respiratory sound recordings with a 1-week interval before the intervention (hereafter referred to as baselines 1 and 2) were collected to confirm the stability of subjects' respiratory acoustics.[18, 19] At baseline 1, socio-demographic, anthropometric (height and weight) and clinical (smoking habits, exacerbations in the previous year) data were first obtained. Dyspnea was assessed with the Modified British Medical Research Council (mMRC) questionnaire.[3] Then, computerized respiratory sounds were recorded.

Dyspnea at rest, self-reported sputum, computerized respiratory sounds, lung function, exercise tolerance, self-reported physical activity, health related quality of life and peripheral muscle strength were assessed at baseline 2 (immediately pre-PR), immediately post-PR and at 3-months post-PR. Subjects' were classified using both the GOLD spirometric classification (mild, moderate, severe-to-very severe) and the GOLD combined assessment (A, B, C and D).[3] All assessments were performed by two physiotherapists and the order was standardized.

Outcome Measures

Secondary outcomes

Dyspnea. Dyspnea at rest was assessed with the modified Borg scale.[20] Subjects were asked to rate their dyspnea from 0 to 10.

Self-reported sputum. Self-reported sputum was assessed using a numerical rating scale from 0 to 10 anchored at either end with a statement ('no sputum at all'=0; 'the worst sputum imaginable'=10). Subjects were asked to select the number that best represented their subjective perception.[21]

Lung function. A spirometric test, using a portable spirometer (MicroLab 3500, CareFusion, Kent, UK), was performed according to standardized guidelines.[22]

Exercise tolerance. Exercise tolerance was measured using the 6-minute walk test (6MWT). Two tests were performed according to the protocol described by the American Thoracic Society[23] and the best performance was considered.

Peripheral muscle strength. The knee extensors muscle strength of the dominant limb was determined by 1 repetition maximum (Multigym Plus G112X, Vitoria-Gasteiz, ES).[24]

Self-reported physical activity. The brief physical activity assessment tool, which consists of two questions assessing the frequency/duration of vigorous and moderate physical activity undertaken in a ''usual'' week, was used.[25] A score higher or equal to 4 indicates that the subject is sufficiently active.[25]

Health-related quality of life. The St. George's Respiratory Questionnaire (SGRQ), with its three domains (symptoms, activities and impact), was used.[26] Scores range from 0 (no impairment) to 100 (maximum impairment).

Primary outcomes

Computerized respiratory sounds. After 5-min of quiet sitting, airflow and respiratory sounds were acquired simultaneously during 20 seconds.[27] Subjects were in a seated-upright position, wearing a nose clip and breathing through a mouthpiece connected to a heated pneumotachograph (3830, Hans Rudolph, Inc., Shawnee, KS, USA). A peak airflow of 0.4–0.6 l/s was selected as computerized respiratory sounds have been shown to be reliable at this airflow range in subjects with COPD.[28] Subjects had visual biofeedback of the flow signal (RSS 100R Research Pneumotach System, Hans Rudolph, Shawnee, KS, USA) and were instructed to maintain the flow between two horizontal lines. Recording was preceded by a training phase of at least 3 breathing cycles.

Recordings were performed simultaneously at right and left posterior chest (5 cm laterally from the paravertebral line and 7 cm below the scapular angle)[29] using the LungSounds@UA interface.[30] Two chest pieces (Classic II S.E., Littmann®, 3M, St. Paul, MN, USA), with a microphone (frequency response between 20Hz and 19kHz - TOM-1545P-R, Projects Unlimited, Inc.®, Dayton, OH, USA) and preamplifier circuit (Intelligent Sensing Anywhere®, Coimbra, PT) in the main tube, were attached to the subject's skin with adhesive tape (Soft Cloth Surgical Tape, 3M, St. Paul, MN, USA). The analogue sound signals were further amplified and converted to digital by an audio interface (M-Audio® ProFire 2626, Irwindale, CA, USA). The signal was converted with a 24-bit resolution at a sampling rate of 44.1kHz and recorded in .wav format.

All generated files were processed using algorithms written in Matlab®R2009a (Mathworks, Natick, MA, USA). Breathing phases were automatically detected using the positive and negative airflow signals. Mean inspiratory and expiratory time were then calculated. The mean airflows and tidal volumes were calculated per breathing phase using flow and volume raw signals. The flow was timed synchronized with the sound to combine the detected breathing phases with sound signals.

Crackles were detected using a multi-algorithm technique based on established algorithms.[31] This multi-algorithm technique showed a 7% performance improvement over the best individual algorithm.[31] Wheezes were detected using an algorithm based on time-frequency analysis.[32] The mean number of crackles and the wheeze occupation rate (proportion of the breathing phase occupied by wheezes) during inspiration and expiration were extracted per chest location (right and left posterior chest).

Normal respiratory sounds were analyzed based on the methodology proposed by Pasterkamp,[33] after excluding adventitious respiratory sounds. The median frequency (F50) and the mean intensity were determined for the two most commonly analyzed frequency bands, i.e., 100 to 300Hz and 300 to 600Hz and extracted per breathing phase and per chest location.[33, 34]

Statistical Analysis

A power calculation was not performed since there is no published data using computerized respiratory sounds to assess the effects of PR in subjects with COPD. Descriptive statistics were used to describe the sample and to examine the outcome measures. Differences between subjects who completed the study and dropouts were tested using independent t-tests for continuous normally distributed data, Mann-Whitney U tests for continuous non-normally distributed data and chi-square tests for categorical data.

Computerized respiratory sounds were explored between right and left posterior chest, however, no significant differences were found. Hence, data from both locations were pooled to simplify the interpretability of the findings.

Computerized respiratory sounds and breathing pattern (inspiratory/expiratory airflow, volume and time) parameters were compared between baseline 1 and baseline 2 with paired t-tests for normally distributed data or Wilcoxon signed-rank test for non-normally distributed data. After confirming that there were no significant differences, baseline 2, hereafter referred as baseline, was used for further analysis.

Subjects were considered to have crackles or wheezes if they had at least a mean of one crackle/wheeze at baseline. To investigate differences in the number of subjects with crackles/wheezes across time points the Cochran Q test was used and the Kendall's coefficient of concordance (Kendall's W) was reported as estimate of effect size.[35] This coefficient was interpreted as follows: very weak (0-.20), weak (.20-.40), moderate (.40-.60), strong (.60-.80) and very strong (.80-1.00) effect.[35] If the effect of time was significant, pairwise comparisons were performed using Bonferroni correction.

Normality was verified for all outcome measures. When data were normally distributed, one-way analysis of variance (ANOVA) with repeated measures was used to establish the effects of time. The effect size was computed via Partial eta-squared as it is the index more commonly reported in the analysis of variance.[36] Partial eta-squared (η^2) was interpreted as a small (≥.01), medium (≥.06) or large (≥.14) effect.[36] When the effect of time was significant, post hoc analyzes were conducted with pairwise comparisons using the Bonferroni correction to assess differences across the three time points (baseline, post-PR and 3-months post-PR).

When data were not normally distributed, the Friedman test was used, together with the effect size estimate Kendall's W.[35] If the effect of time was significant, post hoc analyzes were conducted with Wilcoxon signed-rank tests using Bonferroni correction.

As relationships between computerized respiratory sounds (F50, mean intensity, mean number of crackles and wheeze occupation rate) and secondary outcome measures are yet little understood, correlations with Pearson's coefficient (r) or Spearman's rho (r_s) were explored.

Differences on breathing parameters across time were also explored with ANOVAs for repeated measures, as the breathing pattern can play a role in the genesis of normal[37] and adventitious respiratory sounds.[38, 39]

Statistical analyzes were performed using IBM SPSS Statistics version 20.0 (IBM Corporation, Armonk, NY, USA) and plots were created using GraphPad Prism version 5.01 (GraphPad Software, Inc., La Jolla, CA, USA). The level of significance was set at .05.

RESULTS

Subjects

A total of 51 subjects were enrolled, however the final sample comprised 41 subjects (Figure 1).

(insert Figure 1)

Subjects were mostly male (85%), had a mean age of 67±9 years old and a mean FEV_1 of 69±22% of the predicted (Table 1). There were no significant differences between completers and dropouts with regard to any of the baseline characteristics (p>.05).

(insert table 1)

Secondary outcome measures

There was a significant effect over time in all secondary outcomes ($p<.007$; η^2 from .12 to .61), with the exception of FEV_1 ($p=.16$) and SGRQ impact ($p=.35$) (Table 2).

(insert table 2)

Primary outcome measures

Normal respiratory sounds

The inspiratory and expiratory F50 of normal respiratory sounds changed only in the 100 to 300Hz band ($p=.006$, $\eta^2=.06$ and $p=.01$, $\eta^2=.05$) (Figure 3). Inspiratory F50 was significantly lower immediately after PR and at 3-months post-PR compared to baseline (MD=-2.3(95%CI -4→-0.7)Hz, p=.006 and MD=-2.1(95%CI -3.6→-0.7)Hz, p=.005). Similar changes were observed in expiratory F50 compared to baseline (MD=-1.9(95%CI -3.3→-0.5)Hz, p=.01 and MD=-2(95%CI -3.6→-0.5)Hz, p=.009).

No significant differences were seen in the 300 to 600Hz band (inspiration p=.42 and expiration p=.57) (Figure 2). Also no significant differences in the mean intensity of normal respiratory sounds (p>.05) were found (Figure 2).

(insert figure 2)

Immediately post-PR, there were weak-to-moderate relationships between inspiratory F50 (300 to 600Hz band) and SGRQ symptoms (r=.57; p<.001), SGRQ total (r=.52; p=.001), rest dyspnea (r=.41; p=.008) and self-reported sputum (r=.33; p=.04).

Crackles

All subjects had inspiratory crackles across the different time points, however the frequency of subjects with expiratory crackles decreased across time (p=.005; Kendall's W=.13). Expiratory crackles were present in all subjects before the intervention whereas after PR expiratory crackles were found in 34 (82.9%; p=.004) subjects and at 3-months post-PR in 37 (90.2%; p=.19) subjects. Also no significant difference was found in the frequency of subjects with expiratory crackles between post-PR and 3-months post-PR (p=.49).

The mean number of inspiratory crackles did not change significantly across time (p=.51) (Figure 3). Expiratory crackles, however, changed across the three time points ($p=.01$; $\eta^2=.07$). Their mean number was significantly lower immediately after PR, compared to baseline (MD=-0.8(95%CI -1.3→-0.3), p=.003) (Figure 3).

(insert figure 3)

After PR, weak-to-moderate positive relationships were found between the mean number of inspiratory (r=.4; p=.01) and expiratory (r=.33; p=.04) crackles and rest dyspnea. No other relationships were found.

Wheezes

The frequencies of subjects with inspiratory (p=.006, Kendall's W=.08) and expiratory (p=.002; Kendall's W=.09) wheezes were different across time points. Twelve (29.3%) subjects presented inspiratory and 17 (41.5%) expiratory wheezes before the intervention, whereas immediately after PR they were only 6 (14.6%; p=.06) and 9 (22%; p=.01) and at 3-months post-PR, 4 (9.8%; p=.006) and 8 (19.5%; p=.004), respectively. No significant differences were observed in the frequency of subjects with inspiratory/expiratory wheezes between post-PR and 3-months post-PR (p=1).

Figure 5 shows the behavior of wheeze occupation rate over time of subjects with wheezes at baseline. Inspiratory wheeze occupation rate changed across the three time points (p<0.001; Kendall's W=.51). Post hoc analysis was conducted with a Bonferroni correction. Inspiratory wheeze occupation rate was significantly lower after PR (median 0) compared to the baseline (median 5.9, p=.001). Expiratory wheeze occupation rate changed significantly across time (p<0.003; Kendall's W=.31), however, during post-hoc tests no significant results were found. Only a tendency for lower expiratory wheeze occupation rate after PR (median 0.8) compared to baseline (median 8.9) (p=.04) was observed (Figure 4).

(insert figure 4)

In subjects with no inspiratory (n=29; 70.7%) or expiratory (n=24; 58.5%) wheezes at baseline, no significant differences in the behavior of inspiratory (medians of 0 at baseline, post-PR and 3-months post-PR; p=.77) or expiratory (medians of 0 at baseline and 3-months post-PR and median of 2 post-PR; p=.54) wheeze occupation rates were found across the three time points.

A moderate correlation between expiratory wheeze occupation rate and FEV_1 was verified (r_s=-.35; p=.03) before the intervention. No other relationships were found.

Breathing pattern

No significant differences over time were observed on inspiratory/expiratory flow (p=.06 and p=.12), volume (p=.14 and p=.18) or time (p=.48 and p=.58) during the recordings of respiratory sounds (Figure 5).

(figure 5)

DISCUSSION

To the best of authors' knowledge, this was the first study investigating the effects of PR on computerized respiratory sounds in subjects with COPD. The main findings indicated that F50 of normal respiratory sounds, number of crackles and wheeze occupation rate were able to detect significant differences in lung function immediately post-PR and that most of these effects were not maintained at 3 months.

The mean frequency of normal respiratory sounds was sensitive to PR, while intensity remained unchanged. Similar observations were reported by Malmberg et al. which found respiratory sounds intensity at standardized airflows to be less informative than the F50 as an indicator of flow obstruction in adults with asthma and healthy subjects.[40] Sánchez-Morillo et al. also found that F50 was one of the respiratory sounds parameters to better distinguish between two groups of subjects with acute exacerbation of COPD.[15] Inspiratory and expiratory F50 were significantly lower immediately and at 3-months post-PR. To the authors' knowledge, no published studies have tested the change in normal respiratory sounds after PR. Previous studies have demonstrated that higher F50 are related with pathologic events, such as bronchoconstriction and presence of pneumonia[15, 40] and therefore, the decrease in F50 found in this study may reflect an improvement of lung function after PR. This decrease was only significant in the 100 to 300Hz band, possibly because this frequency band is where, in stable conditions, most of the acoustic energy resides.[11, 41] Nevertheless, as bronchoconstriction and sputum generate flow-turbulent noise, and flow turbulence produce sounds in high frequency ranges,[42] the frequency band of 300-600Hz is also of clinical importance. Positive relationships between inspiratory F50 and subjects' symptoms (SQRQ symptoms, rest dyspnea, self-reported sputum) and health-related quality of life (SGRQ total) were only found at this high frequency band (300-600Hz). Future studies assessing the effects of PR on normal respiratory sounds of subjects with acute exacerbation of COPD should therefore consider both low and high frequency bands.

The mean number of inspiratory crackles did not change across time, but it is well-known that COPD is characterized by inspiratory crackles.[43, 44] Moreover the mean number of inspiratory crackles at the three time points was within the range of previously reported results.[45-47] The mean number of expiratory crackles, however, was significantly lower immediately after PR. No studies have investigated the change in number of crackles in subjects with COPD after PR. Nevertheless, a slight decrease in the number of expiratory crackles (from 0.8±0.8 to 0.7±0.1) after standard medical treatment has been previously reported in 11 subjects with pneumonia.[47] After PR the slight, but consistent, reduction in the number of expiratory crackles may be due to a combination of a number of factors. First, the active airway clearance techniques practiced during the PR program may have enhanced sputum evacuation.[48, 49] A systematic review about the use of airway clearance techniques in subjects with COPD found that active airway clearance techniques were effective removing secretions.[49] Second, the participation in the PR program may have optimized the use of maintenance bronchodilator therapy[6] and it is known that bronchodilators act on airway smooth muscle, reducing air trapping and hyperinflation.[50, 51] Although not yet well understood, these airway changes might have been responsible for decreasing the genesis of crackles. Despite the possible explanatory reasons, the lower mean number of expiratory crackles after PR, seem to point out to an improvement of subjects' lung function. A recent study showed that expiratory crackles are significantly more frequent during periods of increased disease severity (acute exacerbations of COPD) than stable periods (median 3.17 vs. 0.83).[45] Additionally, a positive correlation was found between crackles and rest dyspnea. To date, there are no references in the literature about this correlation. It is believed; however, that hyperinflation may explain this relationship, as it is fundamental to the origin of dyspnea[52] and may contribute to crackles' genesis.

Inspiratory wheeze occupation rate was significantly lower after PR compared to the baseline. A significant decrease in inspiratory wheeze occupation rate (from 9.2±14.1% to 0.4±1.9%) has been previously reported in 9 patients with lower respiratory tract infection after 3 weeks of pharmacotherapy plus respiratory physical therapy.[53] Inspiratory wheezes have also been associated with more severe airway obstruction in patients with asthma[54] and characteristic of acute exacerbations of COPD.[45] Based on this evidence, it is possible that the significant decrease in inspiratory wheeze occupation rate observed in this study reflects an improvement on subjects' airway obstruction after PR. Wheeze occupation rate during expiration did not change with PR. Expiratory wheezes, in contrast with inspiratory wheezes, are a common sign in subjects with COPD[14, 46] and baseline values were in line with earlier studies.[46] It was also verified that severity of airflow limitation was correlated with expiratory wheeze occupation rate, with lower values of FEV_1 producing higher wheeze occupation rate, as previously shown by Fiz et al.

No short- or mid-term improvement in FEV_1 was observed after PR, which is in agreement with previous studies.[55, 56] In light of this research, it has been established that PR does not improve lung function in COPD.[6] However, FEV_1 is only one possible parameter to measure lung function, inspiratory capacity, diffusing capacity and respiratory sound parameters are examples of other possible surrogate outcomes.[4] In this study, the potential of computerized respiratory sounds for assessing the short-term effect of PR on lung function has been shown. This noteworthy finding demonstrates that respiratory sounds are a more sensitive indicator on the status of lung function, than FEV_1, which is in line with the study from Gavriely et al.[57] In this study, half of subjects with a history compatible with COPD had normal spirometry and abnormal respiratory sounds, revealing that airway abnormalities not detectable by standard spirometry generate abnormal acoustic signals.[57] Our results also demonstrate that, in the absence of a maintenance strategy, the significant effects of PR on respiratory sound parameters are no longer present at 3 months post-PR, whilst in the secondary outcomes the decline will probably only be noted later.[58] This finding therefore points out to the importance of keeping subjects motivated in changing behaviors after the program to maintain the benefits.

Strengths and limitations

Recordings of respiratory sounds were made in the sitting position on two standardized chest locations, in line with the CORSA guidelines.[59] This will facilitate the comparison of these results with other studies. It could be argued that changes observed in normal and adventitious respiratory sounds after PR could be due to subjects' breathing pattern changes. However, to account for this bias, airflow was standardized during all respiratory sound recordings. Moreover, an analysis of the breathing pattern parameters showed that no changes over time were observed. In addition, respiratory sounds were recorded at an airflow of 0.4–0.6 l/s, which has already been shown to be reliable in subjects with COPD.[28] Nonetheless, the interpretation of the results from this study should be tempered considering the following limitations. Computerized respiratory sounds have high inter-subject variability among subjects with COPD.[28] To minimize the bias, each subjects served as his/her own control, but a control group was not included. Future research examining changes in respiratory acoustics could use cross-over designs to overcome the high inter-subject variability of computerized respiratory sounds.[28] In these studies, any component that is related to the differences between subjects can be removed from comparisons.[60] To confirm the stability of subjects' respiratory acoustics, two baseline computerized respiratory sound recordings were collected with only 1-week interval. An additional recording (e.g., one month before the intervention) could have been performed, as symptoms in subjects with COPD are characterized by weekly variability[61]. However, as no research has been conducted on this topic, these limitations do not appear to remove the validity and importance of the results found and will inform further study designs. The sample included mainly subjects with early COPD (mild and moderate), and thus it was not possible to explore how the disease severity related to the sensitivity to change of respiratory sound parameters. Future studies should use a more balanced sample of COPD grades to clarify these findings. This study only assessed the short- and mid-term effects of PR on computerized respiratory sounds, thus, the long-term effects of PR could not be established. Future studies with long-term follow-ups are therefore needed. The complex set up used to record respiratory sounds and airflow can also be seen as a limitation of the study and restricts the application of computerized respiratory sounds in day-to-day clinical practice. As computerized RS shows promise, research should focus in developing technological solutions to acquire RS and airflow with minimal setup.

CONCLUSIONS

Median frequency of normal respiratory sounds, mean number of crackles and wheeze occupation rate are sensitive outcomes to measure the short- and mid-term effects of PR in subjects with COPD. Future research is needed to strengthen these findings and to extend these observations to other clinical interventions and respiratory diseases.

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Figure captions:

Figure 1 - Flow of subjects throughout the study.

Figure 2 – Median frequency (F50 – A and B) and mean intensity (Imean – C and D) of normal respiratory sounds at two frequency bands (100-300Hz and 300-600Hz) across time (n=41). Data are presented as mean ± 95% confidence intervals. Significant different from baseline (*). PR, pulmonary rehabilitation; 3M, 3-months.

Figure 3 – Mean number of inspiratory (A) and expiratory (B) crackles across time. Data are presented as mean±95% confidence intervals (n=41). Significant different from baseline (*). PR, pulmonary rehabilitation; 3M, 3-months.

Figure 4 – Wheeze occupation rate during inspiration (A, n=12) and expiration (B, n=17) across time. Data are presented as box and whisker plots with median, interquartile ranges and 5-95% percentiles. Significant different from baseline (*). PR, pulmonary rehabilitation; 3M, 3-months.

Figure 5 – Inspiratory and expiratory flow (A), volume (B) and time (C) across the three time points (n=41). Data are presented as mean ± 95% confidence intervals. PR, pulmonary rehabilitation; 3M, 3-months.

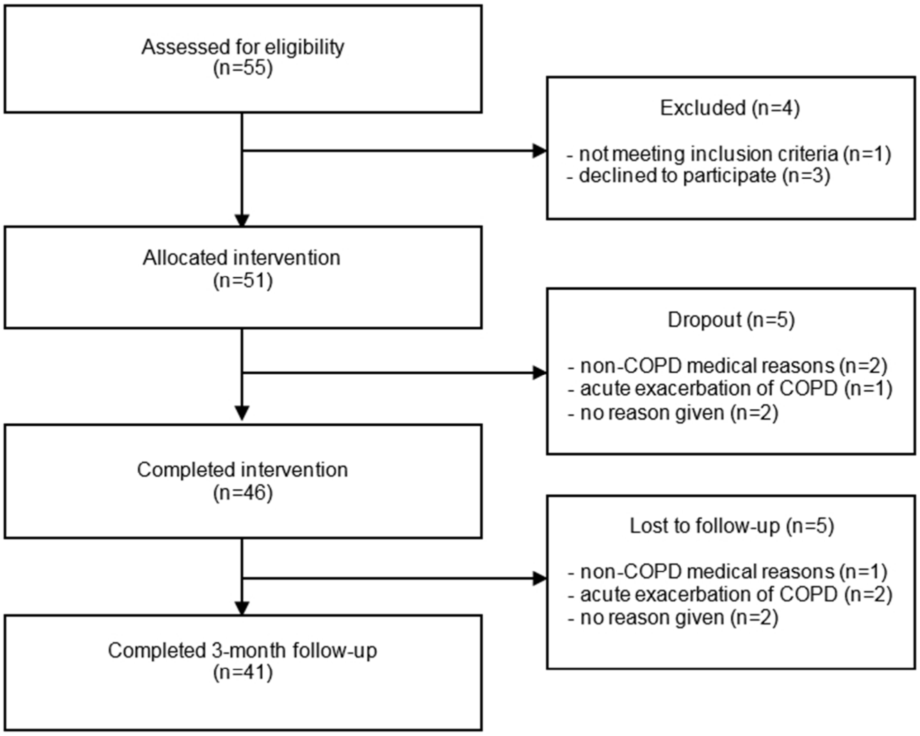
Quick Look

Current knowledge

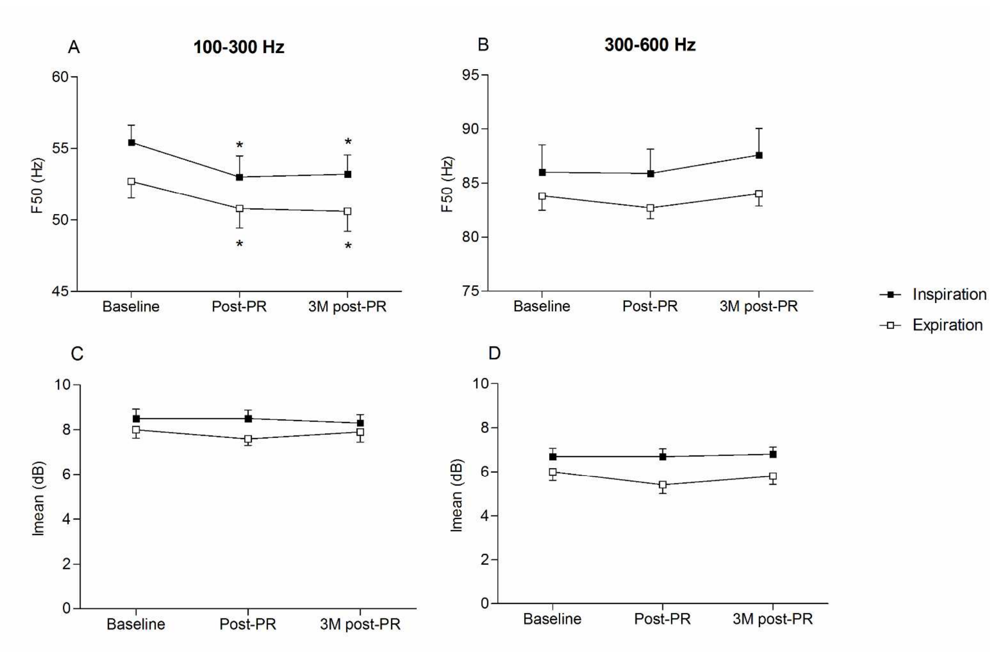
Based on FEV_1, it has been generally established that pulmonary rehabilitation does not improve lung function in COPD. Nevertheless, FEV_1 mainly reflects structural changes in the large airways and it is well-recognized that COPD primarily targets small airways. Computerized respiratory sounds are a non-invasive measure to assess lung function, but their potential to detect changes in lung function after pulmonary rehabilitation is unknown.

What this paper contributes to our knowledge

Computerized respiratory sounds parameters, namely median frequency of normal respiratory sounds, mean number of crackles and wheeze occupation rate, can be used to measure the short- and mid-term effects of pulmonary rehabilitation in subjects with COPD.



Flow of subjects throughout the study.



Median frequency (F50 – A and B) and mean intensity (Imean – C and D) of normal respiratory sounds at two frequency bands (100-300Hz and 300-600Hz) across time (n=41). Data are presented as mean ± 95% confidence intervals. Significant different from baseline (*). PR, pulmonary rehabilitation; 3M, 3-months.
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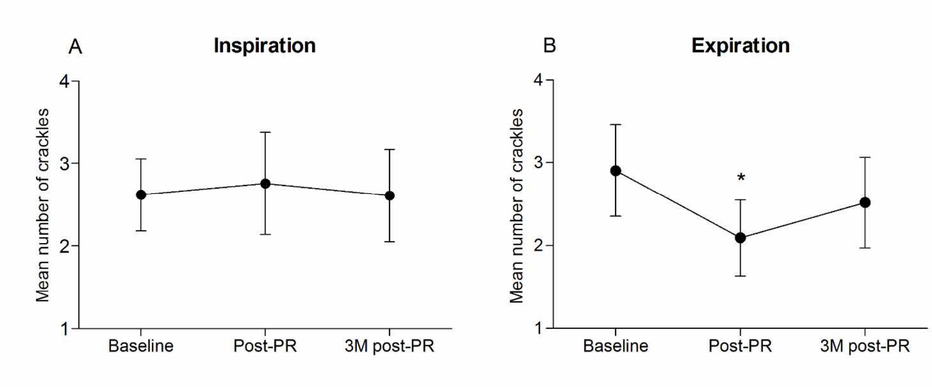

Mean number of inspiratory (A) and expiratory (B) crackles across time. Data are presented as mean±95% confidence intervals (n=41). Significant different from baseline (*). PR, pulmonary rehabilitation; 3M, 3-months.

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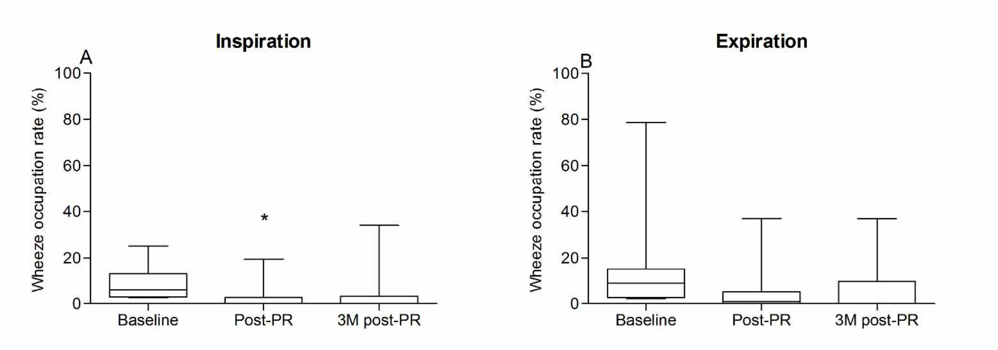

Wheeze occupation rate during inspiration (A, n=12) and expiration (B, n=17) across time. Data are presented as box and whisker plots with median, interquartile ranges and 5-95% percentiles. Significant different from baseline (*). PR, pulmonary rehabilitation; 3M, 3-months.
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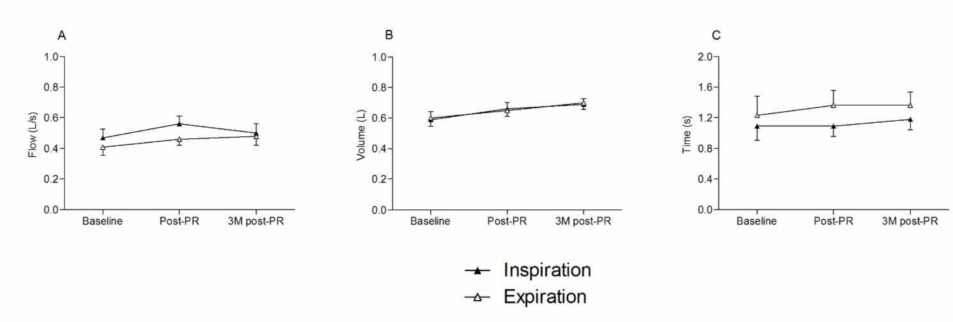

Inspiratory and expiratory flow (A), volume (B) and time (C) across the three time points (n=41). Data are presented as mean ± 95% confidence intervals. PR, pulmonary rehabilitation; 3M, 3-months.
220x71mm (300 x 300 DPI)

Table 1 – Subjects' socio-demographic and clinical characteristics (n=41).

Characteristics	
Sex (male), n (%)	35 (85)
Age (years)	67 ± 9
Current smokers	8 (20)
BMI (kg/m^2)	28 ± 3
mMRC, M [IQR]	1 [1, 2]
FEV_1 (% predicted[52])	69 ± 22
FEV_1/FVC	63 ± 9
GOLD spirometric classification, n (%)	
Mild	17 (42)
Moderate	16 (39)
Severe-to-very-severe	8 (19)
GOLD combined assessment, n (%)	
A	14 (34)
B	15 (37)
C & D	12 (29)

N=41

Values are shown as mean±standard deviation unless otherwise indicated. mMRC, modified British Medical Research Council questionnaire; M, median; IQR, interquartile range; BMI, body mass index; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Table 2 – Secondary outcome measures to assess pulmonary rehabilitation across time.

Outcome measure	Baseline	Immediately Post-PR	3-months Post-PR	p-value	η2
Dyspnea (0-10)	1 [0,2]	1 [0,2]*	0 [0, 1.75]*	.007	.12
Sputum (0-10)	1.5 [0, 4]	1 [0, 2]*	1 [0, 2]*	.003	.15
FEV_1 (% predicted[52])	68.9±21.7	67.1±21.8	68±21.7	.16	.05
6MWD (m)	481.3±76.1	538.8±78.8*	525.2±75.5*, #	<.001	.51
Knee extensors (kg)	37.9±8.5	47.5±11.5*	41.8±11.1*, #	<.001	.61
Physical activity (0-8)	1.8±2.0	5.1±1.6*	3.4±2.3*, #	<.001	.45
SGRQ total (0-100)	31.0±16.8	24.2±17.6*	22.1±12.1*	<.001	.27
SGRQ symptoms (0-100)	40.6±20.8	33.0±18.8*	27.3±20.0*	.003	.14
SGRQ activities (0-100)	46.9±19.6	36.1±22.9	28.6±22.1	<.001	.19
SGRQ impact (0-100)	18.7±16.9	14.5±17.1	15.3±16.5	.35	.03

N=41

Data are presented as mean±standard deviation. 6MWD, 6-minute walk distance; FEV_1, forced expiratory volume in one second; PR, pulmonary rehabilitation; SGRQ, St. George's Respiratory Questionnaire; η^2, partial eta-squared. Significantly different from baseline (*) and from post-PR (#).