Reliability and Minimum Important Difference of Sputum Weight in Bronchiectasis

Beatriz Herrero-Cortina, Victoria Alcaraz-Serrano, Antoni Torres, and Eva Polverino

BACKGROUND: Despite the widespread use of sputum weight to assess the effect of airway clearance interventions, its psychometric properties have not been evaluated. The purpose of this ad hoc analysis was to determine the test-retest reliability of 24-h sputum weight in clinically stable individuals with bronchiectasis. This study also aimed to estimate the minimum important difference of 24-h sputum weight after an airway clearance session in subjects with bronchiectasis. METHODS: Sixty subjects were included in the 24-h test-retest cohort, 42 of whom were part of the airway clearance cohort. For the 24-h test-retest cohort, spontaneously expectorated sputum was collected over 24 h on 2 different days without any airway clearance interventions. For the airway clearance cohort, sputum expectoration was also collected during 3 airway clearance sessions and over the 24 h following these interventions. Intraclass correlation coefficient ($ICC_{3,1}$) and Bland-Altman analysis were used to assess reliability. The minimum important difference was calculated using distribution-based and anchor-based methods, with cough impact as assessed with the Leicester Cough Questionnaire and the global rating of change as anchors. RESULTS: The reliability was acceptable ($ICC_{3,1} = 0.75$) for sputum weight over 24 h without any intervention. The agreement level was wide, particularly for high levels of sputum expectoration. The minimum important difference of the sputum collected in the 24 h after the intervention from baseline was −6.4 g (about −17%), determined using distribution-based methods. There was no correlation between sputum weight and the anchors, thus the anchor-based methodology could not be used. CONCLUSIONS: Multiple measurements should be considered to increase the agreement when sputum weight is used as an outcome measure for short periods in people with bronchiectasis. A reduction of 6.4 g (or 17% from baseline) in sputum collected during the 24 h after the airway clearance intervention may be considered the minimum important difference in people with bronchiectasis. (ClinicalTrials.gov registration NCT02392663; NCT01854788; NCT02614300.) *Key words: bronchiectasis; sputum; airway clearance techniques; reliability; minimum important difference; psychometric properties.* [Respir Care 2020;65(10):1478–1487. © 2020 Daedalus Enterprises]

Introduction

Bronchiectasis is a heterogeneous respiratory disorder characterized by recurrent airway inflammation and infection. Daily sputum expectoration is one of the most common symptoms experienced by people with bronchiectasis, and the incidence of this symptom is similar

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across all age groups and is independent of the time of onset of the productive cough (childhood or adulthood).[1-3] The amount of sputum expectorated tends to increase over time in people with bronchiectasis, and a greater sputum quantity has a negative impact on patients' quality of life.[4-6] In addition, a change in the daily amount of sputum expectoration is recognized as an important factor to identify exacerbations in this population.[7] Strategies to assess and monitor sputum quantity in individuals with bronchiectasis have gained importance, as well as the recommendation to incorporate the use of mucoactive therapies and airway clearance techniques as part of daily treatment to improve symptoms related to the productive cough (eg, sputum expectoration, uncontrollable cough, or sore or irritated throat).[8-10]

Qualitative studies have reported that people with bronchiectasis and cystic fibrosis use airway clearance interventions as a strategy to manage sputum symptoms and improve self-confidence in social settings.[11,12] If they completed interventions prior to engaging in social activities, the need to cough and expectoration will likely be reduced and, thus, embarrassing situations related to sputum are less likely.[11,12] Therefore, the patient's perception might be focused on the change of sputum expectoration experienced after intervention and not during the session itself.

Although sputum quantity is considered a controversial outcome measure because of the likelihood of the presence of salivary contamination or inadvertently swallowed secretions, this outcome measure is often used to assess the short- and long-term effectiveness of interventions in people with bronchiectasis, such as antibiotic therapy, mucoactive treatment, and airway clearance techniques.[13-19] The current widespread use of sputum quantity can be attributed to it being a simple and feasible outcome measure that is relevant to people with bronchiectasis and is easily implemented in clinical practice.[20,21]

Sputum quantity could be measured as sputum weight or sputum volume. The sputum weight (dry and wet) is most frequently used when a calibrated scale is available and subjects are not involved in the measurement process.[22] Findings based on sputum weight may be more accurate because they do not depend on the graduated scale of containers and the assessors' interpretation. Despite dry sputum weight being preferred to wet sputum weight because saliva contamination is completely removed, it is difficult to assess in clinical practice. For that reason, wet sputum weight is a simple and safe outcome measure for monitoring the sputum quantity, although interpreting the clinical importance of changes in wet sputum weight after an intervention remains a challenge.[21]

QUICK LOOK

Current knowledge

Wet sputum expectoration is often used to assess the effects of airway clearance interventions in people with bronchiectasis. The correct interpretation of wet sputum expectoration is still a challenge because its reliability and the minimum important difference have not been evaluated.

What this paper contributes to our knowledge

Most subjects presented a reduced need to expectorate after an airway clearance intervention. The minimum important difference estimated was a reduction of 6.4 g in the amount of sputum expectorated during the 24 h following the intervention, for a relative change of about −17% from baseline, based on distribution-based methods.

There is a knowledge gap in the reliability and the minimum important difference of the wet sputum expectoration in people with bronchiectasis, which are prerequisites for the correct interpretation of this outcome measure and the calculation of an adequate sample size for future studies.[23]

The primary outcome of this study was to examine the reliability of 24-h wet spontaneous sputum expectoration without performing any airway clearance intervention in clinically stable people with bronchiectasis. This study also aimed to estimate the minimum important difference for 24-h wet sputum expectoration after an airway clearance intervention in people with bronchiectasis. We hypothesized that the wet spontaneous sputum obtained over a 24-h period would be an acceptable reliable measure in clinically stable subjects with bronchiectasis and that subjects' response to an airway clearance intervention would be a reduction in the need to expectorate after the intervention (ie, less sputum collected over the 24-h follow-up period after intervention).

Methods

Study Design and Subjects

This study analyzed the test-retest reliability and the minimum important difference of wet sputum weight using data from 2 previous crossover trials and a current, parallel-group, randomized, controlled trial (NCT02614300) applying an ad

Supplementary material related to this paper is available at http://www.rcjournal.com.

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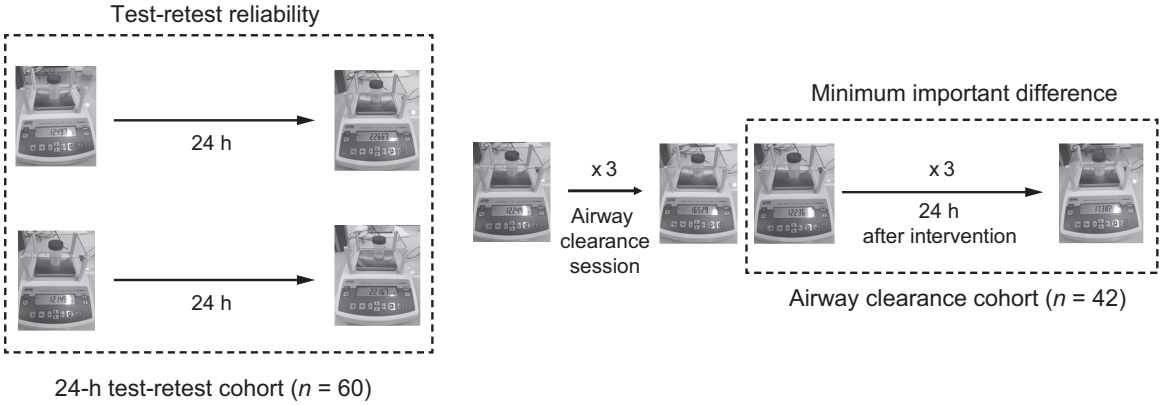

Fig. 1. Overview of sputum collection design for reliability (spontaneous sputum expectorated over 24 h without intervention) and minimum important difference (spontaneous sputum expectorated during the 24 h after airway clearance sessions) based on repeated measures.

hoc analysis.[16,19] All studies recruited individuals with bronchiectasis to assess the efficacy of physiotherapy interventions at Hospital Clinic, Barcelona, Spain. The sputum collection process was similar for all studies.

The inclusion criteria included a confirmed diagnosis of bronchiectasis on computed tomography scan, age ≥ 18 y, clinical stability for 1 month prior to the start of the study (defined as no need for extra antibiotics or changes in usual therapy, no hemoptysis, and no clinical features of exacerbation), and daily spontaneous sputum expectoration. The exclusion criteria were a diagnosis of cystic fibrosis, smoker or former smoker (< 2 y), and regular use of hyperosmolar agents or airway clearance techniques. Finally, the withdrawal criteria were pulmonary exacerbation during the study or any new medical or personal condition that hindered continuation in the study. Written informed consent was obtained from all subjects before data collection began, and all studies were approved by the research ethics committee of the Hospital Clinic.

Procedures

At the baseline visit, all subjects were instructed on the importance of collecting all sputum samples in a transparent container during the different assessment time points. All containers were weighed before and after the sputum collection using the same calibrated scale (VIC 212, Acculab, Germany).

The baseline spontaneous sputum expectorated was collected over a 24-h period (ie, from the beginning of one day until the following day, including the night) on 2 nonconsecutive weekdays (ie, ≥ 24 h apart) within the same week. These sputum samples were collected in 2 transparent containers during the recruitment period from the 3 trials, before starting any intervention (Fig. 1). Although subjects were nonadherent or naïve to airway clearance interventions, they were reminded not to perform any of these treatments during this week.

Salivary contamination and secretions from the sinuses after an inspiratory forced maneuver were not collected in the containers. However, if a small amount of saliva was detected in the containers, it was manually removed using a paper filter before being weighed. The wet sputum weight was chosen as the outcome. All subjects who collected 2 samples at this time point (baseline) were considered the 24-h test-retest cohort.

Subjects from the crossover trials, referred to as the airway clearance cohort, performed 3 airway clearance sessions (once per day) during the same week.[16,19] Each trial explored 3 different treatment arms; however, data from only 1 treatment arm was selected. The treatment arm selection was based on the study purpose, which was to detect the minimum change in the 24-h sputum expectoration after an airway clearance intervention that would likely be important from patients' and clinician's perspectives.[24] Consequently, the treatment arm was chosen according to its efficacy in enhancing sputum expectoration during sessions and the preference reported by the entire group of subjects.[16,19] Subjects recruited in the ongoing randomized controlled trial were not included in the airway clearance cohort because the intervention in this study was not similar to the other 2 trials.

Therefore, there were 2 different airway clearance interventions, one chosen from each trial: (1) a combined intervention using inhalation of a hyperosmolar agent plus airway clearance techniques (ie, hyaluronic acid + hypertonic saline solution [7%] and autogenic drainage technique), or (2) a single intervention with airway clearance techniques (ie, autogenic drainage technique) as previously described.[16,19] Subjects were seated during the inhalation period and were lying in a supine position during the airway clearance intervention. In both studies, an experienced physiotherapist supervised the sessions to guarantee correct performance of the inhalation or autogenic drainage technique.

The time spent doing the combined intervention was approximately 50 min (ie, 20 min for inhalation and 30 min for the autogenic drainage technique), and the total duration of the single intervention was 40 min.[16,19] Each subject received the same airway clearance intervention (combined or single intervention) in all sessions, performed at the same time of day. If a subject participated in both studies, only data from the first study to which they were recruited were used.

The airway clearance cohort was instructed to collect all sputum expectorated during 3 airway clearance sessions and over a 24-h follow-up period after each intervention into different preweighed transparent containers, following the same procedure described above (Fig. 1). Subjects were reminded of the importance of following the sputum collection instructions in each session.

The impact of the cough was assessed with an adapted version of the Leicester Cough Questionnaire (LCQ)[25] at the beginning and end of the sessions (approximately 1 week later) in the airway clearance cohort. The LCQ intraclass correlation coefficient (ICC) range was 0.87–0.96, and their minimum important difference was 1.3.[26,27]

The self-administered global rating of change (GRC) scale was used to evaluate the change in 24-h sputum weight perceived by the airway clearance cohort after completing the week of airway clearance sessions. Subjects were asked if the airway clearance sessions changed their need to expectorate in the 24 h after the intervention (ie, Has your amount of sputum changed over the 24-h follow-up after intervention compared to a day without airway clearance intervention?), which was scored using a Likert scale (scored from −7 to 7).[28] Negative scores indicated a reduction in the need to expectorate, and positive scores indicated a greater need to expectorate. Neither end of the Likert scale was marked as better than the other, nor were subjects informed about the hypothesis of this study (ie, the expected direction of the sputum weight change). The amount of change was classified as follows: ± 0–1 is no change, ± 2–3 is a small change, and ± 4–7 is a substantial change.[29]

Statistical Analysis

A power analysis was performed to estimate the sample needed to achieve reliability. Considering a minimum ICC of 0.9 with a 95% CI of 0.2 ($\alpha = 0.05$, $\kappa = 2$) a sample size of 21 subjects was required. However, according to COSMIN recommendations, a good sample size for reliability studies includes at least 50 subjects.[23] Therefore, we attempted to include this larger number of subjects.

The reliability of the amount of wet sputum collected was estimated using the $ICC_{3,1}$ (a 2-way, mixed-effects, single measurement, absolute agreement)[30] with 95% CI at baseline for the spontaneous sputum collected over a 24-h period without intervention in the 24-h test-retest cohort. The $ICC_{3,1}$ values were interpreted as excellent (> 0.75), moderate-to-good (0.4–0.75) or poor (< 0.4).[31] The agreement for these outcomes was represented with a Bland-Altman plot, including their 95% CI for bias and for the limits of agreement.[32] A regression approach was also included when a relationship between differences and the size of measurement was identified.[32]

The change in the amount of wet sputum collected during the 24-h follow-up period after the airway clearance session was expressed as the absolute weight (measured in grams) and as the change relative to the amount of sputum expectorated over the 24-h baseline period (measured as a percentage). To estimate the minimum important difference, distribution-based and anchor-based methods were used with data from the airway clearance cohort. The mean results for the 3 days were used to ensure greater accuracy of the results. The techniques used for the distribution-based approach are summarized in Table 1. For anchor-based methods, 2 potential anchors were explored: the total LCQ score, because the minimum important difference has been established as 1.3 points and is known to change after airway clearance treatment;[18] and the GRC score, because this is the recommended method for estimating the minimum important difference of an outcome.[28]

A correlation of ≥ 0.4 between the change in the anchor and the change in the amount of sputum collected (weight or percentage) over the 24-h follow-up period was considered necessary to calculate the minimum important difference using the anchor-based method.[33] In the presence of sufficient correlation, sensitivity- and specificity-based approaches with receiver operating characteristic curves would be used. If the correlation requirements are not reached, however, the estimation of minimum important differences can only be calculated using a distribution-based approach.

Within-group differences in total LCQ score and 24-h sputum weight were analyzed using a paired *t*-test and a Wilcoxon signed-rank test, and these values were expressed as the mean difference and median difference along with the respective 95% CIs. A P value < .05 was considered statistically significant in all analyses. Effect size (r) was also estimated and interpreted as small (r < 0.3), moderate (r ≥ 0.3), or large (r ≥ 0.5).

Results

Sixty subjects were recruited and completed the baseline assessment, comprising the 24-h test-retest cohort. Of these, 42 subjects underwent airway clearance treatment, making up the airway clearance cohort. The baseline characteristics of both cohorts are outlined in Table 2.

Table 1. Distribution-Based Approach to Estimate the Minimum Important Difference of Wet Sputum Weight*

Method	Formulas	Minimum Important Difference†			
		Absolute Value, g	Responders, *n* (%)‡	Relative Change from Baseline, %	Responders, *n* (%)‡
0.5 × SD	$0.5 \times SD_{baseline}$	−5.7	28 (66.7)	NA	NA
Cohen effect size	$0.5 \times SD_{\Delta}$	−4.5	30 (71.4)	−16.8	34 (80.1)
Empirical rule effect size	$0.08 \times 6 \times SD_{\Delta}$	−4.4	32 (76.2)	−17.5	34 (80.1)
Standard error of measurement	$SD_{baseline} \times \sqrt{1 - ICC}$	−5.4	28 (66.7)	NA	NA
Minimum detectable change with a 95% confidence level	$1.96 \times \sqrt{2} \times SEM$	−6.4	28 (66.7)	NA	NA

n = 42 subjects.
* Wet sputum weight collected in the 24 h after intervention in the airway clearance cohort.
† Minimum important difference based on the mean value of 3 measurements.
‡ Responders refer to those with ≥ the minimum important difference.
Baseline = mean of the spontaneous sputum expectorated over a 24-h period on 2 different days during the recruitment period (without airway clearance treatment)
Δ = difference between the mean of the sputum expectorated over the 24-h follow-up period after intervention and the baseline/Δ percentage of change from baseline
SEM = standard error of measurement
ICC = intraclass correlation coefficient of the sputum collected during the 24-h follow-up period after intervention
NA = not applicable

Table 2. Baseline Characteristics

Characteristics	24-h Test-Retest Cohort	Airway Clearance Cohort
Subjects, *n*	60	42
Age, y, mean (SD)	62.7 (15.9)	61.0 (17.4)
Female, *n* (%)	41 (68.3)	28 (66.6)
Body mass index, kg/m^2, mean (SD)	24.5 (3.5)	24.2 (3.7)
Etiology of bronchiectasis, *n* (%)		
Idiopathic	20 (33.3)	18 (42.9)
Post-infection	18 (30.0)	12 (28.5)
Associated COPD	10 (16.7)	6 (14.3)
Immunodeficiency	5 (8.3)	4 (9.5)
Primary ciliary dyskinesia	2 (3.3)	2 (4.8)
Others	5 (8.3)	0 (0.0)
Chronic airway infection, *n* (%)*		
Pseudomonas aeruginosa	26 (43.3)	(47.6)
Haemophilus influenzae	6 (10)	4 (9.5)
Long-term antibiotic treatment, *n* (%)		
Oral (macrolides)	13 (21.6)	7 (16.6)
Inhaled	19 (31.6)	17 (40.5)
Lung function, mean (SD)		
FEV_1, L	1.66 (0.8)	1.79 (0.8)
FEV_1 % predicted	64.1 (19.3)	67.3 (19.7)
FVC, L	2.59 (0.9)	2.75 (0.9)
FVC % predicted	76.0 (17.0)	79.3 (17.1)
FEV_1/FVC	0.63 (11)	0.64 (10)
Baseline sputum expectoration, g†		
24-h period, median (interquartile range)	15.4 (11.4–26.1)	15.6 (14.0–27.7)
> 15 g/24 h, *n* (%)	35 (58.3)	29 (69.0)

* Chronic airway infection was defined as pathogen organism cultured in ≥ 2 or more sputum samples, ≥ 3 months apart, in the preceding 12 months.
† Measured on 2 different days within the week prior to start the study.

Test-Retest Reliability

The reliability was found to be acceptable ($ICC_{3,1}$ = 0.85) for the 2 spontaneous sputum samples collected over a 24-h period without intervention, with confidence intervals from 0.76 to 0.91. No bias was identified using Bland-Altman plot, with a mean difference of 1.2 (95% CI−0.7 to 3.0); however, the limits of agreement are not narrow enough, showing larger ranges for greater amounts of expectorated sputum (Fig. 2). After modeling the relationship between mean differences and sputum weight, it was identified that limits of agreement fit better for lower sputum weights (∼ ≤ 15 g) (Fig. 2).

Estimation of the Minimum Important Difference

Distribution-Based Methods. The minimum important difference of the 24-h sputum weight after airway clearance treatment compared to baseline ranged between −4.4 and −6.4 g (being the last value the minimum detectable change with a 95% confidence level). Therefore, the minimum important difference estimate should be a reduction of at least 6.4 g to guarantee a change that exceeds the error of measurement.[34] In addition, a threshold of change from baseline of between −16.8% and −17.5% was estimated using distribution-based methods (Table 1).

Suitability of LCQ and GRC Scale as Potential Anchors for the 24-h Sputum Weight. A reduction in the amount of wet sputum expectorated after the intervention was observed in 38 subjects (90.4%). Less sputum was expectorated during the 24 h following the intervention than at the 24-h baseline assessment, with the effect size ranging from 0.71 to 0.79 (see the supplementary materials at http://www.rcjournal.com). The median (interquartile range) relative change from baseline was −47.8% (−62.9 to −25.8). Three subjects (7.1%) showed a change in sputum weight score of ≥ 85% from baseline, and 4 subjects (9.5%) scored ≤ 15%, indicating that there were no extreme changes. Subjects collected similar amounts

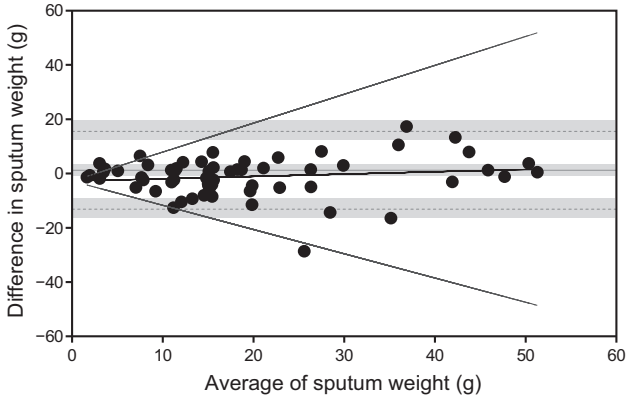

Fig. 2. Bland-Altman plot for absolute reliability of the spontaneous sputum weight collected over 24 h at baseline in the test-retest reliability cohort ($n = 60$). The solid gray line represents the mean difference between both measurements (1.2), dotted lines represent the 95% upper (15.5) and lower limits of agreement (−13.1), shared areas represent the 95% CI for mean (−0.7 to 3.0) and upper (12.2 to 18.7) and lower (−16.4 to −9.9) limits of agreement, and black lines represent the limits of agreement using the regression approach.

of sputum during the treatment period, independent of the intervention performed (hyperosmolar agent inhalation plus airway clearance techniques vs airway clearance techniques alone; all P values $> .05$) (see the supplementary materials at http://www.rcjournal.com), which indicates that pooling the findings from the 2 crossover trials was appropriate.

The total LCQ score improved after 1 week of airway clearance treatment, with a mean difference of 0.6 (95% CI 0.0–1.3) and a median difference of 0.6 (95% CI 0.3–1.0), and the effect size ranged from 0.32 to 0.52 (see the supplementary materials at http://www.rcjournal.com). Nevertheless, the change in total LCQ score did not correlate with the change in the 24-h expectorated mean sputum (absolute weight) from baseline ($r = 0.1$, $P = .53$), nor with the relative change ($r = -0.1$, $P = .34$) (Fig. 3). Most subjects (83.3%) reported a substantial change using the GRC scale, with a median (interquartile range) of −6 (−7 to −5). No significant correlations were observed between patient GRC score and the change in 24-h expectorated sputum (absolute) from baseline ($r = 0.2$, $P = .21$), nor with the relative change ($r = 0.2$, $P = .20$) (Fig. 3). Therefore, neither total LCQ score nor GRC could be used as reliable anchors.

Discussion

This study provides evidence of the test-retest reliability of wet sputum weight as an outcome measure for short periods (ie, 24 h) in clinically stable individuals with bronchiectasis. This study also reports an estimate of the minimum important difference after an airway clearance session based on the mean value of 3 sessions.

Mucociliary clearance rates, assessed in vivo with gamma scintigraphy, is the most widely accepted outcome measure to assess the effects of airway clearance treatments.[14,35] However, only a few previous trials have used this outcome to assess the effects of mucoactive agents or airway clearance techniques in people with bronchiectasis, indicating that poor accessibility to the highly specialized equipment required and the need to inhale radiolabeled markers limits its use in research and, in particular, in clinical practice.[36,37] Although the wet sputum weight is generally considered a controversial measure to assess the effects of airway clearance due to saliva contamination, involuntary swallowing, etc., its use in evaluating short-term efficacy is acceptable even though its psychometric properties have not been established for any specific disease.[13,14]

Subjects were frequently educated and encouraged in our study to avoid sputum swallowing during the assessment time period, and any saliva contamination was manually removed from the sputum samples. Drying sputum samples before weighing is a recommended method for completely removing saliva mixed with sputum; however, we preferred to use wet sputum weight in this study for 3 reasons: (1) it provides immediate information to patients and facilitates response to the GRC score because they could compare the amount of sputum expectoration between different periods of time; (2) the findings may be easily transferred to clinical practice because it is a more feasible measure; and (3) it has been suggested that wet sputum weight is an acceptable predictor of dry sputum weight, although further research is needed on this point, especially when hydrator therapies have been used.

Based on our data, spontaneous sputum collected over 24 h exhibits acceptable reliability with an ICC of 0.85 (95% CI 0.76–0.91)]. However, these results are a bit lower than those described for other widely accepted outcomes in bronchiectasis, such as walking tests,[38] impact of cough on quality of life,[26] and lung clearance index,[39] all of which have a lower limit of 95% CI > 0.9.

The viscoelastic properties and solids content of sputum are alternative biomarkers used to analyze the effect on airway clearance. However, a recent study has reported poor reliability for both of these methods with regard to sputum samples from individuals with cystic fibrosis ($ICC_{3,1}$0.21–0.42).[40] The higher reliability values obtained in our study using sputum weight may be explained by the short interval between sputum sample collections (ie, within the same week), the stable condition of all subjects throughout the study, and the highly standardized sputum-collection process.

Although no systematic difference has been found for the spontaneous sputum collected over a 24-h period without intervention, the agreement intervals are not sufficiently

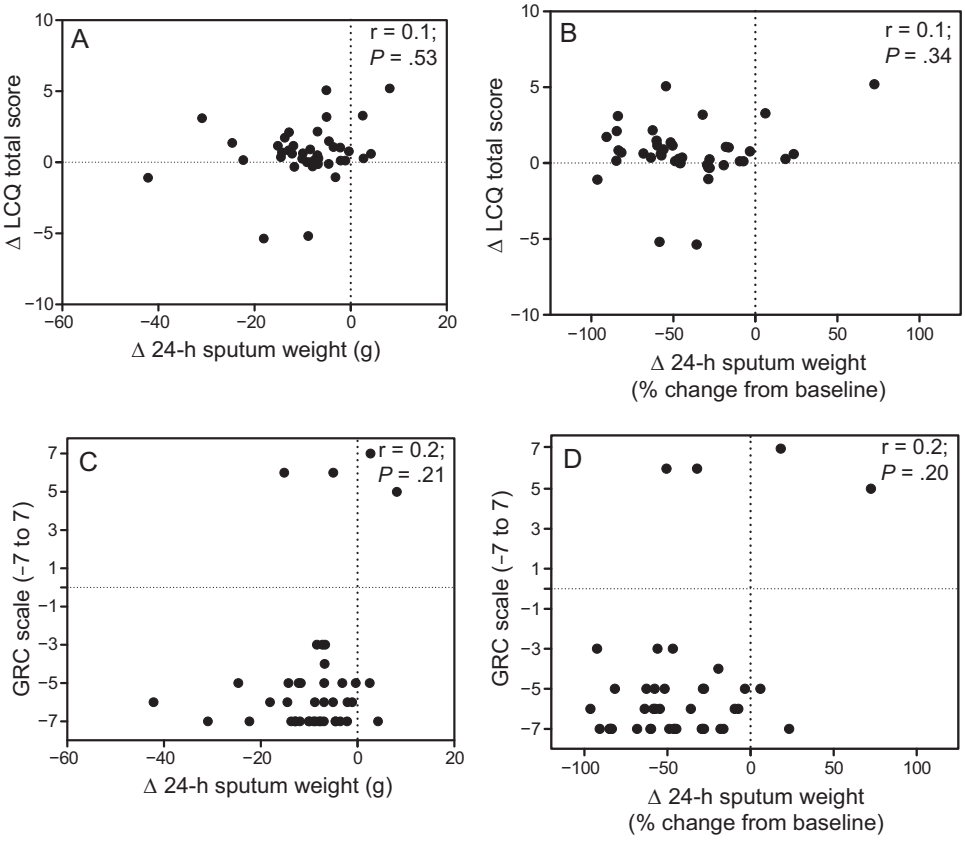

Fig. 3. Correlation (Spearman rank correlation) between change in 24-h sputum weight and anchors (LCQ total score and GRC scale) using airway clearance cohort ($n = 42$). (A) and (C) present the absolute change in sputum weight; (B) and (D) present the percentage of change from baseline (%). LCQ = Leicester Cough Questionnaire; GRC = global rating of change.

narrow, particularly for high levels of sputum weight expectorated (ie, ≥ 15 g). Therefore, the use of repeat measurements to improve the reliability and agreement may be a solution, as have previously been recommended for sputum samples.[40,41] Moreover, the ability to detect differences between groups using sputum weight is limited due to the high variability observed, thus only intrasubject comparisons are recommended, such as clinical practice or crossover designs.

Nevertheless, these results should be interpreted with caution because the number of subjects with lower levels of expectoration was low in this study (ie, 31% of subjects in the airway clearance cohort), and our sample size does not allow stratification of data according to the level of expectoration.[30] Therefore, future research is needed to confirm this finding. In addition, more in-depth analysis of the reproducibility of sputum weight should be conducted by performing longitudinal studies with longer intervals between measurements, similar to clinical practice.

Although the anchor-based methodology is considered the best method to estimate the minimum important difference, the lack of correlation between the change in 24-h wet sputum weight and the anchors selected impeded their estimation in this study.[24] One possible reason for the lack of correlation could be that the short duration of the airway clearance intervention in this study did not enable us to observe greater changes in LCQ than its minimum important difference, which is in contrast to a previous long-term trial.[18]

The potential impact of physiotherapist and subject beliefs regarding the sputum weight on GRC score was minimized because subjects were not informed about the study hypothesis (ie, the expected direction of change); in addition, the question focused on a period of time during which subjects had no contact with the physiotherapist and thus did not receive any feedback, and neither end of the Likert scale was marked as better than the other. However, the fact that subjects did not regularly perform any airway clearance treatment before the study may explain why almost all subjects classified their change in 24-h sputum weight using the GRC score as substantial. More research is needed in the future to assess real impact of airway clearance interventions on social life.

Most subjects ($n = 38$, 90%) presented a reduced need to expectorate after the airway clearance intervention, showing a clear direction of change. Using the distribution-based methodology, the minimum important difference for the 24-h wet sputum weight was found to range from −4.4 to −6.4 g (absolute value), with a relative change of about −17%. Because this estimate was based solely on the statistical criteria (ie, the distribution values of our sample), the selection of the minimum detectable change with a 95% confidence level as the lower limit of minimum important difference estimation is strongly recommended.[34] For that reason, the minimum important difference estimated for the 24-h sputum weight was at least −6.4 g, ensuring the selection of a minimum value that implies a real change and not a measurement error.

The majority of subjects ($n = 28$, 67%) achieved a reduction in sputum collected over 24 h after the intervention of ≥ 6.4 g, and 80% of them achieved a relative change ≥ −17.5% from baseline, showing that the minimum important difference is feasible for airway clearance treatment in stable individuals with bronchiectasis. However, these data should be interpreted with caution because distribution-based methods are not fully able to separate clinical importance from statistical significance.

The availability of a minimum important difference for sputum weight may assist in clinical practice and future research to assess the short-term efficacy of new treatments to enhance sputum expectoration in this target population, in addition to assisting in sample-size calculations for future trials. Nevertheless, future studies are needed to corroborate the minimum important difference estimated using other potential anchors, such as cough frequency, assessed using monitors or computerized respiratory sounds.[42,43] Moreover, the validity of this minimum important difference estimate should be further evaluated with longitudinal studies that include a relevant clinical indicator such as exacerbation frequency or the severity of exacerbations.

The validity of using sputum weight in this manner is not evaluated in this study. Previous studies have noted that self-reported sputum production is an independent factor of cough frequency in people with bronchiectasis.[42] Therefore, if we consider that the main effect of airway clearance interventions is to reduce the need to expectorate after treatment, the number of coughs using objective cough monitors might be a good standardized outcome measure to analyze the construct validity of sputum weight in future studies.[42]

Our study has some limitations. Although the anchor-based method could not be used, the lower limit of the minimum important difference estimate was based on the minimum detectable change with a 95% confidence level to guarantee a real change.[34] Our population was not adherent or were naïve to airway clearance treatment, and the majority of subjects had a moderate level of expectoration (≥ 15 g/24 h), thus, it is not clear whether these results can be extrapolated to individuals adhering to airway clearance treatment or having lower levels of expectoration. Finally, although the direction of change was clear (ie, almost all subjects experienced a reduction in the need to expectorate after the airway clearance intervention), the response to this treatment could differ over longer periods. Further research is needed to clarify these points.

Our study also has notable strengths. First, the interval time of 24 h used to estimate the minimum important difference is in line with previous studies using mucociliary clearance rates or lung clearance index (LCI) as outcome measures to assess airway clearance interventions.[35,44] Because the timing and duration of airway clearance treatments are still unknown, measurements of 24-h clearance have gained interest as a method to assess the possible cumulative clearance effects.[16,18,19] In addition, to improve the accuracy of the findings, repetitive measurements were included to estimate the minimum important difference. Finally, the measurement of wet sputum weight with a calibrated scale seems to provide more accurate results than sputum volume, perhaps because the graduated scale of volume containers requires an assessor's interpretation. Indeed, there may be a tendency to overestimate the findings obtained using the sputum volume compared to the sputum weight.[45] However, both methods have not yet been adequately compared.

Conclusions

Wet sputum weight was an acceptable reliable measure over the 24 h after intervention, but the level of agreement is not narrow enough, particularly for greater levels of expectoration (ie, > 15 g/24 h). Moreover, it is estimated that a reduction of ≥ 6.4 g in the amount of sputum expectorated during the 24 h following the intervention, or a relative change of about −17% from baseline, is needed to achieve a real change in our population, as assessed on the basis of distribution-based methods. Therefore, the use of sequential measurements of sputum weight is recommended to assess the short-term effects of airway clearance treatments in stable individuals with bronchiectasis.

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