Positive Expiratory Pressure Changes Aerosol Distribution in Patients With Cystic Fibrosis

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HYPOTHESIS: We hypothesized that aerosol distribution in the lungs of patients with cystic fibrosis changes with positive expiratory pressure (PEP). METHODS: Eight patients were randomized to one of 2 conditions. On one study day, patients inhaled saline aerosol containing [99m]technetium generated by a Pari LC Plus nebulizer and exhaled through a Pari PEP device. On another day, the same patients exhaled through a low-resistance Pari filter (no PEP). Afterwards, they underwent gamma-camera lung imaging. Images were analyzed for lung deposition fraction, expressed as a percent of the initial nebulizer activity, and deposition pattern, expressed in terms of inner-outer and apical-basal ratios. RESULTS: Lung deposition fraction was significantly lower with the Pari PEP device; the mean ± SD deposition fraction was 6.10 ± 3.05% (median 6.20%) with PEP, compared to 10.76 ± 4.52% (median 10.32%) (p = 0.0078) without PEP. The inner-outer ratio was 2.01 ± 0.69 (median 2.23) with PEP, which was significantly lower than without PEP (2.76 ± 1.33, median 2.55) (p = 0.004). The apical-basal ratio was 0.82 ± 0.31 (median 0.80) with PEP, which was not significantly different from no PEP (1.00 ± 0.49, median 0.90). CONCLUSION: These results indicate that less aerosol is deposited in the lungs of patients with cystic fibrosis when the Pari LC Plus nebulizer is used with the Pari PEP device, as described in these experiments. Nevertheless, aerosol administration with this nebulizer and PEP device also results in a proportional redistribution of aerosol to the peripheral airways, compared to nebulization without the PEP device. The clinical relevance of this subtle redistribution of aerosol in cystic fibrosis patients will probably depend on the drug administered and disease severity. *Key words: cystic fibrosis, positive expiratory pressure, nebulizer, aerosol.* [Respir Care 2005;50(11):1438–1444. © 2005 Daedalus Enterprises]

Introduction

Cystic fibrosis (CF) patients are treated with a variety of aerosolized drugs, including bronchodilators, antibiotics, anti-inflammatories, and mucolytics. Gamma-camera deposition scans in children[1] and adults[2] with CF indicate a range of distribution patterns for inhaled aerosols, such that distribution is most uniform in patients with normal ventilation and more heterogeneous in patients with airway obstruction. As severity of airway obstruction increases, the predominant site of aerosol deposition becomes the central airways.[3] Limited aerosol deposition in

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the smaller, peripheral airways, because of airway obstruction, may contribute to treatment failure or suboptimal treatment outcomes.

Positive expiratory pressure (PEP) is sometimes used to enhance airway clearance in CF.[4–5] PEP also keeps the airways distended during exhalation, slowing airway collapse or early closure. Since aerosol particles typically follow ventilation, we hypothesized that the addition of PEP during aerosol administration would improve aerosol distribution in patients with CF, such that the small, peripheral airways would be targeted for deposition to a greater extent than when aerosol was administered without PEP.

Methods

Eight volunteers who were ≥18 years old, had a documented sweat chloride >60 mEq/L by quantitative pilocarpine ionophoresis, a clinical diagnosis of CF, and forced expiratory volume in the first second (FEV_1) ≥ 40% of predicted values participated in this single-center study. Short-acting bronchodilator medications were discontinued for 12 hours and longer-acting bronchodilators were discontinued for 24 hours before each visit. All other medications were continued as usual. The institutional review board for human studies approved the protocol, and informed consent was obtained from all patients.

Study Protocol

Patients were randomized to one of 2 conditions, which were separated by approximately 3 weeks (range 21–25 d). On one study day, patients slowly inhaled saline aerosol that contained the radioisotope ^{99m}technetium (^{99m}Tc), which was continuously generated by a Pari LC Plus nebulizer and a Proneb Turbo compressor, and exhaled through a Pari PEP device (all 3 devices are made by Pari Respiratory Equipment, Richmond, Virginia), while maintaining an expiratory pressure of 10–20 cm H_2O. Aerosol inhalation continued until the nebulizer sputtered, indicating no more aerosol was being generated. On another day, the same patients inhaled until sputtering occurred and exhaled through a low-resistance Pari filter (no PEP). On both study days, ^{99m}Tc was chelated to diethylene triamine penta-acetic acid (DTPA) (Cardinal Health, Baltimore, Maryland) to slow absorption of the isotope from the lungs and make it possible to acquire a lung image over several minutes. At the beginning of each study day, patients underwent pulmonary function testing, according to the American Thoracic Society guidelines.[6] Forced vital capacity (FVC) and FEV_1 were measured with a computerized 10-L Survey III spirometer (Warren E Collins Inc, Braintree, Massachusetts).

Controlling Expiratory Pressure With PEP

When using PEP, patients were taught to exhale while watching a pressure monitor that was connected in-line with the PEP device. This pressure monitor contained a blue "float." Patients were taught to maintain the float in the area between the black lines during each exhalation. The area between the 2 black lines indicated an expiratory pressure of 10–20 cm of water.

Aerosol Particle Size Determinations

Aerosol particles were characterized in terms of their mass median aerodynamic diameter (MMAD) and their geometric standard deviation (GSD), as described by us previously.[7] Aerosol was generated from 2.5 mL of saline plus DTPA and decayed ^{99m}Tc. Five nebulizers were tested with PEP. Five different nebulizers were tested without PEP. For these experiments, aerosol and ambient room air were continuously drawn through a Marple-Miller impactor (MSP Corporation, Shoreview, Minnesota) at 12 L/min, for 3 min.

MMAD and GSD were determined by extracting the DTPA in the United States Pharmacopeia entry port of the impactor (USP Apparatus 2) and on each of 5 impactor collection cups and a terminal filter, by washing quantitatively with Milli-Q water (Millipore, Billerica, Massachusetts). The amount of DTPA at each location was determined by ultraviolet spectroscopy and comparison to standard curves (wavelength 250 nm). The amount of DTPA was then fitted to a log-normal distribution from which the MMAD and GSD were determined. MMADs and GSDs for all 5 nebulizers with and without PEP were averaged.

Gamma Camera Imaging Procedures

On the first study day, patients underwent 3 lung-imaging procedures: (1) a transmission scan, (2) a ^{133}xenon ventilation scan, and (3) a ^{99m}Tc-DTPA aerosol scan. During the transmission scan, a thin, plastic box (phantom) containing water and ^{99m}Tc was placed in front of the patient's chest while a gamma camera acquired a posterior image of the patient's thorax. Then, a second image was acquired with the plastic box in the same position, but without the patient. Counts within the same region of interest in the 2 images (phantom alone and patient with phantom) were quantified and expressed as a ratio. This lung-transmission ratio was used in a later calculation that determined lung deposition fraction.

During the ventilation imaging procedure, the patient inhaled ^{133}xenon gas, using a Pulmonex xenon system (Biodex Medical, Shirley, New York), while sitting with his or her back to a large-field-of-view gamma camera (ZLC, Siemens Gammasonics, Des Plains, Illinois)
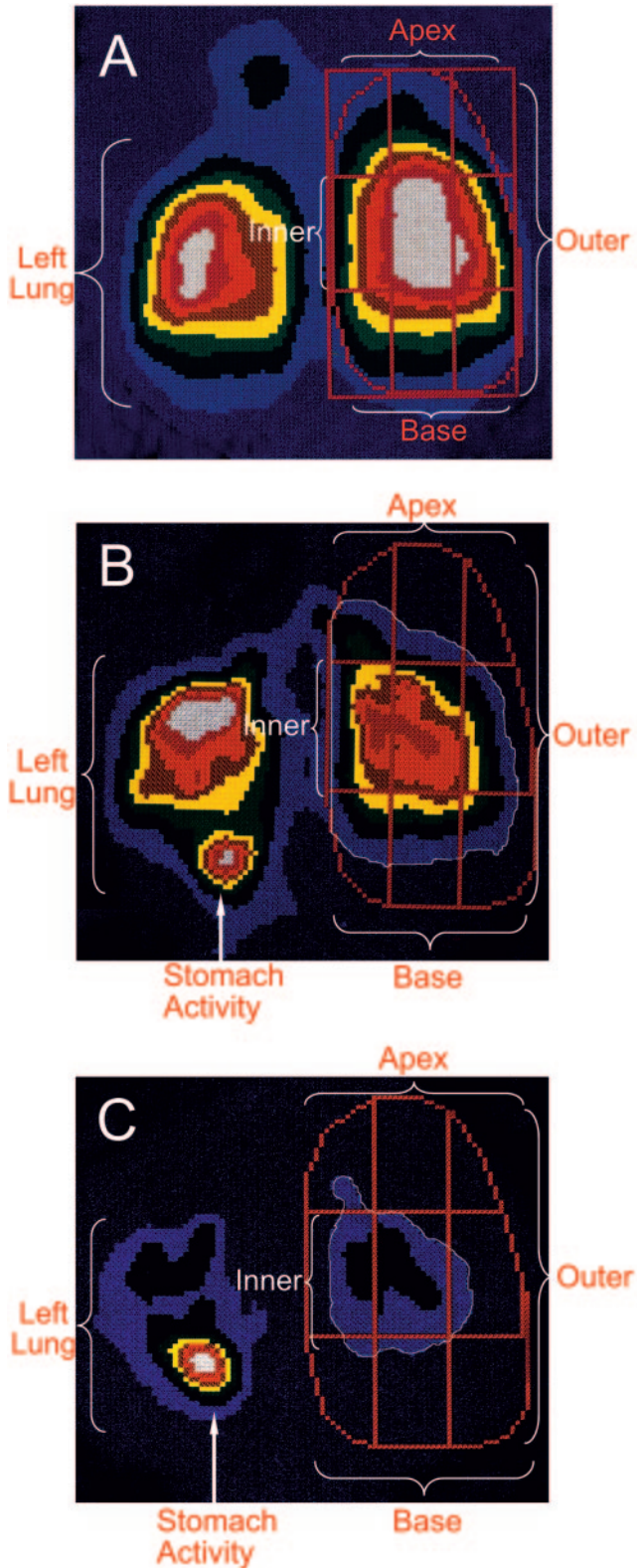
equipped with an all-purpose parallel-hole collimator. The patient rebreathed the radiogas for 90 seconds to promote penetration throughout the lung. Then a 300,000-count image of the posterior lung was acquired and stored on a Sopha computer (SMV, Twinsburg, Ohio) for later analysis. This ventilation image was used to define the functional border of the right lung of each patient.

Then the patient inhaled the ^{99m}Tc-DTPA aerosol, with or without the PEP device. After aerosol administration, the patient underwent a posterior gamma-camera lung scan. Images were stored on the Sopha computer for later analysis. Images from the 2 study days were analyzed in terms of deposition fraction, expressed as a percent of the initial nebulizer activity and deposition pattern, expressed in terms of inner versus outer lung-region count distribution (I-O ratio) and apical versus basal lung-region count distribution (A-B ratio).

Quantification of Deposition Fraction

Deposition fraction was based on the amount of radioactivity detected in the right lung, expressed as counts per min. Total lung counts per min in the right lung were then multiplied by 2 to account for the left lung contribution to total lung counts. This new value was converted to microcuries, using an equation that has been described previously and that incorporates the lung-transmission ratio and a camera sensitivity calculation.[8] Total microcuries deposited in both lungs combined were then expressed as a percent of the total number of microcuries initially in the nebulizer.

Quantification of Deposition Pattern

We analyzed only the right lung for these determinations because it was often difficult to accurately delineate the left lung border from the stomach region on the aerosol scan. Radioactivity that deposited in the oral cavity was swallowed, resulting in a region of high activity in the stomach, which overlapped with the left lung on the image.

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grid containing 9 smaller regions. Subsequent aerosol scans were concatenated and registered with the ventilation scan. The right lung border and the 9-region grid that were delineated on the ventilation scan were then superimposed on each aerosol scan (all shown in red). The smaller bracketed regions are the inner, outer, apical, and basal regions. Deposition in the inner versus outer region and apical versus basal region was expressed as the inner-outer and apical-basal ratios, respectively. Deposition in the inner, outer, apical, and basal regions was also expressed as a percent of total right-lung deposition. B: With positive expiratory pressure. C: Same patient without positive expiratory pressure.

Fig. 1. A: The right lung border (shown in red) was first delineated on the ^{133}xenon ventilation scan. The field within this border was divided horizontally and vertically into thirds, which resulted in a

Regional distribution of the radioisotope was quantified in terms of radioactivity deposited in inner, outer, apical, and basal regions of the right lung, as shown in Figure 1A. Inner, outer, apical, and basal regions were first delineated on the ventilation scan. This was accomplished by dividing the width of the ventilation lung image into 3 vertical regions, as shown in Figure 1A and as described by us previously.[9–10] Similarly, the height of the image was divided into 3 horizontal regions. These divisions resulted in the lung being divided into a total of 9 regions. During automated computer processing, the aerosol image was registered with the ventilation image. All 9 regions delineated on the ventilation image were then superimposed on the aerosol image (all shown in red) (see Figs. 1B and 1C). The smaller bracketed regions indicate the inner, outer, apical, and basal regions.[9–11]

Mean counts per picture element in the inner and outer zones of the ventilation image and the aerosol image were calculated. An I-O ratio was derived for both the ventilation image and the aerosol image. The aerosol image I-O ratio was divided by the ventilation image I-O ratio to correct for differences in lung volume within the 2 regions. Lower I-O ratios indicated enhanced deposition in the smaller, peripheral airways, relative to the larger, central airways.

Anatomically, we assumed that the inner region was predominantly composed of large, central airways and the outer zone was predominantly composed of smaller airways and alveoli. Since these images are 2-dimensional representations, deposition in some small airways and alveoli also appeared in the inner region of the image. However, because of the lung's anatomy, it was assumed that the number of small airways and alveoli in the inner region was much less than the number in the outer region, so we assumed that the 2 zones provided substantially different regional deposition information.

A-B ratios for the aerosol and ventilation images were derived in a similar manner. Lower A-B ratios indicated enhanced deposition in the base of the lung, relative to the lung apex. Counts in the inner, outer, apical, and basal lung regions were divided by total counts in the right lung and multiplied by 100 to yield percent deposition in each region of the right lung.

Data Analysis

Data are presented as mean ± standard deviation and as medians (in parentheses) for study days with and without PEP. The Mann-Whitney test (nonparametric test for unpaired data) was used to compare particle size distribution in terms of the aerosol MMAD and GSD, with and without PEP. The Wilcoxon signed rank test (nonparametric test for paired data) was used to compare deposition fraction, aerosol administration time, and I-O and A-B ratios in patients, following inhalation, with and without PEP. These nonparametric tests assessed differences in the medians of the outcomes between PEP and no PEP. Two-sided hypothesis tests were performed, and differences were considered statistically significant if $p \leq 0.05$.

Results

Patient Characteristics

There were 5 male and 3 female patients, with a mean age of 25 ± 4 y (range 18–30 y). FEV_1 and FVC at the start of each study day were similar. The group's percent of predicted FEV_1 was $51 \pm 9\%$ (range 41–70%) on the study day with PEP, and $53 \pm 11\%$ (range 44–76%) on the study day without PEP. The group's percent of predicted FVC was $66 \pm 7\%$ (range 57–76%) on the study with PEP, and $66 \pm 9\%$ (range 54–76%) on the study day without PEP. All patients were on stable therapies of antibiotics, bronchodilators, steroids, and recombinant human deoxyribonuclease (rhDNase).

Aerosol Particle Size

The MMAD for the saline-plus-^{99m}Tc-DTPA aerosol was 3.26 ± 0.37 μm with PEP and 4.07 ± 0.23 μm without PEP. That difference is statistically significant ($p = 0.008$). The GSDs were not significantly different: 2.61 ± 0.10 with the PEP device and 2.78 ± 0.06 without the PEP device ($p > 0.05$).

Deposition Fraction

Deposition fraction in both lungs combined, expressed as a percent of the initial nebulizer activity, averaged $6.10 \pm 3.05\%$ (median 6.20%) with the PEP device, which was significantly less than the average deposition fraction of $10.76 \pm 4.52\%$ (median 10.32%) without the PEP device ($p = 0.0078$).

Aerosol Administration Time

The time of aerosol administration averaged 6.8 ± 2.2 min (median 6.5 min) with the PEP device, which was significantly longer than without the PEP device (4.5 ± 1.8 min, median 4.5 min) ($p = 0.039$).

Distribution With and Without PEP

Figures 1B and 1C show aerosol distribution (white border) within the right lung (red border) for one of the patients, with PEP (Fig. 1B) and without PEP (Fig. 1C). For that patient, the I-O ratios were 2.20 and 2.69 with and without PEP, respectively, indicating a difference in aerosol distribution, such that more of the aerosol deposited in
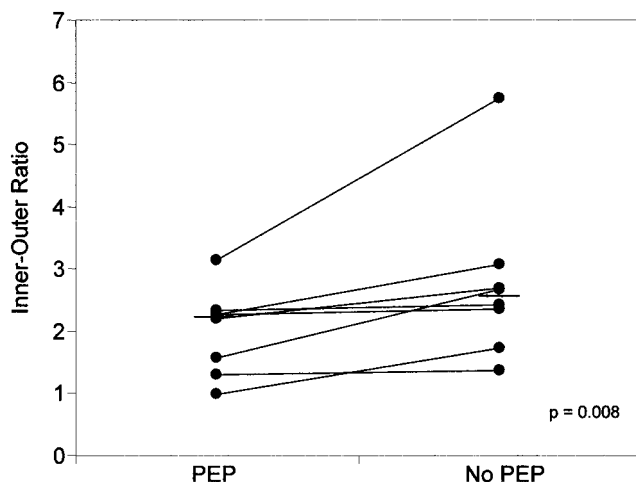
Fig. 2. Inner-outer (I-O) ratios with and without positive expiratory pressure (PEP). The median ratios were significantly lower with PEP (p = 0.008) than with no PEP.
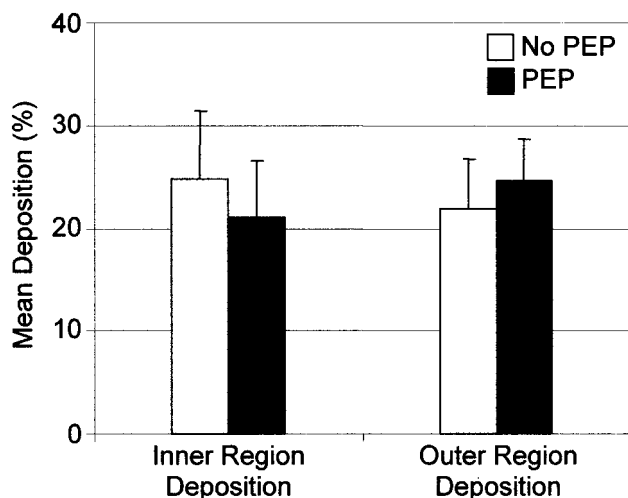

Fig. 3. Mean percent deposition in the inner and outer lung regions with and without positive expiratory pressure (PEP). Deposition decreased in the inner region and increased in the outer region with PEP.
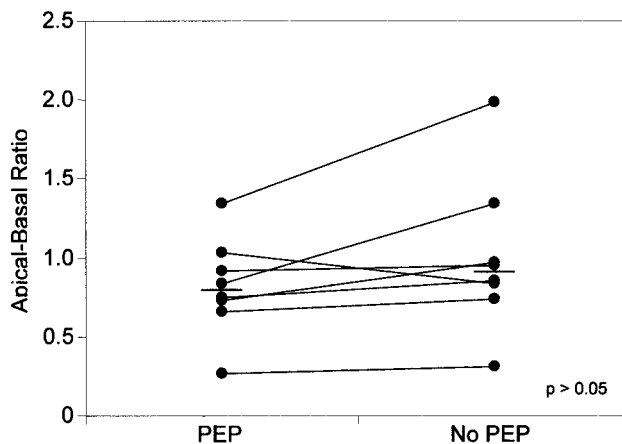

Fig. 4. Apical-basal ratios with and without positive expiratory pressure (PEP). Median ratios were not significantly different with PEP than without PEP (p > 0.05).

aerosol in the outer region of the right lung and an average decrease of 3.6% in the inner region, as shown in Figure 3.

Mean A-B Ratios With and Without PEP

On the study day with PEP, A-B ratios were not significantly different than on the study day without PEP, averaging 0.82 ± 0.31 (median 0.80) and 1.00 ± 0.49 (median 0.90) on the 2 study days, respectively (p > 0.05) (Fig. 4).

A single subject showed consistently higher values for I-O and A-B ratios, compared to the other subjects (see Figs. 2 and 4). Nevertheless, this subject met all the inclusion criteria and was not extreme in terms of FEV_1, age, or therapy.

Discussion

The importance of aerosol distribution in the lung is still unknown. However, it could prove beneficial to target the deposition of drugs such as rhDNase, antibiotics, and protease inhibitors to poorly ventilated airways of CF patients, to slow the progression of the disease. This is because poorly ventilated airways retain mucus, and this appears to be associated with a higher pathogen and neutrophil load.[12] One of the lung regions in which poor ventilation and obstruction first appear in patients with CF is the smaller, peripheral airways. This region showed a proportional increase in deposition when the PEP device was used to deliver saline plus ^{99m}Tc-DTPA aerosol in this study. This was evidenced by the significant decrease in the I-O ratio with PEP, compared to no PEP (see Fig. 2).

The other lung zone that becomes poorly ventilated in patients with CF is the lung apex. However, aerosol deposition in this region was unaffected by the PEP device.

the outer region relative to the inner region with PEP. The A-B ratios were 0.73 and 0.97 with and without PEP, respectively, indicating a difference in aerosol distribution, such that more of the aerosol deposited in the base relative to the apex with PEP.

Mean I-O Ratios With and Without PEP

On the study day with PEP, I-O ratios were significantly lower than on the study day without PEP, averaging 2.01 ± 0.69 (median 2.23) and 2.76 ± 1.33 (median 2.55), respectively (p = 0.008) (Fig. 2). This decrease in I-O ratio with PEP was because of an average increase of 2.8%

This was evidenced by no significant increase in the A-B ratio with PEP, compared to no PEP (see Fig. 4). This finding indicates that, while delivery of aerosolized medications to the lung periphery may be improved by PEP, delivery to the lung apex will probably be unchanged.

Some clinicians and respiratory therapists use positive pressure to "drive" inhaled therapies more distally into the lungs of obstructed patients, or to open closed airways to allow aerosol passage. Our results show that though this may be the case, the magnitude of the deposition change with this PEP device and this nebulizer/compressor system may be small compared to no PEP, and may not be clinically relevant. Other ways of targeting inhaled therapies to the peripheral airways in obstructed patients, such as breathing small particles slowly,[7] may be more effective.

The effectiveness of the nebulizer/PEP combination in terms of aerosol redistribution may have been limited by the number of patients ($n = 8$) and our choice of patient population (ie, young adults with moderately severe lung disease). Thus, this technique might lead to greater increases in deposition in the lung periphery in individuals with less lung disease and less airway damage (ie, young children with CF who have minimal lung involvement). This needs further study.

The dose of radioactivity that deposited in the lungs, relative to the initial activity in the nebulizer, was significantly less with the PEP device (6.10%) than with no PEP (10.76%), making aerosol generation with the nebulizer/PEP combination less efficient for drug delivery than without PEP. Lower deposition fractions with the PEP device may have been due, in part, to considerable loss of aerosol through the flow-limiting orifices of the device during exhalation. This occurred because patients exhaled across the bowl of the device while it continuously generated aerosol for inhalation. Although never quantified, it is likely that losses were substantially reduced when the PEP device was not used, since exhalation occurred through a low-resistance filter located on the mouthpiece of the nebulizer. With this latter configuration, aerosol that was being generated in the nebulizer bowl was conserved during exhalation, leading to enhanced delivery during the next inhalation. The use of an "interrupter" might decrease the losses associated with the PEP device during aerosol exhalation, since aerosol generation would occur only during inhalation.

One explanation for the greater outer-zone deposition with PEP could be the difference in particle size distribution with the PEP device. The particles generated by the nebulizer/PEP combination were significantly smaller (MMAD 3.26 μm) than the particles generated without PEP (MMAD 4.07 μm). Typically, smaller particles deposit more peripherally in the lungs of patients with CF. For example, in another study we quantified the distribution of aerosols with MMADs of 3.68 μm and 1.01 μm in

the lungs of CF patients who were breathing under conditions similar to patients in the current study without PEP.[7] In that study, mean I-O ratio was significantly lower with the 1.01-μm aerosol than with the 3.68-μm aerosol, indicating enhanced deposition in the peripheral airways and alveoli with the smaller particles. Wilson et al also found a difference in deposition pattern as a result of aerosol particle size in CF patients.[13] In that study, an antibiotic aerosol consisting of particles with a mass median diameter of 1.8 μm was more homogeneously distributed in the lungs of children with CF than an aerosol consisting of particles with a mass median diameter of 3.3 μm. It is not known if adding PEP to these approaches would further enhance aerosol distribution to the smaller airways of these patients.

It is of interest that the particle size distributions of 2 other drugs, albuterol alone (Ventolin nebules inhalation solution, GlaxoSmithKline) and rhDNase (Pulmozyme, Genentech) admixed with DTPA, were also affected when aerosol was generated by the Pari LC Plus nebulizer and the PEP device was used, compared to no PEP. Using the same particle sizing technique and nebulizers as described for saline admixed with DTPA, we found that the average MMAD for albuterol alone was also significantly smaller when generated with PEP (2.82 $\pm$ 0.18 μm) compared to no PEP (3.50 $\pm$ 0.18 μm) (p < 0.008). Similarly, the MMAD for the rhDNase/DTPA solution averaged 3.45 $\pm$ 0.28 μm when generated with PEP, which was significantly smaller than without PEP (4.15 $\pm$ 0.13 μm) (p < 0.008). These data suggest that when the Pari PEP device is used in combination with the Pari LC Plus nebulizer, as described in these experiments, the particle size distribution of a number of drugs may be significantly altered, compared to nebulization with the nebulizer alone. The explanation for the alterations in particle size distribution is unknown. As observed in the present experiments, alterations in the particle size distribution of these other drugs could lead to differences in the lung deposition pattern and, potentially, alterations in drug effectiveness.

Conclusions

In summary, these results indicate that aerosol administration takes longer and less aerosol is deposited in the lungs of patients with CF when the Pari LC Plus nebulizer is used with the Pari PEP device, as described in these experiments, compared to nebulization without the PEP device. Nevertheless, aerosol administration with this nebulizer in combination with the PEP device also results in a proportional redistribution of aerosol to the peripheral airways, compared to nebulization without the PEP device. The clinical relevance of this subtle redistribution of aerosol in CF patients is unknown and will probably depend on the drug administered and disease severity.

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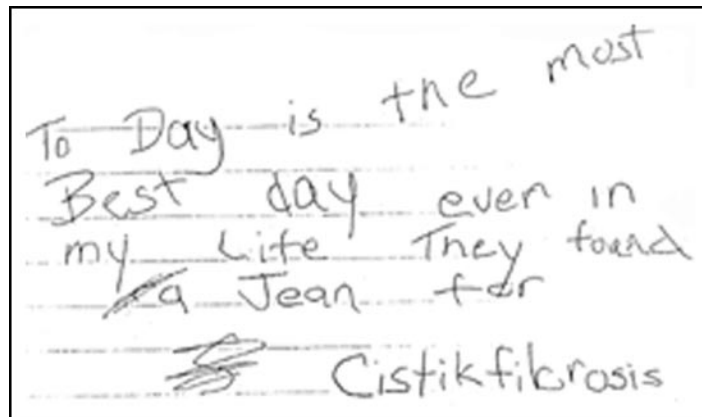
Letter to Dr Francis Collins, one of the researchers who located the gene causing cystic fibrosis, from J.H., an 8-year-old cystic fibrosis patient, August 25, 1989. Courtesy National Human Genome Research Institute, National Institutes of Health