0031-3998/91/2901-082$03.00/0
PEDIATRIC RESEARCH

Vol. 29, No. 1, 1991
Printed in U.S.A.

A Forced Perturbation Method of Assessing Pulmonary Mechanical Function in Intubated Infants

KEVIN J. SULLIVAN, MANUEL DURAND, AND H. K. CHANG

Departments of Biomedical Engineering and Pediatrics, University of Southern California and the Division of Neonatal-Perinatal Medicine, Los Angeles County-USC Medical Center, Los Angeles, California 90089-1451

ABSTRACT. Short pulses in airway pressure were used to assess the pulmonary mechanical function of nine infants suffering acute respiratory distress syndrome or bronchopulmonary dysplasia. All patients were intubated, spontaneously breathing, and mechanically ventilated at the time they were examined. The endotracheal tube was disconnected from the ventilator and connected to a mechanical oscillator that produced brief pulses in airway pressure at a rate of two pulses/s. These pulses were applied to the infants airway for 20–30 s, at which time the infant was replaced on the ventilator. The mean airway pressure during the procedure was maintained at the level of the positive and expiratory pressure that was set on the ventilator. Two classes of patients were identified from the pulse response primarily by the presence or absence of a local resonance in the impedance spectra. Similar results were obtained in five other patients who were examined with zero mean airway pressure, suggesting that the pulse response is little influenced by changes in mean lung volume or total lung compliance. Patient classification appeared related to the duration of ventilation therapy and the transition from one class to another was consistent with the development of high peripheral airway resistance and significant volume shunting in the central airways. These results suggest that brief pulses in airway pressure can be used to detect changes in the pulmonary mechanical function of preterm infants that result from long-term ventilation therapy. (*Pediatr Res* 29: 82–88, 1991)

Abbreviations

BPD, bronchopulmonary dysplasia
PEEP, positive end expiratory pressure
C_{in}, inspiratory compliance of the respiratory system
R_{in}, inspiratory resistance of the respiratory system

Assisted mechanical ventilation has formed the basic therapy for infantile respiratory distress syndrome for nearly 30 years (1), and is largely responsible for the dramatic reduction in the mortality rate of prematurely born neonates (2). Prolonged ventilation therapy in these patients, however, often leads to BPD, which is characterized by a variety of pathologic changes in the lungs that are similar to those found in other forms of severe acute lung injury (2, 3). BPD and ventilation therapy not only retard the recovery and maturation of the lungs, but are implicated in the development of chronic lung disorders that persist throughout the individual's childhood and possibly throughout his entire lifetime (1, 4). For these reasons, the prevention of lung injury has become a predominant health care problem in the neonatal intensive care unit.

To reduce the duration or intensity of ventilation therapy and its damaging effects on the lungs, neonatologists have examined alternative therapies such as the use of exogenous surfactants (5) and high-frequency ventilation (6) and have renewed interest in the diagnostic value of pulmonary function tests in neonates and infants (7, 8). It is widely believed that the information provided by such tests can be used not only to aid in the treatment of lung disorders but also to develop strategies of mechanical ventilation that will reduce chronic ventilator dependence and lung damage. The establishment of a routine test of pulmonary function is also recognized as an important step toward identifying the mechanisms that link mechanical function, gas exchange, and lung development in these patients.

Despite the potential advantages of a routine test of pulmonary function, there is no generally accepted method of obtaining data from neonates and infants. The lack of a standard method is due in large part to a number of imposing constraints that are unique to this group of patients. Among these is the fact that the neonate or infant is uncooperative and the test maneuver must be superimposed upon spontaneous breathing or during a cycle of mechanical ventilation. This may result in a test response that is complicated by variations in the breathing pattern or in the parameters of mechanical ventilation (9). Another constraint involves the measurement of driving pressure. The measurement of esophageal pressure is often not practical in these patients because the placement and calibration of the esophageal catheter greatly increases the time required to perform the test and because the measurement itself is subject to error (10). On the other hand, noninvasive tests that do not require esophageal catheters but rely instead upon measurements of airway (*i.e.* transthoracic) pressure can be affected by changes in the activity of the respiratory muscles with sleep state, respiratory drive, and body position. Finally, for a method to be useful, it must be reliable and easy to implement.

Recently, we examined the use of short pulses of airflow to determine pulmonary mechanical function in rabbits (11). The short duration of these pulses and the noninvasive nature of the measurements led us to consider the pulse method as a way of evaluating pulmonary mechanical function in intubated infants. Unlike other noninvasive methods that rely upon the mechanical ventilator or spontaneous breath to perform the test, the externally applied pulse is independent of the mechanical ventilator or breathing pattern. This feature of the pulse method reduces the influence of ventilation parameters on the test response and forms a basis for comparing the results from different patients. In this report, we present the results of a pilot study in which the pulmonary mechanical function of premature neonates and in-

Received March 26, 1990; accepted August 22, 1990.
Correspondence: Kevin J. Sullivan, Dept. of Biomedical Engineering, University of Southern California, University Park, Los Angeles, CA 90089-1451.

fants was determined from their responses to a free-running pulse train.

MATERIALS AND METHODS

Apparatus and transducers. Figure 1 illustrates the basic components of the apparatus. Pulses generated with a waveform generator were amplified with a power amplifier and used to drive a subwoofer type loudspeaker. A length of flexible but noncompliant tubing (inner diameter 2.5 cm) connected a pneumotachograph with the speaker enclosure and enabled the pneumotachograph to be placed close to the infant. For measurements obtained with zero (*i.e.* atmospheric) mean airway pressure, the speaker enclosure was vented to the atmosphere through two small-bore holes. These openings maintained the mean pressure within the enclosure near atmospheric pressure during the pulse and provided a low-impedance pathway for the spontaneous breathing of the infant. The impedance of the apparatus to the spontaneous flows generated by the patient was 1.5 kPa·L^{-1}·s or roughly equal to one half of the impedance of a standard 3.5-mm inner diameter neonatal endotracheal tube. For measurements obtained with a positive mean airway pressure, the speaker enclosure was pressurized by connecting it to an adjustable source of pressurized air. To maintain the pressure level, the impedance of the enclosure was roughly doubled. The low impedance of the enclosure also limited the amplitude of the pulse pressure to a maximum value of 1.2 kPa. In all subjects, the peak pressure generated by the loudspeaker was considerably less than the peak

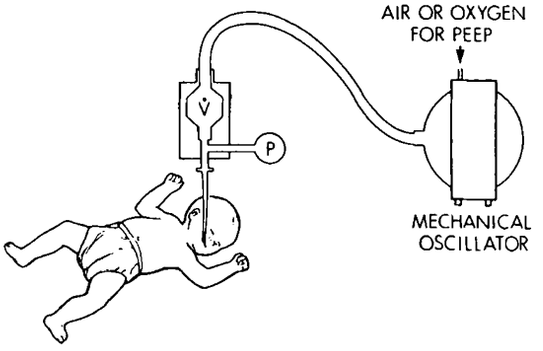

Fig. 1. The basic features of the apparatus. *P*, pressure sensing transducer; V̇, pneumotachograph. See Materials and Methods for details.

Table 1. *Vital statistics of sampled patients**

Patient	Wt (kg)	Gest (wk)	Age (d)	FiO_2	P_aO_2 (kPa)	Diagnosis
Group 1						
1	2.30	34	0.5	0.75	8.67	IRDS
2	2.24	34	0.5	0.30	9.07	IRDS
3	2.23	33	3	0.30	10.67	IRDS
4	2.78	34	4	0.40	11.12	IRDS
5	1.35	29	6	0.80	9.07	IRDS
6	0.98	29	8	0.40	9.20	IRDS
7	1.21	29	10	0.40	8.40	IRDS
8	1.42	29	22	0.55	7.33	BPD
9	0.82	29	61	0.35	6.67	BPD
Group 2						
10	1.85	32	1	0.35	9.33	IRDS
11	1.80	31	5	0.50	12.93	IRDS
12	3.30	38	5	0.80	9.20	MAS, PFC
13	2.20	32	8	0.21	9.33	IRDS
14	1.42	29	17	0.55	7.33	BPD

* Gest, gestational age; FiO_2, fractional content of oxygen in the inspired gas; P_aO_2 arterial oxygen tension (1 kPa = 7.5 mm Hg); IRDS, infantile respiratory distress syndrome; MAS, meconium aspiration syndrome; PFC, persistent fetal circulation.

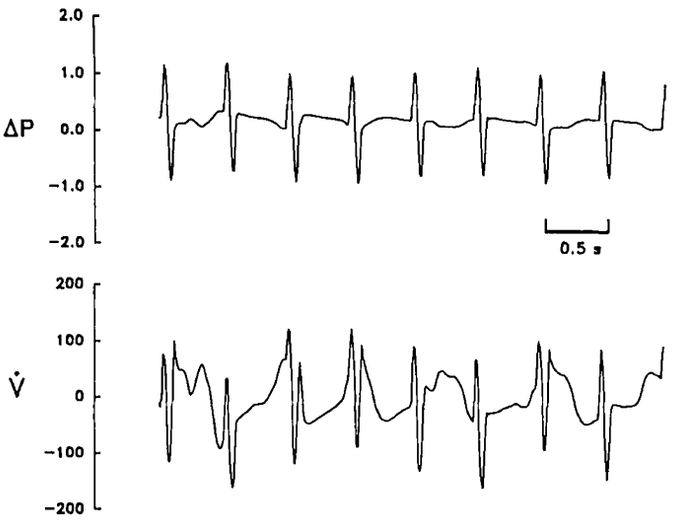

Fig. 2. Tracings of the flow and airway pressure obtained from one patient. ΔP is the change in airway pressure in kPa; V̇ is the airflow in mL·s^{-1}. The superimposition of the pulse on spontaneous breathing is evident in the flow trace but less so in the airway pressure trace due to the low impedance of the speaker enclosure. The mean airway pressure in this example is ~0.2 kPa.

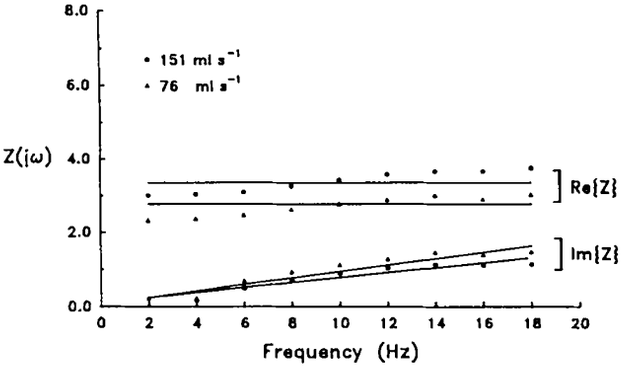

Fig. 3. The impedance of a neonatal endotracheal tube (inner diameter 3.5 mm) determined using a continuous train of pulses. *Re*{*Z*} denotes the real part of the impedance; *Im*{*Z*} denotes the imaginary part of the impedance. The solid lines illustrate the fit of a model composed of a single resistance and inertance components. Units of impedance are kPa·L^{-1}·s.

inspiratory pressures produced by the ventilator.

Airway pressure was measured with a piezoresistive pressure transducer that has a flat frequency response up to 200 Hz. (140PC; Micro Switch, Freeport, IL). The transducer was attached directly to a smooth tube connecting the pneumotachograph with the endotracheal tube. Airflow was measured with a pneumotachograph coupled to a matching transducer through short lengths (<5 cm) of stiff tubing. The output of the pneumotachograph for steady flows was linear up to 180 mL·s^{-1} and the common mode rejection ratio of the combination of pneumotachograph and transducer was greater than 40 dB at 20 Hz. The dynamic response of the pneumotachograph was determined using the plethysmographic technique in which the time-integrated signal from the pneumotachograph was compared with the actual gas volume displaced into a constant-volume plethysmograph. Between 2 and 20 Hz, the magnitude of the pneumotachograph signal decreased by 20% and the phase lag increased by about 16 degrees. The flow signal was corrected for the dynamic response characteristics of the pneumotachograph by a method described elsewhere (12).

Protocol. Parental consent and patient selection conformed to the rules and guidelines as outlined by the Institutional Review

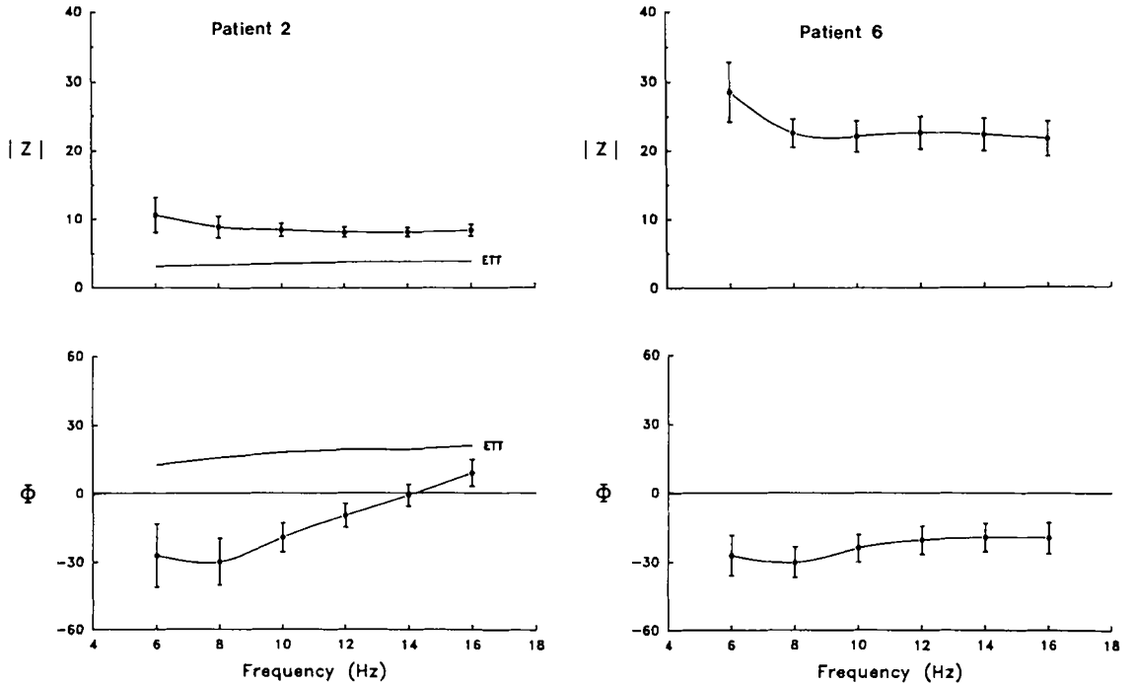

Fig. 4. Examples of the impedance modulus | Z | (*top*) and phase (*bottom*) for patient 2 (*left*) and patient 6 (*right*) from group 1. *Bars* represent the 95% confidence intervals. Units of the impedance modulus are kPa·L^{-1}·s and units of the phase are degrees.

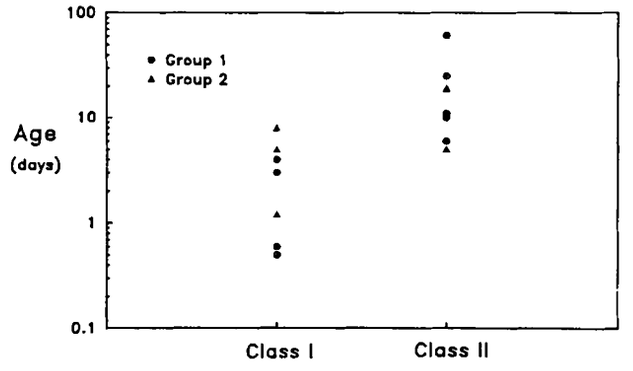

Fig. 5. The relationship between age and the impedance classifications for both groups of patients.

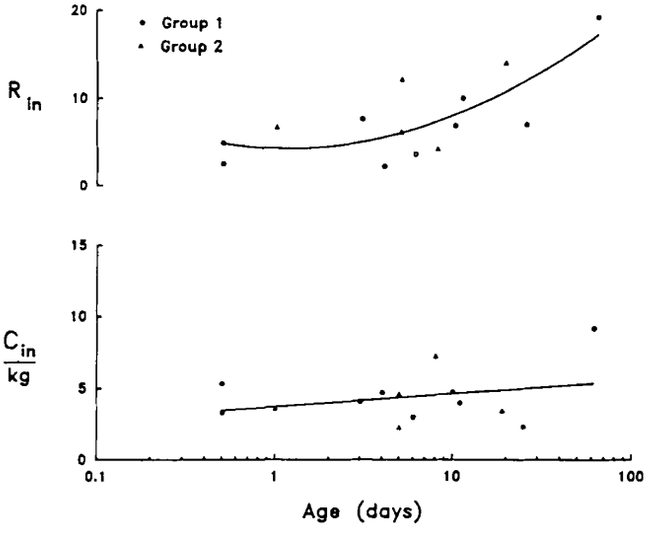

Fig. 6. R_{in} and C_{in} normalized per kg of body weight obtained with conventional analysis for both groups of patients. *Solid lines* illustrate the best-fit linear (for C_{in}) or quadratic (for R_{in}) regression of the measured parameter on log(age). Units of R_{in} are kPa·L^{-1}·s and the units of normalized C_{in} are mL·kPa^{-1}·kg.

Board of the Los Angeles County Women's Hospital. All of the patients were admitted to the intensive care unit within hours of delivery and were intubated and receiving conventional mechanical ventilation at the time they were studied. The patients were divided into two groups, the first of which (group 1) consisted of patients who were examined with a mean airway pressure equal to the level of PEEP that was set on the ventilator. The second group (group 2) consisted of patients who were examined with zero mean airway pressure, regardless of the therapeutic PEEP level. The vital statistics for each group are given in Table 1. Of the 15 patients originally selected, 10 were suffering from acute respiratory distress syndrome, four were diagnosed with BPD, and one presented with a moderate meconium aspiration. The data from one patient who was suffering from BPD was discarded because only very low peak flows (<20 mL·s^{-1}) could be generated in the presence of an extremely high pulmonary resistance. These low-magnitude flows resulted in a poor signal-to-noise ratio that prevented further analysis of the pulse response in this patient.

Each patient was examined while supine and breathing spontaneously and while the vital signs, including blood pressure, oxygen tension, and pulse rate, were stable. Water and mucus secretions that normally accumulate in the endotracheal tube and trachea were removed by suction aspiration shortly before the patient was examined. For a single trial measurement, the infant was disconnected from the ventilator and quickly connected to the pneumotachograph and a continuous train of pulses was applied to the airways for 20 to 30 s after which the infant was replaced on the ventilator (Fig. 2). In most trials, the patient was replaced on the ventilator within 30 s. The protocol was repeated two to four times on each patient, with intervals of resumed mechanical ventilation between trials. Transcutaneous P_{O_2} tension and pulse oximeter oxygen saturation were monitored throughout the procedure and the duration of the trial maneuver was shortened, if necessary, to maintain oxygenation within accepted norms for these patients. These precautions,

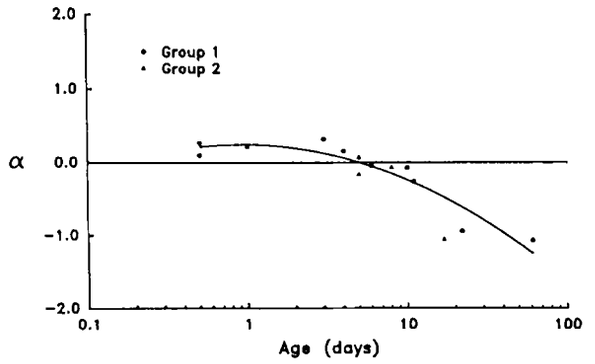

Fig. 7. Relationship between α and age in patients from both groups of patients. *Solid lines* illustrate the best-fit quadratic regression of α on log(age).

Table 2. *Parameter estimates from impedance data**

Group 1		Group 2	
Patient	α	Patient	α
1	0.26	10	0.23
2	0.10	11	−0.16
3	0.32	12	0.07†
4	0.16	13	−0.07†
5	−0.05†	14	−1.06
6	−0.26		
7	−0.07†		
8	−0.94		
9	−1.07		

* Values of the regression coefficient α for each patient. Units of α are $kPa \cdot L^{-1} \cdot s^2$ (1 kPa = 10.2 cm H_2O).

† Values of α that are not significantly different from zero ($p < 0.05$).

Table 3. *Comparisons of lung function indices between two classes of patient**

	Class I	p	Class II
C_{in}	4.28	NS	4.59
	(0.92)		(2.75)
R_{in}	4.31	NS	9.32
	(2.55)		(5.98)
α	0.21	<0.05	−0.48
	(0.10)		(0.49)

* Mean values of C_{in}, R_{in}, and α for two classes of patients from group 1. Numbers in parentheses represent 1 SD. Units: C_{in}, $mL \cdot kPa^{-1} \cdot kg$; R_{in}, $kPa \cdot L^{-1} \cdot s$; α, $kPa \cdot L^{-1} \cdot s^2$.

together with the absence of any adverse reactions to the procedure, suggest that the patients were exposed to no more risk than is normally associated with the routine management of ventilation therapy.

Signal processing and analysis. The amplified signals from the pressure and flow transducers were low-pass filtered using identical eight-pole Bessel type filters (902LPF1; Frequency Devices, Haverhill, MA) set at a cutoff frequency of 50 Hz, and subsequently sampled by a microcomputer (AST Premium 286; AST, Irvine, CA) at a rate of 100 Hz. Transient responses were eliminated by discarding several pulses from the beginning of each trial. The digitized data were high-pass filtered using a finite impulse response type filter with a sharp cutoff at 4.5 Hz to remove the low-frequency components produced by the patient's spontaneous breathing (13). The cutoff frequency of the filter was determined on the basis of preliminary observations that the flow patterns produced by these patients contain harmonics up to about 10 Hz with most of the energy being found in harmonics less than 4 Hz. Flow pulses with amplitudes that varied less than 10 $mL \cdot s^{-1}$ were selected from the filtered pulse train for analysis.

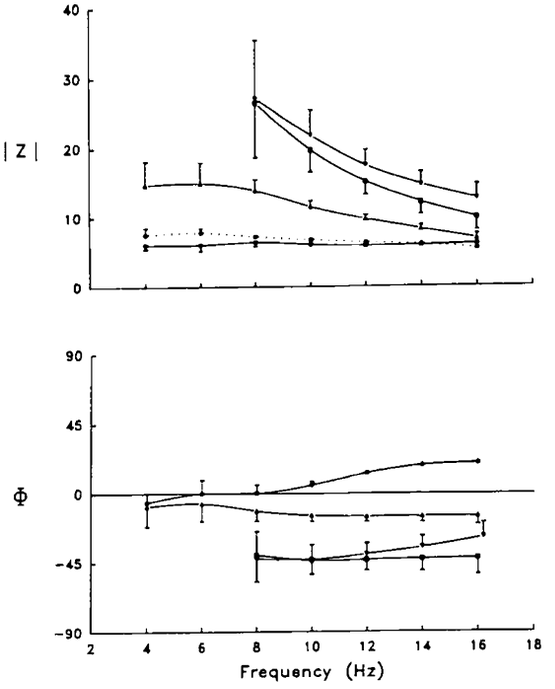

Fig. 8. Effect of peripheral airway resistance and lung volume on the impedance of the respiratory system in a paralyzed adult rabbit. *Circles* represent control measurements; *triangles*, the response to nebulized histamine; *squares*, the response to histamine and decreased lung volume; *inverted triangles*, the impedance of the intrathoracic trachea and main bronchi *in situ*. Data at 6 Hz are not plotted for the two latter measurements due to the lack of acceptable coherence at this frequency. The *dotted line* illustrates the return to control of the impedance modulus after the *in vivo* manipulations.

This procedure eliminated those pulses that were grossly distorted by the spontaneous breathing of the patient and tended to improve the correlation between signals in a manner that is comparable to procedures used by others (14). To identify the pulses, a histogram of the flow amplitudes were constructed from the combined trials of each patient and the pulses were selected from within the range of the most frequently occurring flow amplitude. Selected pulses were extracted from the data in 50-point segments (t = 0.5 s) that were increased in length to 64 by zero padding to obtain a bandwidth resolution of 1.56 Hz. The average impedance spectra, coherence, and confidence intervals were computed according to Michaelson *et al.* (13).

The pulse train consisted of a single 10-Hz sinusoidal waveform repeated at 2-Hz intervals. The power spectrum of this waveform is composed of several harmonics at 2-Hz intervals between 2 and 30 Hz with a maximum power density between 6 and 10 Hz. In all of the patients, the coherence obtained for unfiltered signals tended to decrease below the accepted level (0.8) for frequencies below 6 Hz due to the uncorrelated flow produced by the infants breathing and above 16 Hz due to the low signal energy in the harmonics at these frequencies (15, 16). Consequently, only those frequencies between 6 and 16 Hz were used in the determination of the impedance spectra.

Conventional measurements of compliance and resistance. The C_{in} and R_{in} were obtained during conventional mechanical ventilation with a commercially available pulmonary function computer (PeDS, Medical Associated Services, Hatfield, PA). For these measurements, a pneumotachograph and airway pressure and transducer were inserted between the endotracheal tube and ventilator circuit; they measured the respiratory pressure and flow waveforms produced by the action of the mechanical ventilator. Spontaneous breaths were discarded. The ventilator settings were not adjusted to perform this test and all patients were tested at the level of PEEP that was set on the ventilator.

Estimates of C_{in} and R_{in} were obtained from the inspiratory portion of several ventilator cycles by the least squares minimization (17) of the difference between the data and the lung model;

$$P(t) = \frac{V(t)}{C_{in}} + R_{in} \cdot \dot{V}(t) \quad (1)$$

where P(t) is the airway pressure, V(t) is the tidal volume, and $\dot{V}(t)$ is the flow.

Endotracheal tube impedance. The endotracheal tube contributes to the measurements of pulmonary mechanical function and airflow resistance in intubated patients primarily through: *1*) energy loss related to variations in the kinetic energy of the flow stream that occurs at abrupt changes in airway cross-section and *2*) frictional losses within the tube to steady and oscillating airflows. Experimental (18) and theoretical analysis (19) of these phenomena suggests that the component due to kinetic energy variation is likely small in comparison to the overall tube resistance and may be neglected.

The frictional losses within the endotracheal tube are not constant but vary with both the flow rate and oscillation frequency. To examine the effect of these factors on the tube resistance, the impedance of a standard neonatal endotracheal tube (inner diameter 3.5 mm) was determined in isolation for pulse flows that span the linear range of the pneumotachograph. The results are shown in Figure 3. The impedance of the endotracheal tube resembles that of a linear resistance-inductance system with the exception that it varies with the flow amplitude. The amplitude dependence is rather small, however, inasmuch as doubling the peak flow amplitude resulted in an increase in the effective resistance of the tube by less than 25%. Consequently, the impedance of the tube may be considered constant for the small variations in peak flow (*i.e.* ± 5 mL·s^{-1}) of the pulses selected from each patient.

RESULTS

Figure 4 shows the impedance spectra from two representative patients measured with PEEP (group 1). Note that these impedance spectra can be distinguishing by the presence or absence of a local resonance phenomenon (*i.e.* zero crossing of phase) between 6 and 16 Hz and by the differences in magnitude of the modulus. The modulus of the isolated 3.5-mm inner diameter endotracheal tube is less than half of the total modulus in both patients, suggesting that the mechanical impedance of the respiratory system predominates in pulse response. Using the resonance phenomenon as a reference, the patients from both groups were separated into two classes, where class I represents those patients who exhibited a local resonance and class II represents those patients who did not exhibit local resonance in the respiratory impedance. In either case, a local resonance was defined as a zero crossing in phase that occurs within the 95% confidence limits of the phase spectra. Figure 5 shows the relationship between patient classification and age for both groups. A distinct transition between patient classification appears to occur around 5–6 d in group 1 and, to a lesser extent, in group 2, suggesting that the transition is unaffected by the presence or absence of positive mean airway pressure.

The results of the conventional analysis of pulmonary function for all 14 patients are shown in Figure 6. R_{in} tends to increase with increasing age only after several days of ventilation therapy at which time it begins to increase rapidly with age. The trend for C_{in} normalized per unit of body weight is less well defined, but the slope of the regression curve is significant ($p < 0.05$) and indicates the tendency of C_{in} to increase with age. Over the range in age of these patients, C_{in} roughly doubles but R_{in} increases about 3- to 4-fold. Neither compliance nor resistance obtained by the conventional method show evidence of the abrupt changes at 5–6 days that are demonstrated in the impedance spectra.

The larger change in R_{in} than in C_{in} among these patients suggests that the pressure-flow relations of the respiratory system may be more sensitive than the pressure-volume relations to variations in lung function. The real part (Re{Z}) of the impedance, where $Re\{Z\} = |Z| \cdot \cos\phi$, is the in-phase component of pulse response and thus represents a measure of apparent resistance of the respiratory system. This component of the impedance was examined further to determine its relationship with patient age and duration of ventilation therapy.

In most patients, Re{Z} was found to vary with frequency. The magnitude of frequency dependence was determined by linear least squares regression of the model $y = \beta + \alpha \cdot f$ onto spectrum of Re{Z}, where β is the intercept, α is the slope, and f is the forcing frequency. The slope α, thus defines the magnitude of frequency dependence in Re{Z}. Computed values of α are presented in Table 2. Of the 14 patients who were examined, five had significant ($p < 0.05$) positive frequency dependence, four exhibited no frequency dependence, and five exhibited negative frequency dependence. Values of α are plotted against age in Figure 7 to illustrate the relationship between frequency dependence in the apparent resistance of the respiratory system and the duration of ventilation therapy. The crossover point from positive to negative frequency dependence occurs between 5 and 10 d or roughly at the same age as disappearance of the local resonance (Fig. 5).

Table 3 compares mean values of α, C_{in}, and R_{in} of group 1 patients separated according to impedance classification. Neither C_{in} or R_{in} differed among classes in contrast to α, which was significantly different.

DISCUSSION

The pulse responses of intubated neonates and infants have revealed two classes of patients that are distinguished by differences in the mechanical impedance of the respiratory system. These classes appear related to the age of the patient, suggesting that the pulse response may detect changes in pulmonary mechanical function associated with long-term ventilation therapy and the development of BPD.

To characterize the pulse response obtained from these patients, we relied upon two specific features of the impedance spectra. These were the occurrence of a local resonance and the variations in the real part, or apparent resistance, with frequency between 6 and 16 Hz. Although both indices reflect the mechanical properties of the respiratory system, it is the latter of these, the frequency dependence of resistance, that is most often used to characterize pulmonary mechanical function in health and disease. The increase in resistance with frequency ($\alpha > 0$) observed among class I patients is comparable to the results obtained in intubated and paralyzed infants of the same age by Dorkin *et al.* (20), suggesting that the measured impedance is determined primarily by the passive mechanical properties of the lungs and chest wall rather than the activity or influence of the respiratory muscles. Similarly, the decrease in resistance with increasing frequency ($\alpha < 0$) observed in the older, class II patients has also been found to occur in sedated infants suffering from bronchiolitis, chronic lung disease, and cystic fibrosis (21) and has been observed in adults suffering from obstructive lung disorders (22). In each case, the lungs show clinical and radiologic evidence of severe small airway obstruction, suggesting that the negative frequency dependence of respiratory resistance is linked to the development of high peripheral airway impedance. The fact that negative frequency dependence of resistance has been observed in healthy children as well (21, 23) indicates that factors other than airway obstruction can provoke negative frequency dependence of respiratory system resistance. One factor that appears to contribute to the impedance characteristics obtained from adults and children is a parallel or shunt pathway for flow that is formed by the large, extrathoracic airways (21, 23). Although these airways are bypassed in the intubated neonate and infant, a comparable shunt pathway may arise from the

motion and expansion of the central intrathoracic airways of these patients.

The influence of a shunt pathway for pulse flow can be illustrated by considering the behavior of a simplified model of the lungs that consists of two compartments representing the central intrathoracic airways and lung periphery (24). The airflow entering the lungs with each pulse is divided into two components, the first of which expands the compliant central airways; the second component inflates the lungs. The total change in volume of the respiratory system is equal to the change in volume of airways and of the distal compartment or lung periphery, and the pressure difference across both compartments is assumed to be the same. Under these conditions, the amount of airflow into each compartment is determined by their impedances. Denoting the airway wall shunt impedance as Z_S and the lumped impedance of the lung periphery as Z_L and including a term for the series impedance of the endotracheal tube (predominantly) and central airways, Z_{ETT}, then the input impedance, Z_T, of the lungs becomes

$$Z_T = Z_{ETT} + \frac{Z_S \cdot Z_L}{Z_S + Z_L} \quad (2)$$

Provided the impedance of the chest wall is negligible in comparison to the lungs, equation 2 can be used to approximate the input impedance of the respiratory system. The significance of the hypothetical respiratory system expressed by equation 2 lies in the last term on the right-hand side. The combination of central and peripheral lung impedances in this term leads to the appearance of compliant and inertial components in the real part of the total impedance, resulting in frequency-dependent changes in the apparent resistance of the respiratory system. In the extreme case, when either Z_S or Z_L is very large, then the contribution of the large impedance vanishes and the total impedance becomes

$$Z_T = Z_{ETT} + Z_L \quad \text{for} \quad Z_S \gg Z_L \quad (3)$$

or

$$Z_T = Z_{ETT} + Z_S \quad \text{for} \quad Z_L \gg Z_S \quad (4)$$

Consequently, variations in either airway or peripheral lung impedance will alter the flow distribution within hypothetical lungs and the pattern of impedance of the respiratory system.

The interaction between central and distal compartments of the hypothetical lung suggests that the redistribution of flow between the large central airways and lung periphery in the neonate may be the basic mechanism underlying the change in the impedance characteristics with age. Pathologic changes in the lungs that are characteristics of long-term ventilator support and BPD include necrosis of the distal bronchiolar epithelium, airway fibrosis, regional atelectasis, and edema (2, 3), all of which tend to increase the total impedance of the lungs distal to the central airways and provoke changes in the impedance spectrum by redistributing flow. One may expect that the resultant increase in lung impedance shifts a greater proportion of the pulse flow into the shunt airways and thus provokes changes in the impedance. Because the precise nature of the physical changes within the lungs is not critical to this mechanism, any process that affects primarily the mechanical properties of the lung parenchyma and distal airways may be expected to have a similar effect upon the overall impedance of the respiratory system. To further illustrate this point, we repeated the pulse experiment on a healthy adult rabbit. The rabbit was anesthetized, intubated and placed supine in a pressure chamber that was used to regulate lung volume by varying the mean transthoracic pressure. The instrumentation and analysis of the pulse data were otherwise the same as those used to study the infants. Lung impedance was varied by insufflation of nebulized histamine (25) or by decreasing lung volume coincident with an increase in chamber pressure of 1.0 kPa.

The pulse-derived impedance of the rabbit's respiratory system is shown in Figure 8. The impedance modulus and phase obtained from control measurements are similar to spectra observed in class I patients. Insufflation of nebulized histamine or decreased lung volume (not shown) independently provoked changes in the impedance that are similar to those observed in class II patients. Combining histamine with decreased lung volume resulted in pronounced class II type characteristics that resemble the impedance of the isolated trachea (obtained by ligating the main bronchi at the hilum). The change in respiratory impedance provoked by these maneuvers is consistent with the central airway shunting of the hypothetical lung and suggests that the differences in impedance between the two classes of patients is determined largely by a progressive change in lung impedance that occurs as a result of long-term ventilation therapy.

In summary, we have demonstrated that brief pulses in airway pressure can be used to detect differences in the pulmonary mechanical function in intubated infants. The pulse response appears sensitive to the changes in pulmonary mechanical function that are associated with ventilation therapy and the development of BPD.

Acknowledgments. The authors thank the nurses and staff of the Neonatal Intensive Care Unit of the Women's Hospital for their kind cooperation and assistance with this study.

REFERENCES

1. Fitzhardinge PM 1978 Follow-up studies in infants treated by mechanical ventilation. Clin Perinatol 5:451–461
2. O'Brodovitch HM, Mellins RM 1985 Bronchopulmonary dysplasia. Am Rev Respir Dis 132:694–709
3. Taghizadeh A, Reynolds EOR 1976 Pathogenesis of bronchopulmonary dysplasia following hyaline membrane disease. Am J Pathol 82:214–258
4. Smyth JA, Tabachnik E, Duncan WJ, Reilly RJ, Levison H 1981 Pulmonary function and bronchial hyper-reactivity in long term survivors of bronchopulmonary dysplasia. Pediatrics 68:336–340
5. Fujiwara T, Maeta H, Chida S, Morita T, Yoshitane W, Tadaaki A 1980 Artificial surfactant therapy in hyaline membrane disease. Lancet 1:55–59
6. Marchak BE, Thompson WK, Duffty P, Miykai T, Bryan MH, Bryan AC 1981 Treatment of RDS by high frequency ventilation. A preliminary report. J Pediatr 99:287–292
7. England SJ 1988 Current techniques for assessing pulmonary function in the newborn and infant: advantages and limitations. Pediatric Pulmonol 4:48–53
8. Sly PD, Brown KA, Bates JHT, Spier S, Milic-Emili J 1988 Noninvasive determination of respiratory mechanics during mechanical ventilation of neonates: a review of current and future techniques. Pediatr Pulmonol 4:39–47
9. Fletcher ME, Ewert M, Stack C, Hatch DJ, Stocks J 1990 Influence of tidal volume on respiratory compliance in anesthetized infants and young children. J Appl Physiol 68:1127–1133
10. LeSouef PN, Lopes JM, England SJ, Bryan MH, Bryan AC 1983 Influence of chest wall distortion on esophageal pressure. J Appl Physiol 55:353–358
11. Sullivan KJ, Durand M, Ye TH, Chang HK 1989 Evaluation of lung mechanics in rabbits using short duration flow pulses. Am Rev Respir Dis 140:17–24
12. Delavault E, Saumon G, Georges R 1980 Identification of transducer defect in respiratory impedance measurements by forced random noise. Correction of experimental data. Respir Physiol 40:107–117
13. Michaelson ED, Grassman ED, Peters WR 1975 Pulmonary mechanics by spectral analysis of forced random noise. J Clin Invest 56:1210–1230
14. Daroczy B, Hantos Z 1982 An improved forced oscillatory estimation of respiratory system. Int J Biomed Comput 13:221–235
15. Delavault E, Saumon G, Georges R 1980 Characterization and validation of the forced input method for respiratory impedance measurement. Respir Physiol 40:119–136
16. Landser FJ, Nagels J, Clement J, Van De Woestijne KP 1976 Errors in the measurements of total respiratory resistance and reactance by forced oscillations. Respir Physiol 28:289–301
17. Bhutani VK, Sivieri EM, Abbasi S, Shaffer TH 1988 Evaluation of neonatal pulmonary mechanics and energetics: a two factor least square analysis. Pediatr Pulmonol 4:150–158
18. Perez-Fontan JJ, Heldt GP, Gregory GA 1985 Resistance and inertia of endotracheal tube used in infants during periodic flow. Crit Care Med 13:1052–1055
19. Chang HK, Mortola JP 1981 Fluid dynamic factors in tracheal pressure measurement. J Appl Physiol 51:218–225
20. Dorkin HL, Stark A, Werthammer JW, Strieder DJ, Fredberg JJ 1983 Respiratory system impedance from 4 to 40 Hz in paralyzed intubated infants

with respiratory disease. J Clin Invest 72:903–910
21. Marchal F, Peslin R, Duviviver C, Gallina C, Crance JP 1988 Mechanics of the ventilatory system in sedated infants: forced oscillation *versus* single breath methods. Pediatr Pulmonol 5:19–26
22. Hayes DA, Pimmel RL, Fullton JM, Bromberg PA 1979 Detection of respiratory mechanical dysfunction by forced random noise impedance parameters. Am Rev Respir Dis 120:1095–1100
23. Williams SP, Fullton JM, Tasi MJ, Pimmel RL, Collier AM 1979 Respiratory impedance and derived parameters in young children by forced random noise. J Appl Physiol 47:169–174
24. Eyles JG, Pimmel RL, Fullton JM, Bromberg PA 1982 Parameter estimates in a five element respiratory mechanical model. IEEE Trans Biomed Eng 29:460–463
25. Ludwig MS, Dreshaj I, Solway H, Munoz A, Ingram RH 1987 Partitioning of pulmonary resistance during constriction in the dog: effects of volume history. J Appl Physiol 62:807–815