Bronchodilator Responsiveness in Normal Infants and Young Children

AMY B. GOLDSTEIN, ROBERT G. CASTILE, STEPHANIE D. DAVIS, DAVID A. FILBRUN, ROBERT L. FLUCKE, KAREN S. McCOY, and ROBERT S. TEPPER

Section of Pediatric Pulmonary Medicine, Children's Hospital, The Ohio State University College of Medicine, Columbus, Ohio; and Department of Pediatrics, James Whitcomb Riley Hospital for Children, Indiana University Medical Center, Indianapolis, Indiana

Several studies have demonstrated that normal infants exhibit bronchoconstriction after inhalation of nonspecific agonists and that the induced airway narrowing can be reversed by the inhalation of a β-agonist. However, there are very limited data on baseline airway tone and the airway response to a β-agonist in this subject population. The purpose of our study was to evaluate in normal infants baseline airway responsiveness to the inhaled β-agonist, albuterol, using changes in maximal expiratory flows. Forty-one healthy infant volunteers with no history of respiratory disease or recurrent wheezing (ages 5.4 to 141.4 wk) were studied. Maximal expiratory flow–volume curves were obtained at baseline and 10 min after inhalation of albuterol (n = 28) or placebo (n = 13) using a metered-dose inhaler with a spacer. The mean percent change was significantly greater ($p < 0.05$) in the albuterol versus placebo group for $FEV_{0.5}$ (2.2% versus −1.5%), $FEF_{75\%}$ (10.6% versus −3.1%), and $FEF_{85\%}$ (12.9% versus 0.5%). Six of 28 albuterol-treated infants demonstrated increases in $FEF_{75\%}$ greater than two standard deviations from the mean change in $FEF_{75\%}$ seen in the placebo group. These infants were younger and more frequently exposed to maternal smoking during pregnancy. We conclude that normal healthy infants have overall levels of baseline airway tone that are similar to that reported in adults and older children; however, among the infants we evaluated the response to an inhaled bronchodilator was greatest in the youngest infants and in those exposed to tobacco smoking.

Keywords: airway responsiveness; asthma; tobacco smoke; infant pulmonary function; bronchodilator

Heightened airway reactivity has been proposed as one possible explanation for the increased occurrence of wheezing in infants and young children (1). Bronchoconstrictor responses have been demonstrated in normal infants after challenges with methacholine and histamine (2–6) and these responses have been shown to be reversible with β-adrenergic agonists (6, 7). Montgomery and Tepper also reported that airway sensitivity to bronchoconstrictors declined with increasing age (2). Although there have been several studies of airway responsiveness to bronchoconstricting agents in normal healthy infants, limited data are available on the resting levels of airway tone in this population, as assessed by the response to a bronchodilator. The purpose of this study was to evaluate the baseline airway tone in normal infants and young children, as assessed by the response in maximal expiratory flows to the inhaled β-agonist, albuterol.

METHODS

Subjects

Healthy infants younger than 3 yr of age were recruited from primary care clinics by advertisement within the hospital, and in a local newsletter from both Children's Hospital in Columbus, Ohio and James Whitcomb Riley Hospital for Children in Indianapolis, Indiana. Infants were excluded from the study if they had congenital malformations, had been born prematurely (< 36 wk of gestation), or had a history of two or more episodes of recurrent wheezing with lower respiratory tract illnesses. Infants with chronic respiratory symptoms were excluded from the study. All infants were asymptomatic at the time of pulmonary function testing and had had no upper respiratory symptoms for at least 2 wk before testing. The study was approved by the institutional review boards of both hospitals. Informed consent was obtained from the subject's parents. History of prenatal and postnatal exposures to environmental tobacco smoke as well as immediate and extended family history of prenatal asthma were obtained at the time of testing by questionnaire. A smoking parent was defined as mother, father, or both smoking. Smoking caregiver included any regular caregiver for the child other than a parent. Immediate family history of asthma included asthma in a parent or sibling. Extended family history of asthma included grandparents, aunts, and uncles.

Lung Function Measurements

Infants were sedated with 75 to 100 mg/kg of chloral hydrate given orally. Pulmonary function testing was performed while the infants were sleeping in the supine position. Heart rate and oxygen saturation were monitored continuously using a Nelcor Model N-200 pulseoximeter (Nelcor Inc., Hayward, CA). End-tidal CO_2 was monitored using a Novametrix 2600 CO_2 monitor (Novametrix Systems Inc., Wallingford, CT). A face mask (Rendell Baker no. 2 or no. 3; Gary Hull Anesthesia, Huntington Beach, CA) was applied over nose and mouth and a tight seal obtained using therapeutic putty. A tight seal was confirmed by a test occlusion. The face mask was then connected to a pneumotachometer (Hans Rudolph 3700; Hans Rudolph Inc., Kansas City, MO). The pneumotachometer was attached to a ± 2 cm H_2O pressure transducer (Validyne MP45; Validyne Engineering Corporation, Northridge, CA). Mouth pressure was measured through a port at the mask connector using a Validyne MP45 ± 50 cm H_2O pressure transducer.

Maximal expiratory flow–volume (MEFV) curves were obtained at baseline as described by Feher and coworkers (8). Briefly, a pause in respiration was induced by augmenting the child's normal respiratory efforts. The circuit used to augment respiration consisted of a bias flow of air attached distal to the pneumotachometer and a pressure relief valve (Model IV-317; Sechrist, Anaheim, CA) which was set to 30 cm H_2O. The bias flow was adjusted to equal approximately 1.5 times the child's measured peak inspiratory flow. Occlusion of the expiratory valve resulted in inflation of the respiratory system to an airway pressure of 30 cm H_2O. Positive pressures of 30 cm H_2O were applied to the face mask at the beginning of 2 to 6 successive spontaneous inspirations until a pause in respiration occurred at end-expiration. Once a pause was noted, the child's respiratory system was reinflated to 30 cm H_2O, and forced expiration to residual volume (RV) was produced by rapid thoracoabdominal compression using an inflatable jacket wrapped around the infant's chest and abdomen. An electronic solenoid valve between the jacket and a pressure reservoir controlled jacket inflation. Jacket pressure was monitored with a differential pressure transducer (Validyne MP45 ± 200 cm H_2O) referenced to atmospheric pressure. Analog flow and pressure signals were digitized (Metrobyte DAS 1604; Keithley Corp., Taunton, MA) at 100 Hz and stored using a Dell Dimension XPS T500 Computer (Dell Computer Corp., Round Rock, TX). Volume was obtained by digital integration of the flow signal and stored for subsequent analysis. Forced vital ca-

(*Received in original form May 19, 2000 and in revised form March 15, 2001*)

Supported by Grant HL-54062 from the National Institutes of Health.

Correspondence and requests for reprints should be addressed to Robert G. Castile, M.D., Children's Hospital, Pulmonary Division, 700 Children's Drive, Columbus, OH 43205. E-mail: Castiler@pediatrics.Ohio-State.edu

Am J Respir Crit Care Med Vol 164. pp 447–454, 2001
Internet address: www.atsjournals.org

pacity (FVC) and forced expiratory flows at 25, 50, 75, 85, and between 25 and 75 percent of expired FVC ($FEF_{25\%}$, $FEF_{50\%}$, $FEF_{75\%}$, $FEF_{85\%}$, $FEF_{25-75\%}$) were measured. The forced expired volume in 0.5 second ($FEV_{0.5}$) was also measured.

Functional residual capacity (FRC) was measured using a 75.5-L Plexiglas whole body plethysmograph. Box pressure was measured using a pressure transducer (Validyne MP45 ± 2 cm H_2O). Analog signals were digitized at 100 Hz and stored as previously described. The leak constant of the box was 13 s. Calculations of box volume change were based upon the calibration frequency nearest to the respiratory rate of each child. Occlusions for the measurement of FRC were performed at end-inspiration and held for a minimum of three inspiratory efforts. Box pressure was plotted versus mouth pressure and the slopes of inspiratory efforts were used to calculate FRC. Final FRC represents the mean of measurements made during three separate occlusions matching within 10%. Reported FRC values were corrected to the mean end-expiratory level of the last three breaths before the airway occlusion.

Fractional lung volumes were calculated from FRC, FVC, and expiratory reserve volume (ERV). ERV was obtained from MEFV maneuvers by continuously sampling flow, beginning 15 s before the maneuver and ending 30 s after the MEFV maneuver. The inspiratory flow was corrected for the effects of relative humidity, and the resulting flow signal was integrated to obtain volume. ERV was then calculated by measuring the difference between the volume at the end of the FVC maneuver and the volume at which FRC stabilized. ERV was corrected to BTPS conditions and subtracted from FRC to obtain RV. Total lung capacity (TLC) at 30 cm H_2O was derived from the sum of RV and BTPS-corrected FVC. Measurements of FRC preceded MEFV maneuvers both at baseline and after albuterol or placebo.

Albuterol was then given using a metered-dose inhaler with a spacer (Aerochamber MV; Monaghan Medical Corp., Plattsburgh, NJ) in a dose of 2 puffs (180 μg). Each puff was followed by an inflation of the lungs to 25 cm H_2O. Gentle pressure was applied anteriorly to the cricoid cartilage during inflations to prevent air entry into the stomach. Heart rate was continuously monitored throughout the study. Adequate systemic drug delivery was assumed when a 10% increase in heart rate was achieved. Repeat doses of 2 puffs were given if a 10% rise in heart rate was not achieved by 2 min after the previous dose. The subject received a maximum of 8 puffs over 8 min. MEFV curves and lung volume measurements were repeated beginning at 10 min after the first dose of albuterol. Forced flow maneuvers were repeated with jacket pressures starting at levels where flow limitation had been achieved in the prebronchodilator study. Jacket pressures were then increased or decreased until flow limitation was again observed. Flow limitation was determined during testing by visual inspection of the individual curves and by comparing online calculations of FVC and $FEF_{25-75\%}$ with measured jacket pressures.

A second group of normal infants received a placebo containing propellant only (Glaxo Inc., Research Triangle Park, NC) in the dose of 2 puffs. The same protocol was followed, giving an additional 2 puffs at 2-min intervals to a total of 6 puffs. MEFV curves and lung volume meazurements were repeated at 10 min after the first 2 puffs. The albuterol and placebo inhalations were given in an unblinded fashion.

Analysis

Maneuvers were analyzed using both the single best pre- and postalbuterol flow–volume curves and the mean values of the three prealbuterol and three postalbuterol maneuvers with the highest sums of FVC and $FEF_{25-75\%}$. The single curve with the highest sum of FVC and $FEF_{25-75\%}$ was designated the best curve. All curves used for analysis had FVC measurements within 10% of the highest baseline FVC for that set of baseline and postalbuterol maneuvers. Postinhalation studies with a decline in FVC of greater than 10% of baseline measures were excluded. FVC measurements occasionally decline steadily with repeated maneuvers owing to air entry into the stomach. Intrasubject coefficients of variation were calculated for all spirometric measurements from the best three baseline MEFV curves for each infant. The same methods were used to analyze the pre- and postplacebo MEFV curves.

Responders were chosen by two methods. In Method 1, responders were defined statistically as those infants with a percent increase in $FEF_{75\%}$ greater than two standard deviations (SD) from the mean change in $FEF_{75\%}$ seen in the placebo group. Method 2 used visual inspection of flow–volume curves aligned both at TLC and at RV. Responders were chosen in a blinded fashion by four investigators (R.T., R.C., A.G., D.F.) from both the albuterol and the placebo groups. The selections of these four investigators independently agreed. Group means were compared by using one-way analysis of variance (ANOVA). Repeated measures ANOVA techniques were used to control for the fact that multiple flow measures were made on each forced maneuver. Relationships of responders and nonresponders to smoking history, family history of asthma, and age less than or greater than 1 yr were compared using the chi-square test. A multiple linear regression model was used to test the effects of smoking while controlling for age, length, and weight. Data are reported in mean (± SD) where indicated. Statistical significance was set at $p = 0.05$.

RESULTS

Baseline

Anthropometric, smoking, and asthma family history data, as well as baseline spirometric measurements are presented in Table 1 for both the albuterol and placebo groups. The results are based on the pooled data acquired at both institutions. Baseline spirometric measurements are given as percentage of predicted normal values (9) to control for growth. There were no significant differences between the albuterol and placebo groups in any of the parameters examined except for a greater percentage of smoking parents in the albuterol group. The albuterol group received an average of 4.2 ± 2.2 puffs of albuterol. The number of puffs given to produce a 10% increase in heart rate decreased with increasing infant age ($p < 0.01$). Heart rates were recorded continuously on all subjects studied in Columbus. In this subset of infants, heart rates increased by a mean of 18% ± 8.5% in the albuterol group, and 0.2% ± 2.4% in the placebo group.

Thirty infants received albuterol. Two of these 30 studies were excluded because of a greater than 10% decline in FVC measurements postalbuterol. Eighteen of the 28 remaining infants in the albuterol group were studied in Columbus, and the remaining 10 were studied in Indianapolis. Placebo studies were done in a separate group of 15 normal infants. Two of the 15 studies were excluded owing to a greater than 10% decline in FVC measurements postplacebo. Seven of the remaining 13 placebo infants were studied in Columbus, and six in Indianapolis. Infants from the two centers differed significantly

TABLE 1. CHARACTERISTICS FOR INFANTS RECEIVING ALBUTEROL AND PLACEBO*

	Albuterol (*n = 28*)	Placebo (*n = 13*)
Age, wk	53.5 ± 41.6	65.6 ± 39.3
Length, cm	73.5 ± 11.5	77.3 ± 11.8
Weight, kg	9.3 ± 2.6	9.9 ± 2.8
Sex, M/F	21/7	6/7
Maternal smoking during pregnancy	32%	8%
Smoking parents†	54%	15%
Smoking caregiver	43%	46%
Immediate family history of asthma	32%	31%
Extended family history of asthma	39%	15%
Baseline FVC, % pred	96.5 ± 13.0	94.1 ± 15.4
Baseline $FEF_{25\%}$, % pred	108.4 ± 20.6	98 ± 20.9
Baseline $FEF_{50\%}$, % pred	99.6 ± 18.8	94.5 ± 14.0
Baseline $FEF_{75\%}$, % pred	90.9 ± 21.1	101.7 ± 24.7
Baseline $FEF_{85\%}$, % pred	88.6 ± 23.5	105.3 ± 35.3
Baseline $FEF_{25-75\%}$, % pred	95.6 ± 19.9	93.6 ± 16.6
Baseline $FEV_{0.5}$, % pred	97.4 ± 13.6	104.8 ± 25.6

* Values are mean ± SD.
† $p < 0.04$.

in age, weight, and length, with the Indianapolis children being younger and smaller than the Columbus children ($p \leq 0.001$). Baseline spirometry in percentage of predicted normal values (9) did not differ between the centers for FVC, $FEV_{0.5}$, $FEF_{25\%}$, $FEF_{75\%}$, or $FEF_{85\%}$. There were significant differences in $FEF_{50\%}$ and $FEF_{25-75\%}$ between the two centers, with Columbus infants having lower measurements ($p = 0.043$ and $p = 0.046$, respectively). There were no differences between the two centers in the percentage of children with environmental tobacco smoke exposure or family history of asthma.

In Table 2, mean intrasubject coefficients of variation (± SD) for the baseline spirometric measurements are shown for both the albuterol and placebo groups, as well as the total study population. Mean coefficients of variation did not differ between groups for any of the measurements.

Group Responses to Albuterol and Placebo Interventions

Figure 1 shows the individual pre to post percentage changes in spirometric measurements for both the albuterol and placebo groups. Mean changes in spirometric measurements after albuterol increased significantly for $FEF_{75\%}$, $FEF_{85\%}$, $FEV_{0.5}$ ($p < 0.001$), and $FEF_{25-75\%}$ ($p = 0.011$). None of the mean changes for the placebo group differed significantly from zero. Using the average of the three pre and the three post curves, the mean percent changes (± SD) in the albuterol group were significantly higher compared with the placebo group in $FEF_{75\%}$ (10.6 ± 15.3% versus −3.1 ± 13.7%), $FEF_{85\%}$ (12.9 ± 17.0% versus 0.46 ± 19.2%), and $FEV_{0.5}$ (2.2 ± 4.0% versus −1.5 ± 7.2%), respectively ($p < 0.05$). The mean percent changes in $FEF_{25\%}$, $FEF_{50\%}$, and $FEF_{25-75\%}$ were 3.1 ± 14.3%, 2.4 ± 8.0%, and 3.7 ± 7.2%, respectively, for the albuterol group, and 8.3 ± 27.6%, 1.2 ± 12.8%, and 0 ± 12.0%, respectively, for the placebo group. For these measures there were no significant differences between the two groups ($p > 0.05$). Using only the best pre and post curve instead of the mean value of the three pre and three post values, the results were similar. Repeated measures ANOVA on the individual flow measurements demonstrated that the effects of albuterol were volume-dependent with the increases reaching statistical significance only at $FEF_{75\%}$ ($p = 0.009$) and $FEF_{85\%}$ ($p = 0.042$).

Fractional lung volumes were measured only in Columbus and thus were available for 17 of the 28 infants who received albuterol and six of 13 placebo infants. No significant differences were found between the albuterol and the placebo group means for the percent changes in FVC, FRC, TLC, and RV/TLC ($p > 0.3$).

Albuterol Responders and Nonresponders

Method 1 defined a responder as an individual with an increase in $FEF_{75\%}$ of more than 2 SD from the mean change for the placebo group. By this method, six of 28 infants who received albuterol were identified as responders. Three were from Indianapolis, and three from Columbus. Figure 2 illustrates the percent change in $FEF_{75\%}$ versus age for the albuterol and placebo infants. The *solid horizontal line* is the mean percent change for the placebo group, and the *dashed lines* are ± 2 SD from the mean for the placebo group. The range of responses of normal infants younger than 52 wk of age (−12 to +48%) can be seen to be wider than the range of responses of infants older than 52 wk (−6 to +14%). All of the responders identified by Method 1 were less than 52 wk (1 yr) of age. Six of 16 albuterol-treated infants younger than 1 yr of age were classified as responders, whereas none of the 12 albuterol-treated infants older than 1 yr of age demonstrated increases in $FEF_{75\%}$ greater than 2 SD from the mean of the placebo group ($p < 0.02$). Using the average of three prealbuterol and three postalbuterol curves, the mean percent changes in infants younger than 1 yr of age were significantly higher compared with those in infants older than 1 yr of age for $FEF_{75\%}$ (16.8 ± 17% versus 2.4 ± 7.1%, $p < 0.02$), $FEF_{85\%}$ (18.6 ± 17.9% versus 5.4 ± 12.8%, $p < 0.04$), and $FEF_{25-75\%}$ (6.1 ± 7.5% versus 0.42 ± 5.4%, $p = 0.04$). Among the albuterol-treated infants, the percent change in $FEF_{75\%}$ declined with age ($p = 0.02$). A similar correlation was present for changes in $FEF_{85\%}$ ($p = 0.03$).

Using Method 2, visual inspection of the albuterol and the placebo flow–volume curves, seven infants were identified as responders. This group included all six of the infants identified by Method 1, and one additional infant who also received albuterol. Figure 3 illustrates the flow–volume curves for three of the responders chosen by visual inspection. The six infants selected by both methods were designated as "responders" and the remaining 22 infants who also received albuterol were designated as "nonresponders."

Infants in the responder group ($n = 6$), selected using Method 1, demonstrated significant increases in flows at low lung volumes after inhalation of albuterol compared with the nonresponders. Figure 4 illustrates the individual percent changes in $FEF_{75\%}$ for subjects in the responders, nonresponders, and placebo groups. Mean percent changes in $FEV_{0.5}$, $FEF_{75\%}$, $FEF_{85\%}$, and $FEF_{25-75\%}$ for responders and nonresponders

TABLE 2. INTRASUBJECT COEFFICIENTS OF VARIATION FOR ALBUTEROL AND PLACEBO INFANTS*

	Albuterol (*n = 28*)	Placebo (*n = 13*)	Total (*n = 41*)
FVC	2.5% (1.3%)	2.7% (1.0%)	2.6% (1.2%)
$FEV_{0.5}$	2.1% (1.8%)	2.6% (2.0%)	2.2% (1.9%)
$FEF_{25-75\%}$	4.2% (2.8%)	4.7% (4.2%)	4.4% (3.3%)
$FEF_{25\%}$	9.3% (7.6%)	12.0% (9.7%)	10.2% (8.3%)
$FEF_{50\%}$	6.3% (4.8%)	6.2% (5.6%)	6.3% (5.0%)
$FEF_{75\%}$	6.2% (4.9%)	6.3% (4.5%)	6.2% (4.8%)
$FEF_{85\%}$	7.8% (6.4%)	10.1% (3.8%)	8.5% (5.8%)

* Values are mean (SD).

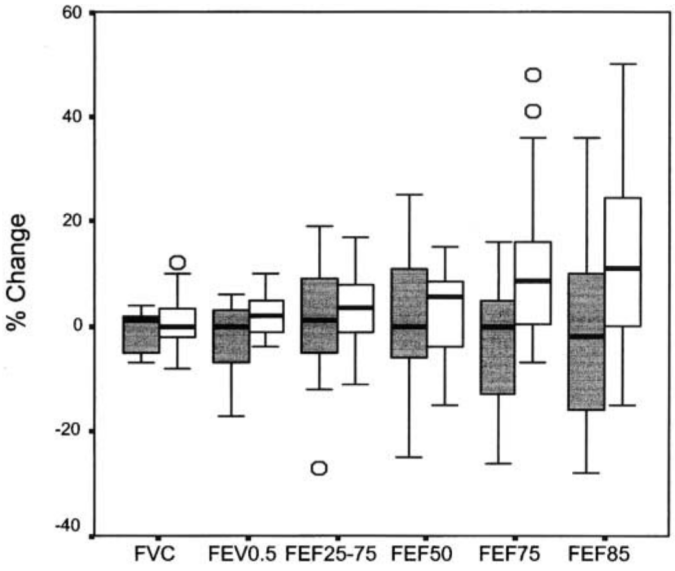

Figure 1. Changes in spirometric measurements for infants who received albuterol (*white*) and placebo (*gray*) shown as box plots. The medians are shown by the *horizontal bars* and the *boxes* indicate the 25 to 75% interquartile range. The 10th to 90th percentile range and outlier points are also shown.

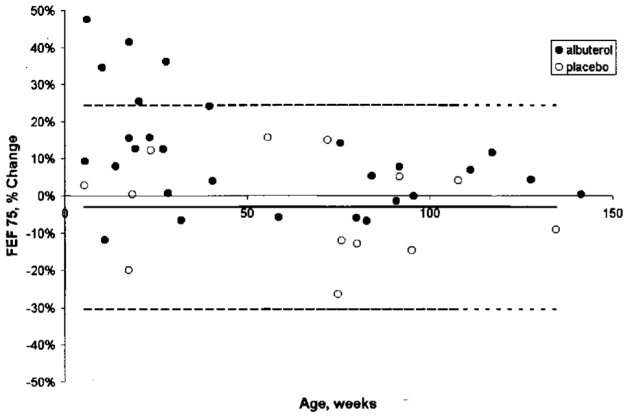

Figure 2. Percent change of $FEF_{75\%}$ versus age for albuterol (*closed circles*) and placebo (*open circles*)-treated infants. The *solid horizontal line* represents the mean percent change of $FEF_{75\%}$ for the placebo group. *Dashed lines* represent 2 SD above and below the mean percent change of $FEF_{75\%}$ for the placebo group.

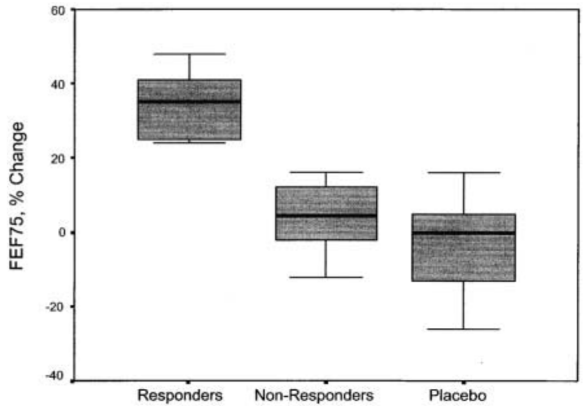

Figure 4. Percent change in $FEF_{75\%}$ for infants designated as responders and nonresponders and for infants who received placebo shown as *box plots* as in Figure 1.

using both the means of the three pre- and three post-values, and values from single best pre- and post-curves are shown in Table 3. The differences in the percent changes between the responders and nonresponders for $FEF_{75\%}$, $FEF_{85\%}$ and $FEF_{25-75\%}$ were significant ($p < 0.05$ for the average of three curves and $p < 0.01$ for single best curves). Fractional lung volumes were measured in three of the six responders, and 14 of the 22 nonresponders. There were no differences in mean percent changes for FVC, FRC, TLC, or RV/TLC for the responder versus nonresponder groups ($p > 0.3$).

Demographics, exposure to environmental tobacco smoke, asthma history, and baseline spirometric values for the responders and the nonresponders are summarized in Table 4. There were no significant differences in baseline spirometric measurements between the groups. As previously noted, the responders were significantly younger than the nonresponders. The responders had a significantly higher percentage of mothers who smoked during pregnancy (4 of 6) compared with the nonresponders (5 of 22) ($p < 0.05$). The responders also had a higher percentage of smoking parents. Five of six responders had parents who smoked in the home compared with 10 of the 22 nonresponders. This difference did not, however, reach statistical significance ($p = 0.10$). For all infants whose mothers smoked during pregnancy ($n = 9$), the mean increase in $FEF_{75\%}$ after albuterol was 19.8 ± 20.3%, whereas for infants born of nonsmoking mothers ($n = 19$), $FEF_{75\%}$ increased by 6.3 ± 10.2% ($p = 0.09$). Using a multiple regression model controlling for age, maternal smoking during pregnancy was associated with a higher mean percent change in $FEF_{75\%}$ ($p < 0.04$). For the entire group ($n = 41$), there were no significant differences in baseline measurements of lung function between infants exposed and nonexposed to tobacco smoking either *in utero* or *post utero*.

The mean jacket pressures used at baseline did not differ significantly between the albuterol and placebo groups (96.2 ± 25.0 and 103.9 ± 22.9 cm H_2O, respectively). After the interventions, mean jacket pressures increased by 4.7 ± 17.6% in the albuterol group, and by 0.6 ± 20.8% in the placebo group. These increases were not significant and did not differ significantly between the two groups. Mean jacket pressures used at

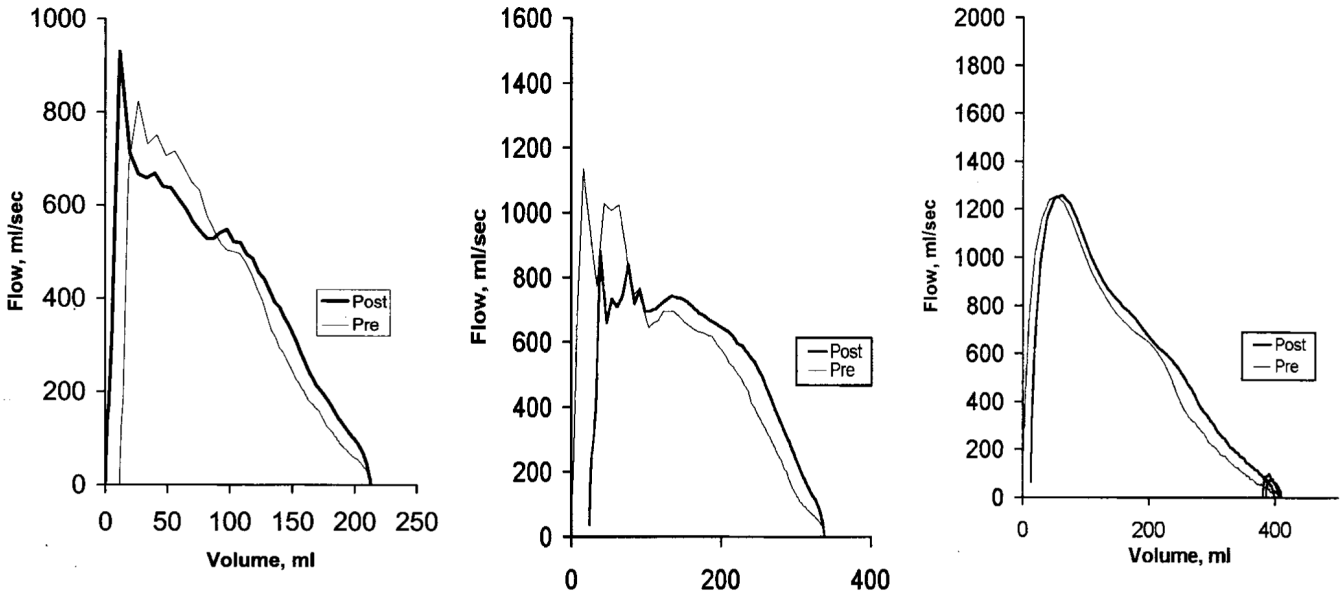

Figure 3. Flow–volume curves for three infants chosen as responders by visual inspection. Single best prealbuterol and postalbuterol curves are shown.

TABLE 3. PERCENT CHANGES IN PULMONARY FUNCTION (± SD) FOR RESPONDERS AND NONRESPONDERS USING THE MEAN OF 3 PRE- AND 3 POSTALBUTEROL CURVES OR SINGLE BEST CURVE

	Average of 3 Curves		Single Best Curve	
	Responders	Nonresponders	Responders	Nonresponders
$FEV_{0.5}$	3.5 ± 4.2%	1.9 ± 3.9%	4.3 ± 4.0%	2.1 ± 5.9%
$FEF_{25–75\%}$	8.8 ± 9.9%*	2.3 ± 5.7%*	11.2 ± 8.2†	1.2 ± 7.4%†
$FEF_{75\%}$	34.7 ± 9.2%*	4.1 ± 8.3%*	38.7 ± 5.3%†,	5.4 ± 8.5%†
$FEF_{85\%}$	38.3 ± 6.5%*	6.0 ± 11.2%*	44.1 ± 11.1%†	9.7 ± 16.5%†

* $p < 0.05$.
† $p < 0.01$.

TABLE 4. CHARACTERISTICS FOR INFANTS RESPONDING TO ALBUTEROL VERSUS THOSE NOT RESPONDING TO ALBUTEROL*

	Responders (*n* = 6)	Nonresponders (*n* = 22)
Age, wk	20.3 ± 12.2	62.5 ± 42.2
Length, cm	65.2 ± 8.1	75.7 ± 11.4
Weight, kg	7.5 ± 2.1	9.8 ± 2.6
Sex, M/F	4/2	17/5
Maternal smoking during pregnancy†	67%	23%
Smoking parents	83%	45%
Smoking caregiver	50%	41%
Immediate family history of asthma	17%	36%
Extended family history of asthma	50%	36%
Baseline FVC, % pred	97.3 ± 9.3	96.3 ± 14.0
Baseline $FEF_{25\%}$, % pred	112.0 ± 27.9	107.4 ± 18.8
Baseline $FEF_{50\%}$, % pred	105.1 ± 20.9	98.1 ± 18.5
Baseline $FEF_{75\%}$, % pred	87.0 ± 24.1	92.0 ± 20.7
Baseline $FEF_{85\%}$, % pred	78.8 ± 19.5	91.3 ± 24.2
Baseline $FEF_{25–75\%}$, % pred	99.4 ± 24.1	94.6 ± 19.1
Baseline $FEV_{0.5}$, % pred	96.5 ± 16.5	97.6 ± 13.2

* Values are mean ± SD.
† $p < 0.05$.

baseline also did not differ between responders and nonresponders (96.7 ± 23.3 cm H_2O versus 96.1 ± 25.9 cm H_2O, respectively). After administration of albuterol, mean jacket pressures increased by 10.3 ± 15.1% in the nonresponder group and decreased by a mean of 15.8 ± 8.1% in the responder group. This difference in changes in jacket pressure was significant ($p < 0.001$). The mean numbers of forced maneuvers performed postalbuterol and postplacebo (5.1 ± 2.1 and 5.1 ± 0.8, respectively) did not differ significantly.

DISCUSSION

In our study, we found that normal healthy infants without respiratory symptoms have baseline airway tone that can be reversed with an inhaled bronchodilator, when assessed with full forced expiratory maneuvers. In addition, younger infants and those exposed to maternal tobacco smoking during pregnancy had greater increases in forced expiratory flows after an inhaled bronchodilator. Although the changes in flow among these normal healthy infants were modest, our findings are consistent with previous reports in normal infants that have shown that younger infants and infants exposed to tobacco smoke have heightened airway reactivity to bronchial challenge agents (10, 11). Our results need to be interpreted in relation to the methodology used for assessing airway responsiveness and existing data on airway responsiveness in this subject population.

Methodological Considerations

Responsiveness to albuterol was assessed in three ways. We first examined the data from the albuterol group alone to see if measurements of pulmonary function increased. Mean changes in $FEV_{0.5}$, $FEF_{25–75\%}$, $FEF_{75\%}$, and $FEF_{85\%}$ all increased significantly after albuterol. We then compared the increases seen to the changes seen in a group of placebo-treated normal infants. Within the range of variability seen after the placebo intervention, the increases in $FEF_{75\%}$ and $FEF_{85\%}$ after albuterol remained significant. Four of the investigators then examined the three preintervention and three postintervention curves of all of the 41 infants studied. Without knowing the treatments given, all four examiners independently picked the same seven infants as responders based upon consistent changes in flows and MEFV curve configurations. All of the infants identified based upon visual inspection were in the albuterol group. Six of the seven infants chosen as responders corresponded with those identified because their changes in $FEF_{75\%}$ measurements were greater than 2 SD from the mean of those observed in the placebo-treated infants. Thus, seven of 28 (25%) normal asymptomatic infants without a history of recurrent wheezing or respiratory symptoms increased their lung function after inhalation of albuterol.

Differences in the methods we used in infants from those used in adults may have impacted measured levels of response. Studies on four infants were excluded because of declines in FVC after albuterol of greater than 10%. Selectively excluding studies with declines in FVC could bias the results in the direction of a positive response. We felt justified in excluding these studies because the source of the observed steady decline in FVC was understood and represented an anticipated source of potential error. The number of studies excluded turned out to be small in number and were equally distributed between the albuterol and placebo groups. Although both FVC and $FEV_{0.5}$ declined in all four excluded infants, forced flows at mid and low lung volumes increased in two and decreased in two subjects. No excluded infant had changes in $FEF_{75\%}$ beyond 2 SD of the mean of the placebo group. Reanalysis of the results including these four infants did not have a significant impact on any of the reported results.

Retesting only 10 min after the delivery of the first puffs of albuterol may have resulted in an underestimation of the degree of responsiveness seen. Although albuterol has activity 10 min after inhalation, peak activity occurs between 30 and 60 min after dosing. The need for sedation in infants limits the time available to complete pre and postbronchodilator studies. Although it would have been preferable to wait longer, this was not practical and would have reduced the number of infants completing postbronchodilator studies during quiet sleep. Studies in adults and older children are usually done from 10 to 60 min after dosing. Thus, the levels of responsiveness that we report may underestimate levels reported from adults and older children.

The placebo and albuterol studies were carried out on different groups of normal infants. We would have preferred to do both interventions on each infant thus using each infant as his or her own control. This would have required sedation on two successive days and was logistically difficult. Using a different group of infants for the placebo studies probably increased intersubject variability. The placebo group was also small. Both of these factors may have widened the limits of the normal range of variability defined in the placebo studies. This increased variability may have diminished our ability to detect changes in function and thus resulted in an underestimation of the frequency of changes beyond the normal range. The two groups did, however, meet the same entry criteria and did not differ significantly in their baseline measurements.

Studies were not blinded. Flows in infants are determined by increasing jacket pressures until an apparent limit is reached, but this assessment is somewhat subjective and controlled by the technician. In relation to the expectation that flows should increase more after albuterol than placebo, technicians could have performed more maneuvers or applied greater jacket pressures after albuterol than after the placebo intervention. The numbers of maneuvers done posttreatment did not differ significantly between the albuterol and placebo groups. Preintervention to postintervention changes in jacket pressures were also not different between the albuterol and placebo groups. When preintervention and postintervention jacket pressures were examined in the infants characterized as responders, it was found that these infants received significantly less rather than more pressure after albuterol than nonresponders. Thus, responders required lower pressures to produce higher flows. Albuterol may have decreased airway resistance and permitted flows to increase above baseline at lower jacket pressures. Recognition of a substantial increase in flows, the anticipated response, may have resulted in a technician decision to prematurely curtail further increases in jacket pressure. Again it would appear that responses may have been underestimated rather than overestimated. It is also not likely that the increased flows in responders were a result of diminished artifact from thoracic gas compression. The mean reduction in postalbuterol jacket pressures in responders was only 15.4 cm H_2O. At lower lung volumes less than half of the pressure in the jacket is transmitted intrathoracically (12, 13), and this would produce a less than 1% change in intrathoracic lung volume. This small difference in volume could not account for the increases in forced flows measured in the responders.

In adults and children, deep inspirations have been shown to produce decreases in airway tone (14). The method for producing MEFV curves in infants requires full inflation of the lungs several times just before performing the forced expiratory maneuver. These inflations may have minimized resting levels of bronchial tone and thus reduced measured responses to albuterol. Most of the technical problems we encountered in making these measurements thus would have caused us to err in the direction of underestimating rather than overestimating bronchodilator responsiveness.

Comparison to Previous Studies

Airway responsiveness is most commonly assessed in older children and adults using measurements of forced flow. MEFV curves, because of the phenomenon of flow limitation, provide highly reproducible measures of airway function and changes in airway function. We have previously shown that MEFV curves produced by the method we used in this study are flow-limited in normal infants (8, 15). The low intrasubject variabilities of our spirometric measurements (Table 2) suggest that forced flows should also be effective for discriminating changes in airway function in infants. Taking into account the long list of reservations previously discussed, the ability to measure MEFV curves in infants permits levels of responsiveness in infants to be compared directly with those observed in older children and adults.

The purpose of this study was to assess levels of albuterol responsiveness in normal infants. In adults and older children the limits of bronchodilator responsiveness are usually defined using the 95% confidence limits of changes in the FEV_1. The upper limits for increases in FEV_1 after bronchodilator challenges in various control groups of adults and children range from approximately 8 to 25% (16). The American Thoracic Society (17) and the Intermountain Thoracic Society (18) have both suggested 12% as the upper limit for change in FEV_1 after bronchodilator challenge. Increases greater than this are considered consistent with an abnormally increased level of response. Less information has been reported regarding changes in $FEF_{25–75\%}$ after bronchodilator challenges in normal adults. The Intermountain Thoracic Society has recommended an upper limit for change of 45% whereas the American College of Chest Physicians (19) suggests that changes between 15% and 25% should be considered significant. Table 5 shows the upper limits of the normal range (defined as 2 SD above the mean) for changes in pulmonary function parameters for our normal infants. Data are based on mean measurements from three preintervention and three postintervention MEFV curves. Data calculated based upon single best preintervention and postintervention curves were not significantly different from those shown. Limits for the total group of infants receiving albuterol are shown in the first column. The limits for infants younger than and older than 1 yr of age are also shown separately (columns 2 and 3) because of the significant difference in responsiveness in these two groups. We have previously found the $FEV_{0.5}$ to be the measure in infants that corresponds best with the FEV_1 (9). It can be appreciated in Table 5 that the limits for changes in $FEV_{0.5}$ after inhalation of albuterol in infants are in the same range as 95% limits for change in FEV_1 in adults. Changes in $FEF_{25–75\%}$ are in the range of limits recommended by the American College of Chest Physicians (19).

Dales and coworkers (20), who measured responses to inhaled terbutaline in a large number of normal adults and children, reported a mean change in the FEV_1 of $1.8 \pm 4.0\%$. This degree of change is similar to the changes in $FEV_{0.5}$ that we measured in our normal infants. In children they reported 95% upper limits of change in FEV_1 ranging between 8% and 12%. Sourk and Nugent (21) made pre- and postplacebo measurements of lung function on 40 adults. They reported changes in FEV_1 and $FEF_{25–75\%}$ of $1.0 \pm 5.6\%$ and $-0.1 \pm 22.4\%$, respectively. From their placebo measurements they derived an upper limit of 12.3% for FEV_1 and 44.1% for $FEF_{25–75\%}$. These limits are similar to those recommended by the Intermountain Thoracic Society (18). Our placebo limit for change in $FEV_{0.5}$ (shown in the far right-hand column of Table 5) is similar to theirs for FEV_1. Our upper limit for mean change in $FEF_{25–75\%}$ is substantially lower than their limit. They did not, however, exclude individuals from their placebo group who were taking bronchodilator medications. Overall bronchodilator responsiveness in our small sample of infants appears to be similar to that seen in children and adults.

The degree of bronchodilator responsiveness observed in our normal infants was mild. Although defined as responders by increases in $FEF_{75\%}$ that were significantly different from those of the placebo group, the level of responsiveness to albuterol in these infants was not in the range that would be considered abnormal in older children and adults. When as-

TABLE 5. TWO STANDARD DEVIATIONS ABOVE THE MEAN FOR PERCENT CHANGES IN PULMONARY FUNCTION FOR INDIVIDUAL SUBJECTS

Pulmonary Function Test	Albuterol (*n* = 28)	Albuterol < 1 yr (*n* = 16)	Albuterol > 1 yr (*n* = 12)	Placebo (*n* = 13)
FVC	10.1	10.1	10.5	7.2
$FEF_{50\%}$	18.5	20.1	16.5	26.7
$FEF_{75\%}$	41.2	50.8	16.5	24.3
$FEF_{85\%}$	46.9	54.3	31.0	38.8
$FEF_{25–75\%}$	18.0	21.1	11.2	24.0
$FEV_{0.5}$	10.1	11.1	8.5	12.8

sessed using best pre- and postalbuterol curves, as is done most commonly in the clinical setting, the mean increases in $FEV_{0.5}$ and $FEF_{25–75\%}$ in the responders were only 4.3% and 11.2%, respectively (Table 3). Declines in function after bronchoconstrictor challenges with histamine and methacholine have clearly demonstrated the presence of airway reactivity in normal infants (2–6). The presence of β-adrenergic responsiveness in normal infants has been demonstrated indirectly by Tepper (6) and Henderson and coworkers (7). In both of these studies β-adrenergic agents appeared to have a bronchodilator effect after a bronchoconstrictor challenge. We could find only one previous report of the measurement of responsiveness to albuterol in normal infants assessed using forced flows. Hiatt and coworkers (22) reported no significant change in flow measured at FRC after administration of nebulized metaproterenol in 22 normal infants. The high degree of variability of this measure of forced flow may have prevented detection of the very modest degree of responsiveness that we measured using MEFV curves. Recently, Hayden and associates (23), using low-frequency forced oscillations applied at the airway opening during an induced airway pause, observed decreases in resistance in seven of eight normal infants given albuterol by metered-dose inhaler. Although the number of infants studied was small, these results also suggest that normal infants have increased levels of resting airway tone.

The decline in albuterol responsiveness with age that we observed is consistent with the findings of Montgomery and Tepper (2) who reported a decrease in airway sensitivity to methacholine with increasing age in 24 normal infants between the ages of 4 and 24 mo. In their study airway function was assessed using measurements of flow at FRC from partial expiratory flow–volume curves. These investigators confirmed the apparent decline in reactivity that they observed in their cross-sectional study by demonstrating longitudinal declines in a subset of 10 infants. Whether bronchoconstrictor reactivity and bronchodilator responsiveness are related in the same subject has not been evaluated. The age relationship in these studies could be a function of selection bias. Children with a history of chronic respiratory disease or recurrent episodes of wheezing were excluded from our study. The older a child becomes, the more time he or she has to have recurrent episodes of respiratory illness or wheezing and thus be excluded from the study. Although the apparent decline in airway tone that we observed fits nicely with the data of Montgomery and Tepper (2) and the observed declines in the frequency of wheezing in infants over the first 2 to 3 yr of life, this relationship will require confirmation by longitudinal studies. In contrast, exclusion of infants with a history of recurrent wheezing may have resulted in underestimation of degree of albuterol responsiveness in children younger than 1 yr of age.

Age may also have had an impact on the dose of albuterol delivered. Each puff of albuterol was delivered to the lungs via an inspiratory capacity breath to an inflation pressure of 25 cm H_2O. As lung capacity increases rapidly early in life, the aerosol concentration delivered to the lung by this method would be higher in younger than older infants. Although the dose delivered was titrated to a specific increase in heart rate, the dose per kilogram may also have been higher in younger infants. The number of puffs required to achieve a 10% increase in heart rate was also higher in younger infants. The greater responsiveness observed in younger infants could potentially be an effect of the relatively larger doses of albuterol delivered in these smaller children.

Although our number of subjects was small, our results demonstrate a significant relationship between albuterol responsiveness and maternal smoking during pregnancy. Previous studies have shown that the infants of mothers who smoke during pregnancy have decreased forced flows (9, 24, 25). It is not known whether this reduction in flows is fixed or reversible. Our results would suggest the latter. Baseline forced flows were not reduced in our tobacco smoke–exposed infants; however, our sample size was substantially smaller than that of previous studies in which this reduction has been demonstrated. Numerous reports suggest a relationship between environmental tobacco smoke exposure and the development of wheezing in infants and children. Wheezing lower respiratory illnesses occur more frequently in the infants of smokers (26, 27). This tendency appears to persist into early childhood (28). Children younger than 5 yr of age exposed to maternal smoking are significantly more likely to have a diagnosis of asthma, take asthma medications, and have developed their asthma before 1 yr of age (29). Frischer and colleagues (10) reported that bronchial hyperresponsiveness, as assessed by exercise challenge, occurred more frequently in children who had been exposed to maternal tobacco smoke in the first year of life. Young and colleagues (11) found that normal infants whose parents smoke have significantly increased airway reactivity compared with infants of nonsmoking parents as assessed by histamine challenge. Our results are consistent with the majority of prior investigations suggesting that exposure to environmental tobacco smoke increases airway responsiveness. Again, exclusion of infants with recurrent wheezing may have resulted in underestimation of the impact of parental smoking on albuterol responsiveness early in life.

In summary, we found that 20 to 25% of asymptomatic normal infants without a history of respiratory problems can be demonstrated to have an increase in forced expiratory flows after inhaled albuterol beyond that seen after placebo. In these infants this appears to be due to baseline levels of airway tone that are reduced by albuterol. In addition, younger infants and infants exposed to maternal tobacco smoking during pregnancy were more likely to demonstrate bronchodilator responsiveness. The relationship of airway tone and bronchodilator responsiveness to the risk of wheezing during infancy remains to be defined.

References

1. Sherrill D, Sears MR, Lebowitz MD, Holdaway MD, Hewitt CJ, Flannery EM, Herbison GP, Silva PA. The effects of airway hyperresponsiveness, wheezing, and atopy on longitudinal pulmonary function in children: a six-year follow-up study. *Pediatr Pulmonol* 1992;13:78–85.
2. Montgomery GL, Tepper RS. Changes in airway reactivity with age in normal infants and young children. *Am Rev Respir Dis* 1990;142:1372–1376.
3. Hayden MJ, Devadason SG, Sly PD, Wildhaber JH, LeSouef PN. Methacholine responsiveness using the raised volume forced expiration technique in infants. *Am J Respir Crit Care Med* 1997;155:1670–1675.
4. Tepper RS, Rosenberg D, Eigen H. Airway responsiveness in infants following bronchiolitis. *Pediatr Pulmonol* 1992;13:6–10.
5. Clarke JR, Reese A, Silverman M. Comparison of the squeeze technique and transcutaneous oxygen tension for measuring the response to bronchial challenge in normal and wheezy infants. *Pediatr Pulmonol* 1993;15:244–250.
6. Tepper RS. Airway reactivity in infants: a positive response to methacholine and metaproterenol. *J Appl Physiol* 1987;62:1155–1159.
7. Henderson AJW, Young S, Stick SM, Landau LI, LeSouef PN. Effect of salbutamol on histamine induced bronchoconstriction in healthy infants. *Thorax* 1993;48:317–323.
8. Feher A, Castile R, Kisling J, Angelicchio C, Filbrun D, Flucke R, Tepper R. Flow limitation in normal infants: a new method for forced expiratory maneuvers from raised lung volumes. *J Appl Physiol* 1996;80:2019–2025.
9. Jones M, Castile R, Davis S, Kisling J, Filbrun D, Flucke R, Emsley C, Goldstein A, Ambrosius W, Tepper R. Forced expiratory flows and volumes in infants: normative data and lung growth. *Am J Respir Crit Care Med* 2000;161:353–359.

10. Frischer T, Kuehr J, Meinert R, Karmaus W, Barth R, Hermann-Kunz E, Urbanek R. Maternal smoking in early childhood: a risk factor for bronchial responsiveness to exercise in primary-school children. *J Pediatr* 1992;121:14–22.
11. Young S, Le Souef PN, Geehoed GC, Stick SM, Turner DJ, Landau LI. The influence of a family history of asthma and parental smoking on airway responsiveness in early infancy. *N Engl J Med* 1991;324:1168–1173.
12. Turner DJ, Lanteri CJ, LeSouef PN, Sly PD. Pressure transmission across the respiratory system at raised lung volumes in infants. *J Appl Physiol* 1994;77:1015–1020.
13. Stick S, Turner D, LeSouef P. Transmission of pressure across the chest wall during the rapid thoracic compression technique in infants. *J Appl Physiol* 1994;76:1411–1416.
14. Fish JE, Ankin MG, Kelly JF, Peterman VI. Regulation of bronchomotor tone by lung inflation in asthmatic and non-asthmatic subjects. *J Appl Physiol* 1981;50:1079–1086.
15. Jones MH, Davis S, Kisling J, Howard J, Castile R, Tepper R. Flow limitation in infants assessed by negative expiratory pressure. *Am J Respir Crit Care Med* 2000;161(3 Pt 1):713–717.
16. Castile RG. Pulmonary function testing in children. In: Chernick V, Boat TF, Kendig EL, editors. Kendig's disorders of the respiratory tract in children, 6th ed. Philadelphia: W. B. Saunders; 1998. p. 212–213.
17. American Thoracic Society. Lung function testing: selection of reference values and interpretation strategies. *Am Rev Respir Dis* 1991;144:1202–1218.
18. Morris AH, Kanner RE, Crapo RO, Gardner RM. Clinical pulmonary function testing: a manual of uniform laboratory procedures, 2nd ed. Salt Lake City, UT: Intermountain Thoracic Society; 1984.
19. Committee report. Criteria for the assessment of reversibility in airways obstruction: report of the committee on emphysema. American College of Chest Physicians. *Chest* 1974;65:552–553.
20. Dales RE, Spitzer WO, Tousignant P, Schechter M, Suissa S. Clinical interpretation of airway response to a bronchodilator: epidemiologic considerations. *Am Rev Respir Dis* 1988;138:317–320.
21. Sourk RL, Nugent KM. Bronchodilator testing: confidence intervals derived from placebo inhalations. *Am Rev Respir Dis* 1983;128:153–175.
22. Hiatt P, Eigen H, Yu P, Tepper RS. Bronchodilator responsiveness in infants and young children with cystic fibrosis. *Am Rev Respir Dis* 1988; 137:119–122.
23. Hayden MJ, Petak F, Hantos Z, Hall G, Sly PD. Using low-frequency oscillation to detect bronchodilator responsiveness in infants. *Am J Respir Crit Care Med* 1998;157:574–579.
24. Hanrahan JP, Tager IB, Segal MR, Castile RG, VanVunakis H, Weiss ST, Speizer FE. The effect of maternal smoking during pregnancy on early infant lung function. *Am Rev Respir Dis* 1992;145:1129–1135.
25. Tager IB, Ngo L, Hanrahan JP. Maternal smoking during pregnancy: effects on lung function during the first 18 months of life. *Am J Respir Crit Care Med* 1995;152:977–983.
26. Tager IB, Hanrahan JP, Tosteson TD, Castile RG, Brown RW, Weiss ST, Speizer FE. Lung function, pre-and post-natal smoke exposure, and wheezing in the first year of life. *Am Rev Respir Dis* 1993;147: 811–817.
27. Wright AL, Holberg AC, Martinez FD, Taussig LM. Group Health Medical Associates. Relationship of parental smoking to wheezing and nonwheezing lower respiratory tract illness in infancy. *J Pediatr* 1991;118:207–214.
28. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995;332:133–138.
29. Weitzman M, Gortmaker S, Klein Walker D, Sobol A. Maternal smoking and childhood asthma. *Pediatrics* 1990;85:505–511.