Analysis of Tidal Breathing Profiles in Cystic Fibrosis and COPD*

Ric L. Colasanti, PhD; M. Jocelyn Morris, MD; Richard G. Madgwick; Linda Sutton; and E. Mark Williams, PhD

Study objectives: To explore the flow and time domain characteristics of resting tidal airflow profiles in the presence of obstructive airway disease.

Methods: Spirometry was performed on 81 adults and 46 juveniles in the lung function laboratory. All the juveniles had cystic fibrosis (CF), as did some of the adults (n = 25), with the remainder having either healthy lungs or COPD. Resting breathing profiles were recorded using a pneumotachograph. Thirty flow and time domain parameters were extracted from each profile. Two new indexes were derived that are influenced by the shape of the post-peak expiratory flow portion of the expirogram. In this expirogram, the first index (change in post-peak expiratory flow at time 20% [TPPEF20]) describes early changes in post-peak flow, while the second index (change in post-peak expiratory flow at time 80% [TPPEF80]) describes later changes in flow. Multiple linear regression techniques were used to define the relationship between body size, flow and time domain parameters, and FEV1, a measure of obstructive airway disease.

Results: In juvenile subjects with CF, body weight and the time to reach peak expiratory flow are the main correlates with FEV1 (adjusted \( r^2 = 0.74 \)). The adult CF group are different with the expiratory flow index (TPPEF20) being the major correlate with FEV1 (adjusted \( r^2 = 0.77 \)). In the COPD group, the second expiratory flow index (TPPEF80) is the major correlate instead (adjusted \( r^2 = 0.6 \)).

Conclusions: Using multiple linear regression techniques has allowed the description of the interrelationships between body size, age, and tidal breathing profile in obstructive airway disease. The relationship between the flow indexes TPPEF20 and TPPEF80 show that in adults with CF, the loss of expiratory flow braking is an important adaptation to disease, while in COPD pulmonary hyperinflation is the predominant factor.

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Key words: expiratory flow braking; FEV1; lung function; pulmonary hyperinflation

Abbreviations: CF = cystic fibrosis; MLR = multiple linear regression; PEF = peak expiratory flow; PIF = peak inspiratory flow; TPPEF20 = change in post-peak expiratory flow at time 20%; TPPEF80 = change in post-peak expiratory flow at time 80%; TPPEF = time from the onset of expiration to peak expiratory flow; TPEF = time from the onset of inspiration to peak inspiratory flow; TOT = total breathing time

Early studies1 with pneumotachographs in the 1950s began noticing differences between the tidal breathing patterns of subjects with healthy lungs and those with COPD. In particular, there was a noticeable change in the expiratory flow profile with increasing airway resistance.2 However, the variability within individual breathing patterns led Gaensler3 in 1955 to note that, “... the normal respiratory pattern is so variable that detailed description of minor changes will never assume clinical importance.”

The advent of modern data-filtering techniques has allowed workers to begin the untangling of patterns within data. Morris and Lane4 were the first to derive indexes that related the severity of airway obstruction to a change in the tidal expiratory flow profile, and found that the time from the onset of expiration to peak expiratory flow (TPPEF) shortened with increasing airway resistance.5 Further studies of the post-peak expiratory flow portion of the breathing cycle have shown how the flow decay time constant lengthens with airway obstruction.6 It has been shown that the post-peak expiratory flow portion of the profile is diagnostic of airway obstruction in COPD and cystic fibrosis (CF).7,8

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The mechanisms for this change in flow dynamics are not fully understood and are thought to result from the interaction between passive lung mechanics and the active neuromuscular control of breathing. In healthy subjects, active expiratory flow braking is used to slow lung emptying.\textsuperscript{9,10} Braking occurs throughout the first third of expiration and thus lengthens T\textsubscript{tpef} and lowers peak expiratory flow (PEF) [Fig 1]. Expiratory braking can be produced by persistent activity of the inspiratory muscles, by increasing expiratory resistance by laryngeal adduction, or by loss of laryngeal abductor activity.\textsuperscript{11} In COPD, expiratory flow braking is largely absent, so T\textsubscript{tpef} is shorter, PEF sharper, and post-peak expiratory flow decays in an exponential manner (Fig 1). In this situation, the time constant of the whole respiratory system largely determines flow rate. Another unique feature of the expiratory flow profile in COPD is related to lung hyperinflation, when inspiration suddenly begins before the expiratory flow has stopped (Fig 1).

The aim of this study was to explore the flow and time domain characteristics of resting tidal airflow.

**Figure 1.** Tidal flow profiles from a subject (top, A) with severe airway obstruction (FEV\textsubscript{1} 27\% predicted) and a subject (bottom, B) with healthy lungs (FEV\textsubscript{1} 103\% predicted). In = inspiration; Exp = expiration.

<table>
<thead>
<tr>
<th>Table 1—Subject Characteristics in the Different Data Sets and Subsets*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>Age, yr</td>
</tr>
<tr>
<td>Height, m</td>
</tr>
<tr>
<td>Weight, kg</td>
</tr>
<tr>
<td>FEV\textsubscript{1}, % predicted</td>
</tr>
<tr>
<td>Male/female gender</td>
</tr>
</tbody>
</table>

*Data are presented as mean (range) or mean ± SD (range) or No.
†The COPD group is a mixture of healthy subjects (n = 7; FEV\textsubscript{1} % predicted, 107 ± 8; range, 99 to 121), patients with moderate COPD (n = 5; FEV\textsubscript{1} % predicted, 61 ± 4; range, 56 to 66), and patients with severe COPD (n = 9; FEV\textsubscript{1} % predicted, 31 ± 7; range, 20 to 47). See Figure 5, C, for individual values.
patterns and how they differ in the presence of obstructive airway disease. A widely accepted measure of airway obstruction is the dynamic measure FEV$_1$. In healthy adults, there is a simple relationship between FEV$_1$ and body size, gender, and age. However, this relationship is more complex in the presence of obstructive airway disease. We used multiple linear regression techniques to explore the interrelationship between FEV$_1$, body size, age, and tidal breathing profile in subjects with obstructive airway disease.

**Materials and Methods**

**Subjects and Data Collection**

In total, 81 adults and 46 children were measured (Table 1). Three sets of breathing profile data collected at different times were used: one set (n = 71) of subjects with CF, one set from subjects with COPD and healthy lungs (n = 21), and one set from healthy adult volunteers only (n = 35). The CF and COPD data sets include subjects used in previous studies. When visiting the lung function laboratory, each subject had their age, weight, and height recorded, before undergoing spirometry when FEV$_1$ was measured. Tidal flow was recorded while the subject was seated, wearing a noseclip, and breathing through a mouthpiece and pneumotachograph connected to a differential-pressure sensor linked to a computer. Resting tidal flow was recorded for 2 min at a sampling frequency of 100 Hz.

**Extraction of Parameters**

A tidal flow signal of a subject with moderate airflow obstruction (FEV$_1$ 57% predicted) is shown in Figure 1, top. In all recordings, the beginning of inspiration and expiration was defined for each breath. The overall mean and SD of peak inspiratory flow (PIF) and PEF rates were calculated for all the breaths in the recording. Then, any breath with a PIF or PEF...
### Table 2—Comparison of Parameters Between Adults With Healthy Lungs or CF and Severe Airway Obstruction

<table>
<thead>
<tr>
<th>Parameters</th>
<th>FEV₁ % Predicted</th>
<th>FEV₁ % Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>106 ± 12; Range</td>
<td>29 ± 7; Range</td>
</tr>
<tr>
<td></td>
<td>77–136 (n = 35)†</td>
<td>19–39 (n = 12)†</td>
</tr>
<tr>
<td>Age, yr</td>
<td>39 ± 14</td>
<td>23 ± 6</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>70 ± 12</td>
<td>54 ± 10</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.7 ± 0.1</td>
<td>1.7 ± 0.1</td>
</tr>
<tr>
<td>Inspiratory time, s</td>
<td>1.9 ± 0.7</td>
<td>1.2 ± 0.2</td>
</tr>
<tr>
<td>Expiratory time, s</td>
<td>2.6 ± 0.9</td>
<td>1.9 ± 0.3</td>
</tr>
<tr>
<td>TTOT, s</td>
<td>4.5 ± 1.5</td>
<td>3.1 ± 0.6</td>
</tr>
<tr>
<td>Breathing rate, breaths/min</td>
<td>15 ± 5</td>
<td>20 ± 4</td>
</tr>
<tr>
<td>PIF, L/s</td>
<td>0.6 ± 0.2</td>
<td>0.9 ± 0.2</td>
</tr>
<tr>
<td>PEF, L/s</td>
<td>0.6 ± 0.2</td>
<td>0.5 ± 0.2</td>
</tr>
<tr>
<td>Tpif, s</td>
<td>0.3 ± 0.1</td>
<td>0.5 ± 0.1</td>
</tr>
<tr>
<td>Tpif, °</td>
<td>0.6 ± 0.2</td>
<td>0.4 ± 0.1</td>
</tr>
<tr>
<td>Tpif/expiratory time ratio</td>
<td>24 ± 10</td>
<td>19 ± 5</td>
</tr>
<tr>
<td>Expired volume, tidal volume</td>
<td>226 ± 198</td>
<td>151 ± 72</td>
</tr>
<tr>
<td>(normalized, arbitrary units)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPF</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.1</td>
</tr>
<tr>
<td>TPPEF₂₀ °</td>
<td>179 ± 19</td>
<td>156 ± 16</td>
</tr>
<tr>
<td>TPPEF₅₀ °</td>
<td>168 ± 16</td>
<td>153 ± 23</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD. TPPEF = integral of post-peak expiratory flow profile.†See Quanjer et al. 13

1Statistical differences were defined using the Student unpaired t test. Pneumotachographic indices represent the average values from all selected breaths from each recording (see text for details).

—1 SD different from the mean was excluded. From the remaining breaths, a number of time domain and flow indexes were extracted and mean ± SD values calculated (Fig 2 top, A). Further expiratory profile indexes were extracted in further processing by normalizing each breath to make the time span for each breath the same (100 U). Each breath was averaged to together to form a single mean breath (Fig 2, bottom left, B). Flow was normalized in the same way with a span between +50 for inspiration and –50 for expiration. Derivation of a "representative" breath by normalization serves to reduce breath-to-breath variability and emphasis the shape. After deriving the normalized post-peak expiratory flow profile from this average breath, the integral of post-peak expiratory flow profile was calculated (Fig 2, bottom right, C). A comparison of all of the above indexes in subjects with healthy lungs and those with severe airway obstruction are shown in Table 2.

Earlier studies6–8 have shown a relationship between the shape of the post-peak flow profile and severity of airway obstruction. Inspection of normalized post-peak flow expiratory flow profiles indicate that this relationship is best described by the change in flow at two common regions of the curve. These regions of changing flow occur at 20% and 80% of the way through the normalized post-peak expiragram. These regions are quantified by two profile indexes (Fig 3). Firstly, the normalized post-peak flow data were split into three time portions (0 to 20%, 21 to 80%, and 81 to 100%), and then a linear regression function was used to fit lines through each portion. The slopes of the three regression lines were used to calculate an angle between each pair of regression line slopes at 20% time and 80% time (Fig 3). These points are referred to as the post-peak expiratory flow at time 20% (TPPEF₂₀) and post-peak expiratory flow at time 80% (TPPEF₈₀). The first index (TPPEF₂₀) measures an outside angle, and the second index (TPPEF₈₀) measures an inside angle (Fig 3). The relationship between these are altered by different flow conditions. If post-peak expiratory flow deceleration is constant, the flow profile is linear (Fig 1, bottom, B) so both indexes will have a value of 180°, as the three fitted lines will form a straight line. However, if expiratory flow decelerates exponentially between time 0 (time at PEF) and time 80, then the index TPPEF₂₀ will have a value < 180. Flow (normalized) at this point is tending toward zero, as shown by the arrow in Figure 3. If the opposite is happening and the flow profile is convex, then TPPEF₂₀ will be > 180, and flow at this point will trend toward 100%6. A high TPPEF₂₀ index is indicative of airflow braking, as the profile is more convex in shape. The second index, TPPEF₈₀, becomes smaller with increasing hyperinflation, as the flow at this point trends toward 100% (Fig 3, arrow).

**Statistical Analysis**

In each data group, the links between the indexes describing tidal flow, breathing profiles, and airway obstruction were investi...
tigated by the construction of multiple linear regression equations (SPSS V11; SPSS; Chicago, IL), and compared against the measured FEV$_1$. The minimum number of parameters was used in the construction of each equation in order to elucidate the maximum amount of information about the contribution of each included parameter (Appendix 1). Unpaired t tests were used to statistically compare differences between individual parameters and groups.

**RESULTS**

The correlation between the FEV$_1$ value derived from the multiple linear regression equations and the measured FEV$_1$ provide information on the degree that each parameter (included in the equations) contributes to the derivation of FEV$_1$.

**FEV$_1$, Age, and Body Stature**

Height and age are important predictors of FEV$_1$ in healthy adults, and accounted for the majority of the adjusted $r^2$ of 0.6 (Fig 4, 5; Table 3). Body weight is the major predictor in subjects with CF, being the principal predictor in the combined data set and in the juvenile subset (Fig 4, 6). In the juvenile CF subset, body weight accounts for 0.74 of the adjusted $r^2$ of 0.81, while in the adult CF subset, age and body weight are secondary predictors to the TPPEF$_{20}$ index (Fig 4, 6). Age and body weight play only a minor role in the relationship between FEV$_1$ in the COPD group (Fig 4, 5).

**FEV$_1$, Flow, and Time Domain Parameters**

In all breathing profiles, flow and time domain parameters were sensitive to FEV$_1$. In the control group and the juvenile CF subset, the contribution was small (Figs 4–6; Table 3), with the index TPPEF$_{80}$ contributing to changing FEV$_1$. In the juvenile CF subset, the time to Tptef lengthens with increasing FEV$_1$.

In the adult CF subset, the multiple linear regression equation produced an adjusted $r^2$ of 0.77, with the TPPEF$_{20}$ index being the major contributor to this correlation (Fig 4; Table 3). A comparison of the TPPEF$_{20}$ index between control subjects and adult CF patients show that the mean (± SD) TPPEF$_{20}$ index

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**Figure 4.** Cumulative contribution of variables to the total $r^2$ adjusted in each group. Juv = juvenile; Ht = height; Wt = weight.
decreases with FEV₁, from 179 ± 19 in the control group to 168 ± 18 in the CF subjects (p = 0.035).

In the COPD group, the major predictor of FEV₁ is different from that found in the adult CF group, the Tppef₂₀ index, rather than the Tppef₈₀ index, being the major contributor to the overall correlation of the multiple linear regression of 0.73 adjusted r² (Fig 4). Analysis indicated that the Tppef₈₀ index decreasing with FEV₁. The time from onset of inspiration to peak inspiratory flow (Tptif) was also a contributory predictor and lengthened with increasing FEV₁.

**DISCUSSION**

This study has explored in detail the flow and time domain characteristics of resting tidal airflow profiles as a function of airway obstruction as measured by FEV₁. The results confirmed the simple relationship between the FEV₁, body size, and age in healthy adults.

Using multiple linear regression techniques, we discovered a more complex interrelationship between FEV₁, body size, and age, and tidal breathing profile in subjects with obstructive airway disease. This was accomplished by extracting from breathing profiles two measurements that contain information specifically about the severity of airway obstruction that describe the change in flow at two common regions of the curve occurring at 20% (Tppef₂₀) and 80% (Tppef₈₀) of the time through the normalized post-peak expirogram. When combined with other parameters in a simple multiple linear regression model, Tppef₂₀ shows a correlation with adult CF and Tppef₈₀ shows a correlation with COPD.

**Healthy Adults and Childhood CF**

The multiple linear regression equations for this group allow the FEV₁ to be derived in healthy adults simply from the subject’s height and age. This is not surprising since regression equations with these parameters plus gender are used universally to predict FEV₁ in both children and adults. In the present study, a stronger correlation may have been obtained if gender had also been included as an independent variable in the adult groups, but to do this we would have to approximately double our sample size. In the juvenile CF subgroup, body weight is the overwhelming factor in calculating FEV₁, with the heaviest subjects having the greatest FEV₁. Most of the juvenile CF subgroup had some airway obstruction (FEV₁ 87 ± 23% predicted; range, 46 to 134%), so the simple relationship between height age and FEV₁ found in healthy children no longer exists. In healthy subjects, weight is not important in determining FEV₁ unless pathologically increased and limiting inspiration. The importance of Tptef in deriving FEV₁ in the juvenile CF subgroup results from the children with the more severe airway obstruction. A reduction in Tptef is a common feature of obstructive airway disease in children and reflects a loss of expiratory flow braking. The preponderance of convex-shaped flow profiles described in an earlier study is confirmed with 41% of juvenile CF subjects having a Tppef₂₀ of > 180.

**Adult CF**

In adults with obstructive airway disease, there are many differences when compared to children. In the adult CF subgroup, the Tppef₂₀ is the major contributor in determining FEV₁. A mean Tppef₂₀ index < 180 signifies that in this group the initial
portion of expiratory flow is exponential in nature, implying that expiratory flow braking is reduced in the presence of airflow obstruction, this exponential decay being described as a predominantly concave flow profile in earlier studies. The lack of contribution from the Tppef index shows that this portion does little to characterize the severity of airway obstruction. This suggests that lung hyperinflation is not a major factor in this adult CF group. This is supported by the observation that resting or tidal expiratory flow limitation (often associated with hyperinflation) has been shown to be present only in CF patients with the severest of reductions in FEV₁ (FEV₁ < 30% predicted).

The importance of body weight and age as predictors of FEV₁ in adults with CF found in this study is to be expected. In CF, lung function and body weight decline with time, these reductions resulting from cumulative bouts of lung infection (particularly by Pseudomonas aeruginosa) and malnutrition through nutrient malabsorption. Indeed, these two factors are the main cause of morbidity and mortality in patients with CF.

Adult COPD

In the COPD group, the major predictor of FEV₁ was the Tppef index. This shows that of all the parameters that are important in the development of pulmonary hyperinflation (pattern of breathing, inspiratory and laryngeal muscle activity), it is the beginning of inspiration before the lungs reach functional residual capacity that is the predominant factor. If the loss of inspiratory muscle activity (expiratory flow braking) during expiration was more important, then the Tppef index would be a contributing factor in the calculation of FEV₁. The premature start of inspiration (indicated by a decreasing Tppef index) supports other studies showing an increase in the time constant of the lung with increasing severity of obstructive airway disease. Supporting the notion that the respiratory timing components of hyperventilation are predominant is the observation that a shortened time to reach PIF is an important indicator of FEV₁. Pulmonary hyperinflation occurs statically because the small airways close at a higher lung volume than normal. In order to increase ventilation (to overcome pulmonary ventilation/perfusion mismatching due to airway obstruction), expiration needs to be prolonged, as increased respiratory muscle activity is ineffective because of expiratory flow limitation. Shortening inspiration, and thus reducing Tptif is one strategy for prolonging expiration and improving ventilation/perfusion mismatch. The contribution of age in the calculation of FEV₁ in this group is

<table>
<thead>
<tr>
<th>Subject Group</th>
<th>r²</th>
<th>r² Adjusted</th>
<th>Regression Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control subjects</td>
<td>0.62</td>
<td>0.59</td>
<td>FEV₁ = - 5.41 + (H × 4.97) + (A × - 0.02) + (Tppef₈₀ × 0.008)</td>
</tr>
<tr>
<td>CF</td>
<td>0.73</td>
<td>0.72</td>
<td>FEV₁ = - 3.95 + (Wt × 0.053) + (Tptide₈₀ × 0.021) + (A × - 0.06) + (Ttot × 0.285)</td>
</tr>
<tr>
<td>All subjects</td>
<td>0.80</td>
<td>0.77</td>
<td>FEV₁ = - 5.88 + (Tppef₂₀ × 0.034) + (Wt × 0.053) + (A × - 0.039)</td>
</tr>
<tr>
<td>Adults only</td>
<td>0.83</td>
<td>0.81</td>
<td>FEV₁ = - 2.4 + (Wt × 0.038) + (Tptide × 1.06) + (Tppef₈₀ × 0.015)</td>
</tr>
<tr>
<td>Juveniles only</td>
<td>0.77</td>
<td>0.73</td>
<td>FEV₁ = - 3.73 + (Tppef₈₀ × 0.031) + (Tptif × 6.08) + (A × - 0.017)</td>
</tr>
<tr>
<td>COPD</td>
<td>0.77</td>
<td>0.73</td>
<td>FEV₁ = - 3.73 + (Tppef₂₀ × 0.031) + (Tptif × 6.08) + (A × - 0.017)</td>
</tr>
</tbody>
</table>

* A = age (years); H = height (meters); Wt = weight (kilograms).

Table 3—Equations Used to Calculate FEV₁ in Individual Groups

Figure 6. The relationship between the measured and derived FEV₁ in adult CF subset (r² = 0.80; top, A) and the juvenile CF subset (r² = 0.83; bottom, B).
not unexpected, as COPD develops over a number of years, with the highest incidence found among the eldest groups of the population.

Multiple Linear Regression Equations

The interrelationship between FEV\(_1\), body size, age, and tidal breathing profile is only revealed through a combination of parameters, as, individually, the correlations are weaker.\(^8\) The even distribution of the residuals of the difference between the calculated and measured FEV\(_1\) (not shown) indicates that the interrelationship of the selected parameters of the multiple linear regression equations is linear for all of the groups. However, a more complex relationship, possibly a nonlinear one, may become apparent in a larger data set, at which point it may be useful to employ more advanced nonlinear regression techniques such as support vector machines.

Our data points to the possibility that, once obstructive airway disease has been diagnosed, it may be possible to monitor changes in obstructive airway disease using breathing profile alone. In the absence of obstructive airway disease, the breathing profile can be variable, with expiratory flow breaking predominating in expiration; however, under these conditions, age, body stature, and gender are sufficient to calculate FEV\(_1\). Only in the presence of significant obstructive airway disease do time and flow domain factors become important. With developing disease, the options for varying respiratory function are reduced and a person’s breathing profile becomes more regular and specific. The multifactorial control of breathing under disease conditions leads to a change in the way we expire. Further studies are therefore required to discover the interplay between how disease alters the interaction between lung mechanics, blood borne and cardiovascular factors, and the musculoskeletal and neurologic systems.

Appendix

Multiple Linear Regression (MLR) Method

(1) With FEV\(_1\) set as the dependent variable, the parameters in Table 2 were set as the independent variables.

(2) A forward method was used to derive each multiple linear regression equation, in order to minimize the number of parameters in the resultant predictive equation.

(3) The entry criteria were set at a probability of F < 0.05.

(4) In order to ensure the best predictive variables and independent variables, the MLR process was repeated several times. When the MLR equation contained two parameters that were highly correlated with one another (ie, a correlation coefficient > 0.5), the parameter that contributed less to the equation (ie, with the lower T value) was excluded and the test rerun. This was repeated until the MLR equation only contained independent variables that were correlated to FEV\(_1\).

(5) The resulting MLR equation describes the relationship between the selected parameters and FEV\(_1\).

(6) The goodness of fit was assessed using the adjusted r\(^2\) value, as this takes into account the number of data points used in comparison with the number of parameters in the equation.

References


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