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Conventional Mechanical Ventilation: Traditional and New Strategies

Waldemar A. Carlo, MD* and Namasivayam Ambalavanan, MD†

OBJECTIVES

After completing this article, readers should be able to:

1. Describe which mechanical properties of the respiratory system affect the interaction between the ventilator and the infant.
2. Delineate the factors on which ventilator adjustments should be based.
3. Describe which effects of mechanical ventilation may cause lung injury.

Introduction

Important breakthroughs in neonatology, particularly in prevention and treatment of respiratory disorders, have extended the limits of viability to lower gestational ages. Despite these advances, conventional mechanical ventilation (CMV) (usually pressure-limited intermittent mandatory ventilation in neonates) remains an essential therapy in neonatal intensive care. Advances in CMV, exogenous surfactant supplementation, and antenatal steroids have resulted in improved outcomes of critically ill neonates. Despite newer alternative ventilatory modes, such as high-frequency ventilation and patient-initiated mechanical ventilation, CMV continues to be the mainstay in the care of neonates.

Improved survival due to advances in neonatal care has resulted in an increased number of infants who are at risk for chronic lung disease and air leaks. Although the etiology of lung injury is multifactorial, recent animal and clinical data indicate that lung injury is largely dependent on the ventilatory strategies used. Optimal ventilatory strategies may improve the benefit-to-risk ratio by providing the best gas exchange with the smallest amount of lung injury. This article highlights the concepts of pulmonary mechanics, gas exchange, control of breathing, and lung injury

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that can be used to optimize CMV. Alternative modes of ventilation also are addressed. This evidenced-based review uses data from integrative studies (eg, meta-analyses, randomized clinical trials) whenever possible. However, because many controversies surrounding CMV have not been resolved with clinical studies, lesser levels of evidence are used as appropriate.

Gas Exchange

The general goal of CMV is to achieve normal blood gases, but ventilator adjustments also should be based on other factors, such as pulmonary mechanics, gas exchange mechanisms, control of breathing, and lung injury. A thorough understanding of these factors can help to guide the selection of ventilatory strategies. Neonates are vulnerable to impaired gas exchange, a common occurrence in this population, because of their high metabolic rate, decreased functional residual capacity, decreased compliance, and potential for right-to-left shunts through the ductus arteriosus or foramen ovale. Hypercapnia and hypoxemia may coexist, although some disorders may affect gas exchange differentially.

HYPERCAPNIA

Hypercapnia usually is caused by hypoventilation or severe ventilation-perfusion mismatch. Carbon dioxide normally diffuses readily from the blood into the alveoli. Elimination of carbon dioxide from the alveoli is directly propor-

tional to alveolar minute ventilation (Fig. 1), which is determined by the product of tidal volume (minus dead space ventilation) and frequency. Thus, the alveolar minute ventilation is calculated as:

$$\text{alveolar minute ventilation} = (\text{tidal volume} - \text{dead space}) \times \text{frequency}$$

Tidal volume is the volume of gas inhaled (or exhaled) with each breath. Frequency is the number of breaths per minute. Dead space is that part of the tidal volume not involved in gas exchange, such as the volume of gas that fills the conducting airways. Because dead space is relatively constant, increases in either tidal volume or frequency increase alveolar ventilation and decrease PaCO_2 . Also, because dead space ventilation is constant, changes in tidal volume appear to be more effective at altering carbon dioxide elimination than alterations in frequency or other ventilatory parameters. For example, a 50% increase of tidal volume from 6 to 9 mL/kg, with dead space at a constant 3 mL/kg, doubles alveolar ventilation (from 3 to 6 mL/kg x frequency). However, increases in tidal volume may augment the risk of "volutrauma." Tidal volume depends largely on the compliance of the respiratory system and on the pressure difference (ie, peak inspiratory

ABBREVIATIONS

CMV:	conventional mechanical ventilation
CPAP:	continuous positive airway pressure
FiO_2 :	fraction of inspired oxygen concentration
I:E:	inspiratory-to-expiratory time
MAP:	mean airway pressure
PEEP:	positive end-expiratory pressure
PIP:	peak inspiratory pressure
RDS:	respiratory distress syndrome
T_E :	expiratory time
T_I :	inspiratory time

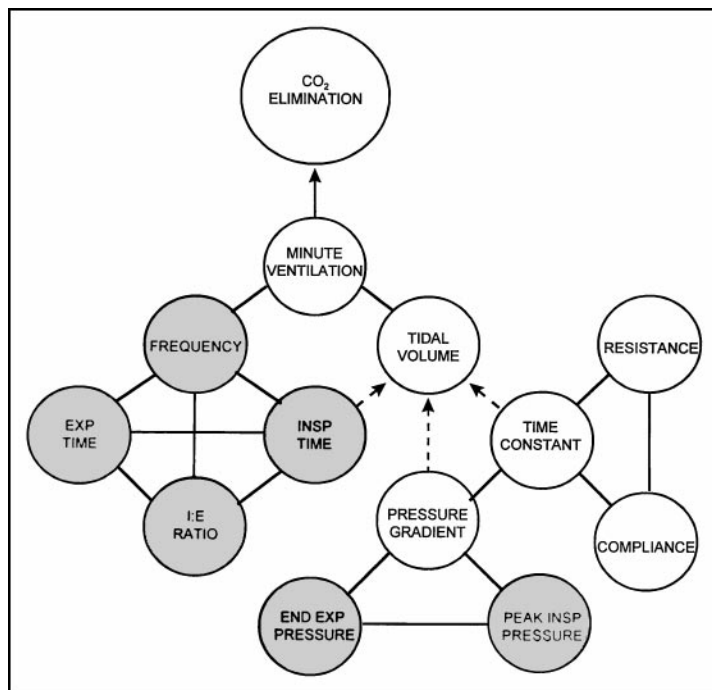


FIGURE 1. Relationships among various ventilator-controlled (shaded circles) and pulmonary mechanics (unshaded circles) that determine minute ventilation during pressure-limited, time-cycled ventilation. The relationships between the circles joined by solid lines are described by simple mathematical equations. The dashed lines represent relationships that cannot be calculated precisely without considering other variables, such as pulmonary mechanics. Thus, simple mathematical equations determine the time constant of the lungs, the pressure gradient, and the inspiratory time. These, in turn, determine the delivered tidal volume, which when multiplied by the respiratory frequency, gives the minute ventilation. Alveolar ventilation can be calculated from the product of tidal volume and frequency when dead space is subtracted from the former. From Carlo WA, Greenough A, Chatburn RL. *Advances in conventional mechanical ventilation.* In: Boynton BR, Carlo WA, Jobe AH, eds. *New Therapies for Neonatal Respiratory Failure.* Boston, Mass: Cambridge University Press; 1994.

pressure minus positive end expiratory pressure).

HYPOXEMIA

Hypoxemia is usually due to ventilation-perfusion mismatch or right-to-left shunting, although diffusion abnormalities and hypoventilation (eg, apnea) also may be at fault. Ventilation-perfusion mismatch is a major cause of hypoxemia in infants who have respiratory distress syndrome (RDS) and other types of respiratory failure. Ventilation-perfusion mismatch usually is caused by poor ventilation of alveoli relative to their perfusion. Shunting can be intra- or extracardiac (eg, pulmonary).

During conventional ventilation, oxygenation is determined by the fraction of inspired oxygen concentration (FiO₂) and the mean airway pressure (MAP) (Fig. 2). MAP is

the average airway pressure during the respiratory cycle and can be calculated by dividing the area under the airway pressure curve by the duration of the cycle, from which the following equation is derived:

$$\text{MAP} = K (\text{PIP} - \text{PEEP}) \left(\frac{T_I}{T_I + T_E} \right) + \text{PEEP}$$

K is a constant determined by the flow rate and the rate of rise of the airway pressure curve, PIP is peak inspiratory pressure, PEEP is positive end-expiratory pressure, T_I is inspiratory time, and T_E is expiratory time. This equation indicates why MAP increases with increasing PIP, PEEP, inspiratory-to-expiratory time (I:E) ratio, and flow (increases K by creating a more square waveform).

The mechanism by which increases in MAP generally improve

oxygenation seems to be the increased lung volume and improved ventilation-perfusion matching. Although there is a direct relationship between MAP and oxygenation, there are some exceptions. For the same change in MAP, increases in PIP and PEEP will enhance oxygenation more than will changes in the I:E ratio. Increases in PEEP are not as effective once an elevated level (>5 to 6 cm H₂O) is reached and may, in fact, not improve oxygenation at all for the following reasons. A very high MAP may over-distend alveoli, leading to right-to-left shunting of blood in the lungs. If a very high MAP is transmitted to the intrathoracic structures, cardiac output may decrease, and thus, even with adequate oxygenation of blood, systemic oxygen transport (arterial oxygen content x cardiac output) may decrease. Blood oxygen content is largely dependent on oxygen saturation and hemoglobin level. It has been common to transfuse packed red blood cells into infants who have impaired oxygenation. Transfusion is most beneficial when anemia is severe (hematocrit <0.25 to 0.30 [$<25\%$ to 30%]). Oxygenation also depends on oxygen unloading at the tissue level, which is strongly determined by the oxygen dissociation curve. Acidosis and postnatal increases in 2,3-diphosphoglycerate and adult hemoglobin levels reduce oxygen affinity to hemoglobin, thereby favoring oxygen delivery to the tissues.

Pulmonary Mechanics

The interaction between the ventilator and the infant is strongly dependent on the mechanical properties of the respiratory system. A pressure gradient between the airway opening and the alveoli must exist to drive the flow of gases during both inspiration and expiration. The necessary pressure gradient is determined by the compliance, resistance, and inertance of the lungs and can be calculated from the equation of motion:

$$\text{pressure} = (\text{volume/compliance}) + \text{resistance} \times \text{flow} + \text{inertance} \times \text{acceleration}$$

Inertial forces during CMV are negligible when compared with compli-

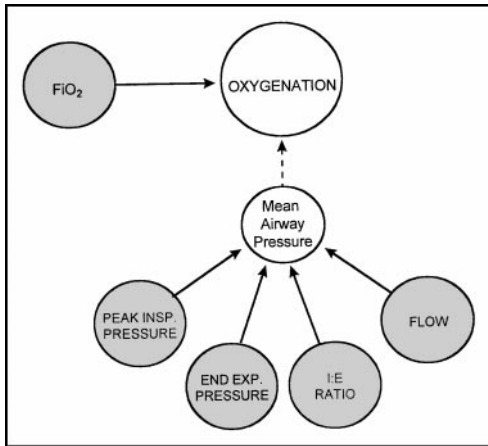


FIGURE 2. Determinants of oxygenation during pressure-limited, time-cycled ventilation. Shaded circles represent ventilator-controlled variables. Solid lines represent the simple mathematical relationships that determine mean airway pressure and oxygenation, and dashed lines represent relationships that cannot be quantified with a simple mathematical method. From Carlo WA, Greenough A, Chatburn RL. *Advances in conventional mechanical ventilation.* In: Boynton BR, Carlo WA, Jobe AH, eds. *New Therapies for Neonatal Respiratory Failure.* Boston, Mass: Cambridge University Press; 1994.

ance and resistance forces. Thus, the equation can be simplified to:

$$\text{pressure} = (\text{volume}/\text{compliance}) + \text{resistance} \times \text{flow}$$

COMPLIANCE

Compliance describes the elasticity or distensibility (eg, lungs, chest wall, respiratory system) and is calculated from the change in volume

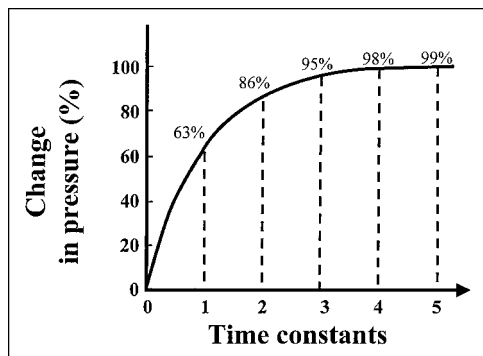


FIGURE 3. Percentage change in pressure in relation to the time (in time constants) allowed for equilibration. As a longer time is allowed for equilibration, a higher percentage change in pressure will occur. The same rules govern the equilibration for step changes in volume.

per unit change in pressure:

$$\text{compliance} = \Delta \text{ volume} / \Delta \text{ pressure}$$

Therefore, the higher the compliance, the larger the delivered volume per unit of change in pressure. Normally, the chest wall is compliant in neonates and does not impose a substantial elastic load compared with the lungs. Total respiratory system compliance (lungs + chest wall) in neonates who have normal lungs ranges from 0.003 to 0.006 L/cm H₂O compared with compliance in neonates who have RDS, which may be as low as 0.0005 to 0.001 L/cm H₂O.

RESISTANCE

Resistance describes the inherent capacity of the air conducting system (eg, airways, endotracheal tube) and tissues to oppose airflow and is expressed as the change in pressure per unit change in flow:

$$\text{resistance} = \Delta \text{ pressure} / \Delta \text{ flow}$$

Airway resistance depends on: 1) radii of the airways (total cross-sectional area), 2) length of airways, 3) flow rate, and 4) density and viscosity of gas breathed. Distal airways normally contribute less to airway resistance because of their larger cross-sectional area, unless bronchospasm, mucosal edema, and interstitial edema decrease the lumen. Small endotracheal tubes that may contribute significantly to airway resistance are also important, especially when high flow rates that lead to turbulent flow are used. Total (airway + tissue) respiratory resistance values for normal neonates range from 20 to 40 cm H₂O/L/s and from 50 to 150 cm H₂O/L/s in intubated neonates.

TIME CONSTANT

Compliance and resistance can be used to describe the time necessary for an instantaneous or step change in air-

way pressure to equilibrate throughout the lungs. The time constant of the respiratory system is a measure of the time necessary for the alveolar pressure to reach 63% of the change in airway pressure (Fig. 3). Time constant is the product of resistance and compliance, as follows:

$$\text{time constant} = \text{resistance} \times \text{compliance}$$

Thus, the time constant of the respiratory system is proportional to the compliance and the resistance. When a longer time is allowed for equilibration, a higher percentage of airway pressure will equilibrate throughout the lungs. For example, the lungs of a healthy neonate with a compliance of 0.004 L/cm H₂O and a resistance of 30 cm H₂O/L/s have a time constant of 0.12 seconds. The longer the duration of the inspiratory (or expiratory) time allowed for equilibration, the higher the percentage of equilibration. For practical purposes, delivery of pressure and volume is complete (95% to 99%) after three to five time constants. The resulting time constant of 0.12 seconds indicates a need for an inspiratory or expiratory phase of 0.36 to 0.6 seconds. In contrast, lungs that have decreased compliance (such as in RDS) have a shorter time constant. Lungs that have a shorter time constant complete inflation and deflation faster than normal lungs. The clinical application of the concept of time constant is that very short inspiratory times may lead to incomplete delivery of tidal volume and, therefore, lower PIP and MAP, resulting in hypercapnia and hypoxemia (Fig. 4).

Similarly, insufficient expiratory time may lead to increases in functional residual capacity and inadvertent PEEP, which are evidence of gas trapping that, in turn, decreases compliance and may impair cardiac output. A short expiratory time, a prolonged time constant, or an elevated tidal volume can result in gas trapping. Gas trapping during mechanical ventilation may manifest as carbon dioxide retention and lung hyperexpansion. Although Pao₂ may be adequate during gas trapping, venous return to the heart and car-

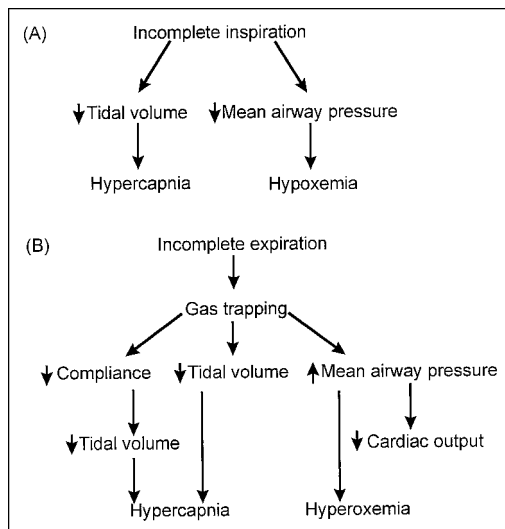


FIGURE 4. Effects of incomplete inspiration (A) or incomplete expiration (B) on gas exchange. An incomplete inspiration leads to decreases in tidal volume and mean airway pressure. Hypercapnia and hypoxemia may result. An incomplete expiration may lead to decreases in compliance and tidal volume and an increase in mean airway pressure. Hypercapnia with a decrease in P_{aO_2} may result. However, gas trapping and its resulting increase in mean airway pressure may decrease venous return, reducing cardiac output and impairing oxygen delivery. From Carlo WA, Greenough A, Chatburn RL. *Advances in conventional mechanical ventilation*. In: Boynton BR, Carlo WA, Jobe AH, eds. *New Therapies for Neonatal Respiratory Failure*. Boston, Mass: Cambridge University Press; 1994.

diac output may be impaired, which can decrease oxygen delivery. Clinical findings that may suggest the presence of gas trapping include: 1) need for high ventilatory rates, 2) a prolonged time constant (eg, high resistance), 3) radiographic evidence of lung overexpansion, 4) decreased thoracic movement despite high PIP, and 5) impaired cardiovascular function (increased central venous pressure, decreased systemic blood pressure, metabolic acidosis, peripheral edema, and decreased urinary output).

Because values of compliance and resistance differ throughout inspiration and expiration, a single time constant cannot be assumed. With heterogeneous lung disease, such as bronchopulmonary dysplasia, different lung regions may have different time constants because of varying compliances and resistances, partly accounting for the coexistence of atelectasis and hyperexpansion. The astute clinician can correlate

changes in the time constant of the respiratory system to clinical events and interventions. Inspiratory or expiratory times then can be adjusted appropriately. In summary, the time necessary for lungs to inflate or deflate depends on the mechanical characteristics of this organ, specifically resistance and compliance.

In addition to using the clinical findings as well as compliance and resistance measurements to calculate time constant, a plot of volume-time or volume-flow can be used to make this estimation. The pattern of volume changes obtained by integrating the signal from a flow transducer can provide an estimate of the time constant. However, flow measurements are somewhat invasive, time-consuming, and frequently not available. Furthermore, pulmonary mechanics are dynamic, frequently changing over time, and affected by adding a flow sensor to the gas delivery circuit.

An alternative technique that may be more useful in clinical practice is using chest wall motion as a semiquantitative estimate of tidal volume. Chest wall motion can be recorded with inductance plethys-

mography or other techniques. At the bedside, chest wall motion can be measured with appropriately placed heart rate/respiration leads used for routine clinical monitoring (Fig. 5). Careful visual assessment of chest wall motion can suffice. The shape of the inspiratory and expiratory phases can be analyzed. A rapid rise in inspiratory chest wall motion (or volume) with a plateau indicates complete inspiration. A rise without a plateau indicates incomplete inspiration. In this situation, prolongation of the inspiratory time results in more inspiratory chest wall motion and tidal volume delivery. A prolonged inspiratory plateau indicates that inspiratory time may be too long; shortening inspiratory time does not decrease inspiratory chest wall motion or tidal volume delivery and does not eliminate the plateau. The expiratory pattern of chest wall motion can be analyzed similarly.

Control of Breathing

Important physiologic concepts of control of breathing need to be considered to understand some aspects of the interaction between the ventilator and the respiratory system. Respiratory drive is servocontrolled by the brain to minimize variations in arterial blood gases and pH despite changes in the efficiency of gas exchange and moment-to-moment changes in oxygen con-

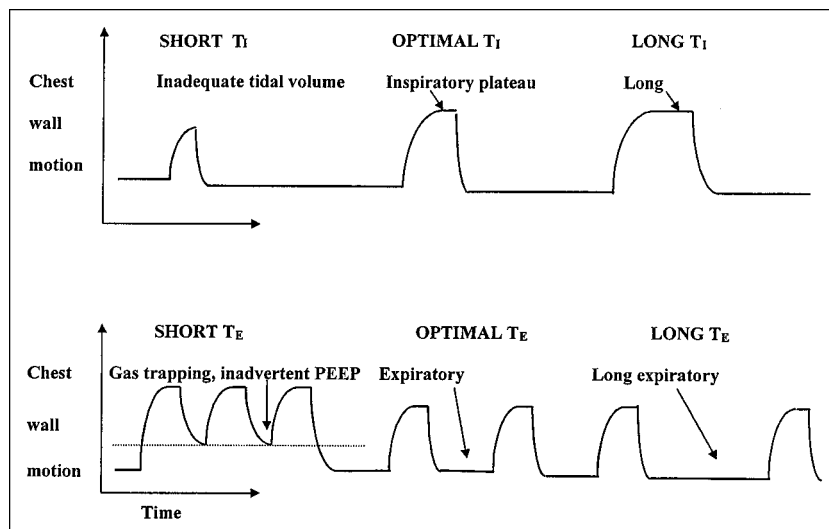


FIGURE 5. Estimation of optimal inspiratory and expiratory times based on chest wall motion.

sumption and carbon dioxide production. Ventilation is maintained by fine adjustments in tidal volume and respiratory rate that minimize the work of breathing. This fine adjustment is accomplished by motoneurons in the central nervous system that regulate inspiratory and expiratory muscles. These neurons receive input primarily from chemoreceptors and mechanoreceptors. These two components of respiratory control provide feedback to adjust ventilation continuously. Mechanical ventilation results in changes in chemoreceptor and mechanoreceptor stimulation.

When $Paco_2$ changes, ventilation is adjusted largely because of the activity of chemoreceptors in the brain stem. An increase in $Paco_2$ increases respiratory drive. Because the chemoreceptors most likely sense the hydrogen ion concentration, metabolic acidosis and alkalosis have strong effects on respiratory drive that are somewhat independent of $Paco_2$ values. In contrast, most of the changes in ventilation and respiratory drive produced by Pao_2 changes depend on the peripheral chemoreceptors, which include the carotid bodies and, to a lesser extent, the aortic bodies. In neonates, acute hypoxia produces a transient increase in ventilation that disappears quickly. Moderate or profound respiratory depression can be observed after a couple of minutes of hypoxia, and it is believed that this decline in respiratory drive is an important cause of hypoventilation or apnea in the newborn period.

It is also important to consider the role of mechanoreceptors in the regulation of breathing, particularly during neonatal life and infancy. Stretch receptors in airway smooth muscles respond to changes in tidal volume. For example, immediately following an inflation, a brief period of decreased or absent respiratory effort can be detected. This is called the Hering-Breuer inflation reflex, and usually it is observed in neonates during CMV when a large enough tidal volume is delivered. The presence of the Hering-Breuer inflation reflex is a clinical indication that a relatively good tidal volume is delivered. This reflex will be absent if the ventilator tidal volume

is very small, such as when the endotracheal tube is plugged. The Hering-Breuer reflex is also time-related (ie, a longer inspiration tends to stimulate the reflex more). Thus, for the same tidal volume, a breath with a longer inspiratory time will elicit a stronger Hering-Breuer reflex and a longer respiratory pause.

At slow ventilator rates, large tidal volumes will stimulate augmented inspirations (Head paradoxical reflex). This reflex reflects improved lung compliance, and its occurrence is increased by administration of theophylline. This may be one of the mechanisms by which theophylline hastens weaning from CMV.

Mechanoreceptors also are altered by changes in functional residual capacity. An increase in functional residual capacity leads to a longer expiratory time because the next inspiratory effort is delayed. High continuous distending pressure (continuous positive airway pressure or PEEP) can prolong expiratory time and even decrease the respiratory rate due to the intercostal phrenic inhibitory and Hering-Breuer reflexes. Also, it is important to remember that during weaning from a ventilator, a high PEEP may decrease the spontaneous respiratory rate.

Other components of the mechanoreceptor system are the juxtamedullary (J) receptors, which are located in the interstitium of the alveolar wall and are stimulated by interstitial edema and fibrosis as well as by pulmonary capillary engorgement (eg, congestive heart failure). Stimulation of the J receptors increases respiratory rate and may explain the rapid, shallow

breathing frequently observed in patients who have these conditions.

Another reflex that affects breathing is the baroreflex. Arterial hypertension can lead to reflex hypoventilation or apnea through aortic and carotid sinus baroreceptors. Conversely, a decrease in blood pressure may result in hyperventilation.

Ventilatory Support

CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP)

CPAP has been an important tool in the treatment of neonates who have RDS. The mechanisms by which CPAP produces its beneficial effects include: 1) increased alveolar volumes, 2) alveolar recruitment and stability, and 3) redistribution of lung water (Table 1). The results are usually an improvement in ventilation-perfusion matching. However, high CPAP levels may lead to side effects (Table 1).

Multiple clinical trials have evaluated the use of CPAP in neonates who have respiratory disorders. Meta-analyses generally conclude that CPAP is most beneficial early in the therapy of neonates who have established RDS. Prophylactic CPAP in preterm infants does not decrease the incidence or severity of RDS and does not reduce the rate of complications or death. Once the diagnosis of RDS is established, the administration of CPAP decreases oxygen requirements and the need for mechanical ventilation and may reduce mortality. However, the incidence of air leaks is increased among infants who receive CPAP. The optimal time to start CPAP depends on the severity of RDS. "Early" CPAP (ie, when the arterial-

TABLE 1. CPAP or High PEEP in Infants Who Have RDS

PROS	CONS
<ul style="list-style-type: none"> • Increased alveolar volume and FRC • Alveolar recruitment • Alveolar stability • Redistribution of lung water • Improved V/Q matching 	<ul style="list-style-type: none"> • Increased risk for air leaks • Overdistention • CO_2 retention • Cardiovascular impairment • Decreased compliance • Potential to increase PVR
<p><i>FRC: functional residual capacity; V: ventilation; Q: perfusion; PVR: pulmonary vascular resistance.</i></p>	

to-alveolar oxygen ratio is approximately higher than 0.20) decreases the subsequent need for CMV and the duration of respiratory assistance. These meta-analyses suggest that CPAP should be initiated in newborns who have RDS, for example, when the P_{aO_2} is approximately less than 50 torr and the F_{iO_2} is 0.40 or more. Studies performed to determine whether CPAP facilitates successful extubation have not shown consistent results.

CMV

Strategies for optimizing CMV have been developed based on principles of pulmonary mechanics and gas exchange. It has been shown that these ventilatory strategies result in more frequent improvement of blood gases than ventilatory changes that follow alternate decisions. Nonetheless, the complexities of the multiple patient presentations and available ventilatory changes result in continued controversy in this area. Much research remains to be done to clarify the relationship between the optimal ventilatory pattern and the underlying lung pathology.

PIP

Changes in PIP affect both P_{aO_2} (by altering the MAP) and P_{aCO_2} (by its effects on tidal volume and, thus, alveolar ventilation). Therefore, an increase in PIP will improve oxygenation and decrease P_{aCO_2} . A high PIP should be used cautiously because it may increase the risk of volutrauma, with resultant air leaks and bronchopulmonary dysplasia. Tidal volume can be measured, but in most clinical settings, breath sounds, chest excursions, and respiratory reflexes are good indicators of appropriate tidal volume.

A common mistake made by clinicians is to relate PIP to weight (eg, the misconception that larger infants need a higher PIP). Rather, PIP requirements are strongly determined by the compliance of the respiratory system, and larger infants tend to have more compliant lungs, therefore requiring a lower PIP. In addition to compliance, the factors that should be considered in selecting the PIP level are blood gas derangements, chest rise, and breath

sounds. In contrast, weight, resistance, time constant, and PEEP should not be considered in the selection of the level of PIP.

PEEP

Adequate PEEP prevents alveolar collapse, maintains lung volume at end expiration, and improves ventilation-perfusion matching. Increases in PEEP will raise MAP and functional residual capacity, thereby improving oxygenation. Nonetheless, use of a very elevated PEEP does not benefit oxygenation consistently (Table 1). For example, older infants who have chronic lung disease may tolerate higher levels of PEEP with improvement in oxygenation, but a very high PEEP may decrease venous return, cardiac output, and oxygen transport and increase pulmonary vascular resistance. It is important to emphasize that although increases in both PIP and PEEP will increase MAP and oxygenation, they usually have opposite effects on carbon dioxide elimination. By altering the delta pressure (PIP minus PEEP), an elevation of PEEP may decrease tidal volume and carbon dioxide elimination and, therefore, increase P_{aCO_2} . However, if functional residual capacity is low, an increase in PEEP may improve ventilation-perfusion matching and relieve both hypoxemia and hypercapnia.

Various approaches have been proposed to optimize the effects of PEEP. These include efforts to reduce the physiologic shunt fraction, improve lung compliance, increase maximal oxygen delivery, and improve cardiac output. PEEP in the range of 4 to 6 cm H_2O improves oxygenation in neonates who have RDS without compromising lung mechanics, carbon dioxide elimination, or hemodynamic stability. Careful assessment of tidal volumes and carbon dioxide elimination

suggests that PEEP levels in the lower end of this range may be preferable in infants who have RDS. PEEP has a variable effect on lung compliance. An initial improvement in compliance occurs in response to low levels of end expiratory pressure, but it may worsen at higher levels of PEEP (>5 to 6 cm H_2O).

RATE

Changes in frequency alter alveolar minute ventilation and, thus, P_{aCO_2} . In large randomized trials, relatively high ventilatory rates (60 breaths/min) resulted in a decreased incidence of pneumothorax in preterm infants who had RDS. An individualized approach should be taken, with the goal of providing adequate minute ventilation using minimal mechanical force. Generally, a high rate, low tidal volume strategy is preferred (Table 2). However, if a very short expiratory time is employed, expiration may be incomplete. The gas trapped in the lungs can increase functional residual capacity and place the infant on the flat part of the pressure-volume curve, thus decreasing lung compliance. Furthermore, tidal volume decreases as inspiratory time is reduced beyond a critical level, depending on the time constant of the respiratory system. Thus, minute ventilation is not a linear function of frequency above a certain ventilator rate during pressure-limited ventilation. Alveolar ventilation actually may fall with higher ventilatory rates as tidal volumes approach the volume of the anatomic dead space when inspiratory or expiratory times become insufficient.

Frequency changes alone (with a constant I:E ratio) usually do not alter MAP or substantially affect P_{aO_2} . In contrast, any changes in T_I that accompany frequency adjustments may affect the airway pres-

TABLE 2. High Rate, Low Tidal Volume (Low PIP)

PROS	CONS
<ul style="list-style-type: none"> • Decreased air leaks • Decreased volutrauma • Decreased cardiovascular side effects • Decreased risk of pulmonary edema 	<ul style="list-style-type: none"> • Gas trapping/inadvertent PEEP • Generalized atelectasis • Maldistribution of gas • Increased resistance

sure waveform and, thus, alter MAP and oxygenation.

I:E RATIO

The major effect of an increase in the I:E ratio is to increase MAP and improve oxygenation (Table 3). However, when corrected for MAP, changes in the I:E ratio are not as effective in increasing oxygenation as are changes in PIP or PEEP. A reversed I:E ratio (inspiratory time longer than expiratory time) as high as 4:1 has been shown to be effective in increasing Pao₂, but side effects may occur (Table 3).

Although one study suggested a decreased incidence of bronchopulmonary dysplasia with the use of reversed I:E ratios, a large, well-controlled, randomized trial has revealed only reductions in the duration of a high inspired oxygen concentration and PEEP exposure with reversed I:E ratios and no differences in morbidity or mortality. Changes in the I:E ratio usually do not alter tidal volume unless T_I and T_E become relatively too short. Thus, carbon dioxide elimination usually is not altered by changes in I:E ratio.

T_I AND T_E

The effects of changes in T_I and T_E on gas exchange are strongly influenced by the relationships of these times to the inspiratory and expiratory time constant, respectively. A T_I that is three to five times

longer than the time constant of the respiratory system allows relatively complete inspiration. A long T_I increases the risk of pneumothorax. Shortening T_I is advantageous during weaning (Table 4). In a randomized trial, limitation of T_I to 0.5 seconds rather than 1.0 second resulted in a significantly shorter duration of weaning. In contrast, patients who have chronic lung disease may have a prolonged time constant. In these patients, a longer T_I (around 0.8 sec) may result in improved tidal volume and better carbon dioxide elimination.

Fio₂

Changes in Fio₂ alter alveolar oxygen pressure and, thus, oxygenation. Because Fio₂ and MAP both determine oxygenation, they can be balanced as follows. During increasing support, Fio₂ is increased initially until it reaches about 0.6 to 0.7, when additional increases in MAP are warranted. During weaning, Fio₂ is decreased initially (to about 0.4 to 0.7) before MAP is reduced because maintaining an appropriate MAP may allow substantial reduction in Fio₂. MAP should be reduced before a very low Fio₂ is reached because a higher incidence of air leaks has been observed if distending pressures are not weaned earlier.

FLOW

Changes in flow have not been well studied in infants, but they probably

affect arterial blood gases minimally as long as a sufficient flow is used. In general, flows of 8 to 12 L/min are sufficient in most neonates. High flows are needed when inspiratory time is shortened to maintain an adequate tidal volume.

Pathophysiology-based Ventilatory Strategies

RDS is characterized by low compliance and low functional residual capacity. An optimal CMV strategy may include conservative indications for CMV, the lowest PIP and tidal volume required, moderate PEEP (3 to 5 cm H₂O), permissive hypercapnia, judicious use of sedation/paralysis, and aggressive weaning (Table 5).

Chronic lung disease is usually heterogeneous, with varying time constants among lung areas. Resistance may be markedly increased, and frequent exacerbations may occur. A higher PEEP (4 to 6 cm H₂O) often is used, and longer T_Is and T_Es with low flow rates are preferred. Hypercarbia and a compensated respiratory acidosis often are tolerated to avoid increasing lung injury with aggressive CMV.

Persistent pulmonary hypertension of the neonate may be primary or associated with meconium aspiration syndrome, prolonged intrauterine hypoxia, congenital diaphragmatic hernia, or other causes. Ventilatory management of these infants often is controversial and varies markedly among centers. In general, Fio₂ is adjusted to maintain Pao₂ between 80 and 100 torr to minimize hypoxia-mediated pulmonary vasoconstriction. Ventilatory rates and pressures are adjusted to maintain an arterial pH between 7.45 and 7.55. Care should be taken to prevent extremely low Paco₂ (<20 torr), which can cause cerebral vasoconstriction. The addition of inhaled nitric oxide to CMV reduces the need for extracorporeal membrane oxygenation.

Strategies to Prevent Lung Injury

Recently emphasis is being placed on the evidence that lung injury is partially dependent on the particular

TABLE 3. High I:E Ratio/Long Inspiratory Time

PROS	CONS
<ul style="list-style-type: none"> • Increased oxygenation • May improve gas distribution in lungs that have atelectasis 	<ul style="list-style-type: none"> • Gas trapping/inadvertent PEEP • Increased risk of volutrauma and air leaks • Impaired venous return • Increased pulmonary vascular resistance

TABLE 4. Short Inspiratory Time

PROS	CONS
<ul style="list-style-type: none"> • Faster weaning • Decreased risk for pneumothorax • Allows use of higher ventilator rate 	<ul style="list-style-type: none"> • Insufficient tidal volume • May need high flow rates

TABLE 5. Suggested Strategies for Conventional Ventilation in RDS

• Conservative indications for conventional ventilation
• Lowest PIP (tidal volume) that inflates the lungs
• Moderate PEEP (3 to 5 cm H ₂ O)
• Permissive hypercapnia (accept Paco ₂ 45 to 60 torr)
• Judicious use of sedation/paralysis
• Aggressive weaning from conventional ventilation

ventilatory strategies used. There is an emerging consensus that CMV leads to lung injury. It has been recommended that clinicians use more gentle ventilatory strategies in which gas trapping and alveolar overdistention are minimized while blood gas targets are modified to accept higher-than-normal Paco₂ values and lower-than-normal Pao₂ values. There has been interest in a variety of strategies of CMV that may reduce the risk of lung injury in neonates.

Ventilator-associated lung injury traditionally has been thought to be due to the use of high pressures; thus, the term barotrauma. However, recent laboratory-based and clinical research has raised questions about this purported mechanism. Experimentally, investigators have used high and low volumes and pressures in an attempt to determine if volume or pressure is the major culprit responsible for lung injury in the immature animal. Using negative pressure ventilation and chest strapping, investigators have dissociated the magnitudes of volumes and pres-

ures. These studies consistently demonstrate that markers of lung injury (pulmonary edema, epithelial injury, and hyaline membranes) are present with the use of high volume and low pressure, but not with the use of low volume and high pressure (Table 6). Thus, many investigators and clinicians prefer the term volutrauma to the more classic term of barotrauma. The heterogeneity of lung tissue involvement in many respiratory diseases predisposes some parts of the lung to volutrauma. Oxidant injury may be another serious cause of ventilator-associated lung injury. Furthermore, immature lungs are particularly susceptible to lung injury.

PERMISSIVE HYPERCAPNIA

Permissive hypercapnia, or controlled mechanical hypoventilation, is a strategy for the management of patients receiving ventilatory assistance. When using this strategy, priority is given to the prevention or limitation of overventilation rather than to maintenance of normal blood gases and the high alveolar ventilation that frequently is used. It is beginning to be recognized that respiratory acidosis and alveolar hypoventilation may be an acceptable price for the prevention of pulmonary volutrauma. Two large retrospective studies designed to determine risk factors for lung injury in neonates concurred on the potential importance of this ventilatory strategy, noting that higher Paco₂ values were associated with less lung injury. Using multiple logistic regression, these two studies independently concluded that ventilatory strategies leading to hypocapnia during the early neonatal course resulted in an increased risk of lung injury. Thus, it is possible that ventilatory strategies that tolerate mild

hypercapnia or prevent hypocapnia, particularly during the first days of life, result in a reduced incidence and severity of lung injury.

We performed a study to determine whether a ventilatory strategy of permissive hypercapnia reduces the duration of assisted ventilation in surfactant-treated neonates. Surfactant-treated infants (birth-weight 854±163 g; gestational age 26±1.4 wk) receiving assisted ventilation during the first 24 hours after birth were randomized to permissive hypercapnia (Paco₂ 45 to 55 mm Hg) or to normocapnia (Paco₂ 35 to 45 mm Hg). The number of patients receiving assisted ventilation during the intervention period was lower in the permissive hypercapnia group (*P*<0.005). During that period, the ventilated patients in the permissive hypercapnia group had a higher Paco₂ and lower PIP, MAP, and ventilator rate than those in the normocapnia group. Larger studies to determine if permissive hypercapnia improves major outcome measures are warranted.

LOW TIDAL VOLUME VENTILATION

Ventilatory strategies for CMV in infants should focus on prevention of overdistention, use of relatively small tidal volumes, maintenance of adequate functional residual capacity, and use of sufficient T_I and T_E. Because high maximal lung volume appears to correlate best with lung injury, selection of an appropriate PIP and the functional residual capacity (or operating lung volume) are critical to preventing lung injury during pressure-limited ventilation. With the recognition that large tidal volumes lead to lung injury, relatively small tidal volumes now are recommended. Studies in healthy infants report tidal volumes to range

TABLE 6. Volume Versus Pressure as a Cause of Lung Injury

	EXPERIMENTAL DESIGN		TYPE OF LUNG INJURY		
	VOLUME	PRESSURE	PULMONARY EDEMA	EPITHELIAL INJURY	HYALINE MEMBRANE
Iron lung	High	Low	Yes	Yes	Yes
Strapping	Low	High	No	No	No

from 5 to 8 mL/kg compared with 4 to 6 mL/kg among infants who have RDS. In our pilot study, tidal volumes of 4 to 5 mL/kg per minute generally were used in infants in the permissive hypercapnia group (unpublished observations). However, insufficient data are available to recommend a specific size of tidal volume in these infants. It should be noted that infants who have severe pulmonary disease should be ventilated with small tidal volumes because lung heterogeneity and unexpanded alveoli will lead to overdistention and injury of the most compliant alveoli if a "normal" tidal volume is used. Nonetheless, maintenance of an adequate functional residual capacity is also necessary.

Strategies Based on Alternative Modes of Ventilation

Technological advances, including improvement in flow delivery systems, breath termination criteria, guaranteed tidal volume delivery, stability of PEEP, air leak compensation, prevention of pressure overshoot, on-line pulmonary function monitoring, and triggering systems, have resulted in better ventilators. Patient-initiated mechanical ventilation, patient-triggered ventilation, and synchronized intermittent mandatory ventilation are being used increasingly in neonates. High-frequency ventilation is another mode that may reduce lung injury and improve pulmonary outcome.

PATIENT-TRIGGERED VENTILATION

The most frequently used ventilators in neonates are time-triggered at a preset frequency, but because of the available bias flow, the patient also can take spontaneous breaths. In contrast, patient-triggered ventilation (also called assist/control) uses spontaneous respiratory efforts to trigger the ventilator. With pressure-triggered ventilation airflow, chest wall movement, airway pressure, or esophageal pressure is used as an indicator of the onset of the inspiratory effort. Once the ventilator detects an inspiratory effort, it deliv-

ers a ventilator breath of predetermined settings (PIP, inspiratory duration, and flow). Although improved oxygenation has been observed, patient-triggered ventilation frequently needs to be discontinued in some very immature infants because of weak respiratory efforts. A backup rate may be used to reduce this problem.

SYNCHRONIZED INTERMITTENT MANDATORY VENTILATION

This mode of ventilation achieves synchrony between the patient and the ventilator breaths. Synchrony easily occurs in most neonates because strong respiratory reflexes during early life elicit relaxation of respiratory muscles at the end of lung inflation. Furthermore, inspiratory efforts usually start when lung volume is decreased at the end of exhalation. Synchrony may be achieved by nearly matching the ventilator frequency to the spontaneous respiratory rate or by simply ventilating at relatively high rates (60 to 120 breaths/min). Triggering systems can be used to achieve synchronization when synchrony does not occur with these maneuvers. Synchronized intermittent mandatory ventilation is as effective as CMV, but no major benefits were observed in a large randomized controlled trial.

PROPORTIONAL ASSIST VENTILATION

Both patient-triggered ventilation and synchronized intermittent mandatory ventilation are designed to synchronize only the onset of the inspiratory support. In contrast, proportional assist ventilation matches the onset and duration of both inspiratory and expiratory support. Furthermore, ventilatory support is in proportion to the volume and flow of the spontaneous breath. Thus, the ventilator can decrease the elastic or resistive work of breathing selectively. The magnitude of the support can be adjusted according to the patient's needs. When compared with conventional and patient-triggered ventilation, proportional assist ventilation reduces ventilatory pressures while maintaining or improving gas exchange. Random-

ized clinical trials are needed to determine if proportional assist ventilation leads to major benefits compared with CMV.

TRACHEAL GAS INSUFFLATION

The added dead space of the endotracheal tube and the ventilator adapter that connects to the endotracheal tube contributes to the anatomic dead space and reduces alveolar minute ventilation, leading to reduced carbon dioxide elimination. In smaller infants or with increasing severity of pulmonary disease, dead space becomes the largest proportion of the tidal volume. With tracheal gas insufflation, gas delivered to the distal part of the endotracheal tube during exhalation washes out this dead space and the accompanying carbon dioxide. Tracheal gas insufflation results in a decrease in P_{aCO_2} , PIP, or both. If proven safe and effective, tracheal gas insufflation should be useful in reducing tidal volume and the accompanying volutrauma, particularly in very preterm infants and infants who have very decreased lung compliance.

HIGH-FREQUENCY VENTILATION

Because of its potential to reduce volutrauma, there has been a surge of interest in high-frequency ventilation in the past few years. High-frequency ventilation may improve blood gases because, in addition to the gas transport by convection, other mechanisms of gas exchange may become active at high frequencies. There has been extensive clinical use of various high-frequency ventilators in neonates. Controlled trials with high-frequency positive pressure using rates of 60 breaths/min (versus 30 to 40 breaths/min for CMV) reported a decreased incidence of air leaks. Small randomized trials suggest that bronchopulmonary dysplasia may be prevented with high-frequency jet ventilation, but results are inconclusive. The largest randomized trial of high-frequency ventilation revealed that early use of high-frequency oscillatory ventilation did not improve outcome. Although various randomized controlled trials show heterogeneous results, meta-analyses largely con-

firm the original findings. However, there are trends toward decreases in bronchopulmonary dysplasia/chronic lung disease, but increases in severe intraventricular hemorrhage and periventricular leukomalacia as well as small increases in air leaks with high-frequency oscillatory ventilation or high-frequency flow interrupters. High-frequency ventilation is a safe alternative for infants who fail CMV.

Summary

Many advances in neonatal care have led to increased survival of smaller and more critically ill infants. CMV is being used on smaller and sicker infants for longer durations. Sound application of the basic concepts of gas exchange, pulmonary mechanics, and control of breathing is necessary to optimize CMV. Employing pathophysiology-based ventilatory strategies, strategies to prevent lung injury, and alternative modes of ventilation should result in further improvement in neonatal outcome.

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