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Abstract

This study analyzed the relationship between total respiratory resistance (Rrs) measured by forced oscillation technique and FEV1 during histamine provocation test in 31 children between seven and 17 years of age. Rrs was measured at frequencies between 6 (R6) and 26 Hz (R26). (R6-R26)/R26 was used as an index of frequency dependency of Rrs. A positive histamine test was defined as PC20 less than 8 mg/ml. Seventeen subjects had a positive test, and all of these had increases from baseline of R6 greater than 50 percent and (R6-R26)/R26 greater than 0.45. Of the 14 subjects whose PC20 was greater than 8 mg/ml, only two had changes in R6 and (R6-R26)/R26 of this magnitude. These two subjects had changes in FEV1 of 16 and 18 percent. There was a strong linear relationship between the changes in FEV1 and both R6 and (R6-R26)/R26 from baseline to the final value at the end of the test (r = 0.87 and 0.91 respectively). In conclusion, this study demonstrated that the evaluation of airway rea...

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Histamine Challenge Test in Children Using Forced Oscillation to Measure Total Respiratory Resistance*

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This study analyzed the relationship between total respiratory resistance (Rrs) measured by forced oscillation technique and FEV_1 during histamine provocation test in 31 children between seven and 17 years of age. Rrs was measured at frequencies between 6 (R_6) and 26 Hz (R_{26}). $(R_6 - R_{26})/R_{26}$ was used as an index of frequency dependency of Rrs. A positive histamine test was defined as PC_{20} less than 8 mg/ml. Seventeen subjects had a positive test, and all of these had increases from baseline of R_6 greater than 50 percent and $(R_6 - R_{26})/R_{26}$ greater than 0.45. Of the 14 subjects whose PC_{20} was greater than 8 mg/ml, only two had changes in R_6 and $(R_6 - R_{26})/R_{26}$ of this magnitude. These two subjects had changes in FEV_1 of 16 and 18 percent. There was a strong linear relationship between the changes in FEV_1 and both R_6 and $(R_6 - R_{26})/R_{26}$ from baseline to the final value at the end of the test ($r = 0.87$ and 0.91 respectively). In conclusion, this study demonstrated that the evaluation of airway reactivity by histamine challenge may be done by forced oscillation technique. It is easy to administer and may allow testing of children unable to perform spirometry.

Asthma in children is frequently underdiagnosed,[1] in part because of the lack of specific tests. The histamine challenge test to demonstrate suspected airway lability or to find an explanation for a cough in the absence of apparent pathology has recently gained favor for use in both adults and children. The degree of positivity is usually assessed by the concentration of inhaled histamine necessary to provoke a 20 percent fall in initial FEV_1 (PC_{20}). In Europe, a 15 percent fall in FEV_1 (PC_{15}) is sometimes used as the marker of a positive test. Because this test depends on the ability of the subject to perform a reproducible forced expiratory maneuver, it is usually limited to children older than six or seven years. For those children too young to cooperate with the usual spirometry of pulmonary function testing, one frequently must rely on history alone. In 1956, Dubois et al[2] described the use of forced oscillation as a measure of total respiratory system impedance which was noninvasive and required minimal cooperation from the subject. Such a technique might lend itself to testing children too young to cooperate with the usual histamine challenge. The purpose of this study was to compare the changes in FEV_1 to the changes in respiratory system resistance as measured by forced oscillation during a histamine challenge test in children.

Since the original description, the technique of forced oscillation has become much easier to perform and can be applied to infants and older children.[3-14] Fourier analysis of the frequency spectrum in the flow signal (resulting from the application of a pressure signal applied to the respiratory system) allows separation of the components of the impedance of the system at various frequencies.[15]

Materials and Methods

The subjects for this study consisted of 31 Caucasian children between seven and 17 years of age who were referred for a histamine challenge test. Twelve were boys and 19 girls. No one was receiving medication at the time of the study. All had baseline values for total respiratory resistance (Rrs), measured by forced oscillation, that were within normal limits,[16] as were their baseline spirometry values.[17] Two-thirds had been referred because of symptoms suggestive of exercise-induced asthma, and one third for investigation of unexplained cough. Informed consent was obtained and the study had ethics committee approval.

Spirometry was done on an Eagle One (Collins, Braintree, MA) automated water seal spirometer. Values derived were forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and forced expiratory flow at 25 and 75 percent of FEV (FEF25-75%). Baseline measures were repeated at least three times and were reproducible within 5 percent for FEV_1. The effort associated with the greatest sum of FVC and FEV_1 was used to derive FEV_1 and FEF25-75%. For this study, lower normal limits were defined as 80 percent of predicted for FVC and FEV_1, 60 percent for FEF25-75% and an FEV_1/FVC ratio of 80 percent. Predicted values were taken from Knudson et al.[18]

Measurement of Rrs by forced random noise used a commercially available unit (Oscillaire, Jones Medical Instrument Co, Oak Brook,

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IL) based on the work of Lándsér and colleagues.[19-21] The device has been described elsewhere in detail.[22-23] With this equipment the subject breathes quietly across a pneumotachograph. A varying pressure signal consisting of pseudorandom noise with a peak never more than 2 cm H_2O and containing energy at all frequencies is superimposed on the regular respirations. The microprocessor in the instrument uses Fourier analysis of the pressure and flow signals to separate the components of impedance into resistive and reactive elements and calculate the frequency spectrum. The values are averaged over 16-sec intervals of quiet breathing, and the resistance and reactance components of the impedance are calculated for even frequencies between 2 and 26 Hz. Reactance (X) is the summation of the elastic and inertial components of the respiratory system which are opposite in sign to each other. For each even frequency the coherence function of the values for the breaths used to derive the results is calculated. It has been empirically determined that when this is greater than 0.95 the relative error in either resistance or reactance will not exceed 10 percent.[19] It is to be noted that a value of 1 for the coherence function indicates the total absence of noise or alinearities. The components of the impedances of interest were the resistances at the relatively low frequency of 6 Hz (R_6) and the higher frequency of 26 Hz (R_{26}), the arithmetic mean resistance between these frequencies (Rm), and the reactance at 26 Hz (X_{26}). Change in resistance as a function of frequency was expressed as $(R_6 - R_{26})/R_{26}$. Only those values where the calculated coherence function was 0.95 or greater were used in the results. Values for measurements at 2 and 4 Hz were not calculated because of the length of time required for adequate data acquisition at these low frequencies.

Prior to the onset of testing, during a period of 20 to 30 minutes, baseline parameters for spirometry and Rrs were measured to acquaint the subject with the procedure. Rrs was measured 21 times in each subject. Each measurement consisted of a 16-sec period during which the subject breathed into a mouthpiece connected to the machine. Each subject wore nose clips and supported his cheeks with his hands, and was encouraged not to swallow or move his head. These maneuvers allowed each child to adopt a comfortable position on the apparatus and to be able to generate reproducible results.

Histamine testing was performed according to the recommendations of Cockcroft et al;[24] the subject inhaled increasing concentrations of histamine during 2 min of tidal breathing at each concentration. Two milliliters of the solution were nebulized by a Hudson nebulizer model 1720 supplied with a constant air flow of 5 L/min[25] and delivered by a mask covering the nose and mouth. The subject did not wear nose clips but was encouraged to breathe through the mouth. The first inhalation consisted of phosphate-buffered saline solution (PBS) and was followed 5 min later by an initial concentration of histamine of 0.5 mg/ml, which was doubled at each 5-min interval until a maximum of 8 mg/ml was reached. Spirometry was done 3 min after the end of each inhalation. At each stage of the histamine test, three or four measurements of Rrs were made over a period of 150 sec prior to the measurement of FEV_1, and the mean of each parameter was used. The test was terminated when FEV_1 fell by at least 20 percent of baseline, or the maximum concentration was reached. Following administration of the concentration of histamine which led to a 20 percent fall in FEV_1, the subject was given an inhalation of 0.5 ml of salbutamol (5 mg/ml in 1.5 ml of normal saline solution) and 5 min later Rrs was determined using the mean of six to eight measurements. FEV_1 was also measured to ensure that it had returned to normal. The concentration of histamine that provoked a 20 percent fall (PC_{20}) was determined graphically[24] from plotting FEV_1 on the Y-axis against the logarithm of the concentration of histamine on the X-axis. The value of the parameters of Rrs at PC_{20} can be determined when plotted against the log dose of histamine. Similarly, PC_{15} and the Rrs values at PC_{15} can be derived.

All data were analyzed by comparing the values measured following the inhalation of histamine to the baseline values. From the baseline measurements, intrasubject and intragroup mean values and standard deviation (SD) for Rrs and Xrs and coefficients of variations for Rrs were calculated. Rrs values obtained following histamine inhalation that were more than ±3 SD of baseline were considered significantly different from baseline.

Table 1—*Anthropometric, Spirometric and Rrs Data*

	Group A (n = 17)		Group B (n = 14)	
	Mean	SD	Mean	SD
Age (years)	11.8	3.1	11.6	1.29
Height (cm)	148.1	15.7	147.6	16.2
FEV_1 (L)	2.43	0.76	2.57	0.86
FEF25-75% (L/sec)	2.56	0.83	3.04	1.21
R_6 (cm H_2O/L/sec)	3.78	1.34	3.53	1.29
Rm (cm H_2O/L/sec)	3.80	1.09	3.59	1.19
R_{26} (cm H_2O/L/sec)	3.68	0.90	3.52	1.01
X_{26} (cm H_2O/L/sec)	1.16	0.47	1.21	0.46
$(R_6 - R_{26})/R_{26}$	0.01	0.21	0.00	0.16

Results

There were 17 patients with a positive response to histamine as indicated by a PC_{20} of 8 mg/ml or less. These constituted group A, and the 14 subjects with negative test results made up group B. Allergic rhinitis was present in five members of group A and one of group B. Anthropometric data and mean baseline values for R_6, R_{26}, Rm, X_{26} and $(R_6 - R_{26})/R_{26}$ for both groups are given in Table 1. There was no significant difference in any of these parameters between the two groups. Range of baseline values for R_6 was 1.99 to 6.99; R_{26}, 2.03 to 5.75; for Rm 2.07 to 6.28; and for X_{26} 0.29 to 2.29, all in cm H_2O/L/sec. The index of frequency dependence of resistance, $(R_6 - R_{26})/R_{26}$, was between −0.2 and 0.4. The mean of individual coefficients of variation for R_6 was 9.3 percent, for R_{26}, was 10.2 percent, and for Rm was 8.4 percent. These latter values were not influenced by the age of the subject or whether the subject had a positive histamine test reaction. Table 2 gives the coefficients of correlation between the resistance values for R_6, Rm, and R_{26}, and the spirometric values for the baseline test values. All of these were significant and and were better for R_6 than for R_{26}. For group A, geometric mean PC_{20} was 3.6 mg/ml of histamine. Following inhalation of PBS solution, FEV_1 fell a mean of 1.6 percent for all subjects.

Figure 1 demonstrates the typical changes in Rrs during a positive test with increasing concentrations of inhaled histamine. In this case, PC_{20} was 4 mg/ml. It

Table 2—*Correlation Coefficients for Parameters Derived from Forced Oscillation and Spirometry**

	FEV_1	FEF25-75%
R_6	.84	.81
Rm	.84	.81
R_{26}	.76	.72

*$p < 0.001$ in all cases

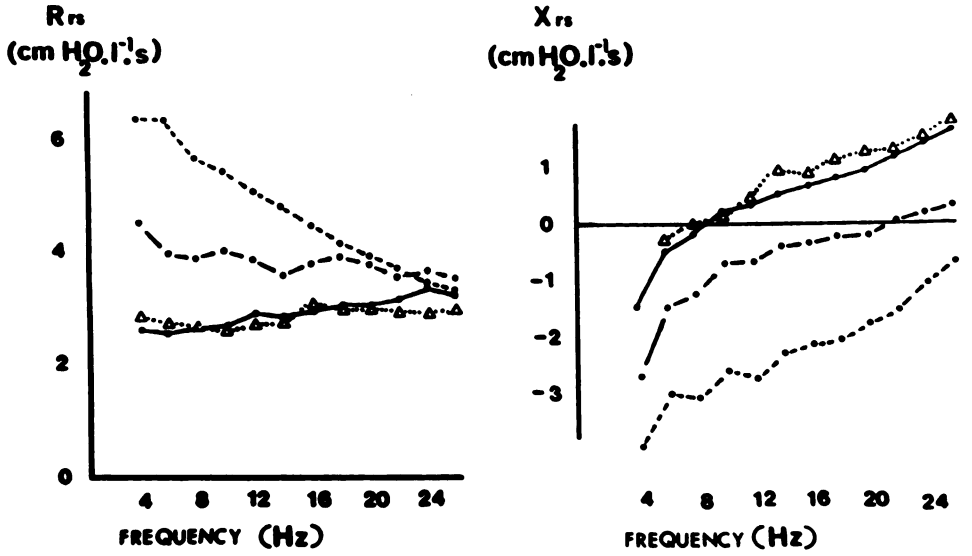

FIGURE 1. Typical response for a positive histamine challenge. Baseline values (dot solid line), the value after 2 mg/ml histamine where the FEV_1 had fallen 9 percent (dot long dash), after 4 mg/ml histamine where the FEV_1 had dropped 20 percent (dot short dash) and after inhalation of salbutamol where the FEV_1 was back to 105 percent of initial (triangle dash) are given for both resistance and reactance plotted against frequency.

can be seen that there is a considerable increase in R_6 but little change in R_{26}; in other words, a marked increase in the frequency dependence of resistance and a progressive diminution of reactance. The mean linear correlation coefficient between Rrs and frequency between 6 and 26 Hz at the end of positive challenges was 0.95 ± 0.02.

Table 3 compares the change in FEV_1, R_6, Rm, X_{26}, and $(R_6 - R_{26})/R_{26}$ from baseline values to those at the final concentration of histamine (paired *t*-test). For group A, all changes were significant ($p<0.005$). At PC_{20} derived from interpolation, the mean increases in R_6, Rm and R_{26} were 78, 42 and 12 percent respectively. There is a striking relation between the change from baseline to that after the highest concentration of histamine administered in R_6 (ΔR_6) and FEV_1 (ΔFEV_1), with $r = 0.87$, $p<0.001$ for the 31 tests (Fig 2). Change in frequency dependence of resistance is also strikingly related to ΔFEV_1 (Fig 3); $r = 0.91$, $p<0.001$. There are similar relationships with lower r-values between ΔFEV_1 and ΔX_{26} ($r = 0.71$, $p<0.001$) and Rm ($r = 0.75$, $p<0.001$) but no significant relation with ΔR_{26}. Using a threshold increase of 50 percent from baseline in R_6 or 0.45 for $(R_6 - R_{26})/R_{26}$, all patients with positive histamine test results (*ie*, PC_{20} less than 8 mg/ml) would be included, giving a test sensitivity for the technique of forced oscillation of unity. In the 14 patients with negative histamine test results, these thresholds were exceeded in only two, giving a test specificity of 0.86. For group A, values for R_6 were 3 SD different from the mean of baseline in all 17 cases; for Rm, X_{26} and $(R_6 - R_{26})/R_{26}$ this difference pertained in 16 of 17 cases. The difference of 3 SD had been reached for these three parameters at a mean of one dose before the final dose of histamine. In group B, the limit of 3 SD had been reached at the end of the test six of 14 times for R_6, five times for X_{26}, four times for $(R_6 - R_{26})/R_{26}$ and three times for Rm.

Finally, Table 4 indicates that the administration of salbutamol at the end of a positive test results in the

Table 3—*Changes in Parameters from Baseline to Final Histamine Concentration**

	Group A (n = 17)		Group B (n = 14)	
	Mean	Range	Mean	Range
ΔFEV_1	−26.9†	−20 to −48	−8	1 to −18
ΔR_6	104†	60 to 194	31.6†	4 to 139
ΔRm	47.8†	28 to 88	17.1‡	−2 to 81
ΔR_{26}	14.6†	−4 to 45	4.6§	−14 to 28
ΔX_{26}	−1.73†	−0.33 to −2.9	−0.70‡	0.1 to −2.74
$\Delta(R_6 - R_{26})/R_{26}$	0.80†	0.50 to 1.56	0.23‡	−0.02 to 0.70

*ΔFEV_1, ΔR_6, ΔRm and ΔR_{26} expressed as percent change; ΔX_{26} and $\Delta(R_6 - R_{26})/R_{26}$ expressed as absolute change.
†$p<0.0005$
‡$p<0.01$
§$p<0.05$

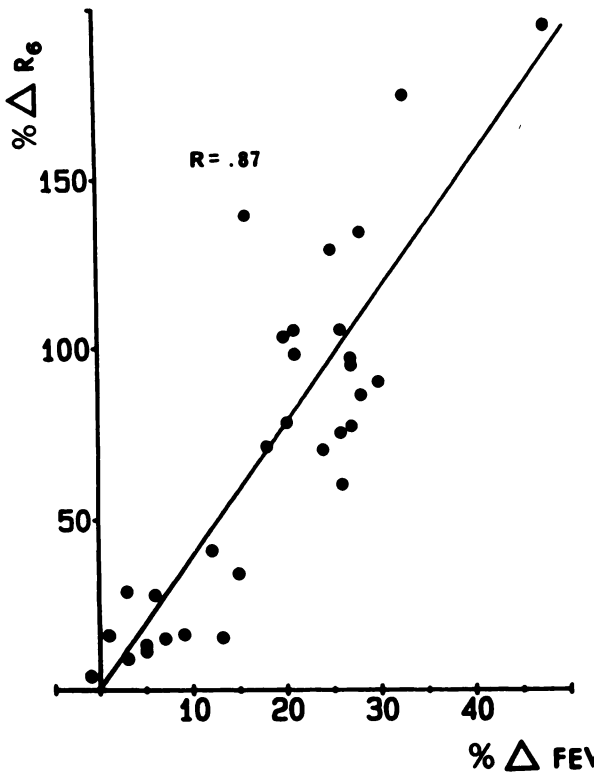

FIGURE 2. Change in R_6 from baseline to the final concentration of histamine, plotted against a similar change in FEV_1. Both are expressed as a percentage of baseline for all subjects. The relationship is highly significant ($r=0.87$, $p<0.001$.)

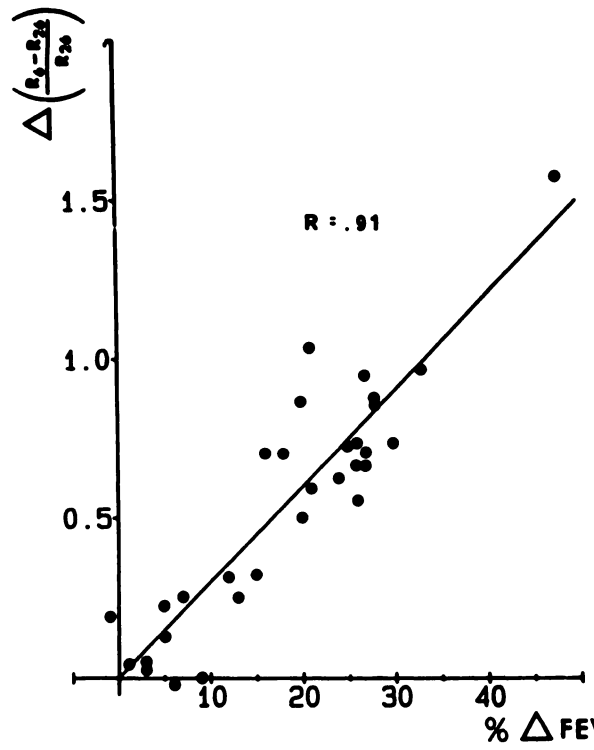

FIGURE 3. Change in absolute values for $(R_6-R_{26})/R_{26}$ before and at the end of the test plotted against the similar change in FEV_1, as in Figure 2. The relationship is highly significant ($r=0.91$, $p<0.001$.)

Table 4—*FEV_1 and Rrs in Group A after Final Dose of Histamine and After Salbutamol Inhalation*

	Before Salbutamol	After Salbutamol
FEV_1*	73.1 (6.5)†	102.5 (6.9)†
R_6*	204 (35.9)†	86.5 (13.2)†
R_{26}*	114.6 (12.7)†	96.4 (15.8)†
Rm*	147.8 (18.1)†	91.5 (12.3)†
X_{25}‡	−6.9	+1.1
$(R_6-R_{26})/R_{26}$‡	+8.9	−1.2

*Expressed as a percentage of the initial value.
†Standard deviation.
‡Expressed as standard deviations from the initial value.

return to baseline of not only FEV_1 but also parameters measured by the oscillatory technique. This can also be seen in Figure 1. The change in FEV_1 with salbutamol administration correlated with the changes in R_6 and in $(R_6-R_{26})/R_{26}$ ($r=0.64$, $p<0.01$ for both).

DISCUSSION

Using the definition of a positive histamine challenge test as a PC_{20} not greater than 8 mg/ml, the method of forced oscillation to measure Rrs using a threshold of an increase in R_6 of 50 percent or greater or an increase in $(R_6-R_{26})/R_{26}$ of 0.45 or greater will include all positive tests; in other words, sensitivity of 100 percent. Those two patients whose PC_{20} was greater than 8 mg/ml but who were positive by the criteria of forced oscillation had changes in FEV_1 of 16 and 18 percent. If, as in many places in Europe, PC_{15} not greater than 8 mg/ml defined a positive test, forced oscillation test results would have resulted in total separation of the groups. In addition, three patients in group A showed changes in R_6 and $(R_6-R_{26})/R_{26}$ exceeding 6 SD from baseline values one dose prior to the provocative dose causing a fall in FEV_1 of 20 percent or more. This increased sensitivity of the forced oscillation technique may be due in part to elimination of changes in bronchomotor tone accompanying maximal inspiration when measuring FEV_1,[28-31] a maneuver that is not necessary when measuring Rrs. The correlations between baseline values of R_6, Rm, R_{26} and FEV_1 were also very acceptable and similar to the observations of Konig et al.[23] In terms of reproducibility, coefficients of variation were similar and on the order of 10 percent; in other words, comparable to that normally seen for FEV_1. These results are in agreement with those of others.[26,27]

There are two theoretic limitations to using Rrs for histamine challenge testing. The first is that Rrs represents the resistance of the thoracic cage and lung tissue, as well as airway resistance (Raw). However, Raw is the predominant factor and there are good cor-

relations between Raw and Rrs in health and disease in adults and children.[16,22,32] Moreover, in determining Rrs by forced oscillation and measuring the combination of lung tissue resistance plus Raw with esophageal balloon techniques, Nagels et al[21] measured the resistance attributable to the thoracic cage and demonstrated that the way this varies with frequency was similar in normal adults and those with COPD. In other words, when comparing normal subjects to those with COPD, this implies that the differences observed in Rrs are due to changes at the level of the airways and pulmonary parenchyma. The other potential handicap is that lung volumes are not determined during the test. Nagels et al[21] have shown in both normal adults and those with COPD that the measurement of Rrs at a volume lower than FRC increases the Rrs and leads to or accentuates the frequency dependence of Rrs. The inverse was also true. In fact, the inhalation of histamine may be accompanied by hyperinflation, which may be due to changes in inspiratory muscle activity[33] or changes in glottic aperture.[34] The latter would lead to an increase in Rrs, while the former would have the opposite effect, rendering physiologic interpretation of the isolated effects difficult if lung volumes were not measured.

A possible advantage of this technique is the help it could provide in locating the site of action of histamine. According to the model of Mead[35] refined by Pimmel et al,[36] the respiratory system is best represented by central and peripheral airway resistive compartments with a capacitative shunt between them. They demonstrated that an increase in the contribution of the peripheral compartment increased the frequency dependency of resistance. In light of these models, it would be tempting to consider accentuation of the frequency dependency of resistance in this study, as well as in studies in adults with challenges by methacholine[37] and cold air[38] inhalation to indicate a peripheral site of action of these stimuli. However, this study does not take into account the effects of shunting of pressure at the level of the upper airways with increasing intrathoracic airways resistance upon the frequency dependency of resistance. Recent works[39-40] caution against an interpretation using this technique of peripheral airway changes. This needs to be explored in more detail.

In conclusion, in the population of children studied we found that airway reactivity to histamine can be assessed as reliably by the method of forced oscillation as by the forced expiratory technique. The results of this study suggest that there may be a role for the evaluation of bronchial reactivity using the forced oscillation technique in those children who are capable of quiet breathing into the mouthpiece of the machine, even though they may be incapable of performing a reproducible forced expiratory maneuver.

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