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Improvement in Lung Mechanics as a Function of Age in the Infant with Severe Bronchopulmonary Dysplasia

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Summary

Pulmonary function tests were performed in two groups of infants with bronchopulmonary dysplasia; a group less than 7 months of age with severe ventilator-dependent respiratory failure (Group A), and a group 7–22 months of age during resolution of their disease (Group B). Group A patients had significantly elevated minute volume, low specific compliance, elevated inspiratory and expiratory pulmonary resistance, and low functional residual capacity. Group B patients also demonstrated elevated minute volume, whereas specific compliance, inspiratory pulmonary resistance and functional residual capacity were within normal limits, and expiratory pulmonary resistance was only slightly above normal. With the exception of minute volume, the differences between the groups were significant ($P < 0.05$). Sequential studies of resistance and compliance over 4–5 months in two patients in the younger group demonstrated values that approached or achieved normal range. It is concluded that pulmonary mechanics improve with age in the infant with severe bronchopulmonary dysplasia.

Speculation

The high minute ventilation demonstrated in children with bronchopulmonary dysplasia results from increased dead space ventilation. With low compliance and high resistance the young infant cannot sustain the high minute ventilation required, and respiratory failure ensues, requiring mechanical ventilation. As the child grows, chest wall strength, compliance, and resistance improve, allowing the infant to sustain a high spontaneous minute ventilation, and thus to tolerate gradual reduction and eventual removal of mechanical ventilatory support.

IMPROVEMENT IN LUNG MECHANICS AS A FUNCTION OF AGE IN THE INFANT WITH SEVERE BRONCHOPULMONARY DYSPLASIA

Seven to 36% of ventilated patients who survive respiratory distress syndrome (RDS) develop bronchopulmonary dysplasia (BPD) (2, 5, 8, 16). This condition varies from mild, requiring increased oxygen concentration for several wk, to severe, with dependence on tracheostomy, intermittent mandatory ventilation (IMV), and supplemental oxygen for many months. Mortality rate for severe BPD during the first year of life is high (3), usually as a result of progressive pulmonary failure or sepsis. However, most survivors show a gradual improvement in pulmonary function and eventually can be weaned from ventilatory support (3).

In a recent study of seven infants with severe BPD, a "turning point" in the clinical course of the disease was noted (12). Before this point, tachypnea and hypercapnea indicated the presence of respiratory failure; reductions in IMV rate during this time resulted in worsening respiratory failure. The turning point, occurring at a mean age of 7 months, was marked by a significant and sustained reduction in spontaneous respiratory rate (RR) and arterial carbon dioxide tension ($Paco_2$). Subsequently, gradual reductions in IMV rate were well tolerated; mean age of weaning from IMV was 14 months.

It is not known if improvements in pulmonary mechanics account for this clinically observed improvement in lung function. Specific pulmonary function abnormalities documented in infants with BPD in the first year of life include high airway resistance (1, 10), low dynamic compliance (1, 3, 10), abnormal lung volumes (3, 22), abnormal gas exchange (3, 7, 22), and elevated minute volume (10). However, improvement in pulmonary mechanics as a function of age and somatic growth has not been documented. Bryan *et al.* (3) performed serial measurements of pulmonary function during the first year of life in 11 infants with BPD. Eight of these patients died in the first year, and the three survivors had persistently increased functional residual capacity (FRC), decreased dynamic compliance (C_L), hypoxia, and carbon dioxide retention throughout the first year. There is little published data documenting changes in pulmonary function with age, and no studies account for the improvement in pulmonary function observed clinically in our patients. The purpose of this study was to determine if improvements in pulmonary mechanics occur in association with clinical improvement in pulmonary function during the first year of life.

MATERIALS AND METHODS

Between July 1979 and April 1980, nine children with severe bronchopulmonary dysplasia were cared for in the Infant Intensive Care and Pediatric Intensive Care Units of The Children's Hospital of Philadelphia. The patient profile is shown in Table 1. All patients were premature and asphyxiated at birth. All developed RDS and required intubation, supplemental oxygen, and mechanical ventilation during the first wk of life. All developed Stage IV radiographic changes as defined by Northway *et al.* (13), and still required mechanical ventilation at age 2 months, when they were considered eligible for study. Of the nine patients, four have been weaned from respiratory support and are now at home. Three patients are still ventilator-dependent, but are improving and are expected to recover. Two patients died: one of pulmonary failure and one of aspiration pneumonia and sepsis.

Permission for study was obtained from the Committee for Protection of Human Subjects. Informed consent was obtained from all parents of patients admitted to the study.

Table 2 presents age, weight, artificial airway type and size, mechanical ventilator settings, inspired oxygen concentration, $Paco_2$ and RR at the time of study. The nine patients were separated into two groups according to age: those less than seven

Table 1. *Clinical profile of nine infants with severe bronchopulmonary dysplasia*

Patient number	Birth weight	Gestational age (Wk)	Apgar 1 min/5 min	Maximum respiratory setting during first wk of life: F_IO_2[2]	PIP[3] (mm Hg)	IMV[4] rate bpm[5]	Radiographic stage (13)	Age weaned (mos)	Current status from IMV
1	1.2	30	1/6	1.0	22	60	IV	4	Home off support
2	0.9	30	6/6	0.5	20	25	IV	5	Home off support
3	1.1	30	3/7	0.7	25	50	IV		On ventilator, age 7 months.
4	1.0	28	3/6	1.0	45	60	IV		Died pulmonary failure, age 7 months
5	1.1	30	3/6	0.6	28	50	IV		Died aspiration pneumonia, age 7 months
6	1.7	31	4/7	1.0	20	42	IV		On ventilator, age 8 months
7	1.2	32	5/7	0.6	14	15	IV	12	Home off support
8	0.9	27	4/5	1.0	22	30	IV		On ventilator, age 18 months
9	1.2	32	N.A.[1]	1.0	28	60	IV	22	Home off support

[1] N.A. = not available.
[2] F_IO_2 = inspired oxygen concentration.
[3] PIP = peak inspiratory pressure.
[4] IMV = intermittent mandatory ventilation.
[5] bpm = breaths per min.

Table 2. *Prestudy age, weight, airway and respiratory status in younger and older patient groups*

Patient no.	Study age (mos)	Study weight (kg)	ID[1] airway	IMV[2] rate (bpm)[3]	IP[4] (cm H_2O)	F_iO_2[5]	$PaCO_2$[6] (mm Hg)	RR[7] (bpm)
Group A								
1	2	1.4	3.0 NTT[8]	10	20	0.32	70	57
2	2	1.2	3.0 NTT	10	24	0.30	59	57
3	2	1.7	3.5 T[9]	36	40	0.70	50	67
4	2	1.5	3.0 NTT	7	17	0.35	41	67
5	4	1.8	3.0 NTT	5	18	0.27	52	60
6	4	3.2	3.5 T	20	26	0.45	55	50
Mean ± S.D.	2.7 ± 1.0	1.8 ± 0.7		14.7 ± 11.6	24.1 ± 8.5	0.39 ± 0.16	54.5 ± 9.7	59.7 ± 6.6
Group B								
7	13	9.5	4.0 T	0		0.24	35	51
8	21	8.0	4.0 T	10	20	0.30	45	63
9	22	11.2	4.5 T	0	2 (CPAP)[10]	0.21	35	32
3	7	3.4	3.5 T	25	35	0.55	48	55
6	8	6.4	3.5 T	16	26	0.47	50	45
Mean ± S.D.	14.2 ± 7.0	7.7 ± 3.0		10.2 ± 10.7	16.6 ± 15.2	0.35 ± 0.15	42.6 ± 7.2	49.2 ± 11.6

[1] ID = internal diameter.
[2] IMV = intermittent mandatory ventilation.
[3] bpm = breaths per min.
[4] IP = inflation pressure.
[5] F_iO_2 = inspired oxygen concentration.
[6] $PaCO_2$ = arterial carbon dioxide tension.
[7] RR = respiratory rate.
[8] NTT = nasotracheal tube.
[9] T = tracheostomy.
[10] CPAP = continuous positive airway pressure.

months (Group A) and those seven months or older (Group B). This age was chosen for several reasons. We had observed clinical improvement in a comparable group of patients at a mean age of 7 months (12). Similarly, the patients in the current study less than 7 months of age were still in the acute phase of their disease, as judged by persistently high values for $PaCO_2$ and RR. Those patients seven months of age or older were in the resolution phase of their disease, with slowly declining $PaCO_2$, RR and requirement for IMV. Finally, there was a marked difference in weight between those patients less than 7 months, and those patients 7 months or greater; sustained weight gain is an important factor in successful weaning from mechanical ventilation (12).

Two patients from Group A (Nos. 3 and 6) remained dependent on IMV at ages 7 and 8 months respectively. Once these patients reached the group B age range (7 months or older), and were improving clinically, they were restudied to determine if significant improvement had occurred in lung mechanics. Table 3 indicates respiratory parameters at the time of the two studies for both patients. Data from the second study on both patients was included with data from other Group B patients.

Intra-esophageal pressure was recorded with a differential pressure transducer (Model 270 Hewlett Packard, Waltham, MA) from a balloon (National Catheter Co., Argyle, NY) placed in the mid-esophagus. The volume of air in the balloon was 0.1 ml.

Table 3. *Age, weight, and respiratory status of two group A patients at initial and followup study*

	Patient no. 3		Patient no. 6	
	Initial study	Followup study	Initial study	Followup study
Age (mos)	2	7	4	8
Weight (kg)	1.7	3.4	3.2	6.4
IMV rate (bpm)[2]	36	25	20	16
IP[3] (cm H_2O)	40	35	26	26
F_{IO_2}[4]	0.7	0.55	0.45	0.47
RR[5] [IMV rate (bpm) + spontaneous breaths]	67	55	50	45
$Paco_2$[6] (mm Hg)	50	48	55	50

[1] IMV = intermittent mandatory ventilation.
[2] bpm = breathes per minute.
[3] IP = inflation pressure.
[4] F_{IO_2} = inspired oxygen concentration.
[5] RR = respiratory rate.
[6] $Paco_2$ = arterial carbon dioxide tension.

Inspiratory and expiratory gas flows were measured with a Fleisch pneumotachograph (Model 2707B Hewlett Packard) from a flow transducer (Model 43304A Hewlett Packard) and amplifier (Model 8811A Hewlett Packard). Flow signals were integrated by a respiratory integrator (Model 47304A Hewlett Packard) to give tidal volume. The three signals were displayed on a four channel recorder (Model 7254A Hewlett Packard).

Patients Nos. 1, 2, 4, and 5 had nasotracheal tubes, whereas all other patients had tracheostomies in place. There was no audible air leak in any patient. Before measurement of FRC, tracheostomy tubes were replaced with cuffed tubes although nasotracheal tubes were not changed. FRC was measured with a helium dilution technique as previously described (6).

Measurements were made on 10 consecutive breaths. For this purpose, those infants with IMV rates in excess of six breaths per min had their rate reduced to six breaths per min. Those infants with IMV rates less than six breaths per min had no change in IMV rate. In this way, measurements could be made on spontaneous breaths during at least ten second intervals between IMV breaths. Peak inspiratory pressure, positive end expiratory pressure and inspired oxygen concentration (F_{IO_2}) remained at prestudy levels. One ml of arterial blood was drawn into a heparinized syringe using a percutaneous sampling technique; $Paco_2$ was obtained from blood gas analysis of this sample (Model 175 Corning Medical Co., Medfield, MA).

Mean data from 10 successive breaths is reported. Minute ventilation ($\dot{V}_E$) was calculated from tidal volume and respiratory rate. Dead space added by our measurement apparatus (3.4 ml in Group A patients and 12.2 ml in Group B patients) does not change the measurement of V_T or $\dot{V}_E$. It may influence that fraction of $\dot{V}_E$ that is alveolar, and thus may alter $Paco_2$. However, assuming that an endotracheal tube or tracheostomy tube reduces anatomic dead space by about 50%, the addition of apparatus dead space represents only a small net increase in anatomic dead space and is unlikely to have had appreciable effect on alveolar ventilation or $Paco_2$.

Inspiratory and expiratory pulmonary resistance and dynamic lung compliance (C_L) were derived according to the methods of Krieger (9). Specific compliance (C_L/FRC) was calculated.

Resistance contributed by the artificial airways was measured as follows: for each patient, either an endotracheal or tracheostomy tube (Table 2) of the same internal diameter, length, and connector size was attached to an air source and the same pneumotachograph, flow transducer, and amplifier as used for patient measurements. Peak inspiratory and expiratory flows were noted from the flow tracing on each patient. Similar flows were introduced into the artificial airway. Pressure drop across the airway was measured with a differential pressure transducer. Resistance in the airway was calculated as the pressure drop across the airway divided by air flow.

An independent students *t* test was performed on the data from the two groups. Differences were considered significant at the $P < 0.05$ level.

RESULTS

Pulmonary function data for both groups is shown in Figures 1 and 2. Figure 1*a* indicates that minute volume was significantly above normal range in the younger infants (mean 378 ± 74 ml/min/kg) and was decreased slightly in the older infants (mean 348 ± 21 ml/min/kg) though still significantly elevated for age. There was no significant difference between the two groups. As shown in Figure 1*b* the high minute volume for both groups resulted from increased respiratory rate [Group A, mean 59.7 ± 12.1 breaths per min (bpm); Group B, 52.8 ± 12.4 bpm] with normal tidal volume (Group A, mean 6.4 ± 0.9 ml/kg; Group B, 7.0 ± 2.4 ml/kg) compared to normal. The differences in tidal volume and respiratory rate between the two groups were not significant.

Figure 2*a* indicates the significant ($P < 0.05$) difference in FRC between Groups A and B, with FRC significantly ($P < 0.01$) below normal for Group A (mean 24.1 ± 6.4 ml/kg), and in the normal range (mean 33.4 ± 5.6 ml/kg) for Group B.

Dynamic lung compliance is related both to body weight and to FRC in Figure 2*b*. For both, compliance was significantly ($P < 0.01$) below normal range in the younger infants (C_L/kg: mean 0.69 ± 0.24 ml/cm H_2O/kg; C_L/FRC: mean 0.030 ± 0.013) and within normal limits in the older group (C_L/kg: mean 1.5 ± 0.73 ml/cm H_2O/kg; C_L/FRC: mean 0.055 ± 0.017). The differences between groups were significant ($P < 0.05$).

A significant ($P < 0.05$) difference also existed between the two groups for both inspiratory and expiratory pulmonary resistance (Fig. 2*c*). The younger infants demonstrated significantly ($P < 0.01$) elevated inspiratory (mean 105 ± 32 cm H_2O/liter/sec) and expiratory (mean 175 ± 102 cm H_2O/liter/sec) resistance. The older infants had inspiratory resistance in the normal range (mean 34 ± 23 cm H_2O/liter/sec), and expiratory resistance only slightly above normal (mean 44 ± 23 cm H_2O/liter/sec). These resistance figures have been corrected for the resistance contributed by the artificial airways which in Group A patients was 14 ± 7 cm H_2O/liter/sec during inspiration and 13 ± 8 cm H_2O/liter/sec during expiration. For Group B patients, the airways contributed 8 ± 2 cm H_2O/liter/sec during inspiration and 6 ± 3 cm H_2O/liter/sec during expiration.

The results of the sequential studies on patients Nos. 3 and 6 are shown in Figure 3*a* and 3*b*. Figure 3*a* shows the improvement in dynamic lung compliance with age. Patient No. 3, with a low compliance at age 2 months, demonstrated compliance within the normal range at age 7 months. Patient No. 6, who started with the lowest compliance of any patient studied, showed improvement at age 8 months.

Both infants also demonstrated improvement in inspiratory and expiratory pulmonary resistance with age (Fig. 3*b*). Patient No. 3 actually reached normal levels for expiratory resistance by age 7 months.

Neither patient demonstrated important changes in minute ventilation, tidal volume, or respiratory frequency at the time of the second study.

DISCUSSION

This study documents significant differences in pulmonary function in two groups of infants with severe bronchopulmonary dysplasia: a group 2–4 months of age in the acute phase of their disease, and a group 7–22 months of age in the resolution phase. The study is consistent with the clinical observation that these infants reach a turning point in the course of their disease, after which, signs of respiratory failure gradually diminish and slow

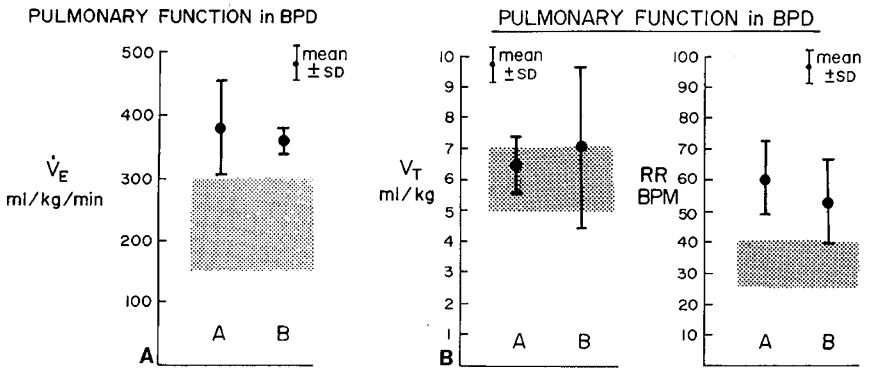

Fig. 1*a* and *b*. Minute ventilation, respiratory rate, and tidal volume in two groups of patients with severe bronchopulmonary dysplasia (BPD). Group A: patients 2–4 months of age. Group B: patients 7–22 months of age. Mean ± S.D. is shown for each group. Normal values ± S.D. (19) are shown by cross hatched areas. (Left hand panel, *a*) minute ventilation ($\dot{V}_E$) and (right hand panel, *b*) respiratory rate (RR) and tidal volume (V_T).

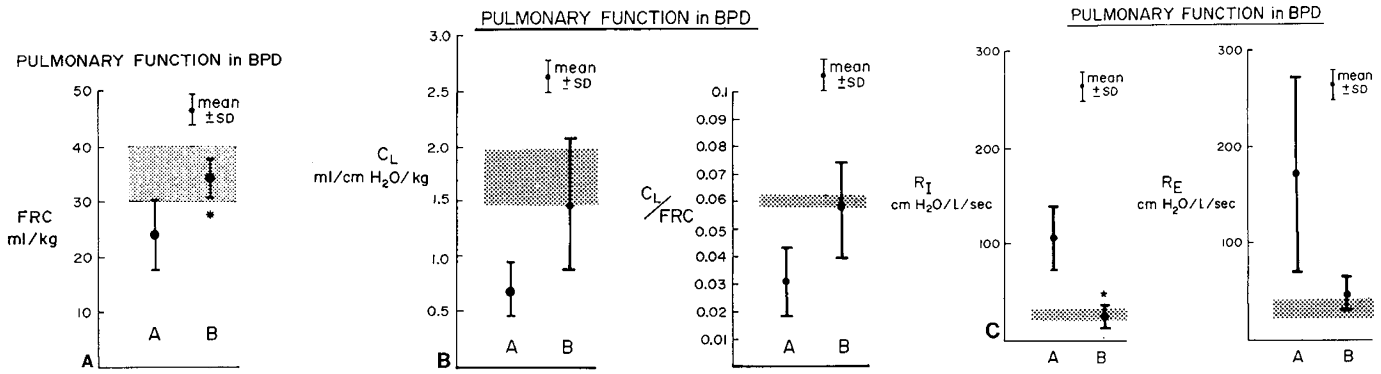

Fig. 2*a*, *b*, and *c*. Functional residual capacity, dynamic lung compliance, specific compliance, and pulmonary resistance in two groups of patients with severe bronchopulmonary dysplasia (BPD). Group A: patients 2–4 months of age. Group B: patients 7–22 months of age. Mean ± S.D. is shown for each group. Normal values ± S.D. (4, 15, 19) are shown by cross hatched areas. $^*P < 0.05$. (Left hand panel, *a*) functional residual capacity (FRC), (middle panel, *b*) dynamic lung compliance (C_L/kg) and specific compliance (C_L/FRC), and (right hand panel, *c*) inspiratory and expiratory pulmonary resistance (R_I and R_E).

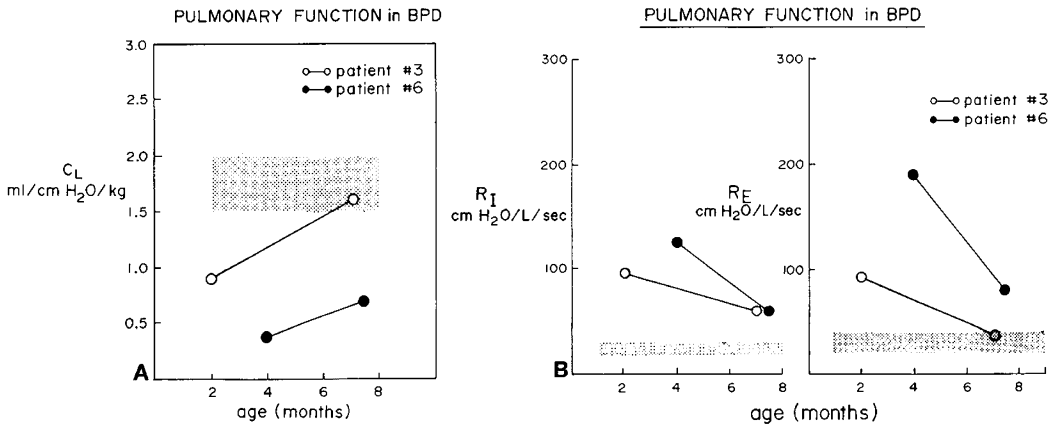

Fig. 3*a* and *b*. Sequential pulmonary function data on two patients with severe bronchopulmonary dysplasia (BPD). For both patients, the initial study was done during the acute phase of their disease, whereas the followup study was done after weaning from intermittent mandatory ventilation (IMV) had begun. Normal values ± S.D. (4, 19) are shown by cross hatched areas. (Left hand panel, *a*) dynamic lung compliance (C_L) and (right hand panel, *b*) inspiratory and expiratory pulmonary resistance (R_I and R_E).

withdrawal of respiratory support can begin (12). Dynamic lung compliance, inspiratory and expiratory resistance, and functional residual capacity, grossly abnormal in the younger infants, approach or achieve normal range in the older infants. Sequential studies of resistance and compliance in two Group A patients verify this difference, suggesting that improvement in pulmonary function occurs as airway and parenchymal disease resolves.

Differences in pulmonary resistance between the two groups

cannot be accounted for by resistance to air flow through an artificial airway. The amount of resistance contributed by the endotracheal or tracheostomy tubes in our patients, which correlates well with previously reported data (21), is small in relation to the total pulmonary resistance and does not change the statistically significant difference in pulmonary resistance between the two groups.

Alterations in lung mechanics and volumes probably result from the pathologic changes in airway and parenchymal architecture associated with bronchopulmonary dysplasia (17, 20). Bronchi and terminal airways are obstructed and narrowed by epithelial hyperplasia and fibroblastic proliferation. Peribronchiolar fibrosis is the dominant parenchymal change, resulting in regions of fibrotic, atrophic, and collapsed lung as well as areas of emphysema. The abnormalities in airway resistance and pulmonary compliance seen in the early phase of the disease are explained in part by these pathologic changes. In infants recovering from RDS without BPD, resistance is elevated, whereas compliance and lung volumes are normal (18). This suggests airway resistance as the most sensitive indicator of airway damage, with abnormalities in pulmonary compliance (1, 3, 10, 11) and lung volume (3) being seen with more severe alterations in lung architecture.

The measurement of a low dynamic compliance is probably as much a reflection of nonuniform distribution of inspired gas as it is of abnormal elastic properties. Otis *et al.* (14) showed that in the face of unequal regional time constants (the product of regional resistance and compliance), as respiratory frequency increases, more gas goes to the short time constant regions and dynamic compliance falls. Even adults with normal lungs exhibit this "frequency dependence of compliance" above 40 breathes per min. Grossly abnormal distribution of ventilation in BPD has been reported (22), making frequency dependence of compliance a likely phenomenon in these children.

Previous studies have shown that FRC is low in the early stages of the disease (3, 22), but increases throughout the first year to values exceeding normal (3). Our older group of patients demonstrates FRC within the normal range. Chest radiographs taken at the same time are consistent with stage IV BPD, showing areas of overdistention as well as collapse. FRC within the normal range may result from the presence of both types of lung pathology. Overdistended areas represent gas trapping in poorly communicating alveoli. As the helium dilution method used in the present study measures only that lung volume which communicates with large airways, it may have underestimated FRC in our older group of patients.

Our study confirms the presence of high minute ventilation, normal tidal volume, and rapid respiratory rate previously reported in children with severe BPD (10). There is no significant difference in these parameters in the two groups of patients. The concurrence of high minute ventilation and hypercapnia in these children implies the presence of increased dead space ventilation, though elevated CO_2 production may play a role. Because of poor lung compliance and high pulmonary resistance, work of breathing is increased. The young infant with severe BPD cannot sustain the high minute ventilation required, and respiratory failure ensues unless he or she is supported with IMV. The older infant gradually develops improved compliance and resistance as well as increased chest wall strength. Over the subsequent months, he becomes more able to sustain the high minute ventilation necessary, and thus no longer needs mechanical ventilatory support.

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