Optimization of Aerosol Deposition by Pressure Support in Children with Cystic Fibrosis
An Experimental and Clinical Study

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Nebulized aerosols are commonly used to deliver drugs to the lungs of patients with cystic fibrosis (CF). The aim of this study was to assess the effectiveness of pressure-support (PS) ventilation in increasing aerosol deposition within the lungs of children with CF. An in vitro study demonstrated the feasibility of coupling a breath-actuated nebulizer to a PS device. An in vivo study was done with 18 children (ages 6 to 21 yr) with clinically stable CF, each of whom underwent both a standard and a PS-driven ventilation session (control session and PS session, respectively). In addition, a perfusion scan was used to determine lung outlines and to construct a geometric model for quantifying aerosol deposition by radioactivity counting in MBq. Homogeneity of nebulization was evaluated from the four first-order moments of aerosol distribution in the peripheral and central lung regions. The time–activity nebulization curve was linear in all patients, with higher slopes during the PS than during the control session (0.43 ± 0.07 [mean ± SD] MBq/min and 0.32 ± 0.23 MBq/min, respectively; p < 0.018).

Quantitatively, aerosol deposition was about 30% greater after the PS session (4.4 ± 2.7 MBq) than after the control session (3.4 ± 2.1 MBq; p < 0.05). Similarly, deposition efficacy (as a percentage of nebulizer output) was significantly better during the PS session than during the control session (15.3 ± 8.3% versus 11.5 ± 5.7%; p < 0.05). No differences in the regional deposition pattern or in homogeneity of uptake were observed. In conclusion, our data show that driving the delivery of a nebulized aerosol by noninvasive PS ventilation enhances total lung aerosol deposition without increasing particle impaction in the proximal airways.

Nebulized aerosols are commonly used to deliver drugs to the lungs of patients with cystic fibrosis (CF). Any potential advantages of aerosol therapy would lie in an ability to deliver smaller doses of drugs directly to the site of interest (i.e., the lungs). However, evaluating both the amount of medication actually delivered to the lung and its exact site of deposition remain crucial problems. Few data are available on quantitative drug deposition in lungs affected by CF (1, 2) or on drug deposition in the lungs of children with CF (3–5). In addition to total lung deposition, the distribution of drug deposition across lung regions is important. In CF, the goal is to deposit a drug in the peripheral bronchi and bronchioles. Bronchoconstriction or airway obstruction by mucus or inflammation diverts more airflow to nonobstructed airways. Heterogeneous drug deposition has been demonstrated in adults with CF (6). Deposition of an aerosol in the lung may vary widely according to many parameters including the type of nebulizer and type of compressor used to produce the aerosol, the nebulizer fill, injected flow, and breathing pattern (7, 8). In particular, the deposition fraction may change substantially when the breathing pattern changes. The optimal breathing pattern for aerosolization combines a large tidal volume (Vt) and a slow inspiratory flow rate; higher flow rates seem to increase drug deposition in the oropharynx. Deep breathing has been shown to increase aerosol deposition in the lungs of both adults and children with CF (7, 9).

Inspiratory pressure-support (PS) ventilation is a method of ventilatory assistance that maintains a constant, preset, positive airway pressure during spontaneous inspiration, with the goal of decreasing the patient's inspiratory work of breathing. Allowing patients with severe chronic obstructive pulmonary disease (COPD) to control their own respiratory rate (RR), Vt, and inspiratory time (Ti) was associated with a significant decrease in the work performed by the inspiratory muscles, especially the diaphragm, and with significant improvements in CO2 elimination and oxygenation (10). One of the main advantages of PS ventilation is its good acceptability by patients, owing to the patient's control of the frequency and duration of inspiratory assistance, rather than control by the machine (10). Recently, we showed that PS ventilation given to CF patients via a nasal mask during chest physiotherapy was beneficial in preventing oxygen desaturation (11). In these patients, we observed a decrease in RR and an increase in both Vt and minute ventilation (Ve). These changes brought the breathing pattern closer to that associated with optimal aerosol deposition. When the present study was begun, the effects of PS ventilation on aerosol transport and particle deposition in the lungs were unknown. We designed the study to evaluate these effects.

The aim of our study was to conduct a precise evaluation of the efficacy of PS ventilation in optimizing aerosol deposition in vitro and in vivo. In the first part of the study, we tested the in vitro performances of two breath-actuated nebulizers of similar design, of which one was used alone (i.e., was triggered by the patient’s inspiratory flow), whereas the other was coupled to the PS device (i.e., was triggered by the positive pressure generated by the PS device). These two nebulizer systems were compared on the basis of: (1) the total nebulizer output; and (2) the amount of solution captured on an absolute filter located at the end of a cranked tube mimicking the upper airways to the site of the carina. The optimal nebulizer and home PS ventilator settings for the clinical study were determined from this bench study.

The second part of the study evaluated the potential clinical utility of nebulization coupled to PS in children with CF by comparing the lung deposition of a radiolabeled aerosol produced by nebulization alone and by nebulization with PS. We quantified total and regional lung depositions of the aerosol and studied the distribution dynamics of the radiolabeled solution delivered by the two systems. Both our in vitro results and

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our in vivo findings in children with CF suggest that aerosol deposition at the sites of interest in CF can be improved by using a nebulizer coupled to a PS ventilator.

METHODS

Experimental In Vitro Study

Apparatus tested. The PS device used in the study was a home ventilator commonly used in our department (Onyx; Mallinckrodt, Les Ulis, France), whose performance is very similar to that of intensive-care PS devices (12). To minimize deposition of the aerosol in the ventilator circuit, PS device was connected by a T-tube to the mouthpiece of the nebulizer used in the study.

Two similar breath-actuated nebulizers were used. Both nebulizers deliver drug in a timed pulse during the inspiratory phase of respiration. The pulse can be timed from 200 ms to 900 ms according to the patient’s breathing pattern. A constant volume of solution is thus available for inhalation during each spontaneous inspiration. The volume of nebulized solution increases with the inspiratory nebulization time. With a 3.6-bar oxygen source, a low-resistance valve is opened at the beginning of inspiration and a 12 L/min peak flow through the mouthpiece is rapidly achieved. The delivery time of the nebulizer must always be set to less than the patient’s inspiratory time to maximize driving of the pulse into the airways. Thus, the number and duration of pulses determine the available mass of drug.

The two nebulizers used in the study are triggered in different ways. The nebulizer used alone in the control session (Optineb; Air Liquide Santé, Paris, France) is actuated by the inspiratory flow of the patient (control session), whereas the nebulizer used with PS in the PS session (Optiplus; Air Liquide Santé) is actuated by the positive pressure generated by the PS device. Great care was taken to obtain similar performances from the two nebulizers to ensure that any differences between the two sessions would be ascribable only to the presence or absence of PS. The mass median aerodynamic diameter (MMAD) and geometric standard deviation (σg) of the generated aerosol, measured with a laser device (MS 1000; Malvern Instruments Ltd, Worcs, UK) at an inspiratory time of 400 ms, were 3.21 ± 0.13 (mean ± SD) μm for the nebulizer alone and 3.16 ± 0.02 μm for the nebulizer coupled to the PS device.

Experimental setup. The output of the nebulizer was driven through a conventional mouthpiece and a glass cranked tube (internal diameter = 18 mm; length of the horizontal and vertical components = 13 cm and 19 cm, respectively) that mimicked the anatomy of the upper airways to the site of the carina. An absolute filter (Type A/E Glass; Pall Gelman Laboratories, Ann Arbor, MI) was placed at the end of the cranked tube.

The nebulizer solution used for the in vitro study was a 2.5% KCl solution. The MMAD of the KCl solution was similar to that of the radiolabeled solution used in the clinical study. Indeed, the MMAD of the KCl solution ranged from 3 μ to 5 μ (i.e., large enough to avoid Brownian oscillations and small enough to avoid impaction in the upper airways). The mass of KCl deposited on the absolute filter was measured using optical spectrometry.

To simulate repeated inspiratory efforts, the PS device was connected to a two-chamber test lung (dual adult T1L 1600 training test lung; Michigan Instruments Inc., Grand Rapids, MI) as previously described (12). One chamber of the test lung (the driving chamber) was connected to and powered by a ventilator (Cesar; Taema, Antony, France), whereas the other chamber (the pressurized chamber) was connected to the PS ventilator being tested. The two chambers were connected to each other by a small metal component that allowed the driving chamber to lift the PS-pressurized chamber, mimicking the patient’s contribution to inspiration. Thus, generation of positive pressure in the driving chamber by the ventilator lowered the pressure in the PS-pressurized chamber to atmospheric levels, simulating the production of negative intracranial pressures in vivo when the inspiratory muscles contract. This effect was detected by the triggering system of the PS ventilator being tested. Because the metal component was not secured to the PS-pressured chamber, this chamber, once effectively pressurized, could rise above the driving chamber. Compliance was set at 50 ml/cm H2O for both chambers. Positive end-expiratory pressure (PEEP) was applied to the driving chamber at a level that ensured synchronism of motion of the two chambers at onset of inspiration. A resistance of 17 cm H2O at 1 L/s was used to connect the PS device being tested to the lung model. The ventilator was set to provide a respiratory frequency of 20 cycles/min, a Ti of 1 s, and a constant inspiratory flow rate of 10 L/min.

Various PS device settings were evaluated. Inspiratory pressure ranged from 8 to 10 cm H2O. The inspiratory trigger was set at -0.7 cm H2O, the lowest value not associated with self-triggering in pediatric conditions. The rate of initial inspiratory flow, or rate of PS insufflation, was set at the highest possible value. Exhalation was totally passive, and began when the inspiratory flow fell below a threshold value of about 30% of the peak inspiratory flow. The PS device and nebulizer settings optimal for the clinical study were determined during this experimental study.

Clinical Study

Apparatus tested. The two nebulizer systems and the home PS ventilator used in the clinical study were the same as those used in the in vitro study.

Patients. Eighteen clinically stable CF patients (seven girls and 11 boys) aged 12 ± 4 (mean ± SD) yr (range: 6 to 21 yr) were studied. The subject’s mean Shwachman score was 74 ± 16 (range: 40 to 100) (13). Their VC and FEV1 were 77 ± 21% and 72 ± 26% predicted, respectively. Four patients were colonized with Pseudomonas aeruginosa and one with Burkholderia cepacia. Inhaled bronchodilators and corticosteroids were used on a long-term basis by eight and nine patients, respectively. Three patients were taking recombinant human deoxyribonuclease. None of the patients changed their usual treatment during the study period. All patients were receiving follow-up at our CF clinic, and were selected on the basis of disease stability, willingness to participate in the study, and availability for spending two afternoons in the hospital for the study.

The study protocol was approved by our institutional review board. Informed consent was given by all patients and their parents.

Imaging protocol. Each subject underwent one control session and one PS session. The two lung scans were performed in random order, during the afternoon, within the same week but at least 3 d apart. Before starting the protocol, the patient and parents were given information on the breath-actuated nebulizers and PS device, and the patient went through a practice session. A perfusion scan was performed after either the control or the PS session.

An anhydrous sodium solution containing 185 MBq of 99mTc-phosphates (Phytacis; CIS Bio International, Gif-sur-Yvette, France), diluted in 4 ml of normal saline, was placed in a lead-shielded unit in the nebulizer (Sidestream; Medic-Aid, Sussex, UK). Before and after nebulization, radioactivity in the nebulizer was counted with a gamma camera (single-headed DS7; Sophia Medical Vision, Buc, France), with the same counting geometry for both counts. The exact amount of nebulized radioactivity (in MBq) was calculated as the count difference divided by the initial activity in the unit. Within the range of radioactivities used in this study, we found a linear relationship between actual radioactivity (x = 30 to 300 MBq with the same counting geometry) and activity measured by the camera (y = 124,415 x; R2 = 0.9994).

Patients inhaled the aerosol solution through a mouthpiece while in the sitting position and wearing a nose-clip. Dynamic aerosol deposition within the lungs was assessed on a posterior view during continuous breathing of Vt for 10 min. Ten consecutive 60-s frames were thus acquired in 64 × 64-pixel matrices. Patient movements were prevented by having the patient sit in a fixed seat with the patient’s back to the camera, and by maintaining the patient’s head and the nebulizer in a sagittal median plane orthogonal to the collimator. Patients were asked to relax, and no attempt was made to control the breathing pattern. Immediately after each session, a garelle was provided for decontamination. After completion of the nebulization, additional, 300-s static images in the anterior and posterior projections were acquired in 256 × 256-pixel matrices.

For practical reasons (essentially decontamination purposes), we were unable to measure patient breathing patterns during the two nebulizer sessions.

An intravenous injection of 99mTc-macroaggregates in an amount providing 18.5 MBq of radioactivity was given via a small peripheral catheter, which was rinsed after the injection. The exact amount of in-
jected radiotracer was determined by measuring syringe radioactivity before and after the injection. Perfusion image acquisition was begun immediately after the injection, with the patient seated, and with the same gamma-camera being used to obtain two 120-s static views (anterior and posterior) in 256 x 256-pixel matrices. Perfusion images were obtained for two reasons: (1) to allow an accurate determination of lung outlines; and (2) to determine an individual counting correction (ICC). This information was then used to calculate the absolute aerosol deposition within the lungs (14, 15).

Dynamic studies were analyzed by plotting the total count within each of the 10 frames against the corresponding acquisition time to produce a time–activity curve. Posterior views were analyzed.

Quantitative aerosol deposition was then assessed. Lung edges were determined automatically on the perfusion images by thresholding at 15% of the maximal count, which in earlier studies (6, 16) gave the best separation between pulmonary activity and background. The lung-edge outlines were then applied to the ventilation scans and were used to define further regions of interest (ROI) and for background subtraction. Each lung was manually included within an elastic grid composed of 40 equal-sized cells, in a five-column and eight-row matrix (Figure 1). This matrix allowed separation of the lung into central, middle, and peripheral regions, as previously described (16). Deposition in the central and peripheral regions was analyzed, the middle region being less informative in patients with obstructive lung disease. Homologous regions in the right and left lungs were used to evaluate the homogeneity of aerosol deposition by calculating the four first-order moments (i.e., mean count per pixel, SD, skew, and kurtosis [6, 17]). These parameters are indices that are corrected for the actual number of pixels, the mean pixel count, and the histogram SD (6, 17). Because these parameters are dimensionless, they allow the comparison of distribution histogram shapes regardless of lung size and total deposited radioactivity. Skew is a measure of asymmetry, and is low when distribution is uniform or symmetric. Kurtosis is considered a measure of the sharpness of distribution, and approaches zero when deposition is peripheral or diffuse. A penetration index was also calculated, as the ratio of peripheral to central counts (16). In addition, each lung was divided into three rectangular ROIs of equal size, consisting of the upper, middle, and lower thirds of the lung, to determine aerosol distribution from the base to the apex within each lung (expressed as the percentage of total lung deposition) (Figure 2) (17). Because of asymmetric pulmonary function caused by heart imitating, the geometric means on the anterior and posterior views were calculated for both the mean count per pixel and for the upper-, middle- and lower-third percentages, and were then used to approximate these parameters in the median coronal plane. Absolute pulmonary deposition was assessed by multiplying these last parameters by the ICC, calculated as follows:

$$ICC = \frac{\text{Injected macroaggregates activity (MBq)}}{\text{Geometric mean of anterior and posterior perfusion views (counts)}}$$

Statistical Analysis

Dynamic aerosol deposition was analyzed by subjecting the time–activity curves to linear regression. All continuous variables (including functional lung volumes, clinical scores, slopes of dynamic uptake, relative and quantitative count statistics, and uptake homogeneity) were compared for the control and PS sessions for each patient, using a paired Student’s t test, and the null hypothesis was rejected if the value of p was less than 0.05. Additionally, patients were separated into two subgroups based on clinical or scintigraphic status, and differences between these subgroups were evaluated with an unpaired t test.

RESULTS

Experimental In Vitro Study

The experimental in vitro study analyzed interactions between the nebulizer and the PS ventilator to determine whether the nebulizer changed the functioning of the PS ventilator or vice versa. We found that when the nebulizer was coupled to the PS ventilator, the generated pressure remained unchanged. Setting the inspiratory time of the nebulizer above 400 ms resulted in premature discontinuation of PS due to the additional flow delivered by the nebulizer. We further found a linear relationship, with both nebulizer systems, between the mass of KCl deposited on the absolute filter and the number of inhalations (Figure 3). The mass of KCl on the absolute filter was larger with the PS system, but the difference did not reach statistical significance.

![Figure 1](image1.png)

**Figure 1.** The elastic grid used for aerosol distribution analysis and shown in the figure is a variant of the grid developed by Agnew and colleagues (16): the outer shaded cells correspond to the peripheral region (alveoli) and the inner shaded cells to the central region (bronchi) of the lung. Since the ventilation image was previously thresholded, all white pixels were assigned a zero value and were not taken into account for the homogeneity analysis.

![Figure 2](image2.png)

**Figure 2.** Grid is used for aerosol distribution analysis from the base to the apex within each lung. Each lung is divided into three rectangular regions of interest of equal size, consisting of the upper, middle, and lower thirds of the lung.
The yield of each system was calculated as the ratio of the amount of KCl that was nebulized for a fixed number of inhalations and the amount of KCl that was deposited on the absolute filter placed at the end of the cranked tube. This ratio remained stable with both systems from 50 to 400 inhalations, and was 70% and 75% for the control and PS session, respectively.

These data indicate that coupling of the nebulizer to the PS device in vitro did not impair the functioning of the nebulizer or PS device provided the nebulization time remained below 400 ms.

**Clinical Study**

All 18 patients completed the clinical study. The PS sessions were well tolerated, without side effects. Radioactivity in the nebulizer was similar before the two sessions (174 ± 8 [mean ± SD] MBq and 171 ± 10 MBq before the control and PS sessions, respectively, p = NS), whereas the amount of radioactivity that left the nebulizer during the nebulization time was slightly greater during the PS session (29 ± 11 MBq) than during the control session (25 ± 6 MBq; p = NS).

**Dynamic lung deposition.** Evaluation of the dynamic lung scans performed during aerosol inhalation showed a linear relationship between nebulization time and aerosol deposition in all patients (Figure 4). Dynamic aerosol deposition was significantly increased during the PS session as compared with the control session (average slopes: 0.43 ± 0.07 MBq/min and 0.32 ± 0.23 MBq/min for the PS and control sessions, respectively; p = 0.018).

**Total aerosol deposition in the lungs.** The absolute radioactivity deposited in the lungs after the nebulization session was about 30% greater after the PS session than after the control session (Table 1). Aerosol lung deposition was also significantly greater after the PS session when deposition was expressed as a percentage of the nebulizer output, which was the difference between the original radioactivity of the solution placed in the nebulizer unit and the residual radioactivity remaining after nebulization, or as the percentage of the total radioactivity present in the nebulizer unit.

**Regional aerosol deposition.** After both the control and PS sessions, approximately one-third of aerosol deposition in the lungs occurred in the central area (Table 1). The penetration index was 2.3 ± 0.5, and was remarkably similar for the two sessions. No difference in lung aerosol deposition between the two sessions was observed when deposition was analyzed from base to apex (Table 1).

**Homogeneity of aerosol deposition.** Skew and kurtosis were similar results after the control and PS sessions (Table 1).

**Correlation of aerosol lung deposition with clinical characteristics of the patients.** The group of 13 patients with larger amounts of deposited aerosol after the PS session (“responders”) did not differ, in terms of clinical characteristics (age, height, Shwachmann score) or lung function parameters, from the group of five patients with unchanged amounts of deposited aerosol (“nonresponders”). However, the nonresponders to PS tended to have poorer lung function than the responders (FEV1 = 57 ± 33% and 77 ± 22% in the nonresponders and responders, respectively; p = 0.1).

When the patients were separated into two groups based on disease severity (mild, FEV1 > 60% predicted; or moderately severe: FEV1 < 60% predicted), the only parameter that differed significantly in the two groups was skew, with the difference being apparent after both the control and the PS session. Skew was 1.3 ± 0.4 and 0.9 ± 0.3 in the mild and moderately severe groups, respectively, after the control session (p = 0.02), and was 1.3 ± 0.4 and 0.9 ± 0.5, respectively, after the PS session (p = 0.04). Dynamic lung deposition, total and regional aerosol deposition, kurtosis, and penetration index showed no significant differences between the two groups.

In the overall study group (n = 18), total aerosol deposition was not correlated with age, height, or the percent predicted VC or FEV1. Neither was the time-course of aerosol deposition

**Table 1**

<table>
<thead>
<tr>
<th>Deposition</th>
<th>Control Session</th>
<th>PS Session</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total deposition, MBq</td>
<td>3.4 ± 2.1</td>
<td>4.4 ± 2.7</td>
<td>0.016</td>
</tr>
<tr>
<td>% Nebulized dose</td>
<td>11.5 ± 5.7</td>
<td>15.3 ± 8.3</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>% Initial dose</td>
<td>1.7 ± 1.2</td>
<td>2.4 ± 1.5</td>
<td>0.011</td>
</tr>
<tr>
<td>Dynamic deposition (slope), MBq/min</td>
<td>0.32 ± 0.23</td>
<td>0.43 ± 0.07</td>
<td>0.018</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** n.s. = not significant; PS = pressure support.
within the lungs correlated with the percent of predicted VC or FEV₁. Skew, which reflects asymmetry and heterogeneity of aerosol deposition, was not correlated with age, but was inversely correlated with the percent predicted FEV₁ after both the control and PS sessions (p = 0.0025 and p < 0.0001, respectively), indicating that poorer lung function, as assessed from FEV₁, was associated with more asymmetric and more heterogeneous aerosol distribution. Skew was inversely correlated with the percent predicted VC after the control session (p = 0.003) but not after the PS session. There was also an inverse relationship between skew and the Shwachmann score, which was significant after the control session (p = 0.008) and of borderline significance after the PS session (p = 0.06). Skew was inversely correlated with the penetration index after both sessions (p = 0.05 and p = 0.02 after the control and PS sessions, respectively). Neither kurtosis nor the penetration index were correlated with any of the clinical or functional parameters studied.

DISCUSSION

The present study was the first in which both a bench test and a clinical study were used to evaluate the effect of PS ventilation on aerosol deposition in children with CF. Our results show that total lung aerosol deposition can be significantly enhanced when aerosol generation and transport through the airways are driven by noninvasive PS ventilation.

The major finding in our clinical study was that the total radioactivity count deposited in the lungs after nebulization, expressed as a percentage of the total radioactivity count initially present in the nebulizer unit, increased by about 30% after the PS session as compared with the control session. The first issue is whether this increased aerosol deposition was related to a difference between the nebulizers used in the control and PS sessions. Two characteristics of aerosols have been shown to affect lung deposition of aerosol particles. One is particle size distribution with smaller particles more likely to deposit within the lungs than larger particles (4, 7). Particle size distributions in the aerosols generated by the two nebulizers used in our study were closely similar and were near the optimal values for aerosol deposition in children with CF (4). The other factor affecting aerosol particle deposition in the lungs is the intrinsic performance of the nebulizer. Better intrinsic performance of the PS-coupled nebulizer in our study would translate into larger values for both the volume of solution and the amount of radioactivity that leave the nebulizer unit during the nebulization time, as compared with the control nebulizer. Although we did find that the amount of radioactivity that left the nebulizer was slightly larger during the PS session than during the control session, this difference did not reach statistical significance, and was too small to explain the 37% increase in aerosol lung deposition during the PS session. These data indicate that the two nebulizers had similar performances and produced similar aerosols. Consequently, the increase in aerosol deposition in the lungs after the PS session can be ascribed to the use of PS.

The most likely explanation for the increased aerosol deposition after the PS session is the change in breathing pattern change induced by PS ventilation. In a previous study, we showed that children with CF had an increase in their VT (from 0.4 L to 1.0 L) and decrease in their RR (from 18 breaths/min to 11 breaths/min) when treated with noninvasive PS ventilation set at an inspiratory pressure of 12 cm H₂O (11). The magnitude of these changes in breathing pattern varied with the level of PS: higher levels of PS ventilation resulted in a higher VT and a lower RR. In the present study, we chose a moderate level of inspiratory pressure (10 cm H₂O) to avoid an excessive increase in inspiratory flow, which would have increased the risk of aerosol particle impaction in the upper and central airways. The velocity of inspired gas is known to be an important determinant of particle transport and deposition. Higher inspiratory flow rates increase turbulent flow and produce stronger inertial forces, leading to impaction of particles in more proximal airways (6). For practical reasons (essentially decontamination), we were unable to study inspiratory flow and VT during the two nebulization sessions. In our previous study, however, the increase in VT (≈ 150%) exceeded the increase in inspiratory flow (≈ 50%) during PS ventilation set at 12 cm H₂O (11). This change in breathing pattern during PS can be expected to minimize particle impaction in the proximal airways. The optimal breathing pattern for drug delivery combines a low inspiratory flow rate and large tidal breaths. During slow, relaxed breathing, particle sedimentation and diffusion are the primary deposition processes, and particle deposition increases in the peripheral airways as a result of the proximity of lung surfaces in these airways. It has been shown that optimal particle deposition in patients with airway obstruction is achieved with flow rates of no more than 0.2 L/s (1). The flow rate providing optimal particle deposition in children with CF is unknown, but we found that “targeting” breath at a predetermined low flow rate by instructing the patient to inhale in such a way that the flow rate was kept between a pair of “tramtracks” on a screen enhanced amikacin deposition in the lungs (9). The most often reported advantage of PS ventilation is control of the frequency and duration of inspiratory assistance by the patients themselves. However, because expiration is unassisted, the decrease in respiratory rate induced by PS ventilation results in an increase in expiratory time. In patients with airway obstruction, increasing the expiratory time may result in less alveolar gas retention and consequently in a decrease in the overall work of breathing. A longer expiratory time may also have an important effect on aerosol droplet deposition, facilitating sedimentation of particles that have entered the lung during inspiration (18).

An important message from this study is that coupling aerosol delivery with PS ventilation can enhance aerosol deposition in the lungs without increasing particle impaction in the proximal airways. One of our concerns was that an excessively high PS ventilation level might generate high axial velocities and higher levels of flow turbulence, thus increasing proximal particle impaction, with radial diffusion from turbulence minimizing the axial dispersion of aerosol. It is interesting to note that the moderate levels of inspiratory pressure (10 cm H₂O) used in the present study provided a meaningful increase in aerosol deposition without altering the aerosol distribution, at least in our group of CF patients. Analysis of local lung deposition of aerosol is important in a disease such as CF (6). We therefore calculated the skew and the kurtosis of aerosol distribution. Skew and kurtosis in adults with CF have been shown to be significantly increased, indicating nonuniform distribution (6). In CF, bronchoconstriction or airway obstruction caused by mucus or inflammation diverts more of the airflow toward the nonobstructed airways. This increases particle deposition in healthy regions as a result of both higher flow rates, which facilitate particle impaction in airways, and longer residence times in the lung periphery, which favor sedimentation and diffusion. Furthermore, deposition immediately proximal to obstructed sites is also increased despite the reduced airflow through these regions, whereas deposition downstream from obstructed sites is severely reduced. At sites of mild to severe obstruction, high axial velocities and higher levels of flow turbulence seem to enhance particle deposition by impaction and by turbulent radial diffusion, resulting in...
concentration of aerosol at “hot spots” immediately down-
stream from the obstructed sites.

Skew and kurtosis have been found effective in separating
normal subjects from CF patients on the basis of aerosol
deposition (6). However, these indices of homogeneity of aerosol
deposition provide no information about which anatomic sites
receive less aerosol. We found an inverse correlation between
skew and severity of lung disease as assessed by the Shwach-
mann score and by the percent of predicted FEV₁. We also
found a significant inverse correlation between skew and the
penetration index, indicating that as the lung disease in CF
progresses, aerosol deposition becomes both more central and
less homogeneous. In contrast to others, we found no correla-
tion between the penetration index and indices of bronchial
obstruction such as FEV₁ (1). This may be because both of the
breath-actuated nebulizers used in our study are designed to
reduce asynchronism between aerosol delivery and inspiration
by the patient.

It would have been of interest to identify a clinical or func-
tional parameter capable of predicting the effect of PS on
aerosol deposition in individual patients. Unfortunately, no
correlation was found between enhanced aerosol deposition
and age, height, the Shwachmann score, VC, or FEV₁. Fur-
thermore, the addition of PS did not increase the amount of
aerosol that was deposited in the lungs in five of the 18 chil-
dren in our study. This troubling result can be explained by
several factors. First, our population was small and heteroge-
neous. Some children had very severe lung disease whereas
others had only moderate lung impairment. Second, not all the
children had routine nebulization therapy at home. Despite
the training session, some children were more familiar with
the PS technique than were others. Third, the variability and
unpredictability of aerosol deposition in healthy humans has
been pointed out (19). This is likely to be even more true in
CF, a disease in which the degree of bronchial obstruction is
highly variable from one day to another (Figure 5). Fourth, we
required a washout period of at least 3 d between the control
and PS sessions because of the decay of the radioactivity in the
radiolabeled aerosol. Despite careful exclusion of those chil-
dren who were not in a stable condition, it is possible that the
clinical condition of some patients was slightly different on the
two sessions. Moreover, accurate analysis of the distribution
of small amounts of aerosol in diseased lungs is even more
difficult in children than in adults. Despite these factors, we
observed a general tendency toward enhanced aerosol deposi-
tion with PS ventilation in patients with better lung function,
but this may merely reflect the limited efficacy of aerosol
transport in severely diseased lungs even with optimal nebuli-
zation techniques. Others also found no correlation between
total lung aerosol deposition and age or height (3); however,
in one study, aerosol concentration within the lungs (defined
as the percentage of nebulizer output deposited normalized
for the predicted TLC) was higher in children and teenagers
than in adults, and in adults was negatively correlated with
height and weight (20).

Our study provides convincing evidence that an in vitro
model incorporating particle diameter, normal breathing fre-
quency, and VT is less accurate than in vivo measurement of
aerosol deposition, which takes into account all the factors
that determine aerosol deposition, including the disease being
treated. However, an important finding in our experimental
study was that coupling the nebulizer to the PS ventilator did
not alter the performances of the nebulizer or PS ventilator.

This study was a feasibility study that assessed the possibil-
ity of combining nebulization and noninvasive PS ventilation
in children with CF. It was not an efficacy study evaluating the
therapeutic potential of a drug (a bronchodilator or an antibi-
otic), but rather a deposition study. It seems important to us to
know, before the routine use of a nebulized drug, the site of its
deposition (especially in diseased lung such as in CF), and the
exact amount of drug that is deposited in the lungs. These es-
sential points are most often lacking in studies of the effect of
a nebulized drug in children.

Future treatments for CF patients will require targeted de-

delivery to specific cell types or specific receptor populations. It
is therefore critical to identify and to learn how to control the
sites of aerosol deposition. For example, similar total deposi-
tion values can mask wide differences in the regional distribu-
tion of an aerosol (7). Our study can be viewed as a first at-
tempt to manage drug distribution with assisted ventilation.
Methods of assisted ventilation other than PS need to be in-
vestigated. Several of these methods have been used in an at-
tempt to enhance aerosol deposition. The effects of continu-
ous positive airway pressure (CPAP) at 10 cm H₂O on aerosol
kinetics and bronchodilator efficacy have been evaluated in
nine stable asthmatic adults (21). Despite a significant reduc-
tion in total aerosol delivery (from 6.85 ± 1.52% to 1.32 ±
0.37%) when a facemask was used, the bronchodilator re-
sponse was not affected, probably because of an intrinsic ef-
cfect of CPAP itself (21). Another study with adults attending
an emergency room for acute asthma exacerbations showed
that the delivery of a β-agonist by noninvasive inspiratory PS
ventilation with PEEP resulted in significantly greater improve-
ment in the peak expiratory flow rate than did delivery of the
drug by nebulization alone (22). Two other studies found that
intermittent positive-pressure breathing and high-frequency
oscillation did not increase drug delivery to the lungs (23, 24).

In conclusion, this study is the first to show that coupling
PS ventilation to a breath-actuated nebulizer enhances aerosol
deposition in the lungs of children with CF. This finding may
have three clinical applications. First, in patients with CF in
whom noninvasive mechanical ventilation is indicated, simul-
taneous administration of aerosol therapy and PS ventilation

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**Figure 5.** Examples of aerosol distributions (posterior view). (A) Homogenous distribution in the control session. (B) Homogenous distribution in the PS session in the same patient as in A. (C) Proximal artifactual deposition. (D) Peripheral artifactual deposition.
can enhance aerosol deposition in the lung, thereby helping to unload respiratory muscles, improve oxygenation, and reduce the time spent in treatment each day, possibly resulting in better compliance with treatment. Second, coupling PS to nebulization may be effective in other lung diseases known to respond to nebulized treatments: in status asthmaticus, for instance, coupling bronchodilator nebulization to noninvasive PS may increase treatment efficacy. Clearly this may require a functional study, which could be the logical continuum of a deposition study as that described here. Third, we suggest that nebulization of a radiolabeled aerosol may be an appropriate means of tailoring the amount of drug deposited in the lungs to the needs of each individual CF patient.

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**References**