Study objectives: The peak inspiratory flow rates (PIFRs) generated by cystic fibrosis (CF) and COPD patients through a range of clinically relevant resistances have not yet been reported (to our knowledge). The objectives of this study were to (1) explore a relevant range of resistive loads and address whether patients with stable CF and COPD can generate the PIFR sufficient to disperse dry-powder inhalants (DPI) and (2) determine whether the optimal inspiratory flow rate effective for delivery of aerosolized pharmacologic therapeutic agents can be attained with a comfort rating acceptable to subjects.

Design: Prospective, controlled, subject-blinded study.

Setting: Pulmonary function laboratory at the VA Palo Alto Health Care System.

Patients or participants: Thirty-six subjects, including 12 healthy volunteers, 12 subjects with CF, and 12 subjects with COPD were studied.

Measurements: Studies of dynamic lung function and PIFR without and with varying resistances were obtained at a single laboratory visit.

Results: Dynamic lung function and PIFR varied inversely with the resistive load for all patient groups and did not correlate with the disease severity, as indicated by FEV1 of percent predicted. The average subjective comfort rating for any given resistive load was similar for subjects with CF and COPD.

Conclusions: These results support the conclusion that subjects with stable CF and COPD of varying severity can comfortably generate the necessary flow rates to operate new and currently available DPIs over a wide range of inspiratory resistances.

(CHEST 1998; 114:988–992)

Key words: chronic bronchitis; COPD; cystic fibrosis; emphysema; inspiratory flow rate; inspiratory resistance; inspiratory volume

Abbreviations: ANCOVA=analysis of covariance; CF=cystic fibrosis; DPI=dry powder inhaler; IC=inspiratory capacity; IFR=inspiratory flow rate; MIP=maximum inspiratory pressure; PIFR=peak inspiratory flow rate; Raw=airway resistance

Dry-powder inhalers (DPIs) have been shown to be equivalent to meter-dose inhalers (MDIs).1–3 Interest in DPIs has increased commensurately with mandated phased removal of fluorocarbon propellant products in medical aerosol delivery devices and replacement with DPIs.4 Many physiologic studies have focused on the expiratory flow dynamics and the features limiting ventilation with scant attention paid to the parameters limiting the inspiratory flow rates (IFRs) in patients with cystic fibrosis (CF) and COPD.5 The IFR could be important in the utilization of DPIs.

DPIs are generally breath activated and require a certain minimum IFR to deaggregate and disperse the drug powder in the inhaled airstream.6 It appears that 0.5 to 2×10^{-3} m^3·s^{-1} may be the necessary peak inspiratory flow rate (PIFR) crucial to the effective delivery of the medication.2,7–12 DPIs vary substantially in their resistance to airflow. The relationship between inhaler resistance...
and inspiratory flow is of immediate importance for the development of DPI devices and ultimately for effective prescribing and compliance practices. Therefore, it is important that patient health-care providers be aware of the minimum allowable IFR necessary to use DPIs effectively.

A prior study of 59 subjects with asthma or COPD has been published describing a poor correlation between IFR and FEV₁. The IFRs generated by CF and COPD patients through a range of clinically relevant resistances have not yet been reported (to our knowledge). The objectives of this study were to (1) explore a relevant range of resistive loads and address whether subjects with stable obstructive airways disease can generate PIFRs sufficient to disperse dry-powder inhalants; and (2) determine whether the optimal IFR effective for delivery of aerosolized pharmacologic therapeutic agents can be attained with a comfort rating acceptable to subjects.

**MATERIALS AND METHODS**

**Subjects**

Thirty-six subjects were enrolled in three groups: 12 age-matched healthy volunteers, 12 patients in stable condition with mild, moderate, and severe CF (within each disease severity strata), and 12 subjects in stable condition with mild, moderate, and severe COPD (within each strata). FEV₁ was expressed as a percentage of the predicted FEV₁ for sex, height, and age. The two patient groups were balanced with regard to baseline severity of physiologic impairment (Table 1). Four COPD patients had mild disease severity as defined by FEV₁=60% to 79% of predicted; four had moderate obstruction with FEV₁=50 to 59% of predicted; and four were in the severe range with FEV₁=35 to 49% of predicted, according to the Knudson classification of severity of pulmonary dysfunction. An identical distribution of subjects with disease severity, as defined above, constituted the CF arm of the protocol and is described in Table 1.

Eligibility criteria included the following: at least 12 years of age; either sex; history of CF or previous diagnosis of COPD; stable respiratory status (>1 week) and receiving regular care as an outpatient; and FEV₁ percent obtained on the day of the study was between 35% and 79% of predicted for patient groups and 80% of predicted for healthy volunteers. Subjects were excluded for the following reasons: if they were hospitalized during 14 days of study enrollment; using any investigational drugs or devices; receiving mechanical ventilation or had an artificial airway; using continuous supplemental oxygen; or being treated with an open- or closed-tube thoracostomy. Subjects were also excluded for the following reasons: if they had a recent asthmatic episode defined as airflow limitation with FEV₁ <80% of predicted with subsequent improvement >15% following bronchodilator documented within the last 12 months; had undergone lung resection; or had lung cancer diagnosed within the past 2 years. This study did not interfere with the patient’s medical therapy, which was continued during and after the conclusion of the study.

Human subject approval was obtained through the Administrative Panel on Human Subjects in Medical Research at Stanford University. Subjects (or guardians) provided written informed consent.

**Procedures and Measurements**

No study drugs were administered in this protocol. Subjects were studied prospectively. On the study day, subjects normally taking bronchodilator medications self-administered the bronchodilator strictly 2 h prior to the pulmonary function study. All studies of dynamic lung function, including PIFR, were obtained at a single visit to the outpatient Pulmonary Function Laboratory at the VA Palo Alto Health Care System, Palo Alto, CA. No follow-up visits were required. No monitoring of patient responses over time was required.

The following measurements were obtained for each subject prior to performing a PIFR maneuver: spirometry, maximum inspiratory pressure (MIP), and airway resistance (Raw). Standard spirometric analyses of FEV₁, FVC, and forced expiratory flow rate between 25% and 75% of the FVC (FEF₁₂⁵₋₇⁵%) were measured with a pneumotach measuring system (Medical Graphics 1070; Medical Graphics, Minneapolis, MN). Each patient had MIP and maximum expiratory pressures measured at the point of zero inspiratory flow that occurred at the end (resting) expiratory level using an occlusion balloon method incorporated in the respiratory monitoring system (Medical Graphics Respiratory Pressure Module; Medical Graphics). Raw was measured by whole-body plethysmography (Quinton Master Lab manufactured by Jeager; Quinton Medical; Seattle). PIFR was determined with and without added resistance (Medical Graphics 1070; Medical Graphics).

In addition to the pulmonary function testing, three PIFR

| Table 1—Pertinent Demographics of Enrolled Subjects* |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Subjects       | Group           | Age, yr         | Sex, M/F        | FEV₁, %         | TLC, %  |
|                 |                 |                 |                 |                 | 10⁻³ m³·s⁻¹ |
|                 |                 |                 |                 |                 | 10³ Pa   |
|                 |                 |                 |                 |                 | 10³ Pa   |
| CF              | Mild            | 25 (16-32)      | 0/4             | 72 (63-79)      | 102 (84-125) |
|                 | Moderate        | 21 (15-30)      | 2/2             | 55 (50-58)      | 108 (93-115) |
|                 | Severe          | 30 (20-46)      | 1/3             | 36 (32-40)      | 91 (77-105)  |
| COPD            | Mild            | 42 (26-62)      | 4/0             | 69 (65-77)      | 94 (77-97)   |
|                 | Moderate        | 63 (44-70)      | 4/0             | 55 (53-56)      | 102 (75-119) |
|                 | Severe          | 62 (44-77)      | 4/0             | 40 (39-47)      | 119 (96-141) |
| Normal          |                 | 36 (14-78)      | 4/8             | 98 (85-124)     | 98 (83-117)  |

*Range of values. TLC=total lung capacity.

1 m³·s⁻¹=10 L·s⁻¹.

1 Pa=10⁻⁵ m²·s⁻¹·cm H₂O/L·s⁻¹.

1 Pa·s=10⁻⁵ m²·cm H₂O.
maneuvers were performed against four resistive loads and were formally randomized, and each PIFR and inspiratory capacity from resting expiratory level were recorded. The selected resisters bracketed the range of typical resistance values of commercially available DPI systems and are listed in Table 2. Subjects were blinded to the resistance sequence chosen. Each exercise consisted of a forced inspiratory breath through the resistor. The subject was asked to breathe normally and then to perform the maximum inspiratory maneuver from the end (resting) expiratory level. Normal maximal expiratory flow-volume curves were determined from the standards established by Knudson et al. An equivalent rest period between tests was provided for each subject. Full flow-volume loop data were stored on computer diskettes. After each spirometry, the subjects were asked to subjectively grade the comfort of the particular resistance. Choices available included the following: 1=comfortable (no difficulty performing maximum inspiratory maneuver); 2=mild discomfort (some slight difficulty); 3=moderate (between mild and severe); and 4=severe discomfort (judged unable to repeat the inspiratory maneuver).

Statistical Analysis

The relationship between mean PIFR and resistive load and the relationship between respiratory function parameters and either mean PIFR or mean inspiratory capacity were examined using regression and correlation methods similar to those used to study these relationships in healthy volunteers. Regression methods were used to examine the relationship between baseline PIFR and dynamic lung function. The statistical methods used to compare the CF vs the COPD groups in the analyses of the respiratory function parameters and comfort rating include repeated, measured analysis of covariance (ANCOVA) and t test.

RESULTS

PIFRs and Pressures

The PIFR showed an inverse relationship with resistive load for all patient groups as shown in Figure 1. The individuals studied were able to generate the flow rates of 0.5 to 2×10⁻³ m³·s⁻¹ reported as necessary to deaggregate and disperse many drugs over this wide range of resistances. PIFR values within the CF group at the two lowest resistance values were significantly lower (p<0.03) than PIFR values at these resistances for the COPD patients and group of normal subjects. PIFR values at each resistance did not show a significant correlation with disease severity as measured by FEV₁ (percent of predicted).

Relationship Between PIFR and Pulmonary Function Values and Disease States

ANCOVA for each resistance revealed that at each resistance level, MIP was the only statistically significant correlate of PIFR (p<0.05) except for Raw at the lowest resistance values. These values were p=0.01 for a zero resistance, and p=0.01 and p=0.02, respectively, for resistor A and resistor B.

Inhaled Volumes

In general, for all patient groups, inhaled volume decreased slightly as the resistive load was increased (Fig 2). This decrease was presumably due to fatigue during inspiration, as the overall inspiration times increased with the higher resistance values. The decrease in inhaled volume with resistors A to D was significant (p<0.001) for each patient group and there were no significant differences between groups.

Comfort Rating

The degree of comfort experienced by the subjects decreased monotonically with increasing resistance (Fig 3). In general, the average “comfort rating” for any given external resistor was similar for all subjects and all patient groups. There were no statistically significant differences between patient groups. Overall, the highest resistance value of 213×10³ Pa⁻⁰·₅·s⁻¹·m⁻³ induced only “moderate discomfort.”

Table 2—Values of Resistive Loads

<table>
<thead>
<tr>
<th>Resistor</th>
<th>Resistance²⁻¹ (Pa⁻⁰·₅·s⁻¹·m⁻³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spirometer</td>
<td>6.54 X10⁻³</td>
</tr>
<tr>
<td>A</td>
<td>16.0 X10⁻³</td>
</tr>
<tr>
<td>B</td>
<td>28.5 X10⁻³</td>
</tr>
<tr>
<td>C</td>
<td>67.1 X10⁻³</td>
</tr>
<tr>
<td>D</td>
<td>212.7 X10⁻³</td>
</tr>
</tbody>
</table>

²Resistance values determined using the methods of Newman et al, assuming the relationship R = V/A – D/Q.

³Pa⁻⁰·₅·s⁻¹·m⁻³ = 1.6827×10⁻⁴ cm H₂O1/2/L·min.

⁴Calculated equivalent at flow rate of 4×10⁻³ m³·s⁻¹.

Figure 1. Inverse relationship of maximum PIFR and resistive load for CF and COPD patients and healthy volunteers.
DISCUSSION

The results of this study demonstrate that PIFR at varying resistive loads is similarly and inversely related to the load in both normal subjects and in patients with stable mild-to-severe CF and COPD. It was observed that PIFR, as a function of resistance, was similar at all levels for both normal subjects and the CF and COPD groups. Similar results were reported by Clark and Hollingworth\textsuperscript{17} in 16 healthy adult volunteers and Hansen and Andersen\textsuperscript{13} in 59 adult subjects with either asthma or COPD. These authors observed that there is a decrease in PIFR, as the device resistance increased.\textsuperscript{13,17,20} A caution must be made in that these data are applicable only for CF and COPD patients in stable condition and should not be extrapolated to patients with acute reversible bronchoconstriction.

Of interest, the inspiratory capacity (IC) in the CF group at baseline spirometry and over varying resistances of up to $60 \times 10^3 \text{ Pa}^{0.5} \text{ s} \cdot \text{m}^{-3}$ tended to be lower, but not significantly different from the values in the other two groups. However, with increasing resistance, the differences in the IC noticeably decreased. This suggests that CF subjects are able to generate ICs at near maximal levels despite increasing resistances, possibly as the result of chronic inspiratory muscle training that may occur in CF subjects with progressive pulmonary deterioration.\textsuperscript{21-27} ANCOVA was used to evaluate the effect of the disease state. Although there were no significant differences between groups or disease severity regarding perceived discomfort with increasing resistance, there was a tendency for the most severe CF

![Figure 2. Relationship of inhaled volume and resistance for CF and COPD patients and normal volunteers.](image)

![Figure 3. Comfort rating vs resistance for CF and COPD patients and normal volunteers. Mean comfort ratings are plotted for the following: 1=comfortable (no difficulty performing maximum respiratory maneuver); 2=mild discomfort (some slight difficulty); 3=moderate discomfort (between mild and severe); and 4=severe discomfort (judged unable to repeat the inspiratory maneuver).](image)
group to have lower perceived ratings for progressive resistances, suggesting an effect of chronic respiratory muscle training or "training stimulus" from chronic lung disease.\textsuperscript{28,29}

Resistance values in this study of $<68 \times 10^3$ Pa$^{0.5} \cdot s \cdot m^{-3}$ corresponded with "mild discomfort" for all subjects except for the patients with COPD, who had ratings approaching "moderate discomfort." These findings are consistent with other researchers who have shown that patients with COPD or asthma preferred a resistance of $\leq 50 \times 10^3$ Pa$^{0.5} \cdot s \cdot m^{-3}$.\textsuperscript{30}

**Conclusion**

The data suggest that CF and COPD subjects with varying severity of lung disease (based on FEV$_1$) can comfortably produce the flow rates required to utilize the currently available DPIs.\textsuperscript{8,19} We have found that the standard expiratory dynamic lung function tests\textsuperscript{31,32} are not predictive of a patient's ICs. The only correlates of PIFR are MIP and Raw only at the lowest resistance value. In view of these data, measurements of these inspiratory maneuvers may be useful in predicting the applicability and benefits of the use of DPIs to the individual patient in stable condition.

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