Forced Random Noise Resistance Determination in Childhood Asthma

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The forced random noise method for measuring respiratory resistance was studied in terms of reproducibility and correlation with spirometry and flow volumes in 30 older children (four to 17 years) with asthma and in 16 infants and children below three years of age. In the 30 older children, the mean value of individual coefficient of variations for three repeated measurements was 7.4 percent. Resistance parameters correlated well with spirometric parameters with all but three correlation coefficients greater than 0.7.

In 20 older asthmatic patients, 180 μg albuterol caused a significant reduction in resistance in 11 subjects. At the same time, FEV₁ increased significantly in nine subjects but showed a paradoxical decrease in five. This paradoxical response is attributed to complex reflexes caused by the maximum inspiration and forced expiration and did not occur with resistance measurements. This method requires little subject cooperation, and therefore, is well suited for infants and children.

Measurement of pulmonary function in infants and young children is particularly difficult because they are unable to perform the necessary maneuvers and do not tolerate the equipment required by standard spirometric and plethysmographic techniques. Also, complex reflexes from the maximum inspiration and forced expiration complicate the interpretation of forced expiratory spirometric data after administration of bronchoconstrictor or bronchodilator drugs. Forced excitation measurements, which require no special maneuvers and only minimal equipment contact, have potential for providing interpretable pulmonary function data in this population. In this approach, either sinusoidal or complex fluctuations are applied to the respiratory system. Resulting pressure and flow signals are detected and processed to obtain measures of effective respiratory resistance and in a more general sense, respiratory resistance as a function of frequency.

In children, several groups have reported effective resistance data using forced excitation approaches. However, only two groups studied children under three years of age, and both used single frequency sinusoidal excitation. One of these, Wohl et al., used a technically complex variation of the forced oscillation approach in which acoustic fluctuations were applied at the body surface using a body box. The other, Rutter, Lenny, and associates, used a much simpler approach with a face mask to couple the acoustic fluctuations to the airway. We are exploring the use of random noise excitation with the latter approach. We believe that this approach can be used routinely to obtain data in these young subjects as well as in children over three years of age.

In this report, data are presented showing the variability of random noise resistance measurements and their correlation with more standard spirometric parameters in asthmatic children over three years of age. Bronchodilator-induced changes are also compared in these two sets of parameters in a similar group of subjects. Finally, prebronchodilator and postbronchodilator random noise resistance data are presented from young children and infants less than three years of age.

MATERIAL AND METHODS

In this study, we used a commercial forced random excitation system based on the work of Landers, Nagels, and associates. This system, which is shown schematically in Figure 1, measured respiratory resistance at 2 Hz intervals in the 2 to 26 Hz range and the coherence of this measurement, a quantitative indication of the reliability of the resistance measurement. It contained a loudspeaker for generating the forced random excitation, pressure and flow transducers for detecting these signals, a computer for processing these signals, a keyboard for entering commands and subject identification, and a printer for displaying the data. In this study, we report the resistances at 6 Hz (R₆) and at 26 Hz (R₂₆) and the average resistance computed using 6 to 26 Hz data (R₆₋₂₆). Data at 2 and 4 Hz were not included because coherence values frequently fell below 0.8, a minimum acceptable value.

We conducted two studies with older asthmatic children (four to 17 years of age with a mean age of 9.4 years, 20 male/ten female) to compare random noise resistance and standard spirometric measurements. All had asthma as defined by the American Thoracic Society and demonstrated a 15 percent increase in FEV₁ after the administration of an inhaled bronchodilator. In 30 subjects with asthma, we obtained three sets of resistance data within a few minutes of each other; from these, we computed mean values and coefficients of variation for R₆, R₂₆, and R₆₋₂₆ for each individual. Coefficients of variation from all individuals were averaged to provide an estimate of the variability of these resistance parameters. After obtaining the three sets of random noise measurements, we obtained maximum forced expiratory spirometric data on all 30 subjects using a computerized spirometric system. Each subject performed three acceptable maneuvers, and the system computed and printed standard spirometric parameters from the one with the largest sum of FVC and FEV₁. Using the data from these 30

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Manuscript received March 21; revision accepted June 14.
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individuals, we correlated mean values of $R_a$, $R_m$, and $R_{50}$ with $FEV_1$, $FEF_{25-75}$, $FEF_{75}$, $FEF_{90}$, and $FEF_{95}$ using linear regression analysis.

The second study involved 20 asthmatic children who had an $FEV_1$ less than 80 percent of predicted or an $FEF_{25-75}$ less than 70 percent of predicted. After baseline measurements, each received 180 μg of albuterol from a metered dose inhaler. Both random noise and forced expiratory measurements were obtained ten minutes after bronchodilator administration. Random noise resistance data was always obtained before the maximum forced expiration to preclude any effect of the latter maneuver on the resistance measurement. Changes in resistance parameters that exceeded two times the average coefficient of variation measured in the study described in the previous paragraph were defined as significant. Similarly, spirometric changes that exceeded two times the average coefficient of variation reported earlier for our laboratory were defined as significant.  

In order to make measurements in supine infants and young children, we modified the forced random excitation system by placing the transducers, bias flow connections, and port for the mouthpiece at the end of a flexible tube, approximately 7.5 cm in length. The lengths and rigidity of all tubes were adjusted so that measurements made on a calibration device supplied with the forced random excitation system after the modification matched those made with the original system. When measuring infants and young children, the transducer assembly was connected to a Bennett seal mouthpiece in place of the standard adult mouthpiece. The rigid mouthpiece ensured a patent airway while the soft "mask" provided a good seal to the face and supported the cheeks. These modifications provided minimal effective dead space, thereby allowing measurements in infants with small tidal volumes. With this modification, we made measurements in several children two years old or younger. In another 12 asthmatic children that were two and three years old, we also made before and after bronchodilator measurements with a standard mouthpiece attached to the extension tubing. The study was approved by the institutional committee on human research and informed consent was obtained from the subjects/parents.

RESULTS

Measured values of $R_a$, $R_m$, and $R_{50}$ in the four to 17-year-old asthmatic children ranged from 2.8 to 11.4, 3.3 to 10.4, and 3.2 to 10.2 cmH₂O·L⁻¹, respectively.

Figure 1. Schematic diagram of the forced random excitation system.

Figure 2 shows a plot of these three parameters as a function of height along with separate regression lines.
for those with normal and abnormal spirometry. It is possible that a curvilinear relationship could have provided a better fit, but we did not feel that the limited amount of data (15 subjects in each group) justified this complexity. Subjects with an FEV₁ less than 80 percent of predicted or an FEF_{25-75} less than 70 percent of predicted generally had higher resistances than individuals with normal spirometry.

Individual coefficients of variation for Rₜ, Rₛ, and Rₛₜ ranged from less than 1 percent to about 20 percent. The variability of these three resistance parameters was similar, and no age dependency in variability was apparent. Table 1 shows the mean values for the coefficients of variation for Rₜ, Rₛ, and Rₛₜ along with their ranges and standard deviations. All three mean values were less than 10 percent, suggesting that the expected variability in these three resistance parameters in asthmatics is less than 10 percent.

Table 2 shows the result of the correlation analysis relating random noise resistance parameters to maximum forced expiratory spirometric parameters. As examples of the observed agreement, Figure 3 presents individual data showing the relationship between the three random noise resistance parameters and FEV₁. In Table 2, correlation coefficients ranged from 0.50 to 0.89; eight of 15 correlation coefficients were greater than 0.8, and all but three were greater than 0.7. All correlations were statistically significant at the 0.0001 level except that between Rₛₜ and FEF_{25-75}, which was statistically significant at the 0.005 level. All spirometric parameters correlated best with Rₜ and worst with Rₛₜ. All three random noise resistance parameters correlated better with spirometric parameters that depended on the early portion of the maximum forced expiration (e.g., FEF_{25-75} and FEV₁) than they did with those spirometric parameters that depended on the late portion of this maneuver (e.g., FEF_{50-75}).

After the bronchodilator, changes in Rₜ (ΔRₜ) ranged from −49 to +16 percent of the individual’s baseline value; corresponding values for ARₛₜ were −49 to +23 percent, and for ARₛₜ they were −51 to +5 percent. Mean values and standard deviation for these changes are given in Table 3. Changes in FEV₁ and FEF_{25-75} (ΔFEV₁ and ΔFEF_{25-75}) ranged from −23 to +48 percent and −37 to +190 percent, respectively; mean values and standard deviations of these two parameters also are given in Table 3 along with those for ΔFEF_{50-75}, ΔFEF_{50-75}, and ΔFEF_{75-85}. The largest average changes occurred in forced expiratory flow rates at mid and low lung volumes, that is, ΔFEF_{50-75}, ΔFEF_{50-75}, and ΔFEF_{75-85}, with mean values of 30.1, 52.1, and 54.2 percent, respectively. At the same time, these parameters had the largest variability among the individual responses as indicated by their large standard deviations, about 60 percent of the mean value. The change in FEV₁ was smaller, 7.4 percent, but it was more consistent among subjects with a standard deviation of 18.8 percent. Mean changes in the three resistance parameters were on the order of 10 percent to 20 percent with standard deviation approximately equal to the mean change; of the three resistance parameter.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Range</th>
<th>SD</th>
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</thead>
<tbody>
<tr>
<td>Rₜ</td>
<td>9.6</td>
<td>1.2-20.6</td>
<td>5.6</td>
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<tr>
<td>Rₛ</td>
<td>8.9</td>
<td>0.8-20.4</td>
<td>4.7</td>
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<td>Rₛₜ</td>
<td>7.4</td>
<td>2.0-21.9</td>
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Table 2—Correlation Coefficients Between Random Noise Resistance Parameter and Forced Expiratory Spirometric Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FEF₁</th>
<th>FEF₁₀⁻⁰₅₀</th>
<th>FEF₇₀⁻₅₀</th>
<th>FEF₅₀⁻₇₀</th>
<th>FEF₅₀⁻₈₅</th>
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<tbody>
<tr>
<td>Rₜ</td>
<td>0.88</td>
<td>0.82</td>
<td>0.89</td>
<td>0.85</td>
<td>0.70</td>
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<tr>
<td>Rₛ</td>
<td>0.77</td>
<td>0.64</td>
<td>0.71</td>
<td>0.65</td>
<td>0.51</td>
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<tr>
<td>Rₛₜ</td>
<td>0.82</td>
<td>0.82</td>
<td>0.86</td>
<td>0.82</td>
<td>0.69</td>
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</table>

*All correlations were significant at 0.0001 level except that between Rₛₜ and FEF_{25-75}, which was significant at 0.005 level.

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Table 3—Bronchodilator-Induced Changes Expressed as Percent

<table>
<thead>
<tr>
<th></th>
<th>$\Delta R_s$</th>
<th>$\Delta R_{sp}$</th>
<th>$\Delta R_{esp}$</th>
<th>$\Delta FEF_{125}$</th>
<th>$\Delta FEF_{250}$</th>
<th>$\Delta FEF_{500}$</th>
<th>$\Delta FEF_{750}$</th>
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<tbody>
<tr>
<td>Mean</td>
<td>-17.3</td>
<td>-12.7</td>
<td>-15.6</td>
<td>7.4</td>
<td>54.2</td>
<td>13.4</td>
<td>30.1</td>
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<tr>
<td>SD</td>
<td>8.2</td>
<td>10.3</td>
<td>13.1</td>
<td>18.5</td>
<td>62.5</td>
<td>56.3</td>
<td>70.7</td>
</tr>
</tbody>
</table>

There was little correlation between bronchodilator-induced changes in the three resistance parameters and those in the maximum forced expiratory spirometric parameters. The largest correlation coefficient, 0.73, was found between $\Delta R_s$ and $\Delta FEF_{750}$. Only three other correlations (ie, $\Delta R_s$ and $\Delta FEF_{125}$, $\Delta R_s$ and $\Delta FEF_{500}$, and $\Delta R_{esp}$ and $\Delta FEF_{750}$) were statistically significant, but the correlation coefficients were less than 0.6.

The bronchodilator induced a significant decrease (ie, greater than two times the expected coefficient of variation) in $R_s$, $R_{sp}$, and $R_{esp}$ in 10, 8, and 11 of the 20 subjects, respectively; changes in the remainder of the subjects were less than two times the expected variation in repeated measurements. At the same time, the bronchodilator induced a significant increase in $FEF_{125}$ in nine subjects and in $FEF_{250}$ in 11 subjects; however, the bronchodilator induced a significant paradoxical decrease in $FEV_1$ in five of the subjects and in $FEF_{250}$ in one of the subjects. Of the 11 subjects who showed a significant decrease in $R_{esp}$, six showed an increase in $FEV_1$, two showed no change in this spirometric parameter, and three showed a decrease. Of the nine who showed no change in $R_{esp}$, five showed a significant increase in $FEV_1$, two showed no change, and two showed a decrease in $FEV_1$.

Figure 4A shows the effective resistance as a function of frequency for a normal three-week-old infant measured with the modified system and the Bannett seal mouthpiece. The curve fluctuated somewhat, but this pattern is typical with forced random noise measurements. In all cases, the coherence values, which provide a measure of data reliability, were greater than 0.8, a minimum acceptable value. The average resistance for this infant was 10.2 cmH$_2$O-L$^{-1}$. Figures 4B and 4C show before and after bronchodilator (nebulized isoetharine, 0.25 ml) data from two asthmatic patients. In the first, an 11-month-old infant with no clinical signs of active asthma, the bronchodilator caused a small decrease in effective resistance with the average going from 11.0 to 10.4 cmH$_2$O-L$^{-1}$. Figure 4C shows data from a two-year-old who was symptomatic at the time of the study. With this patient, the bronchodilator caused a substantial change in the effective resistance at all frequencies, and the average resistance decreased 26 percent from 18.2 to 13.5 cmH$_2$O-L$^{-1}$. Figure 4D shows before and after bronchodilator data from a 23-month-old patient with bronchopulmonary dysplasia and asthma. Again, the bronchodilator caused a substantial decrease in resistance with the average value going from 9.7 to 7.8 cmH$_2$O-L$^{-1}$.

Figure 5 shows the before and after bronchodilator values of $R_{esp}$ for the 12 two- and three-year-old asthmatic patients studied with the modified system with a standard mouthpiece. Prebronchodilator resistances were generally higher than those seen in the older group measured in the standard way (Fig 2), which is consistent with the younger age of the

![Figure 4](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21443/ on 04/18/2017)
subjects represented in Figure 5. All subjects showed a substantial decrease in $R_{50}$ after the bronchodilator with the percent change averaging 38 percent and ranging from 15 percent to 56 percent.

**DISCUSSION**

In general, asthmatic patients with an FEV$_1$ less than 80 percent of predicted or FEF$_{25-75}$% less than 70 percent of predicted had higher resistance values than asymptomatic asthmatic patients with normal spirometry (Fig 2). This is supported by the position of the two regression lines and by the numerical data, for example, the average of $R_{50}$ for the 15 with normal spirometry was 5.55 cmH$_2$O·L$^{-1}$·cm$^{-1}$ and for the other 15 it was 7.53 cmH$_2$O·L$^{-1}$·cm$^{-1}$. Resistance values in our older asthmatic children with abnormal spirometric findings generally were larger than forced oscillatory and random noise resistance values previously reported by others for normal children of comparable ages.$^{11-14}$ For example, at a height of 150 cm, our regression equations for the group with normal spirometry yielded values of 6.4, 4.8, and 5.4 cmH$_2$O·L$^{-1}$·cm$^{-1}$ for $R_{50}$, $R_{50}$, and $R_{15}$ respectively. The corresponding value from the equation of Williams et al$^{15}$ was 3.09 cmH$_2$O·L$^{-1}$·cm$^{-1}$; from that of Mansell et al,$^{16}$ it was 3.48 cmH$_2$O·L$^{-1}$·cm$^{-1}$; and from that of Stanescu et al$^{14}$ it was 5.20 cmH$_2$O·L$^{-1}$·cm$^{-1}$. Our higher resistance values are consistent with the effects of asthma and its magnitude is similar to that reported by Cogswell,$^{20}$ who measured forced oscillatory resistances that were 2 SD above his normal value in 23 of 42 asthmatic children.

In young children, resistance generally decreased with frequency, while in older children, resistance generally increased with frequency. For example, when a separation is made at nine years of age, the difference between low and high frequency resistance averaged $+0.50$ cmH$_2$O·L$^{-1}$·cm$^{-1}$ in the younger children and $-0.45$ cmH$_2$O·L$^{-1}$·cm$^{-1}$ in the older children. This trend in frequency dependence where resistance decreases with frequency up to a certain height after which it shows an increase with frequency is consistent with previous work$^{21}$ (Fullton, personal communication). Furthermore, our regression lines of $R_f$ and $R_{50}$, respectively. These values suggest that the expected variability of repeated measurements of these parameters was on the order of 7 percent to 10 percent and that changes after some intervention that exceeded 15 percent to 20 percent, twice the expected coefficient of variation, indicated altered function. These average coefficients of variation were comparable to 14 percent reported by Williams et al$^{15}$ for normal three to five year old children and the 12 percent reported by Cogswell$^{20}$ also for normal children. This variability is comparable to that seen in forced expiratory spirometric parameters; for example, an earlier study from our laboratory reported coefficients of variation of 4.3 percent and 16.5 percent in FEV$_1$ and FEF$_{25-75}$% in young asthmatic patients.$^{20}$

Random noise resistance parameters showed fairly good correlation with forced expiratory spirometric parameters with correlation coefficients ranging from 0.51 to 0.89 with most greater than 0.80. This suggests that these resistance parameters provide a comparably valid measure of respiratory mechanical function as forced expiratory spirometric parameters, the generally accepted standards.

The three resistance parameters correlated best with high lung volume spirometric parameters, that is, FEV$_1$ and FEF$_{25-75}$%, and poorest with the low lung volume parameter, FEF$_{50}$%. Correlations with mid-lung volume parameters, FEF$_{25-75}$% and FEF$_{50}$% were intermediate between these two extremes. We believe that this pattern simply reflects the increase in variability of forced expiratory flow as lung volume decreased.$^{21}$ Another possible explanation could be the fact that both resistance and high lung volume spirometric parameters are mainly large airway measurements. From the opposite point of view, spirometric parameters correlated better with the low frequency resistance parameter, $R_{50}$, than with its high frequency counterpart, $R_{50}$. Perhaps this is due to the fact that low frequency measurements reflect the resistance of the entire system while high frequency measurements...
reflect only the central resistance.\textsuperscript{a2}

Correlations between bronchodilator-induced changes in the resistance and spirometric parameters were poor with only four correlations being statistically significant, and only one having a correlation above 0.70. Most correlation coefficients fell below 0.60. Kabiraj et al\textsuperscript{a1} reported similar correlation coefficients between changes in forced oscillatory resistance at 10 Hz and changes in FEV\textsubscript{1}, and peak expiratory flow; these coefficients were 0.54 and 0.59, respectively. We believe this lack of correlation between the changes in these two groups of mechanical parameters may be due to two factors. First, the maximum inspiration can cause reflex changes in airway smooth muscle tone.\textsuperscript{1,3} Thus, the maneuver itself actually alters mechanical function so that changes in spirometric parameters reflect the combination of the bronchodilator effect along with the maneuver effect. The second factor concerns secondary effects of the bronchodilator on dynamic airway compression and the site of flow limitation during forced expirations.\textsuperscript{1,3} In this mechanism, the bronchodilator reduces bronchomotor tone in the large central airways, thereby making them more compressible during forced expiration, so that flow actually decreases. Perhaps individual variation in the importance of these two factors accounts for the large variability in the bronchodilator-induced changes in four of the five spirometric parameters as reflected by the large standard deviations in Table 4. Also, these mechanisms provide an explanation for the paradoxical bronchodilator-induced decrease in FEV\textsubscript{1}, that we observed in five subjects. The fact that only one patient showed paradoxic response on FEF\textsubscript{25-75}\textsuperscript{a1} could mean that the site of dynamic compression is mainly in the large airways.

In the results section, data were reported from 16 children three years old or younger. Post-bronchodilator data in these younger children appeared to fit an extension of the post-bronchodilator regression curve for the older children (Fig 3). The marked bronchodilator-induced decrease in resistance in the younger group suggests that bronchospasm is an important component of airway obstruction in children two to three years of age. We attempted to make measurements in several other subjects under two years of age; however, we were unsuccessful with most of them, because the children usually cried when their noses were sealed, and this interfered with the random noise measurement as indicated by low coherence values. In children two and three years old, we generally were able to obtain reliable random noise measurements, and the approach has great potential for characterizing respiratory function and its change with disease and bronchodilator therapy in this age group. It is probable that the problem with those younger than two years old could be overcome with the use of a mild sedative.

ACKNOWLEDGMENT: The authors wish to thank John E. Hewett, Ph.D., for statistical advice, Miss Cynthia Kreutz for technical help, and Ms. Joan Coffland for typing the manuscript.

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