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Educational Aims

In this chapter, we will:

- Consider the problem of bronchiolitis, its pathophysiology, and critical care therapy.
- Restrict discussion to clinical research evidence of RSV-induced lower respiratory tract disease wherever possible.
- Provide rational approaches to bedside mechanical ventilation.
- Focus on potential therapies that target the lower airway problem in respiratory system resistance and compliance.

November in the northern hemisphere, then your first winter exposure to RSV is likely to be when you are less than 4 months of age and vulnerable because of poor respiratory mechanical reserve (Alonso et al. 2007). However, if you are born in May/June, then you will be 7–8 months during your first winter exposure to RSV, much bigger and stronger and have more efficient thoracic and diaphragmatic mechanics. In the PICU, the main predictors of severe outcome in previously well infants appear to be young age, presence of apnea, and pulmonary consolidation on admission chest radiograph (Tasker et al. 2000; Lopez Guinea et al. 2007). Taken together, we can say that more severe RSV bronchiolitis in PICU practice is typically a problem of pulmonary consolidation, poor respiratory mechanics, and poor reserve, in the younger infant.

50.1 Introduction

Everyone on the planet is exposed to respiratory syncytial virus (RSV) infection by the age of 2 years. Most infants admitted to the pediatric intensive care unit (PICU) for respiratory support during this infection are previously healthy, but their principal risk for needing PICU treatment is young age. That is, if you are born in October/

50.2 Typical Features of Bronchiolitis and General Supportive Measures

The typical features of bronchiolitis in an infant less than 2 years of age are acute generalized peripheral airway obstruction, tachypnea, decreased breath sounds on auscultation, and low hemidiaphragms on chest radiograph. RSV is the most frequent cause of bronchiolitis. Other viral causes include adenovirus, influenza and parainfluenza, metapneumovirus, and rhinovirus. Cytomegalovirus can produce a bronchiolitis or pneumonitis-like illness in immunocompromised

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Table 50.1 Assessment and supportive therapies for RSV bronchiolitis

<i>Pulse oximetry should be performed in every child who attends hospital with acute bronchiolitis</i>
Infants with pulse oximetry oxygen saturation (SpO_2) ≤ 92 % require inpatient care
Decision about infants with SpO_2 between 92 and 94 % should be supported by detailed clinical assessment
Infants with $\text{SpO}_2 > 94$ % in room air may be considered for discharge
<i>Supportive therapies for those admitted to hospital</i>
Nasal suction should be used to clear secretions in those with distress due to nasal blockage
Nasogastric feeding should be considered in infants who cannot maintain oral intake or hydration
Infants with $\text{SpO}_2 \leq 92$ % or who have severe respiratory distress or cyanosis should receive supplemental oxygen by nasal cannulae or face mask
Infants may be considered for discharge when they can maintain $\text{SpO}_2 > 94$ % in room air and more than 75 % of their usual daily oral intake
<i>Indication for acute assessment and high-dependency or intensive care referral</i>
Failure to maintain $\text{SpO}_2 > 92$ % with increasing oxygen therapy or cyanosis
Recurrent apnea
Poor feeding (<50 % in the preceding 24 h) or lethargy
Presence of nasal flaring and/or grunting
Severe chest wall recession
Increasing respiratory distress and/or exhaustion despite supplemental oxygen. Blood gas analysis may have a role in the assessment of infants with severe respiratory distress

Based on SIGN (2006) guidelines

children. Rare, nonviral causes of bronchiolitis syndrome include *Mycoplasma pneumoniae* and *Bordetella pertussis* infection. The pathology of RSV infection in the lower airways is characterized by sloughed necrotic epithelium, excessive mucus secretion, bronchial mucosal edema, and peribronchial inflammation.

In this chapter, we will restrict the discussion and clinical research evidence to bronchiolitis and RSV-induced lower respiratory tract disease whenever possible. The focus will be on respiratory failure and PICU management, but the reader should be aware that most affected infants respond satisfactorily to oxygen therapy and general supportive measures. As an overview of this general therapy, Table 50.1 summarizes current guidelines and best evidence concerning assessment and hospital supportive measures for bronchiolitis in children (SIGN 2006).

tion are previously healthy and 10–40 % are less than 36 weeks' gestational age (Law et al. 1997; Carbonell-Estrany et al. 2004). In individual series, prematurity and bronchopulmonary dysplasia have significant impact, and such cases are likely to require either high-dependency or intensive care (Greenough et al. 2001). The prediction of who will require PICU admission is not an exact science. Brooks et al. (1999) found in a population of 542 previously healthy term infants, where 1.8 % required admission, that tachypnea (respiratory rate > 80 /min) and pulse oximetry arterial desaturation ($\text{SpO}_2 < 85$ %) had good specificity (> 97 %) but poor sensitivity (≤ 30 %) for predicting admission. The decision to admit to the PICU should depend on local referral practice and the ability to manage the problems outlined in Table 50.1.

50.3 Respiratory Failure in Bronchiolitis

A small proportion of cases of RSV bronchiolitis develop difficulties that are best managed in the PICU. Studies in the intensive care population suggest that 4–15 % of infants with RSV infec-

50.3.1 Patterns of Disease Requiring Mechanical Ventilation

There are no absolute indications for controlled mechanical ventilation (MV). The clinical situation should dictate what is required. For example, if a patient is being transferred between hospitals, patient safety during transfer may be the overriding

guiding factor. Alternatively, if a patient is being managed in a ward area within easy access of PICU practitioners, then it may be appropriate to wait until the infant demonstrates significant respiratory deterioration, such as those suggested by Rakshi and Couriel (1994):

- Persistent apneas with severe hypoxemia and $\text{pH} < 7.20$
- Altered mental state and $\text{SpO}_2 < 85\%$ with fractional inspired oxygen (FiO_2) above 0.6

The mechanism leading to progressive respiratory failure and apparent exhaustion will be discussed in later sections of the chapter (see Sects. 50.3.2 and 50.3.3). The other patterns of disease requiring MV are peripheral circulatory collapse, recurrent apneic attacks, and generalized convulsions (Simpson et al. 1974; Eisenhut 2006). Recurrent apnea in an infant, in the winter, should lead to the early diagnosis of bronchiolitis at the time of presentation. However, the diagnosis of underlying RSV infection may be overlooked in cases presenting with shock or hyponatremia-related seizures.

Apnea is common in RSV infection, particularly in those with a history of apnea of prematurity; it is usually nonobstructive (Anas et al. 1982). The mechanism of RSV-associated apnea is unclear, but possible explanations include stimulation of laryngeal chemoreceptors, sensitization of airway receptors, respiratory muscle fatigue, and abnormal immunologic responsiveness.

The shock-like state complicating RSV has been described by a number of authors (Simpson et al. 1974; Njoku and Kliegman 1993; Kim and Frankel 1997; Arnold et al. 2000; Checchia et al. 2000). There are some infants where the respiratory features of RSV infection are silent at presentation but can become severe enough to require high-frequency oscillatory ventilation (HFOV) (Arnold et al. 2000). There are others, where cardiac compromise is a consequence of cardiopulmonary interaction that improves with clinical improvement. For example, Sreeram et al. (1991) studied 21 infants with acute bronchiolitis, with normal hearts, and found that half had tricuspid valve regurgitation; many had evidence of raised pulmonary artery systolic pressure. In all such patients, myocardial injury may

contribute to the severity of presentation (Checchia et al. 2000).

Seizures during RSV infection usually result from hyponatremia (Simpson et al. 1974; Hanna et al. 2003), which is a consequence of the derangement in water, electrolyte, and endocrine homeostasis induced by high intrathoracic pressure (Gozal et al. 1990; Poddar et al. 1995). Typically, seizures cease once serum sodium is above 130 mmol/L.

50.3.2 Blood Gases and Respiratory Failure

Respiratory failure is not always present on admission to hospital, and progressive deterioration over a variable time period occurs in many such cases, which confirms the importance of clinical vigilance even in mild to moderately severe cases. Both components of respiration – carbon dioxide (CO_2) clearance and oxygenation – need to be assessed in infants with RSV infection.

In regard to CO_2 derangements in bronchiolitis, respiratory failure is defined as an arterial partial pressure of CO_2 ($P_a\text{CO}_2$) exceeding 65 mmHg (8.7 kPa). Reynolds (1963a) found that when such infants breathed air, there was little increase in $P_a\text{CO}_2$ above 40 mmHg, even when respiratory rates were up to 60 breaths/min (Fig. 50.1). At a breathing rate of 60 breaths/min, the arterial partial pressure of oxygen ($P_a\text{O}_2$) was ~60 mmHg (8 kPa). Downes et al. (1968) found two phases or a progression in CO_2 clearance. In infants with $P_a\text{CO}_2$ below 65 mmHg, the dead space-to-tidal volume ratio (V_D/V_T) was between 0.55 and 0.69. (In normal, spontaneously breathing infants, the ratio is 0.25 ± 0.07 , which is similar to that found in adults.) When increase in V_D/V_T originates within the respiratory system, it represents increase in V_D , decrease in V_T , or some combination of the two. Krieger and Whitten (1964) found lower mean V_T and mean minute volume in 24 infants with acute bronchiolitis; they concluded, “respirations may be considered shallow.” Distinct from these causes, outside of the respiratory system, hypovolemia or shock may also lead to high V_D/V_T . Given this limit to lung physiology in bronchiolitis, avoidance of

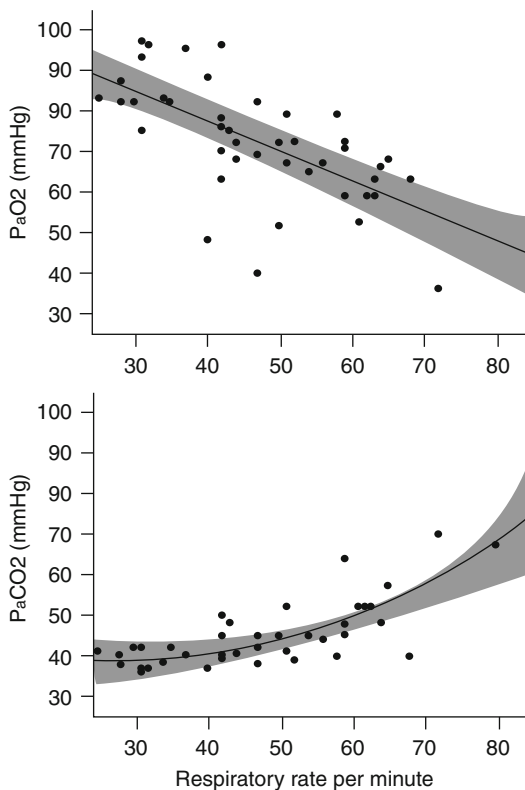


Fig. 50.1 Partial pressure of oxygen (P_aO_2) and carbon dioxide (P_aCO_2) plotted against respiratory rate in infants with bronchiolitis who are spontaneously breathing room air (Figures redrawn from Reynolds (1963a) with additional regression analysis and 95 % confidence interval for fitted lines)

respiratory failure can be accomplished by maintenance of two- to threefold increase in minute volume (Downes et al. 1968). In bronchiolitis, if V_T is limited, then compensatory increase in minute ventilation has to be due to an increase in respiratory frequency (Stokes et al. 1981). It is interesting to note that infants with respiratory failure (based on clinical and blood gas findings) have high V_D/V_T associated with minute ventilation close to predicted basal levels, which implies that the needed increase in minute ventilation has not been maintained. At this point, some infants are extremely tachypneic, so their deterioration represents worsening increase in V_D or lessening of V_T . In other infants, this state represents fatigue or an abnormality in lung mechanics that cannot be overcome. Of note, the V_D/V_T remains raised

(0.46 ± 0.10) even after starting MV, which is due to increase in physiologic dead space caused by hyperinflation or associated hypoperfusion (Almeida-Junior et al. 2007).

Clinical assessment of oxygenation – particularly hypoxia – is difficult in bronchiolitis (Simpson and Flenley 1967). Cyanosis is invariably present when SpO_2 is below 85 %, but this is a late sign. There is a significant inverse relationship between respiratory rate and P_aO_2 (Reynolds 1963a). In those breathing air, respiratory rate increases from 25 to 60 breaths/min as P_aO_2 falls from 90 to 60 mmHg (Fig. 50.1). There is also a significant inverse linear correlation between P_aCO_2 and P_aO_2 , which suggests that alveolar hypoventilation contributes to arterial hypoxemia (Downes et al. 1968). From first principles, in the Downes et al. data, the degree of hypoxemia is as expected from the alveolar gas equation and a normal alveolar-arterial oxygen ($AaDO_2$) gradient: at a time when P_aCO_2 is 65 mmHg (and assuming a respiratory quotient of 0.8), the expected alveolar PO_2 is 68 mmHg, which is consistent with the P_aO_2 of 50 mmHg observed. However, Reynolds (1963b) found much higher $AaDO_2$ in 10 infants with bronchiolitis, ranging from 35 to 57 mmHg, and concluded that since administering oxygen (fractional inspired oxygen, FiO_2 , 0.4) made their P_aO_2 rise to above 100 mmHg (13.3 kPa), the most likely cause of large $AaDO_2$ gradient was ventilation-perfusion inequalities. As the condition becomes extremely severe, intrapulmonary shunt may become the more significant cause of high $AaDO_2$ (Tasker et al. 2000).

Taken together, it is likely that abnormal gas exchange in bronchiolitis is produced by rise in V_D/V_T and worsening ventilation-perfusion inequalities. In less severe states, the former is compensated by increase in minute ventilation. In more severe disease, there is failure in this compensation. The critical questions are as follows: what is driving tachypnea, and what is causing V_D/V_T to increase? Rising P_aCO_2 is not the stimulus for rapid breathing, since respiratory rate is increased despite near-normal levels. Neither is P_aO_2 the stimulus, since this parameter increases respiratory rate when <60 mmHg.

50.3.3 Lung Function and Mechanics in Bronchiolitis

The total work that has to be performed on the lung proper is the work necessary to overcome both elastic and nonelastic resistance. In addition to elastic and nonelastic resistance, respiratory work is a function of rate and V_T . Work of breathing in bronchiolitis is double to six times that of normal infants but similar to that of infants with bronchopneumonia (Krieger and Whitten 1964; Stokes et al. 1981). Interestingly, the latter do not present in extremis, which implies that this increase in work of breathing can be tolerated, but the problem may lie in whether lung mechanics in bronchiolitis permit such work. Since individual clinical features (e.g., auscultation, respiratory rate, and heart rate) do not correlate with total work of breathing, it is difficult to assess (Stokes et al. 1981). The degree of hyperinflation may be helpful in the assessment because it does mirror severity, but the best measure of work is esophageal pressure changes during breathing.

Given the obstructive lesions in terminal bronchioles in bronchiolitis, we would expect high nonelastic resistance. Yet, in general, infants with bronchiolitis do not show prolongation of the expiratory phase. They also breathe rapidly, which is inefficient when there is increased resistance to airflow. In one series of acute bronchiolitis, mean nonelastic resistance was similar to that of normal infants of similar age distribution (~ 0.03 cm H₂O/mL/s) (Krieger 1964). This finding can be explained by the theory of “equality of time constants,” i.e., when flow is rapid in a system of unequally obstructed airways, the measured resistance will approximate that of the large peripheral pathways (Otis et al. 1950).

In contrast to the normal findings in nonelastic resistance, elastic resistance is high in bronchiolitis, which also means that compliance is markedly decreased (Krieger and Whitten 1964; Panitch et al. 1993; Smith et al. 1993). This decrease in compliance is due, in part, to rapid respiratory rates (Helliesen 1958) and bronchiolar inflammation. The most significant factor, however, is the increased retractive force that is

active at a high level of lung inflation; the degree of lung distention (i.e., V_T) influences work expenditure more significantly when compliance is low. (Speed of distention, i.e., respiratory rate, is a more important influence when airflow resistance is increased.) Krieger and Whitten (1964) found that elastic work was less than expected in bronchiolitis. The rapid shallow mode of breathing, therefore, appears to be economical in terms of work expenditure when compliance is low (Otis et al. 1950), because elastic work is conserved through breathing fast. These points are illustrated in the two cases of bronchiolitis depicted in Fig. 50.2. The relationship between elastic ($1/\text{compliance}$), viscous (resistance), and total work of breathing per minute to frequency of breathing during bronchiolitis and on recovery is shown in graphs that have been calculated from first principles according to the equations described by Otis et al. (1950). The acute and convalescent data are from two cases of bronchiolitis reported by Krieger and Whitten (1964). The upper two panels (A and B) are from a 5.5 kg infant with, predominantly, reduced compliance. The lower two panels (C and D) are from a 4.5 kg infant with a mixed abnormality in compliance and resistance. The acute graphs (A and C) show a doubling of total work, due mainly to increased elastic work. The vertical lines show the infant’s respiratory rate and where this rate intersects the work curves.

“Exhaustion” in infants with bronchiolitis does not result from extreme work during breathing. It is more likely a phenomenon of inability to perform the workload necessary for breathing using hyperinflated lungs. In bronchiolitis, hyperinflation places the muscles of inspiration at a mechanical disadvantage; they are unable to shorten sufficiently to produce the necessary reduction in intrapleural pressure. Another physiologic problem that is considered to follow from obstructive breathing with large negative intrathoracic pressure swings (unbalanced by similar positive pressure efforts) is transpulmonary fluid shifts and the development of pulmonary edema (Stalcup and Mellins 1977). Stokes et al. (1981) did not find evidence for this phenomenon in 26 hyperinflated infants with bronchiolitis. Instead,

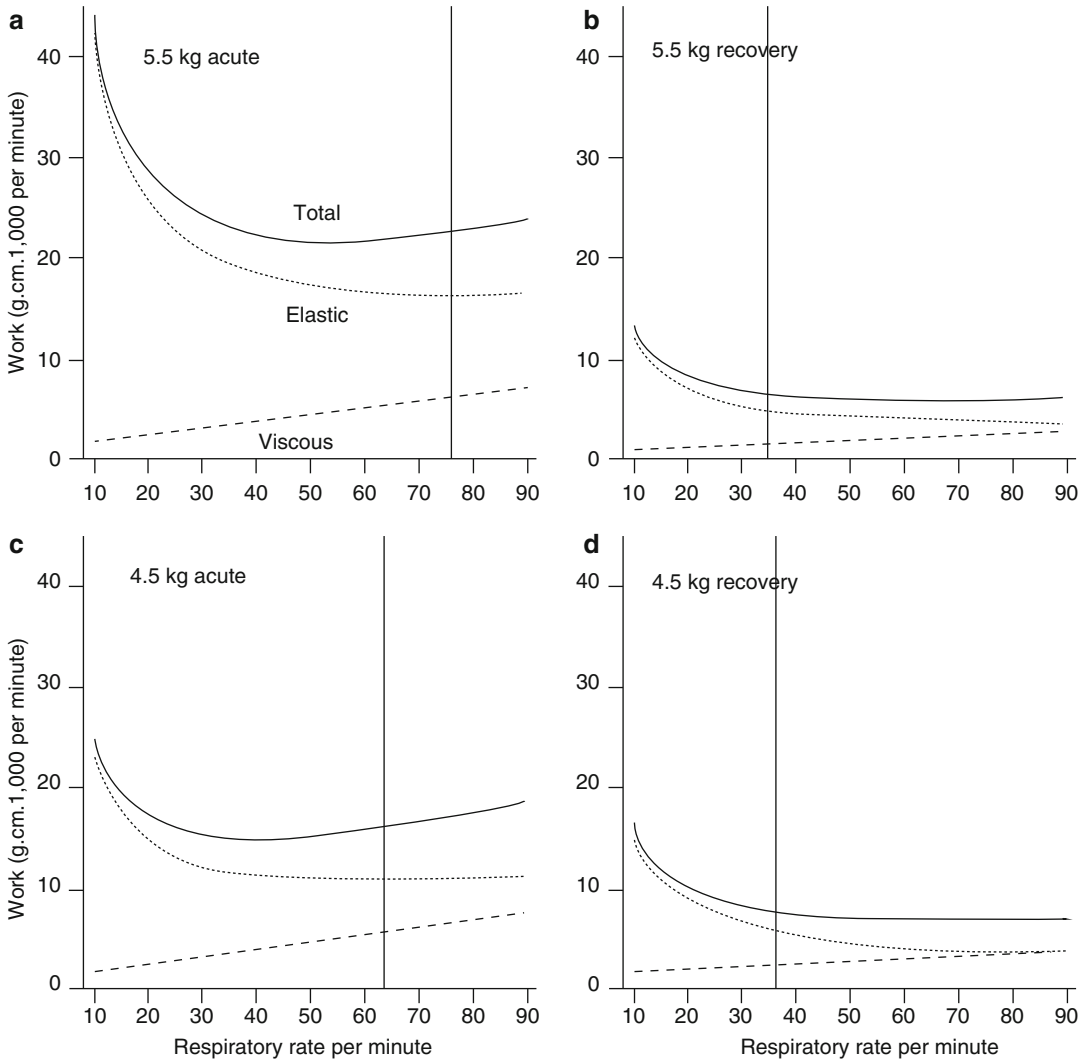


Fig. 50.2 Relationship of elastic, viscous, and total work of breathing per minute to frequency of breathing, during the acute and recovery phase of bronchiolitis. Graphs **a** and **b** refer to a 5.5 kg infant; graphs **c** and **d** refer to a 4.5 kg infant. The data are calculated according to the equations derived by Otis et al. (1950) using real data from two infants reported by Krieger and Whitten (1964) and assuming V_D/V_T changes from acute to recovery, of 0.45–0.25 (see Almeida-Junior et al. 2007). In the acute

graphs (**a** and **c**), total work of breathing is increased compared with the recovery phase. Elastic work decreases with increasing respiratory rate, and viscous work increases with increasing respiratory rate. It is more efficient to breathe at higher respiratory rate during bronchiolitis as demonstrated by the *vertical lines* that show the breathing rate of the infant during each stage of illness. The recovery graphs (**b** and **c**) show optimum respiratory rate as lung mechanics improve

the esophageal pressure monitoring in these infants showed positive values for a large portion of the respiratory cycle, which suggests that positive pressures were produced on expiration. Fluid flux across the alveolar-capillary membrane would be avoided in this state because of limited hydrostatic pressure gradient.

50.4 Respiratory Support for Bronchiolitis

The lung abnormalities in RSV bronchiolitis are hyperinflation, impaired minute ventilation, impaired ventilation-perfusion matching, and an increase in physiologic dead space. As a

consequence, the infant breathes rapidly and has increased elastic and viscous work of breathing. By the time that respiratory support is considered, hypercarbia and hypoxemia are also present. In this setting, *the aim of respiratory support is to overcome the exaggerated work of breathing and abnormal lung mechanics and allow for resolution of the primary pathophysiology.*

Most infants with respiratory failure have “obstructive” lung mechanics, but abnormality in compliance often coexists (Fig. 50.2). The discussion in previous sections (see Sects. 50.3.2 and 50.3.3) indicates that infants with progressive deterioration exhibit a continuum with lessening reserve and compromised homeostasis. A reasonable question, then, is to ask whether this progression can be limited. For example, it is the interaction between the patient’s drive to breathing and abnormal lung mechanics that leads to deterioration and ultimately respiratory failure. So why not intervene early to limit the effect of interaction between drive to breathing and lung mechanics? Altering lung mechanics or altering the effect of interaction between spontaneous breathing and lung mechanics could achieve this result.

50.4.1 Noninvasive Respiratory Support

Sixteen percent of infants hospitalized for RSV have apnea, and its course is usually short-lived. Clinically, these episodes are diaphragmatic or nonobstructive with complete absence of respiratory effort. In these cases, most clinicians would consider that endotracheal intubation with minimal ventilatory support is required until the problem resolves. However, McNamara and Sullivan (1997) reported an improvement in RSV-infection-related apnea with the use of nasopharyngeal prong continuous positive airway pressure (CPAP) alone.

We now know that patients with worsening respiratory distress due to hyperinflation can be supported without using endotracheal intubation. To date, three ways of delivering CPAP have been applied and reported:

- Heated, humidified, high-flow nasal cannulae (HFNC)
- Nasopharyngeal CPAP
- Nasopharyngeal bilevel positive airway pressure (BIPAP)

CPAP maintains positive transpulmonary pressure during spontaneous breathing. It keeps the airways open by moving the equal pressure point more proximal in the airways, such that airway collapse does not occur. It increases secretion clearance. It improves compliance and reduces the work of breathing. Last, it improves gas exchange. However, the cost of these benefits is that its use may lead to lung overinflation.

50.4.2 Heated Humidified High-Flow Nasal Cannulae

HFNC is a relatively new therapy that allows the delivery of high inspired gas flows (1–8 L/min in infants) with or without increased oxygen concentration (McKiernan et al. 2010). Ideally, these devices should deliver flow greater than the patient’s peak inspiratory demand to fully support their minute ventilation. In addition, HFNC provides some level of CPAP, which depends on the flow delivered relative to the size of the patient and on the leak around the nasal cannulae. Flows of 3–5 L/min in term infants have been shown to generate intrapharyngeal pressure of up to 5 cm H₂O (Spence et al. 2007). The advantages of this system over conventional nasal CPAP delivery devices are that it is less cumbersome, better tolerated, and as a consequence used earlier. The disadvantage of this system is that not all attendants may realize that HFNC is CPAP by another name – it isn’t just nasal oxygen. As a consequence, clinical deterioration while receiving HFNC means failed low-level CPAP. McKiernan et al. (2010) reported their PICU experience of managing infants with RSV bronchiolitis before and after the introduction of HFNC to their practice. In the season after the introduction of HFNC, only 9 % of infants required intubation, compared with 23 % in the previous season ($P=0.04$). HFNC decreased respiratory rate to a greater extent than other

devices, and those with the greatest decrease in respiratory rate were least likely to be intubated. The authors also found that median PICU length of stay for cases of bronchiolitis decreased from 6 to 4 days.

50.4.3 Nasal CPAP

We know that in very preterm neonates, early nasal CPAP at birth reduces the number of days of MV (Morley et al. 2008). We also know that application of CPAP to nasal mask better reduces work of breathing when compared with the effect of CPAP applied to an endotracheal tube (Keidan et al. 2000; Pandit et al. 2001). This difference is most likely due to improved patency of the upper airway, rather than major increases in functional residual capacity (FRC) and lung compliance. In view of this theory, we should expect that early intervention with CPAP in bronchiolitis should reduce the work of breathing and may even obviate the need for endotracheal intubation and more invasive support.

Beasley and Jones (1981) reported the use of nasal CPAP early in the course of acute bronchiolitis in 14 infants. They found it improved gas exchange and was free of complications. Thia et al. (2008) showed, in a randomized controlled trial, that there is indeed a reduction in $P_a\text{CO}_2$ when using CPAP. This reduction was better if CPAP was used first than if it was used after a 13-h period with standard treatment. The success rate of noninvasive support in bronchiolitis found in other studies varies from 75 to 83 % (Soong et al. 1993; Campion et al. 2006; Larrar et al. 2006).

50.4.4 BIPAP

Javouhey et al. (2008) reported an approach that bridges the step-up in support between noninvasive airway pressure support and assisted ventilation. These investigators used noninvasive ventilation as their primary form of respiratory support in 27 infants with bronchiolitis. Their initial care was CPAP at 5–10 cm H₂O. If this support failed, they progressed to BIPAP starting

at 12 cm H₂O and, thereafter, gradually increasing to 18 cm H₂O with a backup rate at 30 breaths/min. Compared with their previous experience of similar severity infants, this PICU found that the rate of endotracheal intubation was significantly lower (89 % vs 52 %, $P < 0.01$) and, not surprisingly, the rate of ventilator-associated pneumonia was also much reduced.

50.5 Invasive Conventional Mechanical Ventilation

Mechanical ventilation in RSV bronchiolitis has as its goal patient stability; restoring adequate gas exchange and unloading the work of respiratory muscles bring about this state. The problem is that we are constrained by abnormal lung mechanics and the natural history of the condition. The current practice of respiratory support for bronchiolitis is largely based on clinical judgement and local experience, rather than any consensus (Leclerc et al. 2001). Yet despite this source for variation, the time course of admission on the PICU is remarkably consistent. Cases with no preceding or underlying disease intubated for apnea or respiratory deterioration will require MV for 4–5 days, on average. Cases with preceding disease are ventilated much longer, on average for up to 3 weeks (Stretton et al. 1992; Tasker et al. 2000).

50.5.1 Initial Settings for Mechanical Ventilation

A review of MV settings applied to infants with RSV – reported in the literature 1967–1994 – reveals considerable variation in practice (Table 50.2). Both volume-cycled and pressure-cycled MV are described in the literature with breathing rates varying from 10 to 60 breaths/min, maximum pressures from 20 to 50 cm H₂O, and V_T from 6 to 20 mL/kg (Leclerc et al. 2001). There is no evidence for a superior mode of MV, and it would be difficult to plan such a study since mortality and morbidity are low and, as noted above, time course on PICU is fairly consistent. We are therefore left with a pragmatic

approach that takes account of the prevailing pathophysiology. Figures 50.3 and 50.4 illustrate this point. The inflation-deflation volume curves above FRC are hypothetical for a model 5 kg

infant and based on data presented in the literature. (The curves are a simplification of the ideal situation with a number of assumptions – see figure legend – but they do illustrate the physiology). The “control” cases in Fig. 50.3 represent the mean data for controls in the report by Hammer et al. (1997); if one chose to ventilate a 5 kg infant at a rate of 30 breaths/min with inflation pressure (P_{inf}) of 16 cm H₂O, we may expect P_aCO_2 35 mmHg. The “bronchiolitis” cases in Fig. 50.3 represent the mean data for the unselected cases of bronchiolitis reported by Derish et al. (1998). If we make the assumption that there is an increase in V_D/V_T ratio during

Table 50.2 Ventilator settings used in infants with RSV (1967–1994)

Variable	Value
Ventilator rate (breaths/minute)	10–15 to 30–60
Maximum peak inspiratory pressure (cm H ₂ O)	20–25 to 30–50
Positive end-expiratory pressure (cm H ₂ O)	3–15
Tidal volume (mL/kg)	6–20

Based on data reviewed by Leclerc et al. (2001)

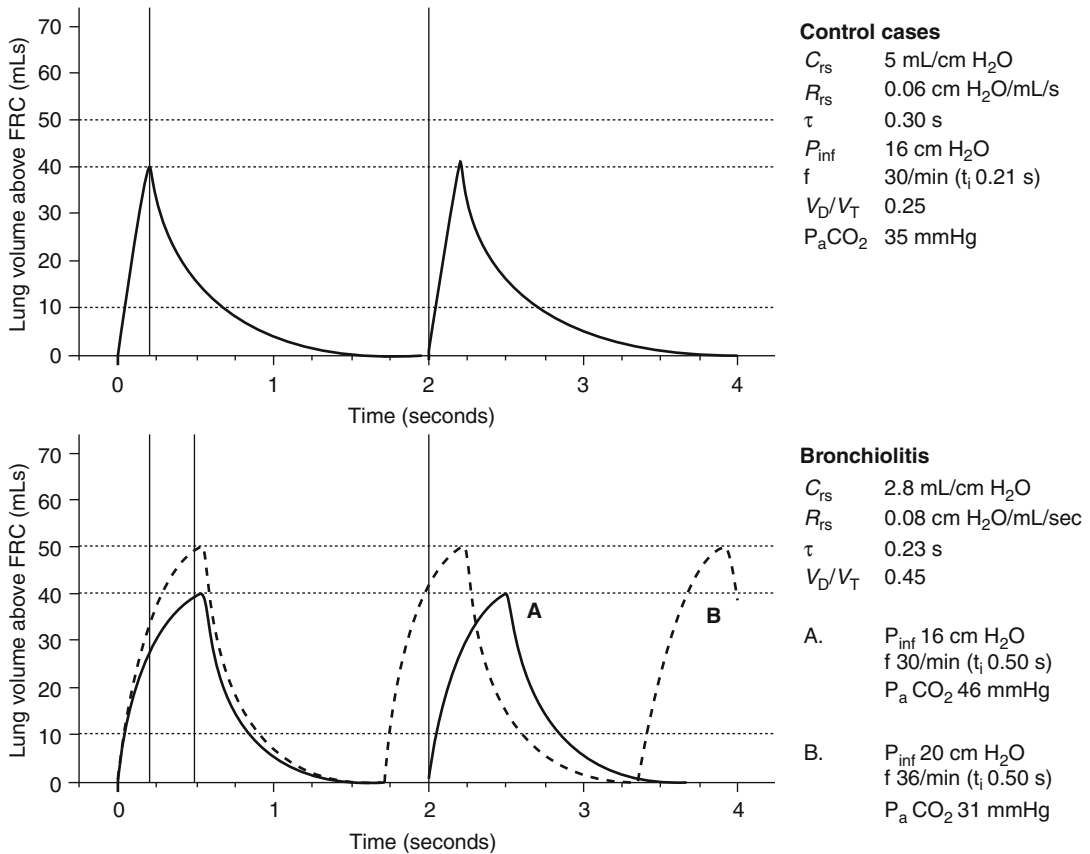


Fig. 50.3 Calculated time course of inflation and deflation curves for artificial ventilation by intermittent application of constant pressure (*square wave*) followed by passive expiration. The graphs are normalized for a model 5 kg infant and assume full sedation and neuromuscular blockade, where C_{rs} is respiratory system compliance, R_{rs} is respiratory system resistance, τ is the time constant, P_{inf} is the inflating pressure, f is the ventilation frequency, t_i is the inspiratory time, and V_D/V_T is the

space-to-tidal volume ratio. The “control” cases are the 26 controls in the series reported by Hammer et al. (1997). The “bronchiolitis” cases are the 25 cases reported by Derish et al. (1998). P_aCO_2 is estimated from the available data and assumes weight of 5 kg and constant respiratory quotient (0.86) and CO₂ production across groups. See text for details. The definitions of curves **A** and **B** are shown in the column

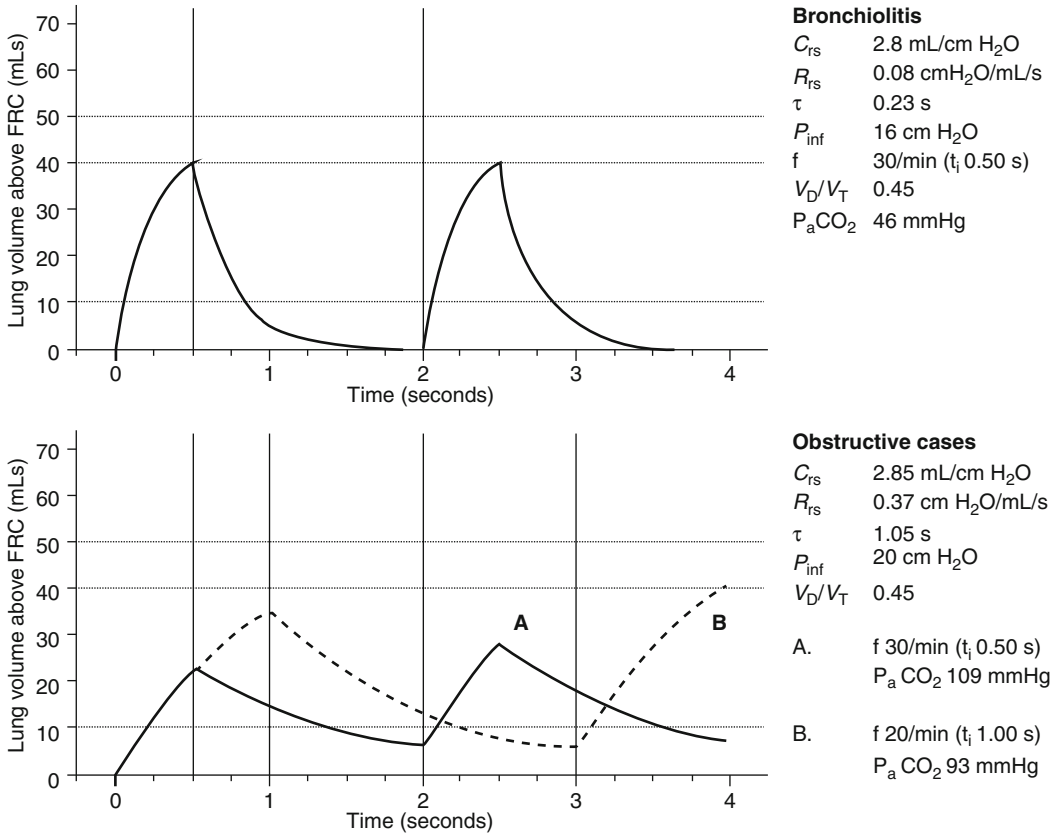


Fig. 50.4 Calculated inflation and deflation curves for “bronchiolitis” and “obstructive” cases. The nomenclature and assumptions are the same as Fig. 50.3. The “bronchiolitis” cases are the 25 cases reported by Derish et al. (1998). The

“obstructive” cases are the 27 selected cases reported by Hammer et al. (1997). See text for details. The definitions of curves **A** and **B** are shown in the column

bronchiolitis (Almeida-Junior et al. 2007) as well as a change in respiratory system compliance (C_{rs}) and resistance (R_{rs}), continuing to ventilate a 5 kg infant at a rate of 30 breaths/min with P_{inf} 16 cm H₂O will result in P_aCO_2 46 mmHg (graph A). Note that the inspiratory time (t_i) has been increased to 0.50 s to allow inflation lung volume above FRC to reach 40 mL (i.e., 8 mL/kg). If the t_i had remained the same as in “controls,” inflation lung volume above FRC would only be 3 mL/kg. Graph B shows the potential danger of responding to P_aCO_2 46 mmHg with simultaneous increases in P_{inf} to 20 cm H₂O and ventilator frequency to 36 breaths/min. Lung volume above FRC rises to 10 mL/kg, and P_aCO_2 falls to hypocapnic level (i.e., 31 mmHg).

Figure 50.4 shows the “bronchiolitis” data from Derish et al. (1998). The upper panel is the

same as graph A in Fig. 50.3 and is used for comparison. The “obstructive” cases represent the mean data for the cases selected as “obstructive” bronchiolitis reported by Hammer et al. (1997). These cases had more severe disease than those reported by Derish et al. (1998). The main difference is that the cases reported by Derish et al. (1998) have an isolated fall in C_{rs} , whereas the cases reported by Hammer et al. (1997) have a fall in C_{rs} and increase in R_{rs} . Graph A shows the inadequacy of ventilation at a rate of 30 breaths/min and a t_i (0.50 s) similar to that for the “bronchiolitis” cases, even though the P_{inf} is increased to 20 cm H₂O. The estimate of P_aCO_2 is now 109 mmHg. The deflation curve also shows the development of dynamic hyperinflation (see end-expiratory volume above zero). Graph B shows the effect of lengthening t_i and decreasing the

ventilator rate. The problem of dynamic hyperinflation continues, but tidal volume is improved. $P_a\text{CO}_2$ is nowhere near being fully controlled (i.e., 93 mmHg), but further increase of P_{inf} , lengthened t_i , and slower ventilator frequency will bring $P_a\text{CO}_2$ to more tolerable levels.

These examples highlight the clinical reality of ventilatory management of bronchiolitis. In less severe cases, with modest decrease in C_{rs} , standard approaches should not cause harm providing ventilator rates are limited to 30 breaths/min. In more severe cases, in the absence of lung function testing, clinical observation of inspiratory and expiratory chest excursion as well as regular auscultation is important. The aim in the “obstructive” lung is to avoid overventilation, with associated hyperinflation, and barotrauma. Ventilatory management should therefore take account of two guiding principles:

- Achieve adequate but not necessarily normal arterial blood gases. Adequate oxygenation is considered present with $P_a\text{O}_2 > 60$ mmHg (8 kPa) or $\text{SpO}_2 > 88\%$. Adequate minute ventilation is considered present with any value of $P_a\text{CO}_2$ that achieves $\text{pH} > 7.25$ (so-called permissive hypercapnia strategy; see Sect. 50.6.1).
- Avoidance of overdistention of hyperinflated lungs by limiting V_T to 6–8 mL/kg. This goal may even necessitate MV at slow ventilation rates (10–15 breaths/min) with prolonged expiratory times to limit ventilator-associated dynamic hyperinflation and impaired minute ventilation. (MV of “restrictive” lungs is discussed in Sect. 50.6). Our recommendation is that ventilator rate should be limited < 30 breaths/min.

All infants will require adequate analgesia and sedation during MV. Morphine (20–40 $\mu\text{g}/\text{kg}/\text{h}$), chloral hydrate (30–50 mg/kg every 4 h), and midazolam (50–250 $\mu\text{g}/\text{kg}/\text{h}$) are commonly used. In combination, these drugs will alter the CO_2 -ventilatory response, with a decrease in the slope and an increase in the apnea threshold (Yaster et al. 1990). These features are useful when applying the permissive hypercapnia strategy (see Sect. 50.6.1). However, these effects may be detrimental after extubation since the expected protective response to worsening gas

exchange will be blunted, hence the need for continued close observation 12–24 h after extubation (see 4.5.3). When neuromuscular blockade is required, vecuronium (50–100 $\mu\text{g}/\text{kg}/\text{h}$) can be used. The main reason for neuromuscular blockade is to enable MV at either very slow rates or fast (HFOV) rates and prevent ventilator-patient asynchrony. As will be discussed later, neuromuscular blockade is not necessarily required during HFOV (see Sect. 50.6.2).

50.5.2 Positive End-Expiratory Pressure

In all intubated patients, the removal of intrinsic positive end-expiratory pressure (PEEP) and lowering of end-expiratory volume necessitates the use of applied PEEP in order to avoid atelectasis. However, the use of PEEP in bronchiolitis is controversial. Not all centers use it, but in those that do, it is used at levels between 3 and 15 cm H_2O (Table 50.2). In bronchiolitis, low-level PEEP during MV is used with the idea that it decreases airway resistance and improves gas exchange (Wren et al. 1982; Frankel et al. 1986). But it is also possible that PEEP may not have these desired effects in bronchiolitis because airways of such infants are smaller and may not be distensible. To date, studies of lung mechanics and PEEP have shown varied results (Smith et al. 1993; Gauthier et al. 1998; Marchal et al. 1998). Smith et al. (1993) studied the effect of increasing PEEP in steps of 3 cm H_2O (0–9 cm H_2O) and found that applied PEEP at any level failed to consistently improve passive expiratory airway resistance or increase compliance from baseline. Inadvertent or auto-PEEP (i.e., the accompanying residual airway pressure at end expiration in MV patients) occurred in all cases (5 ± 2 cm H_2O), but it had no influence on the response of mechanics to applied PEEP, except that peak inspiratory pressures increased when applied PEEP was greater than auto-PEEP. (It should be noted that the presence of auto-PEEP requires that applied PEEP be set at the same level in order to optimize expiratory flow.) In contrast to the Smith et al. (1993) findings, Gauthier et al.

(1998) contend that there may be an optimum level of PEEP in acute bronchiolitis (Marchal et al. 1998).

When RSV lower respiratory tract disease is complicated by parenchymal restrictive disease – usually associated with some obstructive component – an adequate level of applied PEEP is certainly needed (Hammer et al. 1997) (see Sect. 50.6). Last, when significant levels of PEEP are being used, it should not be forgotten that it will further complicate the cardiac-pulmonary-renal interaction of bronchiolitis that results in abnormal water and electrolyte homeostasis (Gozal et al. 1990; Poddar et al. 1995). Therefore, whenever PEEP is used, fluids, electrolytes, and hydration must be closely monitored. Our practice is to restrict water to 67–75 % of maintenance requirements. Careful attention should also be given to cardiac function and the need for volume and inotropes (Simpson et al. 1974; Njoku and Kliegman 1993; Kim and Frankel 1997; Arnold et al. 2000; Checchia et al. 2000).

50.5.3 Airway Obstruction in Mechanically Ventilated RSV Bronchiolitis

A few studies have assessed pulmonary function and the use of bronchodilators to treat airway obstruction during MV for the very acute stage of RSV bronchiolitis (Mallory et al. 1989; Smith et al. 1990; Hammer et al. 1995, 1997). One limitation in assessing R_{rs} , and therefore making some conclusion about airway obstruction, is that the measurement is codependent on airway caliber and lung volume; bronchodilation and decrease in air trapping have opposite effects, and few studies have reported lung volume changes. Hammer et al. (1995, 1997) found that most infants requiring intubation and MV have evidence of obstructive airway disease with reduced flows, air trapping, and a component of restrictive lung disease. Albuterol inhalation affected either all or none of the measured lung functions; if a decrease in R_{rs} occurred, it was always accompanied by a reduc-

tion in air trapping. Figure 50.5 illustrates this point. The nomenclature is the same as Fig. 50.3. The figure uses the mean data of “obstructive” patients reported by Hammer et al. (1997). The upper panel shows that in these selected patients (more severe than the cases reported by Derish et al. (1998); see above), MV with a rate of 20 breaths/min (t_i 1.00 s) and P_{inf} 20 cm H₂O would result in P_aCO_2 93 mmHg. The middle and lower panels show the hypothetical effect of influencing either R_{rs} or C_{rs} or both together. Graph A in the middle panel shows the effect on inflation and deflation of halving R_{rs} from 0.38 to 0.19 cm H₂O/mL/s. Lung volume above FRC is increased, and there is reduction in dynamic hyperinflation. The theoretical consequence on P_aCO_2 is a reduction from 93 to 58 mmHg. Graph B in the middle panel shows the effect of increasing C_{rs} from 2.85 to 4.28 mL/cm H₂O. Dynamic hyperinflation is worsened, and there is no improvement in P_aCO_2 . Graphs A and B in the lower panel show the combined effect of making the above changes in R_{rs} and C_{rs} but simultaneously rather than separately. Graph A shows that dynamic hyperinflation remains, but there is the additional problem of overinflation with tidal volume 12 mL/kg. Initially, P_aCO_2 will be driven down even further to 49 mmHg. Graph B shows that decreasing t_i from 1.00 to 0.75 s will lessen the effect of dynamic hyperinflation (estimated P_aCO_2 62 mmHg), but an even slower ventilator rate may be needed.

Figures 50.3, 50.4, and 50.5 show heterogeneity in the physiology of bronchiolitis. It is therefore not surprising that the usefulness of β_2 -adrenergic drugs (e.g., salbutamol and albuterol) remains controversial in standard clinical practice. The results of studies are mixed, and many infants fail to show clinically significant improvement, but this finding is probably a reflection of the variation in (or lack of) abnormality in R_{rs} (Derish et al. 1998). There is also some evidence that combined β - and α -agonists (e.g., epinephrine) are more effective, because of their additional vasoconstrictor effects, which decrease bronchial mucosal edema and hence airflow obstruction (Sanchez et al. 1993; Menon et al. 1995; Numa et al. 2001). These

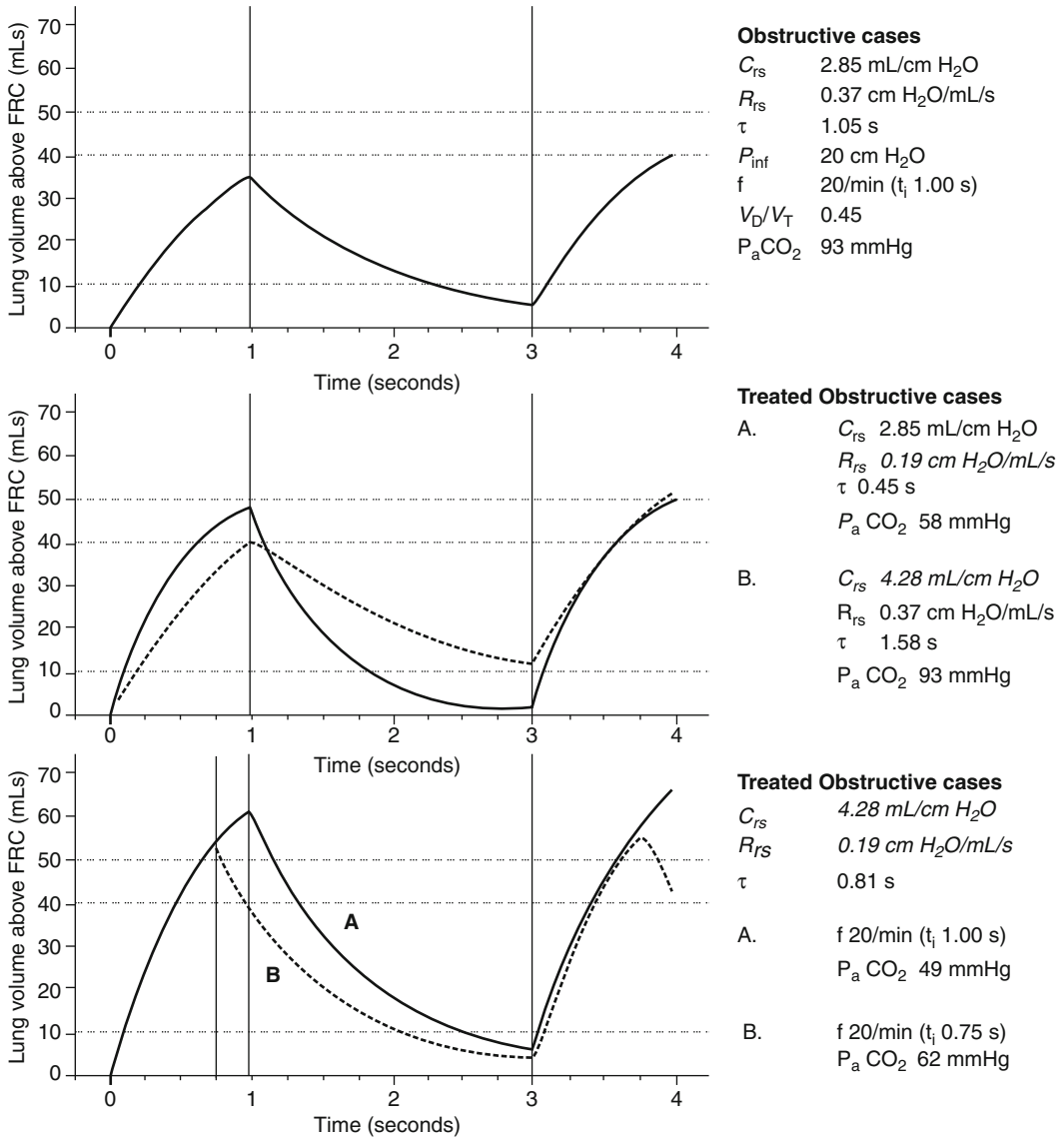


Fig. 50.5 Calculated inflation and deflation curves for “obstructive” bronchiolitis and the theoretical response to changes in lung function. The nomenclature and assumptions are the same as Fig. 50.3. The “obstructive” cases

are the 27 selected cases reported by Hammer et al. (1997). See text for details. The definitions of **A** and **B** curves are shown in the column

potential beneficial effects, however, may be outweighed or masked by other drug effects having an opposite influence on blood gases. For example, all of these drugs increase total body oxygen consumption, minute ventilation, and energy requirement by their direct or indirect effects on other organs through β -receptor stimulation (Newth et al. 1997b).

50.5.4 Weaning from Mechanical Ventilation

Weaning from MV is achieved by the gradual reduction of ventilatory support until spontaneous breathing can be fully resumed. No single variable or marker can predict progression of MV towards extubation. There are a variety of existing surrogate

markers that we use to reflect major components of the respiratory system including ventilatory drive, ventilatory reserve, and efficiency of gas exchange. These include respiratory frequency, V_T , minute ventilation, gas diffusion (P_aO_2 , P_aCO_2 , $AaDO_2$) and pH, muscle strength, SpO_2 , and heart rate.

In practice, patients are removed from ventilatory support when the attendant considers it is safe to do so from first principles. In regard to blood gas parameters, this means adequate oxygenation in a $FiO_2 < 0.4$ and normal pH with good respiratory drive in the absence of hypercarbia. Discharge from the PICU can be considered once the patient has managed at least 12–24 h without any respiratory assistance (see Sect. 50.5.1).

50.6 Acute Respiratory Distress Syndrome and RSV

On average, most MV patients with RSV bronchiolitis will spend less than 7 days on the PICU (Tasker et al. 2000). If there is a deviation from this trajectory, then it is important to consider whether the course of illness is complicated by another process such as infection. For example, up to 40 % of patients admitted with severe RSV bronchiolitis are infected with bacteria in their lower airways and are at increased risk of bacterial pneumonia. Thorburn et al. (2006) undertook a prospective microbiological analysis of lower airway secretions in all RSV-positive bronchiolitis, MV patients on admission to their PICU during three consecutive RSV seasons. Seventy of 165 children (42.4 %) had lower airway secretions positive for bacteria; 36 (21.8 %) were coinfecting. If higher ventilator rates are considered necessary (and tolerated), then the operator should consider whether the infant really does have bronchiolitis physiology. If mean airway pressure is above 10 cm H_2O and $AaDO_2$ above 400 mmHg, then the possibility of pulmonary restrictive disease should be considered (Hammer et al. 1997; Tasker et al. 2000). In this setting, the aim of MV is to recruit lung volume with the addition of PEEP and to limit barotrauma by limiting V_T to less than 8 mL/kg.

In RSV lower respiratory tract disease, two distinct patterns in lung function changes have been

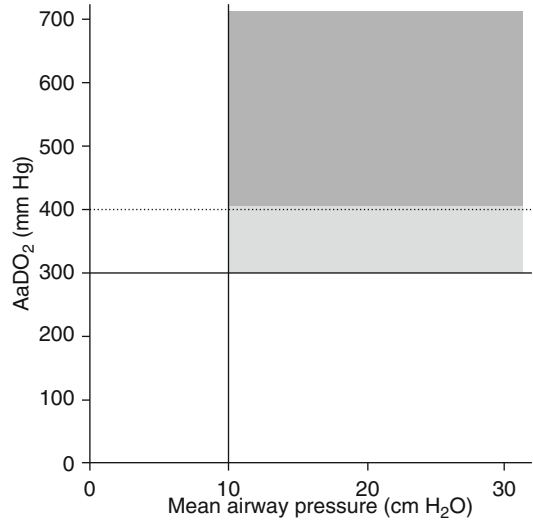


Fig. 50.6 Plot of best mean airway pressure and alveolar-arterial oxygen gradient ($AaDO_2$) from the first 48 h of mechanical ventilation. Patient data that falls within the darker shaded region within the first 24 h or lighter shaded region within the second 24 h reflects severe disease (i.e., likely acute respiratory distress syndrome or severe restrictive disease) with high sensitivity and specificity (Redrawn from Tasker et al. (2000))

identified (Hammer et al. 1997; Newth et al. 1997a). As noted above, most infants suffer from an “obstructive” pattern of disease (i.e., mixed change with modest fall in C_{rs} and increase in R_{rs}). Severe “restrictive” parenchymal disease (i.e., severe fall in C_{rs}), usually referred to as pneumonitis, is seen in those whose condition is often compatible with a diagnosis of acute respiratory distress syndrome (ARDS) (Patel et al. 1999; Tasker et al. 2000). ARDS is defined clinically using the criteria recommended by the American-European consensus (Bernard et al. 1994): acute disease onset, P_aO_2/FiO_2 ratio ≤ 200 mmHg, bilateral infiltrates on chest radiograph, and the absence of clinical evidence of left atrial hypertension. Patients with RSV-induced ARDS are, in general, younger and have a longer time course on MV. Tasker et al. (2000) reported that 20 % of MV infants have this pattern of disease and their usual time course is at least 2 weeks on the PICU. These infants demonstrate significant intrapulmonary shunt with best $AaDO_2 > 400$ mmHg within the first 48 h of MV (Fig. 50.6). The strategies that are used in RSV-related ARDS are discussed below.

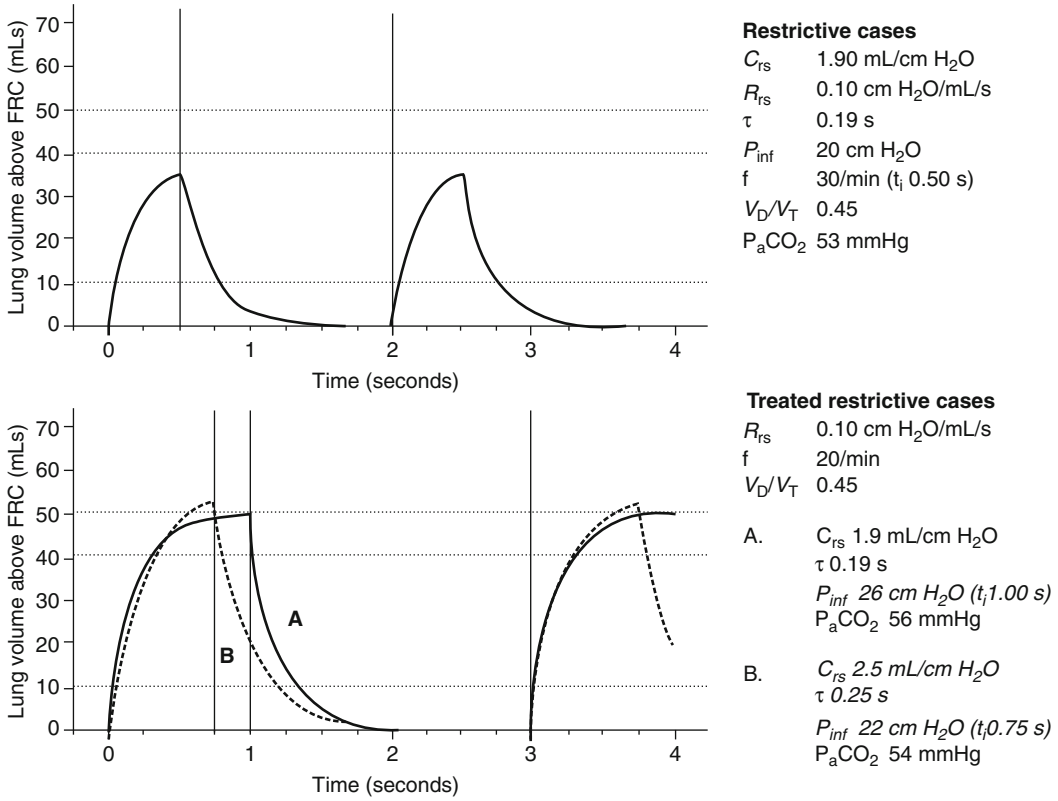


Fig. 50.7 Calculated inflation and deflation curves for “restrictive” bronchiolitis and theoretical response to changes in lung function. The nomenclature and assumptions are the same as Fig. 50.3. The “restrictive” cases are

the 10 selected cases reported by Hammer et al. (1997). See text for details. The definitions of curves **A** and **B** are shown in the column

50.6.1 Permissive Hypercapnia

Permissive hypercapnia has been suggested as a lung protective strategy for adults with ARDS. The strategy allows for a degree of hypercapnia provided the arterial pH does not fall below a preset minimum value; it may be used in combination with a degree of permissive hypoxemia with SpO₂ ~88 % in order to minimize mean airway pressure and hence barotrauma. Reda et al. (1997) reviewed their experience of this strategy in 29 infants with RSV bronchiolitis and reported significantly less barotrauma and shorter duration of MV and hospital stay. In contrast, Tibby et al. (1999) had a different experience in their 28 infants. They could achieve the strategy – as demonstrated by mean P_aCO_2 7.6 kPa (57 mmHg), mean pH 7.34, and maximal peak inspiratory pressure 25 cm H₂O – but it did not result in

improved survival, less barotrauma, or less nosocomial infection, when compared with their experience before using this strategy. Furthermore, the duration of MV was longer, although not statistically significant. The authors concluded that since they could not show a benefit of permissive hypercapnia, a prospective randomized controlled trial is needed. These reports are over 10 years old, and it is likely that equipoise is now lost. Most attendants incorporate a version of permissive hypercapnia in conventional MV for bronchiolitis (see Sect. 50.5.1). Again, it comes down to the mechanical cost of trying to achieve normal P_aCO_2 and the benefit of permitting higher values so that reduced ventilator settings can be applied.

Figure 50.7 uses the same nomenclature as Fig. 50.3. The figure uses the mean data of “restrictive” patients reported by Hammer et al. (1997). The upper panel shows that MV with a

rate of 30 breaths/min (t_i 0.50 s) and P_{inf} 20 cm H₂O would result in P_aCO_2 ~50 mmHg. Graphs A and B show that there is little or no effect on P_aCO_2 with a variety of theoretical manipulations in P_{inf} or C_{rs} . In comparison with “obstructive” patients and “controls,” FRC is low (Hammer et al. 1997). The implication of Fig. 50.7 is that recruitment of lung volume with consequent fall in C_{rs} should be the initial strategy.

50.6.2 High-Frequency Oscillatory Ventilation

High V_T and minute ventilation during MV result in high peak airway pressures and risk of air leak, as well as the necessity to use neuromuscular blockade. HFOV has been described as a rescue intervention for severe cases of RSV bronchiolitis since it may reduce these risks (Thompson et al. 1995; Medbo et al. 1997; Duval et al. 1999; Kneyber et al. 2005).

In a large multicenter review of HFOV, 18 of 27 patients with RSV infection had a successful response and were weaned to conventional MV (Arnold et al. 2000). Interestingly, the authors found that infants with RSV had significantly longer periods on HFOV compared with those with other causes of lower airway disease (10.5 vs 6.8 days). Recently, however, Berner et al. (2008) reported much shorter duration of HFOV (5.0 ± 1.6 days) in nine infants with RSV bronchiolitis (5.0 ± 1.6 days). The authors attributed this result to better P_aCO_2 control brought about by their practice of allowing infants to breathe spontaneously while on HFOV. This practice is used sometimes in neonatal care (Froese and Kinsella 2005). There are reasons why this approach is beneficial in infants. In children and adults, spontaneous breathing during HFOV leads to discomfort and distress which is probably due to the high level of imposed work of breathing (van Heerde et al. 2006a, b). In bench testing, with simulators, the level of imposed work of breathing in “patients” heavier than 25 kg exceeds normal physiologic work of breathing by ~200 % (van Heerde et al. 2006b). In contrast, simulations for infants weighing

3.5 kg show a low level of imposed work of breathing; hence, infants are able to tolerate spontaneous breathing during HFOV.

50.6.3 Extracorporeal Membrane Oxygenation

Despite maximal MV management, a small subgroup of infants with RSV bronchiolitis develop profound hypoxemia and a need for extracorporeal membrane oxygenation (ECMO). This form of support was first successfully applied to such infants in the period 1983–1988 (Steinhorn and Green 1990). Since then, it has been recognized as a potential alternative to MV for life-threatening RSV (Khan et al. 1995; Flamant et al. 2005). Steinhorn and Green (1990) reported that the need for ECMO during RSV bronchiolitis was observed mainly in previously premature infants, and their survival was 58 %. Khan et al. (1995) had a similar series, but only seven of their 24 cases had bronchopulmonary dysplasia – the survival rate was 96 %. Flamant et al. (2005) reported a survival rate of 70 % in a series of 14 cases.

This collected experience, over 20 years, raises two important questions. Why do some infants have such severe course of illness? Does our MV management make lung disease worse? It is beyond the scope of this chapter to review the literature on the biology of severity of RSV disease and genetic predisposition. Khan et al. (1995) and Flamant et al. (2005) suggest that bronchopulmonary dysplasia is an important risk factor. The question of whether attendants can make lung disease worse is also important and concerns us here. The series reported by Khan et al. (1995) was collected during 1989–1995, a time when HFOV was not in general use. This fact is reflected in the pre-ECMO summary measures of MV, which indicate high-pressure ventilation: mean peak inspiratory pressure 36 ± 5.5 cm H₂O (mean \pm standard deviation), mean PEEP 5.8 ± 2.2 cm H₂O, and mean airway pressure 20 ± 4.7 cm H₂O. In addition, the normal pre-ECMO pH 7.43 ± 0.13 and P_aCO_2 5.8 ± 2.1 kPa (44 ± 16 mmHg) suggest that the contemporary target for MV was normal gas exchange even at the cost of high MV pressures, rather than a more

permissive approach to hypercapnia that we would now accept (see also Sect. 50.6.1). Given that 96 % of these infants survived, the implication is that many such infants would not need ECMO where current standards are applied. The Flamant et al. (2005) supports this notion. This series was collected during 1996–2003 and 70 % of their ECMO cases had been on HFOV and 64 % had received inhaled nitric oxide before ECMO (see also Sect. 50.7.2). The authors do not provide any pre-ECMO pH or $P_a\text{CO}_2$ data for comparison.

50.7 Other Lung-Directed Therapies

There have been numerous clinical trials on treatments for bronchiolitis, such as bronchodilators, corticosteroids, and ribavirin (King et al. 2004). However, to date, little evidence exists for the effectiveness of any of these interventions. Most studies are underpowered and not of sufficient size or quality to rule out effectiveness. There is even less evidence in infants receiving these therapies during MV (Davison et al. 2004). In these cases, there is the added problem of clinical heterogeneity and lack of readily available bedside tools to classify or stratify severity. The illustrations in this chapter (see Figs. 50.3, 50.4, 50.5, and 50.7) indicate that targeting R_{rs} , or R_{rs} and C_{rs} together, should ease MV support. The question is whether these manipulations alter the time course of MV and PICU stay (outcomes often used in clinical trials). We have already discussed altering R_{rs} with bronchodilators (see Sect. 50.5.3). Another strategy that could be used to decrease R_{rs} is helium-oxygen gas mixture for ventilation. Also, we could use surfactant to increase C_{rs} . Last, we could use inhaled nitric oxide to match lung perfusion to ventilation, i.e., to reduce V_D/V_T . Each of these approaches is discussed.

50.7.1 Helium-Oxygen Gas Mixtures

Helium is an inert gas with a density that is one-seventh that of air. Carbon dioxide diffuses more

easily through helium than through air. Laminar flow in narrowed airways is more likely to be preserved when helium is used instead of air (Gupta and Cheifetz 2005). Taken together, helium and oxygen (heliox) mixtures should decrease resistance to gas flow and theoretically reduce the work of breathing in conditions where increased resistance plays a part.

In the early stage of RSV lower respiratory tract disease, the use of heliox has had varied effects. An early pilot study of 18 infants with bronchiolitis showed that after 20 min of heliox, there was a reduction in clinical score and a 1.8 % improvement in SpO_2 , although six infants went on to require CPAP (Hollman et al. 1998). A multicenter, randomized controlled trial in 39 non-intubated infants using a heliox mixture with 78 % helium within 8 h of admission to PICU showed no difference in the proportion that required MV (19 % controls vs 22 % heliox group) (Liet et al. 2005). A crossover study showed that 30 min of CPAP with or without 70 %:30 % helium-oxygen reduced clinical score and transcutaneous PCO_2 (Martinon-Torres et al. 2008). Patients receiving heliox nasal CPAP had a greater decrease in clinical score compared with air-oxygen nasal CPAP (2.12 vs 1.08 points) and a greater decrease in transcutaneous PCO_2 (9.7 vs 5.4 mmHg or 1.3 vs 0.7 kPa). Most recently, a Cochrane review of four quasi-trials involving 84 infants concluded: “the addition of heliox therapy may significantly reduce a clinical score evaluating respiratory distress in the first hour after starting treatment... nevertheless, there was no reduction in the rate of intubation, in the need for MV, or in the length of PICU stay” (Liet et al. 2010).

There is even less evidence for using heliox in MV cases of RSV bronchiolitis. Gross et al. (2000) studied 10 infants each given a sequence of heliox mixtures (50 %:50 %, 60 %:40 %, and 70 %:30 %) and found that increasingly higher doses failed to improve gas exchange. In contrast to these findings, Kneyber et al. (2009) studied 13 infants and found that R_{rs} was significantly decreased by MV with 60 %:40 % heliox, although this improvement was not accompanied by improved CO_2 elimination, decreased peak

expiratory flow rate, or decreased end-expiratory lung volume.

50.7.2 Surfactant Therapy

Endogenous surfactant activity can be impaired in the course of RSV disease for several reasons: (a) the virus-induced damage of type II pneumocytes results in a reduction of surfactant synthesis, (b) the protein-rich edema causes an inactivation of surfactant by specific inhibitors and plasma components, (c) damage to the alveolar-capillary membrane may cause loss of surfactant into the interstitium and blood, (d) MV with large V_T and high FiO_2 can deplete further or damage surfactant, and (e) lack or inactivity of surfactant favors bronchiolar and alveolar collapse and lung permeability to macromolecules (Luchetti et al. 2002).

The theoretical rationale for using surfactant treatment in RSV bronchiolitis is to restore the surfactant pool, so that while MV with PEEP recruits alveoli, surfactant may stabilize them, maintain their patency, and thus restore ventilation of non-ventilated regions of the lung. It should improve lung compliance. A Cochrane review of three trials (Luchetti et al. 1998, 2002; Tibby et al. 2000) of natural surfactant in bronchiolitis demonstrates a trend towards a decrease in the duration of ventilatory support (mean 2.6 days, $P=0.07$) and a decrease in PICU stay (mean 3.3 days, $P=0.04$) without adverse effects, but only 79 infants were included in the review (Ventre et al. 2006).

50.7.3 Inhaled Nitric Oxide

Inhaled nitric oxide may improve oxygenation in certain infants with RSV bronchiolitis, but it does not appear to have any overall benefit in groups of patients (Patel et al. 1999). It does not function as a bronchodilator, and no studies have looked at its effect on V_D/V_T . In the wider context of treatment during acute hypoxemic respiratory failure, it does result in improvement in oxygenation, but there is no improvement in outcome (Dobyns et al. 1999).

Future Perspectives

Viral bronchiolitis accounts for almost 10 % of PICU admissions in the UK, some 1,000 infants per year (O'Donnell et al. 2010); perhaps it is time to get the evidence for how best to manage such patients. For example:

- How do we decide when to intervene with noninvasive support?
- Does noninvasive support limit the progression in worsening lung mechanics?
- Can we better characterize the clinical phenotypes of “bronchiolitis” requiring conventional MV using widely available techniques?
- Can we standardize MV settings according to clinical phenotype and lung function parameters?
- Can the intrapulmonary consequences of bronchiolitis (e.g., ventilation-perfusion inequalities and shunt, raised V_D/V_T , increased resistance, decreased compliance, prolonged time constant) be targeted by specific therapies?

Essentials to Remember

Respiratory support of infants with bronchiolitis is complicated, and we have the potential for making a patient worse after endotracheal intubation if we do not pay attention to the interaction between lung mechanics and the time course of mechanical ventilation. The essential points to remember are:

- The progression in deteriorating pulmonary mechanics is decrease in respiratory system compliance (“bronchiolitis”), followed by combined decrease in respiratory system compliance and increase in respiratory system resistance (“obstructive”), followed by a state where low lung volume and very low respiratory system compliance predominate (“restrictive”).
- The acute deterioration in pulmonary mechanics – bronchiolitis and obstructive – is accompanied by increased dead

space-to-tidal volume ratio and pulmonary ventilation-perfusion inequalities.

- Before endotracheal intubation, the aim of respiratory support is to overcome the exaggerated work of breathing and abnormal lung mechanics and allow for resolution of the primary pathophysiology. Various forms of noninvasive CPAP have a role.
- After endotracheal intubation, each phase of the condition – bronchiolitis, obstructive, and restrictive – requires different strategies. In the acute phase, focus on the time course of lung inflation, respiratory system resistance, and the pulmonary time constant for deflation will limit overinflation and dynamic hyperinflation. Read the whole chapter for more details!

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