

Comparison of the Lung Flute[®] with the Acapella[®] in the Treatment of COPD with
Chronic Bronchitis

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Word count: 2554

Source of support: Medical Acoustics, Inc.

ABSTRACT

Chronic obstructive pulmonary disease (COPD) is characterized by mucus hypersecretion that contributes to the morbidity and is associated with increased mortality. The Lung Flute[®] is a new oscillatory positive expiratory pressure (OPEP) device that produces a low frequency acoustic wave with vigorous exhalation that increases mucociliary clearance. We hypothesized that the Lung Flute[®], used on a twice daily basis will provide clinical benefit to patients with COPD with chronic bronchitis. Acapella[®], an OPEP device which is currently available and approved for the clearance of respiratory secretions was used as a comparator in a randomized open label eight week trial in 40 COPD patients. Thirty seven patients completed the study. For the primary end point, change in 24 hour dry sputum weight from baseline, the two treatments were equivalent. At 8 weeks, both devices improved symptoms as assessed by the Chronic COPD questionnaire as well as quality of life as assessed by St. George Respiratory questionnaire, with the Lung Flute[®] associated with larger changes than the Acapella[®]. There was no change in baseline lung function over 8 weeks in both arms. Adverse effects were minor, with only 1 patient discontinuing treatment because of musculoskeletal chest discomfort related to blowing vigorously in the Lung Flute[®] in the initial week of treatment. The Lung Flute[®] is a safe and effective OPEP treatment for mucus hypersecretion in COPD, and is equivalent to the Acapella[®] for this purpose.

Abstract Word Count: 234

Mucus hypersecretion and impaired mucociliary clearance is a common problem in patients with COPD, and contributes significantly to the morbidity and mortality of this disease (1, 2). In spite of the need for efficacious, convenient and safe treatment for mucus hypersecretion, current choices are few with limited data to support their efficacy in COPD (3, 4). The Lung Flute[®] is a new small self-powered audio device that belongs to the family of Oscillatory Positive Expiratory Pressure (OPEP) devices, which includes the Flutter[®] and the Acapella[®] (5, 6). When blown into with an exhalation vigorous enough to make the reed oscillate, the Lung Flute[®] generates a sound wave of 16 to 22Hz with an output of 110 to 115 dB using 2.5cms H₂O of pressure. This sound wave has the ability to travel down the tracheobronchial tree and vibrate tracheobronchial secretions. This vibration enhances mucociliary clearance of the lower respiratory tract thereby resulting in the induction of sputum. This functionality of the Lung Flute[®] has been applied to sputum induction for diagnostic testing, for which it is currently a Food and Drug Administration (FDA) approved device.

We hypothesized that the ability of the Lung Flute[®] to enhance mucus clearance from the lower airways could be used for therapeutic purposes in COPD, if the device was used on a chronic basis. This report is the first systematic evaluation of the therapeutic application of the Lung Flute[®] in human subjects. The efficacy and safety of the Lung Flute[®] in a group of COPD patients with chronic bronchitis was compared with a predicate device, the Acapella[®] (Smiths Medical), which works on a similar principle and is available for therapeutic use in lung hypersecretory disorders. The primary end point of the study was the comparison of 24 hr dry sputum weights with the use of the Lung Flute[®] as compared to the Acapella[®]. Several secondary end points were assessed for efficacy and safety, including COPD symptoms, health status, spirometric lung function and daily albuterol use.

Methods

Study Design

This was an eight-week, randomized, controlled, two arm parallel study that was powered to demonstrate equivalency of the new device, the Lung Flute[®], to the predicate device, the Acapella[®]. The study was open label. The clinical trial registration number of this trial is NCT00560105.

Subjects

The study was approved by the Human Studies subcommittee for the VA WNY Healthcare system. We planned to enroll 40 subjects with COPD with chronic bronchitis at a single center (Buffalo VA Medical Center). Inclusion criteria were: a) at least 40 yrs of age, b) presence of airflow obstruction by spirometry (GOLD Stage 2-4), c) presence of chronic bronchitis, i.e. cough productive of sputum on most days of the week, d) current smoker or ex-smoker with at least 10 pack yrs of smoking history (7). Exclusion criteria were a) exacerbation of COPD or hospitalization for COPD within 8 weeks prior to enrollment, b) predominant asthma and bronchiectasis by clinical assessment, c) history of cough syncope d) pregnant or nursing women e) inability to comply with study procedures.

Procedures

The study consisted of a screening visit, two weeks of intervention-free run-in, a randomization visit and then on treatment clinic visits at 1, 2, 4, 6, and 8 weeks. Participants who met the inclusion/exclusion criteria on screening were enrolled and provided with a daily

paper diary to record symptoms and rescue albuterol use. In addition they were instructed to provide two 24 hr sputum collections over the next 2 weeks. A randomization visit was done within 2 weeks of the enrollment visit. Participants who were compliant with the 24 hr sputum collection and at least 50% of the daily diary entries were randomized to either the Lung Flute[®] or the Acapella[®]. Randomization was done by a pre-specified randomization table. Detailed instructions for the use of either device were provided as follows. For the Acapella[®], participants were instructed to watch the instructional video provided by the manufacturer, the device was adjusted for the participant as per the manufacturer's instructions, and they were instructed to use the device twice a day for 2 cycles consisting of 20 breaths followed by 3 huff coughs. For the Lung Flute[®], participants were instructed to blow twice in to the device vigorously enough to make the reed oscillate, followed by 5 normal breaths. This was repeated 10 times, followed by 3 huff coughs to complete 1 cycle. Two such cycles were recommended twice a day. Baseline Spirometry, Clinical COPD questionnaire (CCQ) and St. George's Respiratory Questionnaire (SGRQ) were obtained at the randomization visit (8-10).

Participants were instructed to complete a daily diary every evening in which they recorded their breathlessness, cough and sputum severity on the breathlessness, cough and sputum scale (BCSS), as well as the number of puffs of rescue albuterol used in the past 24 hrs (11). At each subsequent on therapy clinic visit, 24 hour sputum samples were collected, a clinical examination was performed, adverse effects were recorded and daily diaries were collected. In addition, at the end of therapy 8 week visit, spirometry, CCQ and SGRQ were completed. The Lung Flutes[®] were replaced at every visit and the patient was instructed to use each Lung Flute[®] for 1 week.

Dry Sputum Weights

Twenty four hr sputum collections were transferred to pre-weighed centrifuge tubes and weight of total sputum was measured. All samples were then centrifuged at 10,000g for 10mins at 4°C, and the supernatant obtained was removed. The residual pellet and tube were re-weighed and the dry sputum weight was obtained by subtracting the tube weight from the value obtained.

Data analysis

The primary endpoint of dry sputum weight was assessed by using mixed models. Mixed models were also used to determine changes in daily BCSS scores and use of inhaled albuterol from baseline in the two groups of patients. Secondary end-points of changes between baseline and week 8 in spirometric measures, SGRQ and CCQ were assessed by paired t tests. A $p < 0.05$ was considered significant.

Results

Participants

We enrolled 45 subjects, of which 5 subjects either did not meet the initial inclusion/exclusion criteria (n=3) or did not meet the compliance criteria between the enrollment and randomization visit (n=2). Of the 40 subjects who were randomized, 20 each were randomized to the 2 devices. Of these 40 subjects, 37 completed the study. Of the 3 subjects who did not complete the study, one was randomized to the Acapella[®] (participant was non-compliant with study instructions) and 2 were randomized to the Lung Flute[®] (1 discontinued

Lung Flute[®] after 1 week of use because of musculoskeletal chest discomfort with use of the device and 1 was non-compliant with study instructions).

Baseline clinical characteristics of the forty subjects randomized into the study are described in Table 1. There were no statistically significant differences in the demographics, smoke exposure history and lung function between the subjects enrolled in the two arms of the study.

Comparison of dry sputum weights between the Lung Flute[®] and the Acapella[®]

In order to test the overall treatment effect on dry sputum weight over the course of the study, mixed effects analysis were performed. These models allow us to account for the longitudinal nature of the data. We assumed that the observations collected within each patient were correlated; however, observations collected across patients were assumed to be independent. Dry sputum weights obtained prior to and at randomization were regarded as baseline measurements, while those obtained at week 1, 2, 4, 6 and 8 were examined for treatment effects. Neither device use had a statistically significant sustained effect on 24 hr sputum volumes (Figure 1). Furthermore, we did not find any difference between the effects of the Lung Flute[®] vs. Acapella[®] on the dry sputum weight over the course of the study ($p = 0.94$).

Spirometry Results

Spirometric data was collected primarily to document safety of the interventions. Pre- and Post-bronchodilator spirometry was obtained at the randomization visit and at Week 8. Though there were small improvements in the parameters in both arms, there were no

statistically significant differences in the post-bronchodilator values from baseline in any of the spirometric measures (Table 2).

CCQ Results

The CCQ is an objective validated tool to assess COPD symptoms. CCQ was measured at the randomization visit and at the end of the study visit at week 8. There was a significant improvement in the CCQ (3.24 ± 0.30 at randomization, 2.82 ± 0.26 , mean decrease of 0.41 units, $p = 0.007$, paired t-test) in patients who were using the Lung Flute[®]. A smaller and statistically non-significant improvement in the CCQ (2.53 ± 0.20 at randomization, 2.29 ± 0.25 , mean decrease of 0.24 units, $p = 0.16$) was seen in patients who were using the Acapella[®] (Figure 2). The change in CCQ was not statistically different between the two treatments ($p=0.44$). The minimal important difference (MID) for the CCQ is 0.4 units, which was met on an average by the patients in the Lung Flute[®] arm but not the Acapella[®] arm. These results demonstrate a greater efficacy of the Lung Flute[®] in improving COPD symptoms as compared to the Acapella and this efficacy was clinically meaningful.

SGRQ results

SGRQ is a well validated, widely used health status questionnaire specific for COPD. Its MID is 4 units. With the Lung Flute[®], an improvement in health status of 4.71 ± 2.53 (SEM) units in the total SGRQ score was seen at the end of study (8 weeks) visit as compared to the randomization. This difference in total SGRQ score was however not statistically significant ($p = 0.08$). Improvements were noted in all 3 domains of symptoms, activity and impact of the SGRQ (Table 3). With the use of the Acapella[®], small non-statistically significant changes in

total SGRQ (0.44 ± 1.82 units), as well as in the domain scores were seen (Table 3). The change in SGRQ total score was not statistically different between the two treatments ($p=0.19$). These results suggest that the Lung Flute[®] had a larger effect on improvement of quality of life in COPD than the Acapella[®].

BCSS and Albuterol use

Breathlessness cough and sputum score is a well validated measure of daily symptoms of COPD, with a MID of 0.3 units. In a mixed model analysis, with the Acapella[®], a mean \pm SEM decline of 0.35 ± 0.18 units in the BCSS from 2.82 ± 0.10 units pre-treatment to 2.43 ± 0.05 units during treatment was seen ($p=0.05$). Use of Lung Flute[®] resulted in a mean \pm SEM decline of 0.26 ± 0.18 units in the BCSS from 3.79 ± 0.10 units pre-treatment to 3.63 ± 0.05 units during treatment was seen ($p=0.16$). The changes were statistically similar in the two treatment arms ($p=0.72$). Both devices improved symptoms assessed by the BCSS score, with the Acapella[®] showing a larger effect which reached the threshold of a minor clinically important improvement. Reported daily albuterol use did not change significantly in either arm.

Adverse effects

There were no serious adverse events or mortality in this study. Only 1 person dropped out of the study at week 1, because of musculoskeletal chest discomfort with blowing in the Lung Flute[®]. Three other patients complained of similar discomfort at week 1, however, these 3 patients continued in the study and the chest discomfort resolved spontaneously in spite of continuing use of the device. The Acapella[®] was not associated with such chest discomfort. The most common adverse effect were cold symptoms, 6 episodes were seen in the Acapella[®] arm while 3 such episodes were seen in the Lung Flute[®] arm. Two COPD exacerbations occurred

during the study, both in patients using the Lung Flute[®]. Table 4 lists all the adverse effects observed in the study that were respiratory or thought to be possibly related to the study devices.

Discussion

The Lung Flute[®] has been shown to be efficacious in inducing sputum when used once and is approved for such use to obtain diagnostic sputum samples. In this first study of repeated use for therapeutic purposes, the Lung Flute[®] was equivalent to a similar device, the Acapella[®], in its effects on 24 hour dry sputum weight. However, a consistent increase in dry sputum weight was not seen with either device in this study, which is consistent with observations made in other studies with other mechanical treatments of lung hypersecretory disorders (3, 5, 6). In this and other studies, patients do appear to benefit from these treatments. This would suggest that dry sputum weight is not a good correlate of clinical efficacy of measures to improve lung clearance. The measurement of dry sputum weight is confounded by salivary contamination, day to day variability, swallowing, and its inability to detect changes in ease of expectoration.

Clinical benefit was also assessed in several secondary end points in this study. Both the Lung Flute[®] and the Acapella[®] improved COPD symptoms, which were assessed with two different measures, the CCQ and the BCSS. A larger reduction in symptoms was seen with the Lung Flute[®] with the CCQ, while the reverse was true with the BCSS. However, the differences between the two devices were not statistically significant. Disease related health status is an important efficacy end point in COPD. The Lung Flute[®] did show larger improvements in health status than the Acapella[®] as measured by the SGRQ, though the difference did not reach statistical significance. Though dry sputum weight did not change, subjective benefit in health status and symptoms is seen with OPEP treatment in COPD.

The Lung Flute[®] and Acapella[®] were both well tolerated. As the Lung Flute[®] required vigorous exhalations to achieve oscillation of the reed, musculoskeletal discomfort was seen in 20% of patients in the first week. However, only 1 of 20 (5%) patients discontinued use of the device because of this discomfort, while in the other 3 patients it was transient. Other adverse events were minor and appeared to be unrelated to treatment. Transient throat irritation, which was the most common adverse effect with single use of the Lung Flute[®], was not seen with chronic use.

The mechanism of action that results in clinical benefits of Lung Flute[®] and Acapella[®] in COPD is presumed to be increased mucociliary clearance of tracheobronchial secretions. However, a limitation of this study was the absence of measurement of mucociliary clearance. Other limitations of this study include the lack of blinding, which is difficult in device studies. The duration of the interventions was not long enough and the study was not large enough to determine if other parameters such as lung function and exacerbation frequency were impacted with the Lung Flute[®] or the Acapella[®].

There is a paucity of treatments that have demonstrated efficacy in the treatment of mucus hypersecretion in COPD. Currently available mucolytics and expectorants are of unproven efficacy in COPD, and the beneficial effects of agents such as n-acetylcysteine and carbocysteine are more likely related to their antioxidant effects rather than their mucolytic effects (12, 13). Mechanical means to improve mucus clearance in hypersecretory lung conditions including Oscillatory PEP devices such as the Acapella[®] and Flutter, chest vibration and percussion and breathing techniques have not been tested systematically in stable COPD . This study demonstrates that oscillatory PEP devices are of potential benefit in COPD patients

with mucus hypersecretion. Further studies with the Lung Flute[®] should explore mechanisms and clinical benefit with longer term use in COPD and other hypersecretory lung diseases.

Table 1. Subject demographics.

Characteristic	Lung Flute [®]	Acapella [®]	p value
Age	64.0 ± 2.4	60.9 ± 1.6	0.28
Sex	13 men 7 women	15 men 5 women	0.73
Race	17 white 3 African American	15 white 5 African American	0.69
Pack yrs smoking	50.8 ± 3.5	58.3 ± 6.6	0.32
Current smoker	11 ex, 9 current	7 ex, 13 current	0.34
FEV ₁ (liters)	1.41 ± 0.16	1.43 ± 0.12	0.91
FEV ₁ %predicted	48.3 ± 3.6	46.6 ± 3.0	0.72
FVC (liters)	3.07 ± 0.23	2.95 ± 0.18	0.67
FVC%	83.4 ± 4.5	75.2 ± 3.4	0.16
FEV ₁ /FVC ratio	45.3 ± 2.8	48.4 ± 2.8	0.43

FEV₁ = Forced expiratory volume in 1 second, FVC = Forced vital capacity in 1 second.

Table 2. Comparison of spirometric lung function at Randomization visit and Week 8 visit in the Lung Flute[®] and Acapella[®] patients.

Parameter	Lung Flute [®]			Acapella [®]		
	Randomization	8 week visit	p value	Randomization	8 week visit	p value
FEV ₁ (liters)	1.38 ± 0.14	1.44 ± 0.19	0.55	1.43 ± 0.13	1.49 ± 0.14	0.48
FEV ₁ % predicted	46.23 ± 3.65	47.9 ± 4.83	0.56	46.8 ± 4.37	48.6 ± 4.16	0.48
FVC (liters)	3.27 ± 0.25	3.27 ± 0.27	0.95	3.01 ± 0.18	3.17 ± 0.20	0.13
FVC % predicted	83.9 ± 4.39	84.6 ± 5.45	0.80	75.9 ± 4.58	80.5 ± 4.35	0.09
FEV ₁ / FVC	42.6 ± 2.60	44.0 ± 3.51	0.43	46.8 ± 2.95	47.5 ± 3.04	0.77

Table 3. SGRQ total and domain scores at baseline and week 8 (End of treatment, EOT).

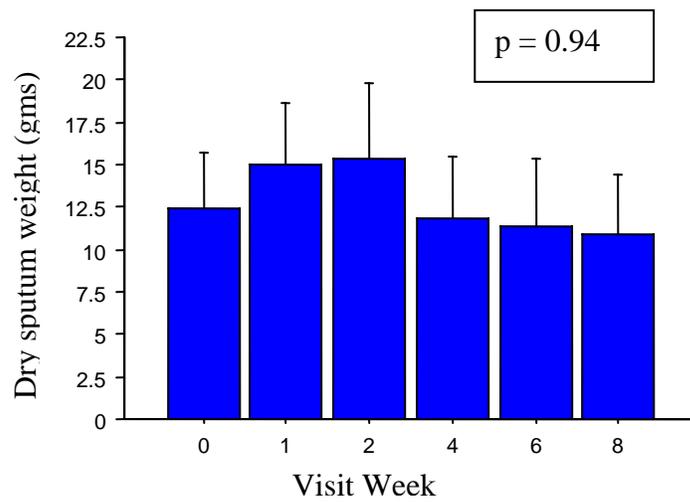
Score	Total Baseline	Total EOT	P value	Symptoms Baseline	Symptoms EOT	p value	Activity Baseline	Activity EOT	P value	Impact Baseline	Impact EOT	p value
Lung	51.9 ±	47.2 ±	0.08	68.5 ± 2.7	65.1 ± 3.9	0.24	73.8 ±	67.8 ±	0.09	33.8 ±	29.3 ±	0.15
Flute [®]	3.1	4.1					3.0	4.9		3.7	4.5	
Acapella [®]	45.5 ±	45.0 ±	0.81	63.6 ± 4.2	58.1 ± 4.7	0.18	61.8 ±	59.4 ±	0.38	29.7 ±	32.2 ±	0.25
	3.6	4.2					4.4	4.3		4.1	4.5	

Table 4. Respiratory and treatment emergent adverse events during the course of the study.

Adverse Event	Lung Flute [®]	Acapella [®]
Cold	3	6
Exacerbations of COPD	2	0
Musculoskeletal chest discomfort	4	0
Decreased sputum	2	1
Generalized Weakness	0	1
Throat Discomfort	0	1

Figure 1. Twenty four hours dry sputum weights (mean \pm 1 SEM) during the course of the study. Week 0 represents averaged values from 2 sputum collections obtained between the screening and randomization visit.

a) Lung Flute[®]



b) Acapella®

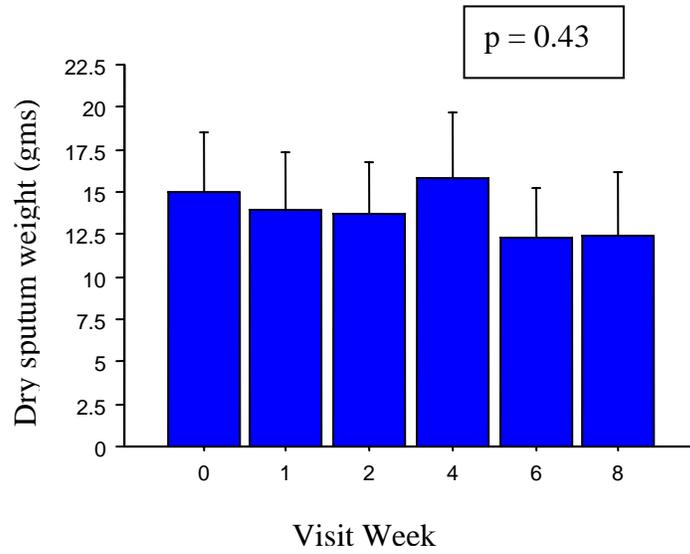
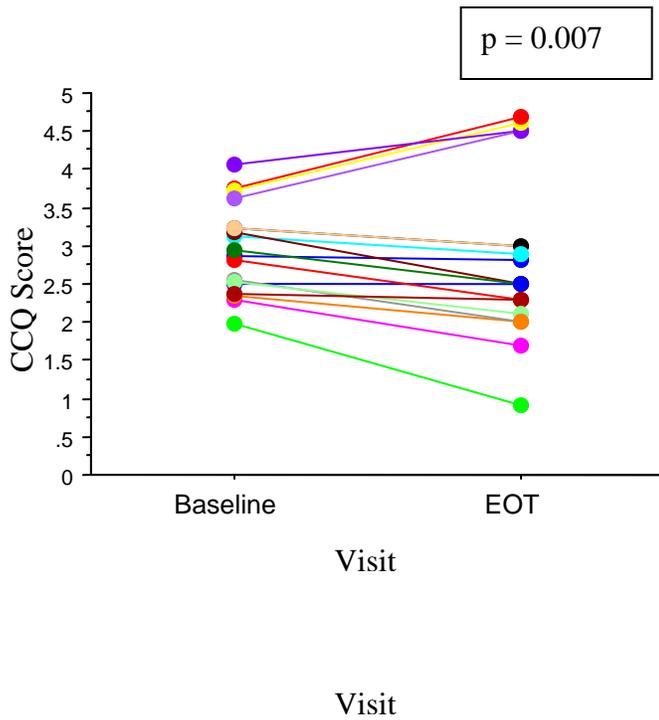
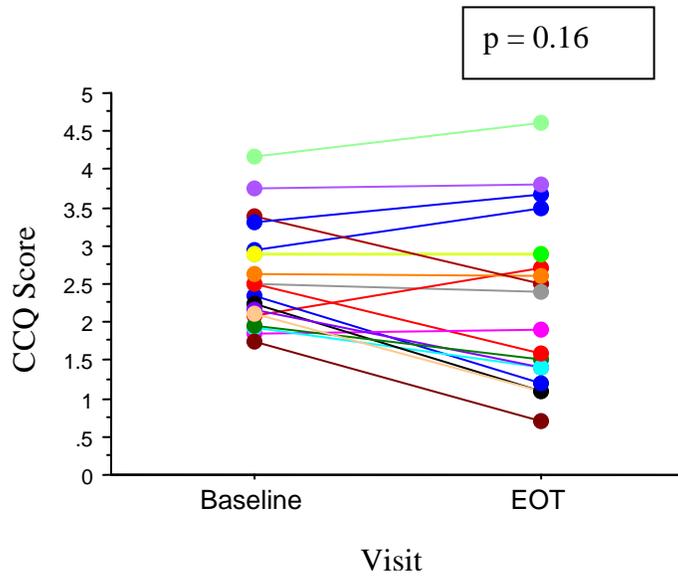


Figure 2. Change in Chronic COPD questionnaire scores from Baseline to Week 8 (End of treatment, EOT). Each horizontal bar represents an individual patient. The p values are from paired t-tests.

a) Lung Flute[®]



b) Acapella®



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