Forced Expiratory Flows and Volumes in Infants
Normative Data and Lung Growth

MARCUS JONES, ROBERT CASTILE, STEPHANIE DAVIS, JEFF KISLING, DAVE FILBRUN, ROBERT FLUCKE, AMY GOLDSTEIN, CHRISTINE EMSLEY, WALTER AMBROSIUS, and ROBERT S. TEPPER

Department of Pediatrics, James Whitcomb Riley Hospital for Children, and Department of Bio-statistics, Indiana University Medical Center, Indianapolis, Indiana; and Columbus Children's Hospital, Ohio State University, Columbus, Ohio

Forced expiratory flows (FEF) can be measured in infants from lung volumes initiated near total lung capacity. In order to establish reference values and to evaluate lung growth, we obtained measurements in 155 healthy subjects between 3 and 149 wk of age. Forced vital capacity (FVC) was highly correlated with body length; however, after accounting for length, age was also significant. When subjects were divided at the median age (40 wk) younger compared with older subjects had a significantly larger slope for length (3.7 versus 2.8; $p = 0.002$). The flow parameters (FEF_{50}, FEF_{75}, FEF_{85}, and FEF_{25-75}) were highly correlated with length, and those infants whose mothers smoked had lower flows. For FEF_{75}, male subjects had lower flows than female subjects. The relationship between FEF and volume was assessed using $FEV_{0.5}/FVC$, which decreased with increasing length. Smaller subjects emptied their lung volume proportionately faster. We conclude that our study provides reference values for this age group and demonstrates that smoke-exposed infants and male subjects have decreased FEF. In addition, our findings indicate that lung volume increases most rapidly during the first year of life and that airways are large relative to lung volume very early in life. Jones M, Castile R, Davis S, Kisling J, Filbrun D, Flucke R, Goldstein A, Emsley C, Ambrosius W, Tepper RS. Forced expiratory flows and volumes in infants: normative data and lung growth.

AM J RESPIR CRIT CARE MED 2000;161:353–359.

Respiratory diseases such as asthma, bronchopulmonary dysplasia, and cystic fibrosis are present early in life. Our ability to quantify the severity of these pulmonary diseases and the efficacy of therapeutic interventions is currently very limited. In older children and adults, forced expiratory maneuvers initiated from TLC are routinely used to diagnose pulmonary dysfunction, to assess the efficacy of therapeutic interventions, and to follow patients longitudinally. In infants, partial expiratory flow volume (PEFV) maneuvers obtained by the rapid thoracoabdominal compression technique have been used to assess airway function in this age group (1–4). However, PEFV curves assess only the tidal lung volume range, and it has been unclear whether flow limitation is achieved in healthy infants (5, 6).

Recently, the measurement of forced expiratory flows in infants has been extended to lung volumes above the tidal range (7, 8). For maneuvers that are initiated near TLC, it has been demonstrated that flow limitation can be achieved in healthy infants (7, 8). Therefore, full forced expiratory maneuvers offer the same potential for the assessment of lung function of infants as it does for older children and adults. In order for forced expiratory measurements to be used clinically for the assessment of lung disease in infants, it is important to establish reference values in healthy subjects. In addition, measurements obtained in healthy subjects will offer important insights into how the lung grows early in life and the potential influence of genetic and environmental factors upon lung growth.

METHODS

Subjects

Healthy infants were recruited at James Whitcomb Riley Hospital for Children in Indianapolis, Indiana, and the Children's Hospital in Columbus, Ohio. Subjects were recruited from general pediatric clinics within the two hospitals, from pediatricians within the city, and from advertisements. Infants were excluded from the study if they were premature at birth (< 36 wk gestation), had congenital malformations, or recurrent lower respiratory illnesses. Subjects were also without upper respiratory symptoms for at least 3 wk prior to pulmonary function testing. History of exposure to tobacco smoking during pregnancy, postnatal environmental tobacco smoke exposure by parents or caregivers, and family history of asthma were obtained at the time of testing. The Institutional Review Boards at both hospitals approved the study, and informed consent was obtained from the subjects' parents.

Forced Expiratory Maneuvers

Infants were weighed and their length was measured with a stadiometer while awake. Subjects received 50 to 75 mg/kg of chloral hydrate orally, and measurements of forced expiratory flows were obtained while the infant was sleeping in the supine position. Forced expiratory maneuvers from elevated lung volumes were performed using the rapid thoracic compression technique as previously described (8). Forced

---

(*Received in original form March 2, 1999 and in revised form July 14, 1999*)

Supported by Grant No. HL-54062 from the National Institutes of Health.

Correspondence and requests for reprints should be addressed to Robert S. Tepper, M.D., Ph.D., Department of Pediatrics Indiana University Medical Center, James Whitcomb Riley Hospital for Children, Rm. 2750, 702 Barnhill Drive, Indianapolis, IN 46223. E-mail: RTEPPER@iupui.edu

Am J Respir Crit Care Med Vol 161. pp 353–359, 2000
Internet address: www.atsjournals.org

expiratory flows were initiated from a lung volume at which the airway pressure was 30 cm H_2O (V_{30}) and proceeded to residual volume (RV). Inflating the respiratory system to V_{30} several times prior to the forced expiratory maneuver inhibited respiratory effort during forced expiration. The circuit used to obtain forced maneuvers contained an adjustable continuous flow of air that was set between 15 and 20 L/min and a pressure relief valve set at 30 cm H_2O. Occlusion of the expiratory valve resulted in inflation of the respiratory system to an airway pressure of 30 cm H_2O. Forced expiration was initiated at this elevated lung volume by rapidly inflating the jacket, which was wrapped around the infant's chest and abdomen. An electronic solenoid valve between the jacket and the pressure reservoir controlled jacket inflation, and jacket pressure was monitored with a differential pressure transducer (Validyne MP-45-871; Validyne Corp., Northridge, CA) referenced to atmospheric pressure. A pneumotachometer (Model 3700; Hans Rudolph, Kansas City, MO) and differential pressure transducer (Validyne MP-45-871) were used to measure the inspiratory and expiratory flow. The analog signals of flow and pressure were amplified and filtered above 50 Hz (Validyne CD 19-A) and digitized at 100 samples per second. Volume was obtained by digital integration of the flow signal, and the signals were displayed on the computer monitor in real time and stored for subsequent analysis. Forced expiratory maneuvers were repeated with increasing jacket compression pressures between 40 and 120 cm H_2O until the highest expired volume and flow was obtained.

The forced vital capacity (FVC) was calculated as the expired volume between V_{30} and residual volume. Forced expiratory flows were measured at 50, 75, and 85% expired volume (FEF_{50}, FEF_{75}, FEF_{85}), as well as the forced expiratory flow between 25 and 75% expired volume (FEF_{25-75}). The forced expired volume in the initial 0.5 s ($FEV_{0.5}$) was measured, and the ratio of $FEV_{0.5}$/FVC was calculated. In addition, the rate constant for forced expiration was calculated as the ratio of the differences in flows and volumes between 50 and 75% expired volume (RC_{50-75}). From the multiple technically acceptable flow-volume curves obtained for each subject (range, 2 to 4) the best flow-volume curve was selected as the curve with the highest product of FVC and FEF_{25-75}.

Statistical Analysis

Demographics for the two sites were compared using *t* tests for continuous variables and chi-square tests for categorical variables. Multiple linear regression models were used to examine the effect of length, age, sex, and race (Caucasian versus other), maternal smoking during pregnancy, postnatal tobacco smoke exposure by caregivers or parents, family history of asthma, and study site on the various pulmonary function tests. For a subgroup of subjects in whom measurements were obtained at several different ages, only the values obtained at the last evaluation was used in the cross-sectional analysis. A natural log transformation was performed on all pulmonary function parameters and on length and age. The log transformations were used because the relationships were more nearly linear on this scale. This was evaluated using residual plots (plot residuals on the y-axis and predicted values on the x-axis). Normality and homogeneity of variance assumptions were examined graphically for all models. The assumption of equal variances across the whole range of age/length did not hold for the untransformed data and it did hold for the log-transformed data. A model including all of the factors listed above was run for each pulmonary function parameter. A stepwise selection procedure was also run for each model to validate results (p value for entry $<$ 0.15, p value for exit $>$ 0.15).

When age was significant independent of length we divided the subjects into two groups at the median age. We then used an analysis of covariance model to test for differences in slopes of the response versus length for younger versus older infants.

Reference plots were generated using a regression equation of each pulmonary function parameter with length. Again, natural log transformations were performed on each pulmonary function parameter and length. The prediction intervals were calculated using the standard error of prediction (9).

For a subgroup of infants followed longitudinally, pulmonary function values were transformed to z-scores. We then analyzed the z-scores longitudinally using a mixed model analysis of variance with random intercepts and a fixed slope (10).

RESULTS

We obtained technically acceptable forced expiratory maneuvers in 155 healthy infants. The ages of the subjects ranged from 3 to 149 wk, with a mean age of 48 wk (Table 1). Forty-three percent of the subjects were female and 69% were Caucasian. The percentage of Caucasian infants tested was lower in Indianapolis than in Columbus (57 versus 78%; $p < 0.01$) and the Indianapolis infants were younger than the Columbus infants (42.7 versus 55.3 wk; $p = 0.03$). A positive extended family history of asthma (parents, siblings, aunts, and uncles) existed in 56.8% of the infants. A history of maternal smoking during pregnancy was positive in 26.5% of the infants, and postnatal environmental tobacco smoke exposure by caregivers or parents was present in 49% of the infants. Postnatal tobacco smoke exposure occurred in a higher fraction of the infants from Columbus than the infants from Indianapolis (65 versus 38%; $p < 0.001$).

Results from the multiple linear regression models using natural log-transformed data, including statistically significant variables, are summarized in Table 2. Forced vital capacity was highly correlated with body length; however, age was also significant after accounting for length. For the same body length, older infants had greater FVC. Sex, race, body weight, smoke exposure, and family history of asthma were not significant. When the sample was divided at the median age (40 wk) the younger group had a significantly larger slope for length than the older age group (3.7 versus 2.8; $p = 0.002$).

Similar to FVC, the volume expired in 0.5 s ($FEV_{0.5}$) correlated most strongly with body length, whereas age was also a significant independent variable after accounting for length (Table 2). For the same body length, those infants who were older had a greater $FEV_{0.5}$. Sex, race, body weight, smoke ex-

TABLE 1

DEMOGRAPHICS FOR SUBJECTS AND STUDY SITES

	Overall (*n* = 155)	Indianapolis (*n* = 90)	Columbus (*n* = 65)	p Value*
Age, wk,[†]	48.0 (34.0)	42.7 (28.8)	55.3 (39.2)	0.03
Length, cm[†]	71.8 (10.6)	70.5 (9.7)	73.6 (11.4)	0.08
Race, % Caucasian	69.0	77.8	56.9	$<$ 0.01
Sex, % Female	43.2	43.3	43.1	0.98
Smoking during pregnancy, % yes	26.5	23.3	30.8	0.30
Smoke exposure, % yes	49.0	37.8	64.6	$<$ 0.01
Asthma (family history), % yes	56.8	55.6	58.5	0.72

* From comparison of institutions, Indianapolis versus Columbus.

[†] Values are means with SD shown in parentheses.

TABLE 2

REGRESSION EQUATIONS FOR PULMONARY FUNCTION

Parameter	Equation*	R^2	RMSE
ln(FVC)	$-5.804 + 2.614 \times \ln(\text{length})^{\dagger} + 0.144 \times \ln(\text{age})^{\dagger}$	0.92	0.15
$\ln(\text{FEV}_{0.5})$	$-3.880 + 2.113 \times \ln(\text{length})^{\dagger} + 0.139 \times \ln(\text{age})^{\dagger}$	0.90	0.14
$\ln(\text{FEF}_{50})$	$-1.404 + 1.850 \times \ln(\text{length})^{\dagger} - 0.079 \times \text{smoke}^{\S}$	0.66	0.21
$\ln(\text{FEF}_{75})$	$-4.846 + 2.484 \times \ln(\text{length})^{\dagger} - 0.162 \times \text{smoke}^{\ddagger} + 0.092 \times \text{sex}^{\S}$	0.66	0.28
$\ln(\text{FEF}_{85})$	$-5.095 + 2.432 \times \ln(\text{length})^{\dagger} - 0.239 \times \text{smoke}^{\dagger}$	0.61	0.32
$\ln(\text{FEF}_{25\text{–}75})$	$-2.128 + 1.995 \times \ln(\text{length})^{\dagger} - 0.108 \times \text{smoke}^{\ddagger}$	0.69	0.21
$\ln(\text{RC}_{50\text{–}75})$	$10.143 - 2.079 \times \ln(\text{length})^{\dagger}$	0.49	0.32
$\ln(\text{FEV}_{0.5}/\text{FVC})$	$1.965 - 0.515 \times \ln(\text{length})^{\dagger}$	0.37	0.10

* Length in cm; age in wk; RMSE = root mean square error. Smoke = 1 for smoked during pregnancy, 0 for did not smoke; Sex = 1 for female, 0 for male.

[†] $p < 0.001$; [‡] $p < 0.01$; [§] $p < 0.05$.

posure, and family history of asthma were not significant. Dividing the sample by the median age (40 wk), the younger age group had a significantly larger slope for length than the older age group (3.2 versus 2.4; $p < 0.001$).

The flow parameters (FEF_{50}, FEF_{75}, FEF_{85}, and $\text{FEF}_{25\text{–}75}$) were highly correlated with body length. In addition to body length, maternal smoking during pregnancy was a significant variable for each flow parameter (Table 2). Infants whose mothers smoked during pregnancy had lower flows than did infants whose mothers did not smoke during pregnancy. After correcting for smoking during pregnancy, postnatal exposure to tobacco smoke (ETS) was not significant. For FEF_{75}, there was also a significant effect of sex; males had lower flows than females (Table 2). We also found a small but statistically significant Center effect for FEF_{75} ($p = 0.01$), FEF_{85} ($p = 0.004$), and $\text{RC}_{50\text{–}75}$ ($p = 0.01$). For FEF_{75} and FEF_{85}, infants from Columbus had lower values than infants from Indianapolis after adjusting for other significant factors. For $\text{RC}_{50\text{–}75}$, infants from Indianapolis had lower values than infants from Columbus after adjusting for body length.

The regression equations for each of the pulmonary function parameters versus body length using log-transformed data are summarized in Table 3. The variables of age, sex, smoking exposure, and Center are not included since the magnitude of these effects are small relative to that of body length. Using these equations, the data was back-transformed in order to create plots in the original measurement units (Figures 1 to 6). Reference lines were plotted at the upper and lower 90% individual confidence limits (5th and 95th percentiles), the upper and lower 50% individual confidence limits (25th and 75th percentiles), and the mean (50th percentile).

The relationship between flow and volume during forced expiration was assessed from $\text{FEV}_{0.5}/\text{FVC}$ and the rate constant between 50 and 75% of expiratory volume ($\text{RC}_{50\text{–}75}$). Both $\text{FEV}_{0.5}/\text{FVC}$ and $\text{RC}_{50\text{–}75}$ decreased with increasing body length. The larger or older subjects emptied their lung volume proportionately slower than the smaller or younger subjects (Figures 7 and 8).

TABLE 3

PULMONARY FUNCTION TEST VARIABLES VERSUS BODY LENGTH*

Variable	Equation	R^2	RMSE[†]
ln(FVC) =	$-8.746 + 3.424 \times \ln(\text{length})$	0.91	0.16
$\ln(\text{FEV}_{0.5})$ =	$-6.713 + 2.893 \times \ln(\text{length})$	0.90	0.15
$\ln(\text{FEF}_{50})$ =	$-1.548 + 1.878 \times \ln(\text{length})$	0.65	0.21
$\ln(\text{FEF}_{75})$ =	$-4.938 + 2.505 \times \ln(\text{length})$	0.63	0.29
$\ln(\text{FEF}_{85})$ =	$-5.549 + 2.524 \times \ln(\text{length})$	0.56	0.33
$\ln(\text{FEF}_{25\text{–}75})$ =	$-2.323 + 2.035 \times \ln(\text{length})$	0.68	0.21
$\ln(\text{RC}_{50\text{–}75})$ =	$10.143 - 2.079 \times \ln(\text{length})$	0.49	0.32
$\ln(\text{FEV}_{0.5}/\text{FVC})$ =	$1.965 - 0.515 \times \ln(\text{length})$	0.39	0.08

* All models were highly significant ($p < 0.0001$).

[†] RMSE = root mean square error.

During the course of this study, 26 infants had repeated measurements at least 3 mo apart. We used the measurements in this subgroup of infants to determine whether their longitudinal data tracks along the regression equations derived from cross-sectional data. For each infant, the individual values of FVC, FEF_{50}, FEF_{75}, FEF_{85}, and $\text{FEF}_{25\text{–}75}$ at each testing were transformed into z-scores, defined as the difference between the actual and the predicted value divided by the standard deviation of the predicted value. A mixed model was then run using the longitudinal z-scores fit with a random intercept and fixed slope. The estimated slopes from the mixed model for the z-scores of pulmonary function parameters are listed in Table 4. None of the z-scores of pulmonary function parameters had a slope for length that was significantly different from zero.

DISCUSSION

In this study, pulmonary function was assessed in a large group of healthy infants using a relatively new methodology for obtaining full forced expiratory maneuvers. This study is unique in that it evaluated more healthy infants than any previous study, testing was performed as a collaborative effort at two

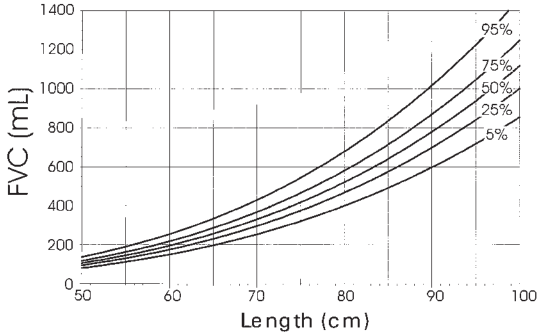

Figure 1. Forced vital capacity (FVC) (ml) versus body length (cm) using the log-transformed regression equation in Table 3. The equation was back-transformed in order to plot FVC in the original measurement units. Reference lines are plotted at the upper and lower 90% individual confidence limits (5th and 95th percentiles), the upper and lower 50% individual confidence limits (25th and 75th percentiles), and the mean (50th percentile).

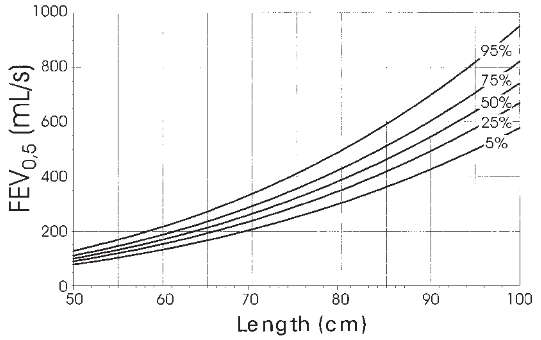

Figure 2. Forced expiratory volume in 0.5 s ($FEV_{0.5}$) (ml/s) versus body length (cm) using the log-transformed regression equation in Table 3. The equation was back-transformed in order to plot $FEV_{0.5}$ in the original measurement units. Reference lines are plotted at the upper and lower 90% individual confidence limits (5th and 95th percentiles), the upper and lower 50% individual confidence limits (25th and 75th percentiles), and the mean (50th percentile).

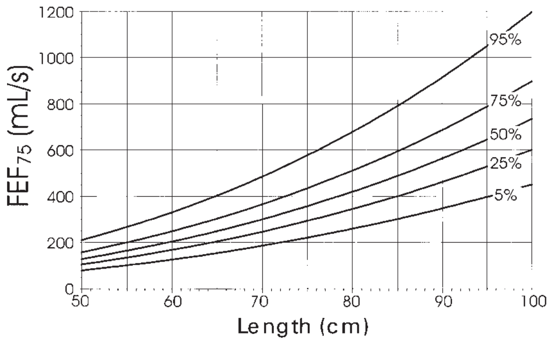

Figure 4. Forced expiratory flow at 75% expired vital capacity (FEF_{75}) (ml/s) versus body length (cm) using the log-transformed regression equation in Table 3. The equation was back-transformed in order to plot FEF_{50} in the original measurement units. Reference lines are plotted at the upper and lower 90% individual confidence limits (5th and 95th percentiles), the upper and lower 50% individual confidence limits (25th and 75th percentiles), and the mean (50th percentile).

different institutions, and the type of measurements obtained, full forced expiratory maneuvers, were similar to those routinely obtained in older children and adults. Our measurements of forced expiratory flows and volumes were highly correlated with body length and our regression equations can serve as reference values for similar populations. In addition, our results offer additional insights in lung growth early in life, as will be discussed below. Lastly, our results confirm previous reports that maternal smoking during pregnancy is associated with lower forced expiratory flows at low lung volumes, and extends this observation to flows at higher lung volumes (8).

The group of healthy infants we evaluated was recruited from community and hospital-based pediatric practices, as well as from advertisements. Our group is not a random sample of a well-defined population, although the sex and racial distribution of our group does approximate that for the two cities where subjects were recruited. Our healthy subjects were representative of healthy infants and do not represent an "ideal" group of infants. We did not exclude subjects with a single episode of wheeze if the illness lasted only a few days, did not require hospitalization, and they were not treated with bronchodilators. Epidemiologic studies report that nearly 20% of subjects younger than 3 yr of age experience a single episode of wheeze (11). In addition, we did not exclude infants exposed to tobacco smoke. In our sample, 30% of infants were exposed during pregnancy and 50% were exposed postnatal. This incidence of tobacco exposure is similar to that reported in other studies (12–16). Our assessment of health status was limited to interviewing the parents and a physical examination prior to testing. We have no way of validating parental history, and thus there is the potential to include infants that had repeated lower respiratory disease in our "healthy" group of subjects since important information might have been omitted. Inclusion of some "unhealthy" infants could potentially increase our intersubject variability and decrease the predicted values.

Our measurements of lung function were obtained from full forced expiratory maneuvers generated by the rapid com-

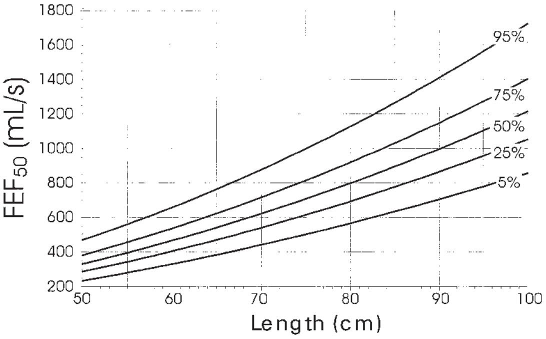

Figure 3. Forced expiratory flow at 50% expired vital capacity (FEF_{50}) (ml/s) versus body length (cm) using the log-transformed regression equation in Table 3. The equation was back-transformed in order to plot FEF_{50} in the original measurement units. Reference lines are plotted at the upper and lower 90% individual confidence limits (5th and 95th percentiles), the upper and lower 50% individual confidence limits (25th and 75th percentiles), and the mean (50th percentile).

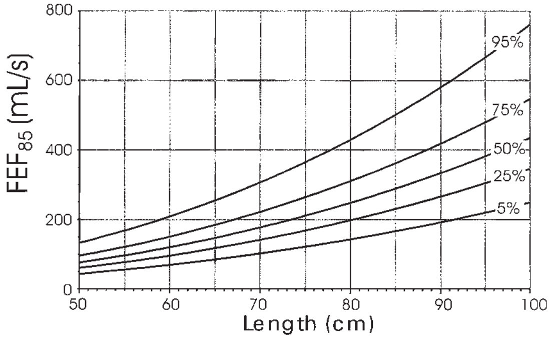

Figure 5. Forced expiratory flow at 85% expired vital capacity (FEF_{85}) (ml/s) versus body length (cm) using the log-transformed regression equation in Table 3. The equation was back-transformed in order to plot FEF_{85} in the original measurement units. Reference lines are plotted at the upper and lower 90% individual confidence limits (5th and 95th percentiles), the upper and lower 50% individual confidence limits (25th and 75th percentiles), and the mean (50th percentile).

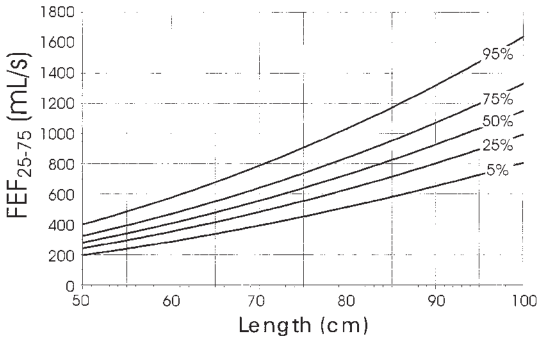

Figure 6. Forced expiratory flow between 25% and 75% expired vital capacity (FEF$_{25-75}$) (ml/s) versus body length (cm) using the log-transformed regression equation in Table 3. The equation was back-transformed in order to plot FEF$_{25-75}$ in the original measurement units. Reference lines are plotted at the upper and lower 90% individual confidence limits (5th and 95th percentiles), the upper and lower 50% individual confidence limits (25th and 75th percentiles), and the mean (50th percentile).

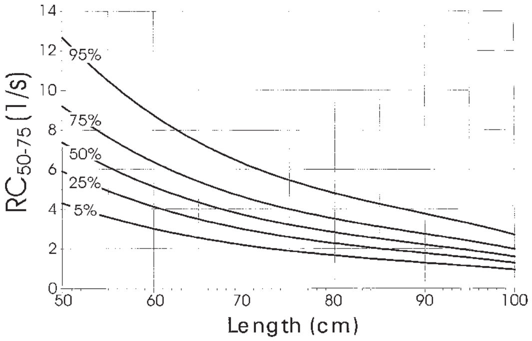

Figure 8. The rate constant between 50% and 75% expired vital capacity (RC$_{50-75}$) (l/s) versus body length (cm) using the log-transformed regression equation in Table 3. The equation was back-transformed in order to plot RC$_{50-75}$ in the original measurement units. Reference lines are plotted at the upper and lower 90% individual confidence limits (5th and 95th percentiles), the upper and lower 50% individual confidence limits (25th and 75th percentiles), and the mean (50th percentile).

pression technique. We have previously demonstrated that this technique achieves flow limitation in healthy infants (8). In this study the methodology was used in two centers to enroll an adequate number of subjects for establishing reference data and evaluating lung growth in this age group. We found no differences between the two centers for FVC, FEF$_{50}$, and FEF$_{25-75}$; however, there was a small but significant difference for flows at low lung volumes (FEF$_{75}$, FEF$_{85}$). This center difference was present after accounting for length and smoking exposure; however, the two centers also differed in the fraction of infants exposed to tobacco smoke. We did not quantify tobacco exposure, and it is possible that the center with the greater fraction of infants with exposure also had a greater quantitative exposure, thus accounting for the lower flows at that center. Although we did not find a race effect for flows, there was also a difference in the racial composition between the two centers that may have also contributed to the small difference between the two centers for flows at low lung volume. Finally, the center effect may have been related to methodologic differences between the two centers. Although we made frequent visits between laboratories to review methodology, equipment, and analysis, there is no "test" infant that can be evaluated in both centers to confirm that the same values are obtained at both centers.

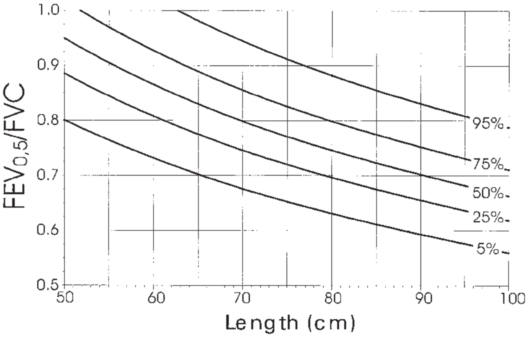

Figure 7. The ratio FEV$_{0.5}$/FVC versus body length (cm) using the log-transformed regression equation in Table 3. The equation was back-transformed in order to plot FEV$_{0.5}$/FVC in the original measurement units. Reference lines are plotted at the upper and lower 90% individual confidence limits (5th and 95th percentiles), the upper and lower 50% individual confidence limits (25th and 75th percentiles), and the mean (50th percentile).

Our regression equations for the different parameters measured from the flow-volume curve were derived from the best curve obtained from each subject. From the several technically acceptable curves the best curve was chosen as the one with the highest product of FVC and FEF$_{25-75}$. Similar to previous results of pulmonary function obtained from infants and from older children, the lung function parameters were highly correlated to body length (17). In addition, we found that using a natural log transformation provided the best fit of our data.

Our finding that FVC was not significantly different for male and female infants and very young children is consistent with morphometric measurements in post-mortem, excised lungs by Thurlbeck (18). He found greater total lung capacity in boys than in girls older than 2 yr of age but did not find a difference for younger subjects. Our findings for FVC are also consistent with other physiologic measurements in infants and very young children that have not found a sex-related difference in functional residual capacity early in life (19–21). Lung volumes are greater in older boys than in older girls (17). This difference if present in infants is too small to be detected by current measurements with the number of subjects evaluated. Conversely, a sex-related difference in lung volume may not be present until after 2 yr of age when most of the alveoli have

TABLE 4

TRACKING PULMONARY FUNCTION (Z-SCORES)

Variable	Slope of Length	Standard Error	p Value
FVC	0.005	0.0146	0.73
FEF$_{50}$	0.019	0.0140	0.18
FEF$_{75}$	0.002	0.0106	0.85
FEF$_{85}$	−0.0008	0.0129	0.95
FEF$_{25-75}$	0.017	0.0135	0.21
RC$_{50-75}$	0.014	0.0130	0.29
FEV$_{0.5}$	0.012	0.0157	0.45
FEV$_{0.5}$/FVC	0.005	0.0121	0.69

been formed and when lung growth primarily results from an increase in alveolar size.

For our group of infants and very young children, FVC increased as the 3.4th power of body length (Table 3). We found that FVC was dependent upon age as well as upon body length. There was a significant difference between the slopes for the two age groups; the younger group having a higher slope. Our data suggest that lung volume increase most rapidly during the first year of life; however, by the second year of life the rate of increase in FVC is similar to that reported in older children, 2.6 to 3.3 (17).

Forced expiratory flows (FEF_{50}, FEF_{75}, FEF_{85}, and $FEF_{25\text{–}75}$) increased with body length. In addition, for all of these parameters, smoking during pregnancy was associated with significantly lower flows. This finding is consistent with previous reports that maximal flows at FRC ($\dot{V}max_{FRC}$) are lower in infants exposed to tobacco smoke (12, 14). However, our study extends these findings to measurements of forced expiratory flows at lung volumes above and below FRC. In our analysis, postnatal exposure was not significant after accounting for smoking during pregnancy. This finding is consistent with previous studies assessing the effect of smoking during pregnancy on pulmonary function during infancy; however, we are not able to distinguish the effects of prenatal versus postnatal exposure as they are highly correlated (14). Sex was only significant for FEF_{75}; girls had higher flows than boys did after accounting for body length and smoking during pregnancy. Previous studies measuring $\dot{V}max_{FRC}$ suggested that infant girls had higher flows than the infant boys; however, in those studies the difference did not reach statistical significance (19–22).

Race was not statistically significant for any of the pulmonary function parameters. Older Caucasian children have approximately 15 to 20% higher values for FVC and FEV_1 than did African-American and Asian children (23–25). It has been suggested that in older children and adults that the differences in body proportion, leg-to-trunk ratio, and chest dimensions (26, 27) may account for part of the ethnic differences observed between lung volume and height. Stocks and colleagues (22) reported that there were no differences in the crown-heel/crown-rump ratio between black and white infants. If differences in body proportion account for most of the ethnic differences in older children, a difference in lung volume is not likely to be detected in infants. The rate constant for emptying of the lung during forced expiration decreased with growth whether measured as the ratio $FEV_{0.5}$/FVC or as the slope between 50 and 75% expired volume. This decrease in the rate constant was most prominent for infants younger than 40 wk of age compared with those older than 40 wk of age. Our findings are consistent with those of Bryan and Wohl (28) who estimated that rate constant from forced expiratory maneuvers decline from higher values in newborns ($7.8\ s^{-1}$) to the lowest value in adults ($1.7\ s^{-1}$). The decrease in $FEV_{0.5}$/FVC and the rate constant strongly suggests that lung volume increased more rapidly than airway caliber during the first year of life. This finding is consistent with the concept of dysanaptic lung growth, that is, dissociation between the growth of the lung parenchyma and the airways (29).

For the subgroup of healthy infants assessed longitudinally, the increases in flows and volume did not significantly differ from the expected increases with growth predicted from the regression equations developed from cross-sectional data. This finding suggests that our cross-sectional data can be used to assess airway function longitudinally; however, we acknowledge that because there were only 26 subjects with longitudinal data there may not have been sufficient power to detect a non-zero slope. Our longitudinal data also provide estimates of longitudinal variability for designing studies to detect changes in normal lung growth for evaluating early lung disease and/or the effects of therapeutic interventions.

In summary, our study has provided reference values for measurements of full forced expiratory maneuvers in infants and toddlers and has demonstrated the ability of the method to detect differences in lung function related to tobacco smoke exposure and sex. In addition, our data are consistent with the concept of dysanaptic lung growth early in life, with lung volume increasing more rapidly than flow.

References

1. Tepper, R. S., W. J. Morgan, K. Cota, and L. M. Taussig. 1986. Expiratory flow limitation in infants with bronchopulmonary dysplasia. *J. Pediatr.* 109:1040–1046.
2. Tepper, R. S., H. Eigen, J. Brown, and R. Hurwitz. 1989. Use of maximal expiratory flows to evaluate central airways obstruction in infants. *Pediatr. Pulmonol.* 6:272–274.
3. Tepper, R. S. 1987. Airway reactivity in infants: a positive response to methacholine and metaproterenol. *J. Appl. Physiol.* 62:1155–1159.
4. Hiatt, P., H. Eigen, P. Yu, and R. S. Tepper. 1988. Bronchodilator response in infants with cystic fibrosis. *Am. Rev. Respir. Dis.* 137:119–122.
5. England, S. 1998. Current techniques for assessing pulmonary function in the newborn and infant: advantages and limitations. *Pediatr. Pulmonol.* 4:48–53.
6. American Thoracic Society and European Respiration Society Committee. 1993. Respiratory mechanics in infants: physiologic evaluation in health and disease. *Am. Rev. Respir. Dis.* 147:474–496.
7. Turner, D. J., S. M. Stick, K. L. Lesouef, P. D. Sly, and P. N. Lesouef. 1995. A new technique to generate and assess forced expiration from raised lung volume in infants. *Am. J. Respir. Crit. Care Med.* 151:1441–1450.
8. Feher, A., R. Castile, J. Kisling, C. Angelicchio, D. Filbrun, R. Flucke, and R. Tepper. 1996. Flow limitation in normal infants: a new method for forced expiratory maneuvers from raised lung volumes. *J. Appl. Physiol.* 80:2019–2025.
9. Weisberg, S. 1985. Applied Linear Regression. Wiley, New York.
10. Little, R., G. Milliken, W. Stroup, and R. Wolfinger. 1996. SAS System for Mixed Models. SAS Institute, Cary, NC.
11. Martinez, F. D., A. L. Wright, L. M. Taussig, C. J. Holberg, M. Halonen, and W. J. Morgan. 1995. Asthma and wheezing in the first six years of life: The Group Health Medical Associates [see comments]. *N. Engl. J. Med.* 332:133–138.
12. Hanrahan, J. P., I. B. Tager, M. R. Segal, T. D. Tosteson, R. G. Castile, H. Van Vunakis, S. T. Weiss, and F. E. Speizer. 1992. The effect of maternal smoking during pregnancy on early infant lung function. *Am. Rev. Respir. Dis.* 145:1129–1135.
13. Tager, I. B., J. P. Hanrahan, T. D. Tosteson, R. G. Castile, R. W. Brown, S. T. Weiss, and F. E. Speizer. 1993. Lung function, prenatal and postnatal smoke exposure, and wheezing in the first year of life. *Am. Rev. Respir. Dis.* 147:811-817.
14. Tager, I. B., L. Ngo, and J. P. Hanrahan. 1995. Maternal smoking during pregnancy: effects on lung function during the first 18 months of life. *Am. J. Respir. Crit. Care Med.* 152:977–983.
15. Wang, X., I. B. Tager, H. Van Vunakis, F. E. Speizer, and J. P. Hanrahan. 1997. Maternal smoking during pregnancy, urine cotinine concentrations, and birth outcomes: a prospective cohort study. *Int. J. Epidemiol.* 26:978–988.
16. Hoo, A. F., M. Henschen, C. Dezateux, K. Costeloe, and J. Stocks. 1998. Respiratory function among preterm infants whose mothers smoked during pregnancy [see comments]. *Am. J. Respir. Crit. Care Med.* 158:700–705.
17. Quanjer, P. H., J. Stocks, G. Polgar, M. Wise, J. Karlberg, and G. Borsboom. 1989. Compilation of reference values for lung function measurements in children. *Eur. Respir. J. Suppl.* 4:184S–261S.
18. Thurlbeck, W. M. 1982. Postnatal human lung growth. *Thorax* 37:564–571.
19. Tepper, R. S., W. J. Morgan, K. Cota, A. Wright, and L. M. Taussig. 1986. Physiologic growth and development of the lung during the first year of life. *Am. Rev. Respir. Dis.* 134:513–519.
20. Hanrahan, J. P., I. B. Tager, R. G. Castile, M. R. Segal, S. T. Weiss, and F. E. Speizer. 1990. Pulmonary function measures in healthy infants: variability and size correction. *Am. Rev. Respir. Dis.* 141:1127–1135.
21. Tepper, R. S., and T. Reister. 1993. Forced expiratory flows and lung volumes in normal infants. *Pediatr. Pulmonol.* 15:357–361.

22. Stocks, J., M. Henschen, A. F. Hoo, K. Costeloe, and C. Dezateux. 1997. Influence of ethnicity and gender on airway function in preterm infants. *Am. J. Respir. Crit. Care Med.* 156:1855–1862.
23. Hsu, K. H., D. E. Jenkins, B. P. Hsi, E. Bourhofer, V. Thompson, N. Tanakawa, and G. S. Hsieh. 1979. Ventilatory functions of normal children and young adults: Mexican-American, white, and black: I. Spirometry. *J. Pediatr.* 95:14–23.
24. Schwartz, J., S. A. Katz, R. W. Fegley, and M. S. Tockman. 1988. Sex and race differences in the development of lung function [see comments]. *Am. Rev. Respir. Dis.* 138:1415–1421.
25. Wang, X., D. W. Dockery, D. Wypij, M. E. Fay, and B. G. Ferris, Jr. 1993. Pulmonary function between 6 and 18 years of age. *Pediatr. Pulmonol.* 15:75–88.
26. Donnelly, P. M., T. S. Yang, J. K. Peat, and A. J. Woolcock. 1991. What factors explain racial differences in lung volumes? *Eur. Respir. J.* 4: 829–838.
27. American Thoracic Society. 1991. Lung function testing: selection of reference values and interpretative strategies [see comments]. *Am. Rev. Respir. Dis.* 144:1202–1218.
28. Bryan, A. C., and M. Wohl. 1986. Respiratory mechanics in children. *In* P. Macklem and J. Mead, editors. Handbook of Physiology, Section 3: Vol. 111, Part 1: Mechanics of Breathing. American Physiological Society, Bethesda, MD. 179–191.
29. Green, M., J. Mead, and J. M. Turner. 1974. Variability of maximum expiratory flow-volume curves. *J. Appl. Physiol.* 37:67–74.