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Research Article

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Respiratory System Impedance from 4 to 40 Hz in Paralyzed Intubated Infants with Respiratory Disease

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ABSTRACT To describe the mechanical characteristics of the respiratory system in intubated neonates with respiratory disease, we measured impedance and resistance in six paralyzed intubated infants with respiratory distress syndrome, three of whom also had pulmonary interstitial emphysema. We subtracted the effects of the endotracheal tube after showing that such subtraction was valid. Oscillatory flow was generated from 4 to 40 Hz by a loudspeaker, airway pressure was measured, and flow was calculated from pressure changes in an airtight enclosure mounted behind the flow source (speaker plethysmograph). After subtraction of the endotracheal tube contribution, resistance ranged from 22 to 34 cmH_2O $liter^{-1}$ s; compliance from 0.22 to 0.68 ml/cmH_2O; and inertance from 0.0056 to 0.047 cmH_2O $liter^{-1}$ s^2. Our results indicate that, for these intubated infants, the mechanics of the respiratory system are well described as resistance, compliance, and inertance in series. Most of the inertance, some of the resistance, and little of the compliance are due to the endotracheal tube. When the contribution of the endotracheal tube is subtracted, the results are descriptive of the subglottal respiratory system. These data characterize the neonatal respiratory system of infants with respiratory distress syndrome (with or without pulmonary interstitial emphysema) in the range of frequencies used during high frequency ventilation.

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INTRODUCTION

The mechanical characteristics of the neonatal respiratory system have been well studied during tidal breathing and at frequencies up to the current limits of standard assisted ventilation (1–4). Factors such as resistance, compliance, and inertance are undefined, however, in the frequency range used during small tidal volume, high frequency ventilation (HFV).[1] Reports of infants with respiratory distress syndrome (RDS) or pulmonary interstitial emphysema (PIE) ventilated successfully with HFV include little information concerning the mechanical factors of the respiratory system and their frequency dependence (5, 6). Because gas exchange during HFV is thought to be closely coupled to mechanical factors (7, 8), a better understanding of gas exchange mechanisms and ventilation strategies may depend upon better definition of the high frequency mechanics pertaining to the infant respiratory system.

The respiratory system is a complex interconnection of inertive (L), resistive (R), and compliant (C) mechanical elements. Such L-R-C elements combine to give the respiratory system a characteristic impedance (Z) and resistance (R), both of which can vary as a function of the oscillating frequency. Obtaining these impedance and resistance measurements over a wide range of frequencies allows the mechanical characteristics of the respiratory system to be determined.

To describe these properties in six intubated infants

[1] *Abbreviations used in this paper:* C, compliance; HFV, high frequency ventilation; L, inertance; PIE, pulmonary interstitial emphysema; R, resistance; RDS, respiratory distress syndrome; Z, impedance.

with RDS, three of whom also had PIE, we measured the frequency dependence of impedance and resistance over the range of 4 to 40 Hz. We then computed values for the inertance, resistance, and compliance of the intubated respiratory system. To determine the mechanical characteristics of the unintubated respiratory system, we partitioned the impedance and resistance between respiratory system and endotracheal tube and validated this partitioning method in vitro. The oscillatory impedance and resistance measurements were performed with a speaker plethysmograph devised by Jackson and Vinegar (9).

METHODS

Measurement system. The loudspeaker plethysmograph functions both as the oscillatory flow generator and the detector by which the impedance and resistance are measured. This method avoids the frequency response problems often associated with the use of a pneumotachometer for oscillatory flow measurements at high frequencies (10). The loudspeaker plethysmograph is separated into two chambers by the loudspeaker (Fig. 1). The volume of the reference chamber (1, Fig. 1) is measured by water displacement and the compliance of the equivalent gas volume is calculated. Speaker movement generates either gas compression or rarification in this chamber, developing pressure changes proportional to the volume of the speaker excursion. Compression of air in chambers of this size and geometry have been shown to be adiabatic over the frequency range of interest (9). From this plethysmographic relationship of pressure and compliance, the volume of speaker displacement per unit time (flow) can be determined at each frequency.

The outlet of the test chamber (2, Fig. 1) can either be closed or connected to an experimental load. When the outlet is closed, speaker movement produces gas compression and rarification in the test chamber as it does in the reference chamber. The volume changes in the two chambers are equal in magnitude but 180° out of phase; the pressure change in the test chamber is proportional to the gas volume change. When an experimental load, such as in intubated infant, is connected to the test chamber, speaker displacement causes both gas compression and rarification in the test chamber and gas flow into the infant's respiratory system. Pressure measured in the test chamber under these conditions is less than that measured when the outlet is closed. The decrease in pressure is proportional to the volume of gas flowing from the test chamber into the intubated infant.

The ratio of the pressure developed in the test chamber to the flow exiting is by definition the input impedance of the infant's respiratory system. The component of impedance in which pressure and flow are in phase is by definition the resistance. By measuring the pressure at the airway opening, flow, and their phase relationship, the oscillatory resistance and impedance magnitude of the intubated respiratory system can be computed. In all cases, pressure at the airway opening was <0.4 cmH_2O and was usually in the range of 0.15 to 0.2 cmH_2O.

Signal processing and data analysis. The equipment and data analysis used have been described in detail previously (11). Briefly, a computer-generated sinusoidal function is established at the minimum frequency (4 Hz in all but one case) and increased in steps of 2 Hz over the range of frequencies desired. The signal is amplified, converted into an oscillatory pressure by the loudspeaker plethysmograph, and directed into the subject. The resultant pressure signals in the reference and test chambers of the plethysmograph are then amplified, filtered, and returned to the computer where the pressure magnitude and the phase relationship between impedance and flow are computed and stored.

In vitro experiments. To calculate the impedance and resistance of the unintubated respiratory system we subtracted the endotracheal tube contribution from measurements made in intubated infants. To validate this method in vitro, we measured impedances and resistances of (*a*) 12-cm lengths of 3.0- and 3.5-mm i.d. endotracheal tubes; (*b*) 0.5- and 1.15-liter glass bottles; and (*c*) endotracheal tube-bottle combinations. The bottles were chosen to have compliances similar to those of infants with RDS (1). The endotracheal tubes were chosen to have dimensions equal to those of the infants studied.

In vivo experiments. We studied six newborn infants with RDS, three of whom also had PIE (Table I). All were patients in the Neonatal Intensive Care Unit of The Children's Hospital, Boston. Patients were selected who were being treated with intubation, conventional mechanical ventilation, oxygen, and muscle relaxation. The gestational ages ranged from 31 to 36 wk and the weights ranged from 1.6 to 2.3 kg. All infants were between 1 and 7 d old. The study was approved by the Hospital Committee on Clinical Investigation.

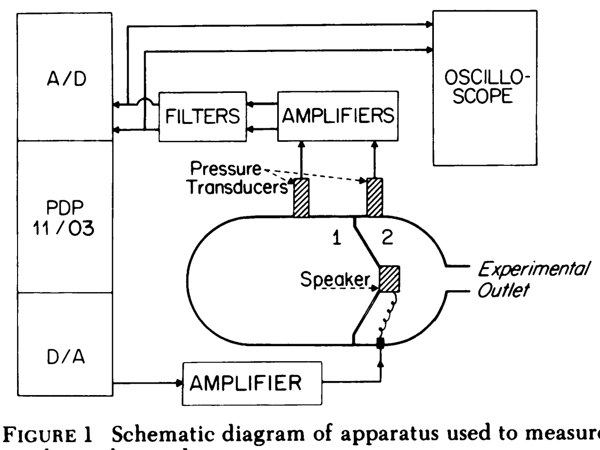

FIGURE 1 Schematic diagram of apparatus used to measure mechanical impedance.

TABLE I
Clinical Characteristics of Subjects

Subject	Birth weight	Gestational age	Postnatal age	Diagnosis
	kg	*wk*	*d*	
A	1.65	32	3	RDS, PIE
B	1.70	31	7	RDS, PIE
C	2.02	36	1	RDS
D	1.64	32	2	RDS
E	2.16	34	2	RDS
F	2.30	36	5	RDS, PIE

Parameters estimation. Any model of the respiratory system must take into account the components of inertance, resistance, and compliance, which are contributed to the entire system by the airways, gas, lung tissue, and chest wall. The simplest model is a lumped parameter L-R-C series combination. If the respiratory system is represented as such a series combination of inertance, resistance, and compliance, then the impedance magnitude, |Z|, is given by the equation:

$$|Z| = \{R^2 + [2\pi fL - 1/(2\pi fC)]^2\}^{1/2}, \tag{1}$$

where f is frequency of oscillation in Hertz. The frequency at which inertial and elastic elements cancel and impedance magnitude is least is the resonant frequency (f_0):

$$f_0 = 1/[2\pi(LC)^{1/2}]. \tag{2}$$

We fit our impedance data to such a simple L-R-C model of the respiratory system to estimate the values of inertance, resistance, and compliance that fit the data with the least mean square error over the frequency range studied.

Protocol. Before proceeding, blood pressure, pulse rate, and transcutaneous O_2 tension were observed to ensure a stable clinical setting. No infant was studied unless the initial transcutaneous O_2 tension was >60 torr. The patient's endotracheal tube was then disconnected from the ventilator at end expiration and attached to the experimental outlet of the air-filled test chamber. The system was vented transiently to allow the child to reach functional residual capacity at atmospheric pressure. The vent was then closed and the measurement of impedance and resistance made by forced oscillation. Studies were made in 2-Hz increments generally between 4 and 40 Hz limits. Total time of ventilator disconnection was ≦30 s. The patient was reconnected to the ventilator and the study repeated after the child returned to base-line transcutaneous oxygen tension. Endotracheal tubes of equal length and internal diameter to those used in ventilating four of the six infants were studied separately. The endotracheal tube impedance and resistance were then subtracted from the impedance and resistance of the intubated subject to yield results for the respiratory system alone.

RESULTS

In vitro measurements. Results for the two endotracheal tubes were similar, as were the results from individual bottles and bottle-endotracheal tube combinations. Therefore, we present results for only one endotracheal tube (3.0-mm i.d.) and one bottle (0.5 liter). The impedance and resistance for a single measurement with the 3.0-mm endotracheal tube are plotted vs. frequency (Fig. 2). At low frequencies, the impedance is predominantly resistive, but at higher frequencies the major portion of impedance is inertive. For the endotracheal tube and bottle coupled together, the impedance displays compliancelike behavior at low frequencies, falling with increasing frequency (Fig. 3). Impedance reaches a minimum at the resonant frequency (13 Hz) and thereafter displays inertancelike behavior, rising with increasing frequency. Resistance increases slightly with frequency.

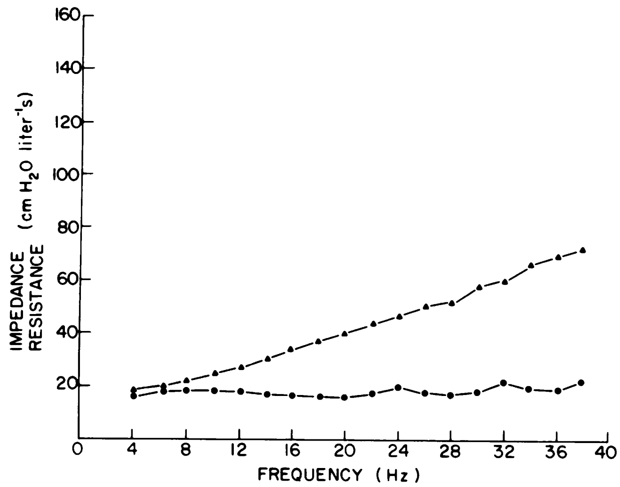

FIGURE 2 Oscillatory impedance (▲) and resistance (●) as a function of frequency for a single measurement using the 3.0-mm i.d. endotracheal tube.

The impedance and resistance for the endotracheal tube and bottle coupled together were well approximated by the sum of the impedances of the endotracheal tube and the bottle measured individually (Fig. 3). The results were similar for all bottle and endotracheal tube combinations. Therefore, for the pressures and flow amplitudes used in this study, it was considered valid to subtract the impedance and resis-

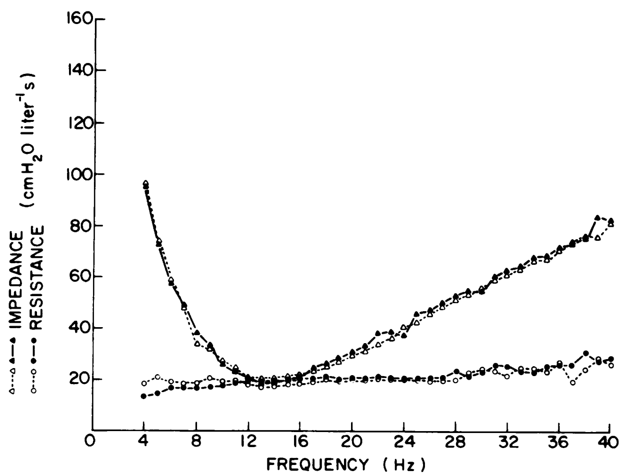

FIGURE 3 Oscillatory impedance and resistance as a function of frequency for a single measurement using the 3.0-mm i.d. endotracheal tube and the 0.5-liter bottle. Solid line represents a measurement of the endotracheal tube and bottle combination. The dashed line represents a measurement of each separately and the results summed as vectors.

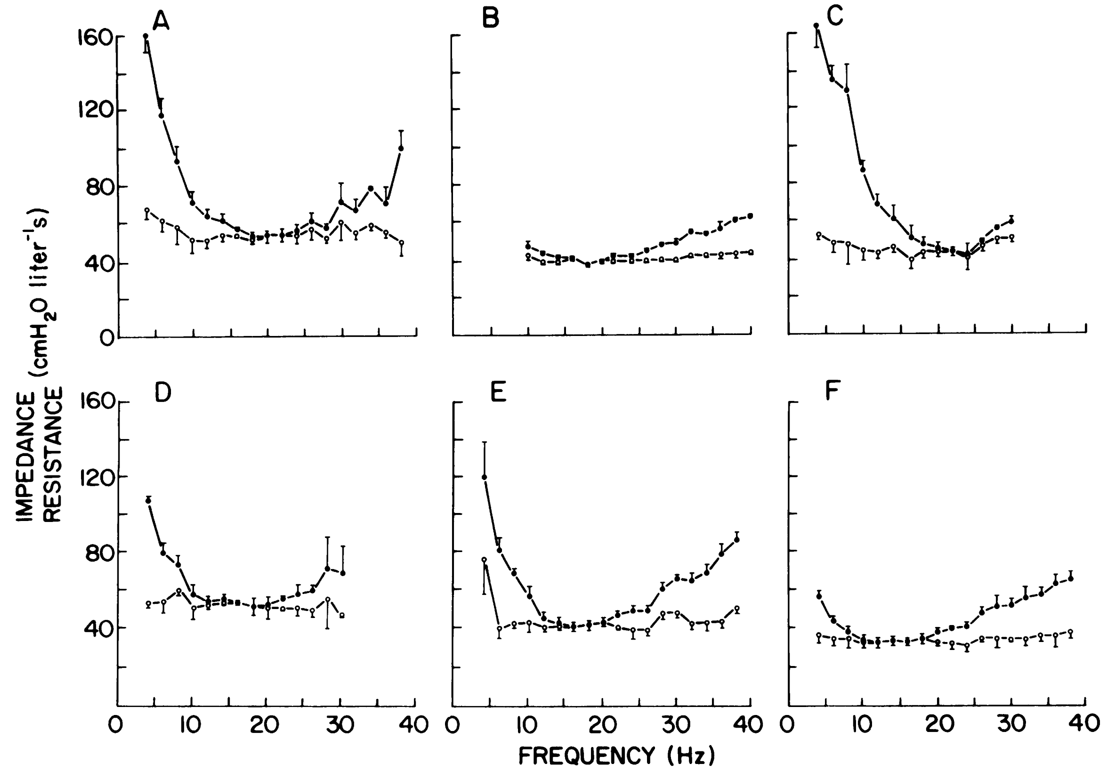

FIGURE 4 Oscillatory impedance (●) and resistance (O) as a function of frequency for six intubated infants with respiratory disease. Results are expressed as mean±1 SD. Letter identification corresponds to that of Table I.

tance of the endotracheal tubes from the measurements of the intubated infant to determine the impedance and resistance of the respiratory system alone.

In vivo measurements. Two to four sets of data were obtained on each infant. Transcutaneous oxygen tension decreased no more than 10–12 torr during each study, then returned promptly to base line. Measurements < 10 Hz were not obtained in one infant.

Impedance and resistance of the intubated respiratory system are plotted vs. frequency for each infant (Fig. 4). Like the studies in vitro, the impedance of the intubated infant displays compliancelike behavior

TABLE II
Mechanical Characteristics of the Neonatal Respiratory System

Subject	Resonant frequency		Resistance at resonance	Parameter estimates					
				Resistance		Compliance		Inertance	
	Intubated	Unintubated*	Intubated	Intubated	Unintubated	Intubated	Unintubated	Intubated	Unintubated
	Hz		*cm H_2O liter^{-1} s*	*cm H_2O liter^{-1} s*		*ml/cmH_2O*		*cm H_2O liter^{-1} s^2*	
A	20	143	53	54	34	0.23	0.22	0.28	0.0056
B	17	60	38	40	29	0.39	0.39	0.216	0.018
C	23	—	40	46	—	0.17	—	0.289	—
D	16	—	53	51	—	0.35	—	0.307	—
E	17	44	41	42	33	0.28	0.28	0.335	0.047
F	13	36	33	34	22	0.69	0.68	0.246	0.028

* Inferred resonance based on parameter estimates.

below the resonant frequency and inertancelike behavior above the resonant frequency. Resistance was largely frequency invariant with the exception of the range below 10 Hz. For six infants, resonant frequency ranges from 13 to 23 Hz and resistance at resonance ranges from 33 to 53 cmH_2O $liter^{-1}$ s. The range of compliance is from 0.17 to 0.68 ml/cmH_2O and the range of inertance is from 0.216 to 0.335 cmH_2O $liter^{-1}$ s^2 (Table II).

Impedance and resistance of the respiratory system after subtraction of the endotracheal tube contribution are plotted vs. frequency (Fig. 5) for the four infants where the endotracheal tube data were obtained. Resonant frequency is higher than in the intubated respiratory system and, in three of four cases, lies beyond the range of frequencies studied (Table II). A resonant frequency could be inferred nonetheless by the parameters estimates (Table II). Compared to results before subtraction of the endotracheal tube contribution, there is little change in compliance but resistance falls by 30–50% and inertance by 80–90% (Table II).

DISCUSSION

Mechanics of the respiratory system in diseased infants. Using a speaker plethysmograph we have determined the respiratory system mechanical characteristics between 4 and 40 Hz in endotracheally intubated infants with RDS, three of whom also had PIE. We have shown that the oscillatory properties of the endotracheal tube may be subtracted from the measurements of the intubated subject to determine the mechanical characteristics of the respiratory system alone.

To a reasonable approximation, our data in vitro and in vivo (both before and after subtraction of the endotracheal tube contribution) fit the series L-R-C model. For the intubated infants, a resonant frequency is observed below which elastic behavior is dominant (Z falls with increasing frequency) and above which inertial behavior is dominant (Z rises with increasing frequency). We observed a small, reproducible increase in resistance as a function of frequency, which is not accounted for by a simple L-R-C model. Possible

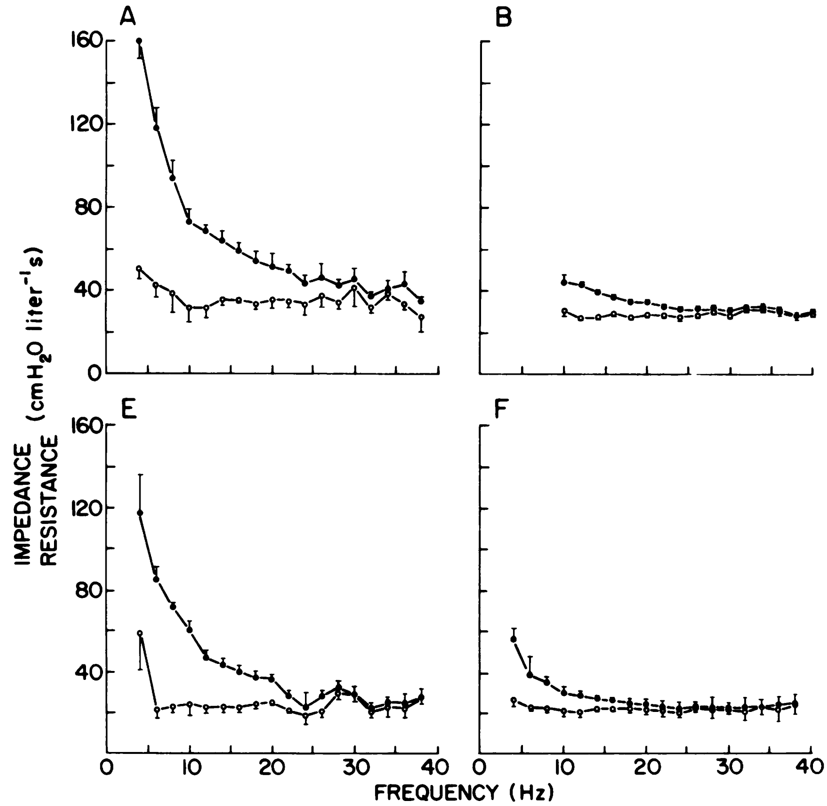

FIGURE 5 Oscillatory impedance (●) and resistance (O) as a function of frequency for four infants after subtraction of the effects of the endotracheal tube. Results are expressed as the mean±1 SD. Letter identification corresponds to that of Table I.

explanations for this frequency dependence of resistance include velocity profile distortions, inhomogeneous parallel pathways, and airway wall compliance (11, 12). We also observed that the infants, in contrast to the endotracheal tube and bottle combination, demonstrated a higher resistance and broader impedance minimum at the resonant frequency. The cause for this is the higher intrinsic resistance of the infant as compared with that of the bottle (Eq. 1).

Finally, our in vitro results suggest the validity of partitioning impedance and resistance between the endotracheal tube and infant. When the impedance of the endotracheal tube was subtracted from the values measured for the intubated infant, the data exhibited compliant and resistive behavior with little inertance. The decrease in inertance causes the resonant frequency to rise substantially (Eq. 2 and Table II). Indeed, no resonant frequency was directly observed within the frequency range studied, although a resonant frequency of the unintubated respiratory system could be inferred from inertance and compliance values using Eq. 2 (Table II).

We found no comparable studies that address the oscillatory mechanical properties at high frequencies for the respiratory system in sick infants. Wohl et al. (13) studied 27 healthy infants in the first week of life and measured oscillatory resistance of the respiratory system between 3 and 7 Hz. They found resonance for most of the infants to be between 3 and 5 Hz, with no frequency dependence of resistance in this narrow band. Respiratory system resistance was 69±25 cmH_2O $liter^{-1}$ s (mean±SD) on inspiration and 97±52 cmH_2O $liter^{-1}$ s on expiration. These subjects, however, were unintubated and larger than ours. Even after subtracting the endotracheal tube and adding a correction for nasal resistance (14), glottal variations alone would still make comparison difficult.

Respiratory mechanics have been studied in infants with RDS but these measurements were of pulmonary (not total respiratory system) resistance and compliance at breathing frequencies below our range of measurement. Cook et al. (1) studied two infants breathing 40–50 breaths/min. They found the mean resistance to be 25 cmH_2O $liter^{-1}$ s in one and 41 cmH_2O $liter^{-1}$ s in the other while mean compliances were 0.7 ml/cmH_2O and 2.5 ml/cmH_2O, respectively. Hjalmarson (15) reported on serial measurements in 18 infants with RDS. Maximum resistance during the first week of life ranged from 30 to 125 cmH_2O $liter^{-1}$ s. Although these patients were more comparable to ours in both size and degree of parenchymal disease, the contribution of the glottis to the resistance cannot be estimated.

In RDS, the lungs are less compliant as a result of surfactant insufficiency (16). There may be a small degree of airway narrowing secondary to interstitial edema but the effect on airway resistance and inertance is much smaller than that of surfactant deficiency on compliance. Since compliance is decreased in RDS, we would expect the resonant frequency of the respiratory system to be higher than in normal subjects. Our results demonstrate that a clear resonance is not achieved below 40 Hz. This is in contrast to the range of resonant frequency, 3 to 5 Hz, found by Wohl et al. (13) in healthy subjects. As expected from Eq. 2, additional inertance in the form of the endotracheal tube should lower the resonant frequency (Fig. 4).

Measurement uncertainty. Possible sources of uncertainty in our study must be considered. While measuring oscillatory properties in straight tubes and an airway cast, Dorkin et al. (11) maintained constant flow amplitude from the loudspeaker at each frequency by means of a feedback loop in the computer program. This was done to avoid flow-dependent changes in oscillatory resistance. We were unable to use this approach here because it would require the subject to remain unventilated for an excessively long time.

Dynamic head loss resulting from step changes in cross-sectional area at the distal tip of the endotracheal tube could contribute to overestimation of the input pressure. One would expect, however, that this would be minimal at the pressures and flows developed in our study. Indeed, calculated dynamic head loss was found to be 3–5% of the measured resistive pressure drop, in the worst possible case using the highest pressure and lowest impedance attained in the study.

Uncuffed endotracheal tubes are used in infants, usually placed 2 cm above the carina. Leakage could have occurred between the endotracheal tube and the tracheal wall. The inertance of such a pathway should be considerable, even at the lowest frequency studied (4 Hz), and accordingly leakage would be minimal.

Of more concern is the effect of the endotracheal tube placement on the inertance calculated for the unintubated subject. When the endotracheal tube contribution to impedance is subtracted, the remainder includes only that portion of the trachea and respiratory system distal to the endotracheal tube. As much of the respiratory system inertance resides in the trachea, we may be underestimating the total inertance of the unintubated infant respiratory system. This may explain the relatively low inertance in subject A and his high predicted resonant frequency (Table II). Furthermore, since the inertance of the endotracheal tube itself is considerably larger than that of the respiratory system, small errors in inertance measurement for either the endotracheal tube or the intubated patient would have a large effect on the calculated inertance for the unintubated subject. This problem is less severe in computation of the unintubated infant's compliance or resistance because in either case the value for the infant alone is much greater than for the endotracheal tube contribution. The resonant frequency calculated after the subtraction of the endotracheal tube must therefore be interpreted with caution.

Our method of measurement precluded the presence of the 5–6 cmH_2O positive end-expiratory pressure used in ventilating these patients. Such end-expiratory pressure would maintain the infant at a lung volume higher than that maintained during our impedance measurements. Airway cross-sectional area may have been smaller during impedance measurement than during ventilation. Resistance is inversely proportional to the fourth power of the airway radius and inertance is inversely proportional to the second power of the airway radius. Therefore, resistance, and to a lesser degree inertance, might have been slightly lower had the higher lung volume been maintained during impedance measurement.

Relevance to HFV. To limit barotrauma during HFV it would be advantageous to choose ventilator settings with which the smallest possible peak pressure differences would be applied across airway walls and across lung tissue. The impedance of the intubated respiratory system represents the pressure amplitude per unit ventilation (flow) at the proximal end of the endotracheal tube. The impedance of the respiratory system after subtraction of the endotracheal tube impedance represents the pressure amplitude per unit ventilation in the trachea distal to the endotracheal tube, which may be more relevant to production of airway barotrauma. We infer from the data in Fig. 5 that the pressure amplitude in the trachea (relative to atmosphere) would fall with increasing frequency until at least 40 Hz, if tidal volume and ventilatory frequency were adjusted such that oscillatory flow amplitude in the trachea remained constant. If CO_2 elimination were proportional to tracheal flow in these infants, as has been shown in normal dogs (17) and adult humans (18), there may be some advantage in ventilating at frequencies at least as high as 40 Hz. The relationship of tracheal pressure amplitude to pressure across small airways and alveolar units is not yet known but may also be relevant to selection of frequencies for HFV.

Marchak et al. (5) studied eight infants with RDS and ventilated them between 7 and 20 Hz. Because the piston pump tidal volume and therefore the oscillatory volume of their system varied as a function of frequency and endotracheal tube resistance, no attempt was made to correlate optimal oxygenation with frequency. Frantz et al. (6) ventilated 10 patients with RDS and 5 with PIE at a mean frequency of 10 Hz. Although a different ventilator system was used, similar output changes as a function of ventilator frequency were noted. If gas exchange is adequately maintained, it would appear from our results that the potential for barotrauma in these patients might be diminished at higher ventilation frequencies.

In summary, we have measured the oscillatory impedance and resistance of infants with severe respiratory disease to determine the frequency-dependent characteristics of the intubated respiratory system. Further, we have shown in vitro that the impedance may be partitioned between the endotracheal tube and the subject, allowing determination of oscillatory properties in the subglottal respiratory system alone. With the contribution of the endotracheal tube subtracted, it appears that the pressure cost of flow decreases throughout the range of frequencies studied. We hypothesize from these data that higher ventilatory frequencies may offer some protection from barotrauma if the product of frequency and tidal volume remains fixed and gas exchange is adequate.

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