Chest Physiotherapy With Positive Airway Pressure: A Pilot Study of Short-Term Effects on Sputum Clearance in Patients With Cystic Fibrosis and Severe Airway Obstruction

Giulia Placidi RRT, Marta Cornacchia RRT, Guido Polese MD, Luisa Zanolla MD, Baroukh M Assael MD, and Cesare Braggion MD

BACKGROUND: The periodic administration of positive airway pressure combined with directed cough could aid mucus clearance in patients with cystic fibrosis (CF) and severe airway obstruction. OBJECTIVE: To compare the short-term effect of positive expiratory pressure (PEP) physiotherapy via mask (mask PEP), continuous positive airway pressure (CPAP), and noninvasive positive-pressure ventilation (NPPV) physiotherapies on amount of sputum collected. METHODS: Directed cough was standardized for each patient and used as the control treatment. We studied 17 patients with CF (mean ± SD age 28 ± 7 y) and severe airway obstruction (forced expiratory volume in the first second 25 ± 6% of predicted) admitted for pulmonary exacerbation. Mask PEP, CPAP, NPPV, and the control treatment (directed cough) were administered in a random sequence. Each patient received each treatment twice a day (in 70-min sessions) for 2 consecutive days. We measured the wet and dry weight of sputum collected and the number of directed and spontaneous coughs during each session. Spirometry and pulse oximetry were conducted before and after each session. For mask PEP, CPAP, and NPPV, each patient gave a subjective score for the efficacy and tolerability of the treatment, compared to the control treatment. RESULTS: There was no statistically significant difference in the dry weight of sputum collected: mask PEP 0.9 ± 0.6 g, CPAP 0.8 ± 0.4 g, NPPV 0.9 ± 0.6 g, control treatment 1.0 ± 0.8 g. There was a statistically significant difference in the wet weight of sputum collected: mask PEP 15.8 ± 5.5 g, CPAP 13.7 ± 5.5 g, NPPV 13.2 ± 5.0 g, control treatment 14.0 ± 5.0 g ($p < 0.05$), but that difference became nonsignificant when we took into account the number of spontaneous coughs. There were no statistically significant changes in the spirometry and pulse-oximetry values. The patients' subjective efficacy scores were similar for mask PEP, CPAP, and NPPV. Less fatigue was reported after NPPV and CPAP than after mask PEP. CONCLUSIONS: There were no differences in sputum clearance or pulmonary-function measures between mask PEP and short-term administration of either CPAP or NPPV combined with directed cough. After mask PEP these patients felt more tired than after CPAP or NPPV secretion-clearance therapy. *Key words: airway clearance, cystic fibrosis, noninvasive positive-pressure ventilation, sputum, directed cough.* [Respir Care 2006;51(10):1145–1153.

Introduction

Various techniques are available to aid mucus clearance in patients with cystic fibrosis (CF).[1,2] Positive-expiratory-pressure mask physiotherapy (mask PEP) consists of cycles of active breathing through a face mask against an

Giulia Placidi RRT, Marta Cornacchia RRT, Guido Polese MD, Baroukh M Assael MD, and Cesare Braggion MD are affiliated with the Cystic Fibrosis Center, and Luisa Zanolla MD is affiliated with the Cardiology Department, Ospedale Civile Maggiore, Verona, Italy.

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Correspondence: Cesare Braggion MD, Cystic Fibrosis Center, Ospedale Civile Maggiore, Piazza le Stefani 1, 37126 Verona, Italy. E-mail: cbraggion@qubisoft.it.

expiratory resister. Mask PEP, as with any airway-clearance technique, might ideally suit the needs of patients with mild-to-moderate airway obstruction, but it might not be equally suitable and effective for patients with CF and severe airway obstruction.[3] Radioaerosol studies showed that mucociliary and cough clearance were more impaired in patients with severe airway obstruction than in patients with mild-to-moderate lung disease.[4] Moreover, adverse effects could be associated with airway-clearance techniques when severe airway obstruction is present: airway-clearance techniques impose additional respiratory work that may carry a risk of respiratory-muscle fatigue and can be associated with oxyhemoglobin desaturation.[5–7] The effectiveness of airway-clearance techniques tailored to the pathophysiology of severe lung disease should therefore be addressed in clinical studies.

Continuous positive airway pressure (CPAP) therapy decreases the respiratory work and improves oxyhemoglobin saturation.[8,9] Periodic CPAP therapy aids in mobilizing retained secretions and in preventing and treating atelectasis after thoracic and abdominal surgery.[8,10] During CPAP therapy the patient breathes from a pressurized circuit against a threshold resister that maintains a constant preset airway pressure of 5–20 cm H_2O during both inspiration and expiration.[8] There are no data about the effectiveness of CPAP in removing airway secretions in patients with CF, and periodic CPAP therapy might represent an alternative to conventional airway-clearance techniques in patients with CF and severe lung disease.

Preliminary experience with noninvasive positive-pressure ventilation (NPPV) has been reported in CF patients awaiting lung transplantation.[11,12] Both inspiratory and expiratory positive airway pressure (IPAP and EPAP, respectively) are usually administered via nasal mask, using NPPV. The short-term and long-term improvement of gas exchange and the decrease in respiratory work associated with NPPV are promising and warrant further evaluation in randomized controlled clinical trials in CF patients with severe lung disease and respiratory failure.[11–15] Two studies[5,6] showed no difference in collected sputum weight between the short-term administration of noninvasive pressure-support ventilation combined with either forced expiratory technique or active-cycle-of-breathing technique and the administration of either forced expiratory technique or active-cycle-of-breathing technique used as single airway-clearance techniques. The advantage of noninvasive pressure-support ventilation was the relief of respiratory-muscle fatigue and oxyhemoglobin desaturation, compared with standard treatments.[5,6] Those studies proposed the combination of NPPV and an airway-clearance technique as a potential indication for NPPV in CF patients.

Ventilated patients suffer impairment of mucociliary transport, which is associated with the development of pulmonary complications.[16] The possibility of detrimental effects of either CPAP or NPPV on mucus clearance in CF patients may give rise to concern. Fauroux et al[5] found no difference in sputum weight between two 20-min sessions of conventional airway-clearance technique and nasal pressure-support ventilation.[5] Airway obstruction in CF patients included in that study ranged from severe to mild, and the amount of sputum was not measured in subsets of patients with different severities of lung disease. Moreover, patients were assessed in stable clinical conditions. During pulmonary exacerbations the amount of sputum may be increased and sputum clearance may be further impaired by more severe airway inflammation and obstruction and greater viscosity and adhesion of secretions than in stable condition.[17,18] Holland et al included patients with CF and severe airway obstruction hospitalized for acute respiratory exacerbations.[6]

The main purpose of the present study was to evaluate the short-term effects of directed cough combined with mask PEP, CPAP, and NPPV, on wet and dry weight of collected sputum. We considered the short-term changes in spirometry and oxygen-saturation values as a safety evaluation during the treatments. We were also interested in assessing patients' feelings regarding the effectiveness of these treatments in clearing sputum and the fatigue associated with the various treatments. Directed cough, used as single airway-clearance technique, was standardized for each patient and used as the control treatment.

Methods

Patients

Patients with CF and severe airway obstruction, who were admitted to the hospital for treatment of a pulmonary exacerbation, were eligible for the study. In all the patients, the diagnosis was established via repeated positive sweat tests.[18] Each patient had to meet the following inclusion criteria:

1. Age $>$ 15 y
2. "Best" value of forced expiratory volume in the first second (FEV_1) in the last 6 months $<$ 40% of predicted
3. Ability to expectorate sputum and reliably perform pulmonary function tests
4. More than 30 mL sputum volume expectorated per day
5. Proficiency in mask PEP

Patients were excluded if they had:

1. Severe respiratory failure with need of fraction of inspired oxygen $>$ 31% and/or symptoms or signs of right heart failure
2. Airway infection with *Burkholderia cepacia complex* and/or oxacillin-resistant *Staphylococcus aureus*

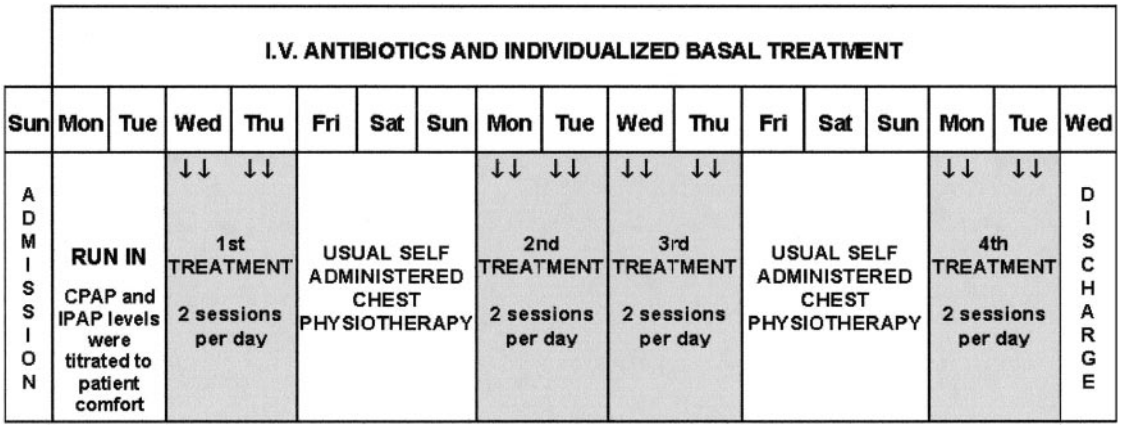

Fig. 1. The 4 treatment periods were distributed over a 16-day study period during hospitalization. The treatments were administered with a cross-over randomized design, twice a day, starting at 9 AM and 3 PM on 2 consecutive days. I.V. = intravenous. CPAP = continuous positive airway pressure. IPAP = inspiratory positive airway pressure.

3. Need for more than 2 physiotherapy sessions a day
4. Gastroesophageal reflux, pneumothorax, or massive hemoptysis
5. Need for surgical or endoscopic procedures during the study period
6. Symptoms of asthma in the last year or FEV_1 increase $>$ 12% of predicted after inhalation of albuterol
7. Known or suspected tympanic rupture or other middle-ear pathology[19]
8. Headache, earache, or recurrent epistaxis associated with administration of positive airway pressure
9. Inability to tolerate CPAP and NPPV via nasal mask

A sample size of at least 15 patients was calculated, considering a statistically significant difference of 1.5 standard deviations in dry weight of sputum, a power of 0.90 and a type-1 error of 0.05, based on the results of a previous study.[20]

The study was approved by our institutional ethics committee, and informed consent was obtained from the patients.

Study Design and Schedule

The study was crossover and randomized. Mask PEP, CPAP, NPPV, and directed cough (control treatment) were administered in a random sequence, and each patient was treated with each regimen twice a day (starting at 9 AM and 3 PM) for 2 consecutive days. The 4 treatment periods were distributed over 16 days (Fig. 1). During the weekends the patients carried out their usual self-administered physiotherapy. Randomization of the treatments was done according to the Latin square design described by Williams, which provided a balanced assignment to each treatment and a balance in the sequence of treatments.[21]

During the first 2 days of hospitalization (run-in period, see Fig. 1) the patients underwent 2 mask-PEP sessions to determine the number of directed-cough maneuvers. Moreover, CPAP and NPPV (IPAP plus EPAP) were administered via nasal mask, using a bi-level pressure-support generator (BiPAP ST30, Respironics, Murrysville, Pennsylvania) to evaluate patient tolerance and comfort. During the physiotherapy sessions of the run-in period, arterial oxygen saturation was measured via pulse oximetry (S_{pO_2}, N-20PA, Nellcor Puritan Bennet, Hayward, California) to evaluate the need for supplementary oxygen. Oxygen was administered via nasal cannula or nasal mask during CPAP and NPPV, to obtain an S_{pO_2} of 92–95%. During every subsequent session of the hospitalization period, pulse oximetry was monitored to adapt the oxygen therapy.

Antimicrobial therapy was given intravenously 3 times daily to all patients, according to individual sputum culture sensitivities. Steroids were administered intravenously during the hospitalization (prednisolone at a maximum dosage of 50 mg/d for 7 d and thereafter tapering the dosage in the second week), if diabetes was excluded. Pancreatic enzymes and vitamins were given in accordance with individual pre-admission dosage. Nutrition management was individualized. All aerosolized medications (bronchodilators, steroids, antibiotics, recombinant human deoxyribonoclease) were withdrawn.

Lung-function testing, chest radiograph, body-mass-index evaluation, and standard blood and sputum culture investigations were carried out at admission and discharge. Lung-function testing included spirometry and constant-volume whole-body plethysmography (MasterLab Body, Jäger, Würzburg, Germany), S_{pO_2}, partial pressure of carbon dioxide in arterialized capillary blood (model 855, Chiron Diagnostics, Medfield, Massachusetts), peak inspiratory pressure maintained for at least 1 s (best value

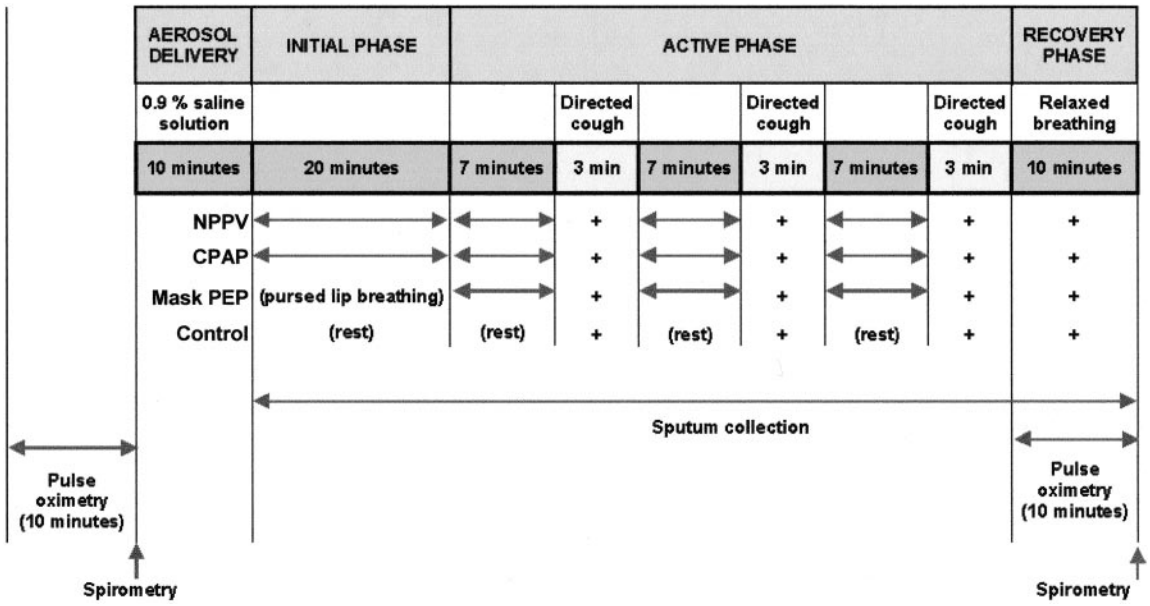

Fig. 2. Each 70-min treatment period consisted of: aerosolized-saline-inhalation period; initial phase; active phase; and recovery phase (see text). Sputum was collected during the initial, active, and recovery phases. We recorded the number of both spontaneous coughs and directed-cough maneuvers separately for each session. Spirometry and pulse oximetry were conducted before and after each session. NPPV = noninvasive positive-pressure ventilation. CPAP = continuous positive airway pressure. Mask PEP = positive-expiratory-pressure therapy via mask. Control = directed cough.

of at least 8 maneuvers) and measured during maximal inspiration beginning at residual volume (Pmax mouth-pressure monitor, PK Morgan, Rainham, United Kingdom). The spirometry and maximum-inspiratory-pressure measurements were recorded as percent-of-predicted values.[22,23] Thoracic gas volume, total lung capacity, and residual volume were measured via constant-volume whole-body plethysmography.

Mask PEP, CPAP, NPPV, and Directed Cough

Each treatment session (Fig. 2) lasted 70 min and consisted of:

1. For 10 min the patient inhaled 0.9% saline solution from a jet nebulizer (MB2, Markos, Monza, Italy).

2. During the initial phase (20 min) CPAP or NPPV was administered while the patient sat comfortably on a chair. During the mask-PEP session, 2-min periods of pursed-lip breathing were followed by 2-min periods of relaxed breathing. During the control treatment session, the patient rested in the sitting position. For all treatments, only spontaneous coughing was allowed during this phase.

3. The active phase of 30 min consisted of three 7-min treatment periods (mask PEP, CPAP via nasal mask, or NPPV via nasal mask), each followed by a 3-min period of directed cough and expectoration. During the control treatment session the patient rested in the sitting position and three 7-min periods with relaxed breathing were followed by 3-min periods of directed cough and expectoration.

4. The recovery phase lasted 10 min and consisted of relaxed breathing for all treatments. Only spontaneous coughing was allowed.

Huffing (forced expiration technique) is a forced expiration from mid-to-low lung volume, with the glottis open.[24] In our study, directed cough was the sequence of one or two huffs, followed by a single cough and sputum expectoration.[25] This sequence was always followed by relaxed breathing. The number of directed-cough maneuvers was standardized for each patient during the various treatments. During the first 2 mask-PEP sessions (run-in period) the physiotherapist asked the patient to repeat directed cough and expectoration during 3-min periods, to optimize the efficacy of the session. Directed-cough maneuvers were repeated the same number of times during the 3-min periods of the active phase as during the following sessions and with the different treatments.

The following treatments were administered in a random sequence to each patient during the hospitalization:

Mask PEP. Mask PEP was performed during the 7-min periods of the active phase, while the patient sat comfortably on a chair.[20] The patient breathed through a face mask with a one-way valve and an expiratory resister (Medipep MV6000, Nuova Tecnomedica, Verona, Italy). The diameter of the resister was determined for each patient to give a steady PEP of 10–20 cm H_2O. That pressure plateau was maintained for at least 5–6 s during expiration, after an inspiration to mid-lung volume and holding the breath for

3–4 s.[20] The resister diameter range was 1.5–4.5 mm. After 8–10 breaths with PEP, 8–10 relaxed breaths were taken.

CPAP. The nasal mask was applied with adhesive strips. The patient wore the mask while sitting, throughout the initial phase for 20 min and during the 7-min periods of the active phase. Directed cough and expectoration performed during the 3-min periods of the active phase were done with the nasal mask removed. The CPAP level between 6 and 10 cm H_2O associated with maximum patient comfort, as determined during the run-in period, was maintained for the 4 sessions.

NPPV. The NPPV administration times and modalities were similar to that with CPAP. EPAP of 4 cm H_2O was administered to all patients, mainly to avoid the rebreathing effect and consequent carbon-dioxide accumulation caused by the dead space of the mask, connectors, and circuit.[26] The IPAP level between 8 and 12 cm H_2O associated with maximum patient comfort, as determined during the run-in period, was maintained for the 4 sessions.

Directed Cough (Control Treatment). During the 3-min periods of the active phase, directed cough and expectoration were performed, whereas in the other phases of the session the patients breathed relaxedly and only spontaneous coughing was allowed.

Two respiratory therapists (GP and MC) took part in the study. Each patient had only one respiratory therapist supervise and conduct all the treatment sessions.

Measurements

The wet and dry weight of sputum collected were our primary measurements. The physiotherapist collected the sputum from the beginning of the initial phase to the end of the recovery phase of each session (see Fig. 2). Each sputum sample was measured to an accuracy of 0.01 g, both in wet and dry form. The dry weight was obtained by storing the sputum in dry air at 60°C for at least 48 h. The technician was blinded to the patient's physiotherapy treatment.

The number of both spontaneous coughs and directed-cough maneuvers was recorded during each session.

Forced expiration was measured, using a standardized method, before saline-solution inhalation and at the end of the recovery phase of each session (Fig. 2).[22] The values of forced vital capacity, FEV_1, and forced expiratory flow during the middle half of the forced vital capacity were recorded. The technicians of the pulmonary function laboratory were blinded to the patient's physiotherapy treatment. The mean S_{pO_2} was recorded during the 10 min before spirometry and during the recovery phase of each session (see Fig. 2).

At the end of mask PEP, CPAP, and NPPV treatment, the patient was asked to report his or her subjective impression of the effectiveness of and fatigue induced by the treatment, in comparison with the usual airway-clearance technique they performed daily at home. The tolerance scale was: 0 = very exhausting, 1 = somewhat exhausting, 2 = as tiring as the usual airway-clearance technique, 3 = less tiring than the usual airway-clearance technique. The efficacy scale was: 0 = useless (same as doing nothing), 1 = somewhat effective in removing secretions, 2 = as effective as the usual airway-clearance technique, 3 = more effective than the usual airway-clearance technique.

Statistical Analysis

The continuous response variables were analyzed using repeated-measures analysis of variance, with the sequence of treatments as a between-patient factor. The sequence was never a statistically significant factor, so the analysis was repeated without its inclusion. The treatment and the 4 session times (day 1 at 9 AM and 3 PM, day 2 at 9 AM and 3 PM) were included in the model as within-patient factors, according to a split-plot factorial design.[27] The session time was never a statistically significant factor, so the reported analysis considered only the treatment. The comparison between the control treatment and each of the other treatments, which was a pre-planned comparison, was performed with Dunnett's test. The comparison between mask PEP, CPAP, and NPPV was done with Scheffé's multiple-comparison test.

Tolerance and effectiveness scores were analyzed with the Wilcoxon signed-rank test. The relationships between sputum weight and the number of directed and spontaneous cough maneuvers were assessed via simple linear-regression analysis. The comparison between the clinical data at admission and discharge was performed with the paired *t* test. The data are reported as mean ± SD.

Results

Seventeen patients (5 male, 12 female, age range 19–41 y) took part in the study (Table 1). Mean ± SD FEV_1 at admission was 25 ± 6% of predicted. Strains of *Pseudomonas aeruginosa* were identified at admission in 15 patients. One strain of *S. aureus* was found in 4 patients, including in 2 patients without *P. aeruginosa* strains. In 4 patients, oxygen was needed during the day, the night, and the airway-clearance-technique sessions to maintain S_{pO_2} of 92–95%, and oxygen was also prescribed at discharge for administration at home. Methylprednisolone was administered intravenously in 14 of the 17 patients, with a

Table 1. Clinical Characterization at Admission and Discharge of 17 Patients With Cystic Fibrosis

	At Admission		At Discharge	
	Mean ± SD	Range	Mean ± SD	Range
Age (y)	27 ± 7	19–41	27 ± 7	19–41
FEV_1 (% of predicted)	25 ± 6	18–41	29 ± 9*	14–48
TGV/TLC (% of predicted)	143 ± 13	121–161	133 ± 13†	112–147
RV/TLC (% of predicted	232 ± 29	188–281	214 ± 28†	180–282
P_{cCO_2} (mm Hg)	41 ± 8	33–63	42 ± 6	35–58
S_{pO_2} (%)	94 ± 2	90–96	96 ± 2†	93–99
MIP (% of predicted)	87 ± 17	62–117	90 ± 22	52–128
BMI (kg/m^2)	18 ± 3	15–23	19 ± 4†	15–24
Wet weight of sputum (g)	15 ± 5	5–23	14 ± 5	6–24

* = $p < 0.05$ via paired *t* test between variables at admission and discharge
† = $p < 0.01$ via paired *t* test between variables at admission and discharge
FEV_1 = forced expiratory volume in the first second
TGV = thoracic gas volume
TLC = total lung capacity
RV = residual volume
P_{cCO_2} = partial pressure of carbon dioxide in arterialized capillary blood
S_{pO_2} = arterial oxygen saturation measured via pulse oximetry
MIP = maximum inspiratory pressure (measured during maximal inspiration, beginning at RV)
BMI = body mass index

mean daily dosage of 30–40 mg in the first week and thereafter tapered in the second week. In 3 diabetic patients, steroids were not administered. During the hospitalization there was a statistically significant improvement in FEV_1, ratio of thoracic gas volume to total lung capacity, ratio of residual volume to total lung capacity, S_{pO_2}, and body mass index (see Table 1). Mean CPAP was 10 ± 1 cm H_2O (range 8–10 cm H_2O). NPPV was administered with a mean IPAP of 12 ± 0 cm H_2O (range 8–12 cm H_2O), whereas EPAP of 4 cm H_2O was used with all patients.

Table 2 shows the mean values of sputum weight collected with the various treatments. During the sessions, the wet-weight difference was statistically significant ($p < 0.05$), but the dry-weight difference was not ($p = 0.46$). More wet-weight sputum was expectorated with mask PEP (15.78 ± 5.49 g) than with the control treatment (13.98 ± 4.96 g, $p < 0.05$, mean difference 1.80 g, 95% confidence interval [CI] −0.19 to 3.80 g), whereas there was no significant wet-weight difference between CPAP and the control treatment (mean difference −0.32 g, 95% CI −1.25 to 0.62 g) or between NPPV and the control treatment (mean difference −0.77 g, 95% CI −2.09 to 0.54 g). The wet weight of the mask-PEP sessions was higher than that of the NPPV sessions ($p < 0.05$), but there was no statistically significant wet-weight difference between the mask PEP and CPAP sessions or between the CPAP and NPPV sessions.

Table 2 shows the mean values for number of spontaneous and directed coughs. The effect of treatment was statistically significant for spontaneous cough ($p < 0.001$), but not for directed cough ($p = 0.81$). The number of spontaneous coughs was higher during the mask-PEP sessions (13 ± 9) than during the control treatment sessions (8 ± 6, $p < 0.01$, mean difference 4, 95%, CI 1 to 8). There was no difference in the number of spontaneous coughs between CPAP and the control treatment (mean difference −3, 95% CI −5 to 0) or between NPPV and the control treatment (mean difference −1, 95% CI −3 to 1). Spontaneous cough was more frequent during mask PEP than during CPAP ($p < 0.01$) or NPPV ($p < 0.01$), whereas there was no difference in spontaneous cough between CPAP and NPPV.

We found a statistically significant correlation between the wet weight and the number of spontaneous coughs ($r = 0.22$, $p < 0.001$). There was no statistically significant correlation between the wet weight and the number of directed coughs, or between the dry weight and the number of both spontaneous and directed coughs. The difference in wet weight between the treatments became nonsignificant when we took into account the number of spontaneous coughs, using analysis of covariance ($p = 0.30$).

Table 2 shows the spirometry and S_{pO_2} values before and after the 4 treatments. Considering the changes in the various lung-function variables, there were no statistically significant differences between the 4 treatments.

Comparing the subjective effectiveness scores for mask PEP (median 1, interquartile range 1–1), CPAP (median 1, interquartile range 1–1), and NPPV (median 1, interquartile range 0.5–1), we found no statistically significant differences. The patients reported feeling less tired after NPPV (median 3,interquartile range 2.5–3) than after mask PEP (median 1, interquartile range 0.5–3, $p < 0.01$). Less fatigue was also reported after CPAP (median 3, interquartile range 2–3) than after mask PEP, but that difference was not significant ($p = 0.054$). There was no difference in the tolerance scores between CPAP and NPPV.

Table 2. Sputum Weight, Number of Spontaneous and Directed Coughs, and Lung Function Values*

	Mask PEP	CPAP	NPPV	Control	p (via ANOVA) for Treatment vs Control
Sputum					
Wet weight (g)	15.78 ± 5.49†	13.66 ± 5.47	13.20 ± 5.00	13.98 ± 4.96	< 0.05
Dry weight (g)	0.94 ± 0.57	0.77 ± 0.43	0.88 ± 0.62	0.97 ± 0.76	0.29
Spontaneous coughs (*n*)	13 ± 9‡	6 ± 5	8 ± 7	8 ± 6	< 0.001
Directed coughs (*n*)	50 ± 17	50 ± 17	50 ± 17	50 ± 17	0.42
FVC					
Before (L)	1.94 ± 0.63	1.97 ± 0.59	1.88 ± 0.57	1.89 ± 0.57	
After (L)	2.00 ± 0.62	2.03 ± 0.63	1.93 ± 0.57	1.95 ± 0.58	0.99
FEV_1					
Before (L)	0.99 ± 0.27	0.98 ± 0.25	0.95 ± 0.25	0.96 ± 0.26	
After (L)	1.00 ± 0.27	1.01 ± 0.26	0.95 ± 0.25	0.99 ± 0.29	0.19
$FEF_{25–75}$					
Before (L/s)	0.28 ± 0.12	0.28 ± 0.10	0.27 ± 0.11	0.28 ± 0.11	
After (L/s)	0.27 ± 0.11	0.29 ± 0.10	0.27 ± 0.11	0.28 ± 0.12	0.20
S_{pO_2}					
Before (%)	95.1 ± 1.5	94.9 ± 1.6	94.7 ± 1.8	94.8 ± 1.7	
After (%)	94.9 ± 1.2	94.7 ± 1.3	94.8 ± 1.4	94.6 ± 1.4	0.007

* Values are mean ± SD.

† When analysis of variance identified a significant difference, we employed Dunnett's test. For wet weight the difference between the control treatment and mask PEP was statistically significant ($p < 0.05$) via Dunnett's test.

‡ For spontaneous coughs, the difference between the control treatment and mask PEP was statistically significant ($p < 0.01$) via Dunnett's test.

ANOVA = repeated-measures analysis of variance

Mask PEP = positive-expiratory-pressure therapy via mask

CPAP = continuous positive airway pressure

NPPV = noninvasive positive-pressure ventilation

Control = control treatment (directed cough)

FVC = forced vital capacity

FEV_1 = forced expiratory volume in the first second

$FEF_{25–75}$ = forced expiratory flow in the middle half of the FVC

S_{pO_2} = arterial oxygen saturation measured via pulse oximetry

Discussion

We found no statistically significant difference in sputum dry weight between mask PEP, CPAP, NPPV, and directed cough. The wet weight was significantly greater with mask PEP than with directed cough, but the wet-weight difference became nonsignificant when we took into account the number of spontaneous coughs. Considering the changes in spirometry and S_{pO_2} values after each treatment, there were no statistically significant differences between the 4 treatments. These findings were obtained from patients with CF and severe airway obstruction during hospitalization for pulmonary exacerbations, and in these circumstances these patients felt less tired after CPAP and NPPV sessions than after mask PEP.

We choose sputum weight as the primary measure to compare the short-term sputum-clearance effect of directed cough combined with mask PEP, CPAP, or NPPV. In studies on the short-term efficacy of airway-clearance techniques, radioaerosol techniques, or simple indices such as the weight of expectorated sputum can be used. The radioaerosol techniques are noninvasive but time-consuming and suitable only in patients with stable clinical conditions.[28–31] In hospitalized patients and in the clinical setting, sputum weight can be used to evaluate mucus clearance, for reasons of patient safety and practicality. There was a weak correlation between sputum weight and percent radioactivity retention in 2 radioaerosol studies that compared these 2 mucus-clearance indices.[28,30] Measuring sputum weight might be inaccurate or misleading because saliva might be included in the sputum and some patients might swallow some of their sputum. The patients in our study were adults and were all very accustomed to and skilled with huff, cough, and expectoration maneuvers. All sessions were supervised by a physiotherapist, and it was quite unlikely that sputum was swallowed. The crossover randomized design and the measurement of sputum dry weight limited the problem of saliva contamination. Other limitations of sputum weight in the evaluation of efficacy of airway-clearance techniques are discussed below.

In our study, directed cough was the sequence of one or two huffs, followed by a single cough and sputum expectoration. Directed cough is considered an airway-clearance technique, and it is used alone or combined with other

techniques, such as breathing through a PEP mask.[20,25,28] Various radioaerosol studies showed that coughing and huffing, used as single standardized techniques, improve tracheobronchial clearance and may influence sputum weight.[28–30] For this reason the standardization of directed cough is an important methodologic aspect in short-term studies that compare airway-clearance techniques that include coughing and huffing. Spontaneous coughs also need to be taken into account. In our study, the higher number of spontaneous coughs with mask PEP (than with the control treatment, NPPV, or CPAP) explained the wet-weight difference between mask PEP and the other treatments. Interestingly, the dry weight was not affected by the number of directed or spontaneous coughs.

When directed cough is standardized, as in this study, to compare the short-term effectiveness of various airway-clearance techniques, sputum weight mainly represents mucus clearance by directed cough. This was reflected in our study by the fact that similar amounts of sputum were collected during the mask PEP, CPAP, NPPV, and control treatment sessions. This finding can be appreciated, as we planned to evaluate the effect of directed cough on sputum clearance, considering directed cough a single component of a treatment (control treatment). Directed cough and other components of airway-clearance regimens, such as positive airway pressure and control of breathing, could be effective to promote mucus clearance in small airways. The removal of mucus plugs from small airways can improve alveolar ventilation and regional gas distribution. These positive short-term effects of airway-clearance techniques are not reflected by sputum weight; rather, high-resolution chest computed tomography, radioaerosol studies, and lung-function methods for testing distribution of ventilation should be performed with this aim.[31–34] The limitations of sputum weight for assessing the effectiveness of airway-clearance techniques should make us cautious in choosing one technique over another. A comprehensive evaluation, including oxygen saturation and fatigue, is necessary to choose the suitable airway-clearance technique for any individual patient with severe CF. Moreover, the findings of the present study are specific for the airway-clearance techniques we investigated and specifically for patients hospitalized for pulmonary exacerbation.

Although our sample size was determined from a power calculation, the possibility of a type-II error cannot entirely be ruled out. Our study should be considered a pilot study, and our findings should be confirmed with a higher-powered study or a different study design. With a cross-over design, a major drawback is the possibility of a carry-over effect. The supervision of treatments by physiotherapists, concomitant medications, and the progression of recovery during hospitalization may also have resulted in possible bias. However, in a study of various airway-clearance techniques, methodological advantages include the measurement of the dry weight of sputum collected during 4 sessions of each treatment, an appropriate randomization of the sequential airway-clearance techniques and control treatment, standardization of directed cough, and the recording of the number of spontaneous coughs.

Our study shows that sputum clearance was not impaired by the short-term administration of either CPAP or NPPV combined with directed cough. To our knowledge, our study is the first report on CPAP used to clear bronchial secretions in CF. A similar amount of sputum was expectorated during CPAP, mask PEP, and NPPV treatment. We considered the short-term changes in spirometry and S_{pO_2} values after the 4 treatments as a safety evaluation, permitting us to identify possible adverse effects of these airway-clearance techniques in patients with severe airway obstruction. We found neither statistically significant improvement nor decrease in spirometry or S_{pO_2} values with CPAP or NPPV, compared with mask PEP and the control treatment.

Weakness of inspiratory muscles can be a feature of CF.[35–38] Fauroux et al found a statistically significant decrease in maximum inspiratory pressure during an airway-clearance technique and a statistically significant increase of inspiratory muscle strength during a pressure-support-ventilation session of similar length.[5] Holland et al found similar results with peak expiratory pressure.[6] We did not assess inspiratory-muscle performance in relation to the various treatments administered to clear bronchial secretions. Both CPAP and NPPV decrease inspiratory muscle work,[5,8,13,14] which may explain why in our study patients felt less tired after the CPAP and NPPV sessions than after mask PEP. Based on these benefits from CPAP and NPPV and our results of comparable sputum clearance with these various treatments, we could consider the short-term administration of either CPAP or NPPV combined with directed cough as a possible airway-clearance regimen that might be clinically relevant and justifiable if a patient feels tired and uncomfortable using conventional airway-clearance techniques during a lung-disease exacerbation.

Conclusions

We found no difference in sputum clearance between mask PEP, CPAP, and NPPV in patients with CF and severe airway obstruction hospitalized for pulmonary exacerbation. The combination of CPAP and NPPV with directed cough was not associated with adverse effects, as assessed by short-term changes in spirometry and S_{pO_2} values. Further studies are necessary to evaluate the physiologic effects of CPAP and NPPV in the context of airway-clearance techniques, in both stable clinical conditions and during pulmonary exacerbations of CF. Moreover, the effect of nocturnal and long-term NPPV on sputum clearance should be addressed in future studies.

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