Innovative practices of ventilatory support with pediatric patients

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Objectives: **The recognition that alveolar overdistension rather than peak inspiratory airway pressure is the primary determinant of lung injury has shifted our understanding of the pathogenesis of ventilator-induced side effects. In this review, contemporary ventilatory methods, supportive treatments, and future developments relevant to pediatric critical care are reviewed.**

Data Synthesis: **A strategy combining recruitment maneuvers, low-tidal volume, and higher positive end-expiratory pressure (PEEP) decreases barotrauma and volutrauma. Given that appropriate tidal volumes are critical in determining adequate alveolar ventilation and avoiding lung injury, volume-control ventilation with high PEEP levels has been proposed as the preferable protective ventilatory mode. Pressure-related volume control ventilation and high-frequency oscillatory ventilation (HFOV) have taken on an important role as protective lung strategies. Further data are required in the treatment of children, confirming the preliminary results in specific lung pathologies. Spontaneous breathing supported artificially during inspiration (pressure support ventilation) is widely used to maintain or reactivate spontaneous breathing and to avoid hemodynamic variation. Volume support ventilation reduces the need for manual adaptation to maintain stable tidal and minute volume and can be useful in weaning. Prone positioning and permissive hypercapnia have taken on an important role in the treatment of patients undergoing artificial ventilation. Surfactant and nitric oxide have been proposed in specific lung pathologies to facilitate ventilation and gas exchange and to reduce inspired oxygen concentration. Investigation of lung ventilation using a liquid instead of gas has opened new vistas on several lung pathologies with high mortality rates.**

Results: **The conviction emerges that the best ventilatory treatment may be obtained by applying a combination of types of ventilation and supportive treatments as outlined above. Early treatment is important for the overall positive final result. Lung recruitment maneuvers followed by maintaining an open lung favor rapid resolution of pathology and reduce side effects.**

Conclusions: **The methods proposed require confirmation through large controlled clinical trials that can assess the efficacy reported in pilot studies and case reports and define the optimal method(s) to treat individual pathologies in the various pediatric age groups. (Pediatr Crit Care Med 2003; 4:8–20)**

KEY WORDS: hemofiltration; plasma filtration; sepsis

Mechanical ventilation was first introduced during the polio epidemics of the 1950s and since then has been of undoubted value in improving the survival of many patients, including newborns and children. However, problems can stem from its use, particularly if inappropriate ventilatory modes are chosen. This can result in pressure and volume damage to the lungs, hemodynamic instability, oxygen toxicity, and nosocomial infection.

Ventilation-Induced Lung Injury

Ventilatory modes should be carefully selected to minimize ventilator-induced lung injury. The recognition that alveolar overdistension rather than high proximal airway pressure is the primary determinant of lung injury (i.e., volutrauma rather than barotrauma) has constituted a substantial shift in the pathogenesis of ventilator-induced side effects (1–6).

Mechanical ventilation with high pressure and volume induces changes in endothelial and epithelial permeability, formation of pulmonary edema, and alterations in pulmonary microvascular permeability. Severe alveolar damage, alveolar hemorrhage, and hyaline membranes have been noted in animals that die after lung overinflation injury (4, 7–9) and in a series of ventilated adult patients (10). The most important factors that have been proposed as being responsible for ventilation-induced lung injury are, first, high lung volume associated with elevated transpulmonary pressure and alveolar overdistension, and second, repeated alveolar collapse and reopening because of low end-expiratory volume. Other factors that contribute to injury include preexisting lung damage and/or inflammation, high inspired oxygen concentration, the level of blood flow, and the local production and systemic release of inflammatory mediators (11–13).

Innovative and protective lung strategies are proposed to avoid alveolar overdistension by limiting tidal volume and/or plateau pressure. Lung overstretching and overdistension are significant in causing lung injury rather than high pressures alone; volume trauma is at least as important as barotrauma (14). Acute respiratory distress syndrome (ARDS) (15–19), asthma (20), acute lung injury (21), and severe air flow obstruction (20, 21) should be taken into account, with tidal volumes and peak pressures reduced to a minimum.

Positive end-expiratory pressure (PEEP) should be used appropriately to maintain alveolar recruitment throughout the respiratory cycle (2, 3, 22), and complementary therapies such as nitric oxide and surfactant should be used to improve ventilation and oxygenation. Lower end points for ventilation may be accepted, e.g., a Pa_{O_2} of 50–60 mm Hg and moderate hypercapnia (45–50 mm Hg). Ventilation should be adapted to

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changing lung pathology and supportive treatments, such as physiotherapy and prone positioning, nitric oxide, and surfactant, used to improve the lung pathology and to reduce the duration of mechanical ventilation (23–25).

CONTROLLED VENTILATION

Small Tidal Volume—High Respiratory Rate: Continuous Positive Volume-Controlled Ventilation

Local inhomogeneities of ventilation result in large shear forces applied to lung units undergoing cyclic opening and closing. The repeated collapse and reopening of the lung units at low lung volume may contribute to ventilation-induced lung injury. A strategy combining recruitment maneuvers, low-tidal volume, and higher PEEP have been demonstrated to decrease the incidence of barotrauma (6, 9, 26–30).

Given that appropriate tidal volumes are critical in determining adequate alveolar ventilation and also in avoiding lung injury, volume-control ventilation is the safer and preferable ventilatory mode. Pressure-limited ventilation is not highly indicated in pediatric patients and for neonatal ventilation because the tidal volume cannot be controlled in every breath and reduced tidal volume (hypoventilation) can be alternated to large tidal volume (hyperdistention). This method is widely applied in neonatology because of the simplicity of use and because lung barotrauma is supposed to be connected with peak inspiratory pressure.

In volume-controlled ventilation, the target tidal volumes (6–8 mL/kg or 5 mL/kg, if necessary) are selected based on ideal body weight and lung pathology while minute volume remains stable. It is adjusted to maintain the pressure-volume curve below the upper inflection point. It should be noted that tidal volume less than or close to total deadspace can produce an insufficient exchange of alveolar gases (hypercapnia). By using uncuffed endotracheal tubes, a large discrepancy between set and delivered tidal volumes is present. To avoid hypoventilation, this discrepancy and poor compliance of infant lung compared with the ventilatory circuit compliance must be evaluated.

Respiratory rate can be adapted to maintain normocarbia in case of contraindication of permissive hypercapnia (human immunodeficiency virus in premature babies, brain hemorrhage, pulmonary hypertension). Generally, the respiratory rate for a specific patient is increased by 20% to 25% of the normal range.

PEEP has to be adjusted to maintain the pressure-volume curve above the lower inflection point, to avoid repeated alveolar collapse and reopening resulting from low end-expiratory volume, and to maintain alveolar recruitment throughout the respiratory cycle. Hemodynamic implications can be reduced by maintaining an euvolemia and avoiding high PEEP levels.

Pressure-Regulated Volume Control (PRVC) Ventilation

PRVC ventilation is a mode of ventilation now available in newer ventilators. This method delivers a controlled tidal and minute volume in a pressure-limited manner, using the lowest possible pressure, which is constant during the inspiratory phase. The gas flow is decelerated and pressure and flow constantly vary, breath by breath, to achieve the preset tidal volume at a minimum peak inspiratory pressure. It is particularly useful in patients ventilated when there are rapid changes in lung compliance and airway resistance, for instance, when surfactant and bronchodilators are used (31–34).

Methodology. The ventilator tests the first breath at 5 cm H_2O above PEEP and calculates the compliance. The inspiratory pressure changes breath by breath until the preset tidal volume is reached at a maximum of 5 cm H_2O below the set upper pressure limit. At this stage, the measured tidal volume corresponds to the preset value and the pressure remains constant. If the measured tidal volume increases above the preset level, inspiratory pressure is reduced until the set tidal volume is reached.

Indications. This mode of ventilation appears to be indicated: a) if within the lung compliance and resistance vary rapidly; b) if there is an initial requirement of high flow to reopen closed pulmonary areas (e.g., atelectasis, etc.); c) to reduce high ventilatory peak pressure (e.g., in premature infants, interstitial emphysema); d) to control ventilatory pressures from the moment nonventilated alveoli and bronchioles are reopened (e.g., surfactant, theophylline, or nitric oxide administration); e) in the presence of bronchospasms and bronchiole spasms (e.g., asthma, bronchiolitis); f) in all patients in whom PEEP levels must be reduced to avoid hemodynamic complications.

Advantages of PRVC Ventilation. This method appears to be useful in improving respiratory mechanics and gas exchange, in reducing the barotrauma caused by peak inspiratory pressure, in limiting oxygen toxicity because of the possibility of using reduced F_{IO_2} to maintain adequate gas exchange compared with conventional mechanical ventilation (34–36). The use of decelerating gas flows favors opening of closed areas of the lung and laminar flow, which allows the reduction of PEEP levels in case of hemodynamic implications (37–40). It also appears to be beneficial when drugs, such as surfactant, bronchodilators, and nitric oxide, which bring about a rapid change in compliance and airway resistance, are used.

Clinical controlled trials are required to evaluate the benefits of PRVC ventilation in acute lung pathology, in ventilation of healthy lungs (i.e., neurosurgical patients), and during weaning from the ventilator, in which this method appears to be indicated.

High-Frequency Oscillatory Ventilation (HFOV)

High-frequency ventilation has been one of the most studied ventilation techniques during the past two decades. Despite its theoretical benefits, it has not received unanimous consensus and has not been widely used.

The most fundamental difference between high-frequency ventilation and intermittent positive-pressure ventilation is that with high-frequency ventilation, the tidal volume required is approximately 1–3 mL/kg/body weight compared with 6–10 mL with intermittent positive-pressure ventilation. During high-frequency ventilation, minute ventilation is proportional to ventilator frequency $\times$ the square of the tidal volume. The increase in the ventilation rate to frequencies of 60 bpm or more in high-frequency ventilation is obviously mandatory if even comparable minute volume ventilation is to result (41, 42).

Three models are currently under investigation: high-frequency positive-pressure ventilation, high-frequency jet ventilation, and HFOV (43, 44). The first two are no longer used in intensive care therapy because of their poor results in trials compared with conventional me-

chanical ventilation. High-frequency jet ventilation has found an important place in tracheobronchial surgery. HFOV is proving to be highly successful, mainly because adequate equipment capable of solving the problem of humidification of ventilated gases is now available.

High-Frequency Positive-Pressure Ventilation. Tidal volume is delivered via a normal sized tracheal tube, with inspiration being the only active part of the ventilatory cycle (i.e., expiration achieved by passive lung recoil). Frequencies are usually in the range of 60–120 cpm (1–2 Hz).

High-Frequency Jet Ventilation. Tidal volume is delivered via a narrow cannula or injector, resulting in a jet of high velocity gas, normally at frequencies of 60–600 cpm (1–10 Hz).

High-Frequency Oscillation. Tidal volume is delivered via normal sized tracheal tubes, and both inspiration and expiration are active and of approximate equal power, such as would occur with an oscillating piston or loudspeaker-based ventilator. Frequencies range from 2 Hz to 50 Hz (300–3000 cpm). Prototype ventilators with a frequency range of 100 Hz (6000 cpm) have been described (45).

High-Frequency Oscillation

High-frequency oscillation differs in several respects from the other two techniques. Cyclic pressure changes are applied to the trachea by connecting a piston pump or the cone of a loudspeaker system driven by an electronic oscillator, directly to the patient's endotracheal tube to generate approximately a sinusoidal flow waveform. The pump is used to produce a reciprocating flow in the airways, whereas an auxiliary gas flow (bias flow) is used to clear the extracted carbon dioxide and to provide fresh gases to the system. These systems behave as a T-piece circuit, and the efficiency of carbon dioxide removal is a function of the magnitude of the bias flow.

Both inspiration and expiration are active, in contrast to high-frequency jet ventilation and high-frequency positive-pressure ventilation, in which expiration is passive and the flow profiles have a square or triangular waveform, respectively. From this, it follows that the inspiratory/expiratory ratio is usually fixed at 1:1, but pumps with variable ratios are now available.

There are a number of mechanisms proposed to explain the gas exchange in HFOV. Direct alveolar ventilation, asymmetric velocity profiles, Taylor dispersion, pendelluft, cardiogenic mixing, accelerated diffusion, and acoustic resonance appear to participate in gas exchanges both individually and/or together (42, 46).

Clinical Considerations

Gas Trapping. Tidal volume amplification resulting from pressure swings in the alveoli, delivering a larger tidal volume than the one generated by the oscillator, may contribute to gas trapping. Air trapping may occur if the ventilatory frequency increases and if the expiratory time is reduced to <250 msec.

Gas trapping is less likely to occur in HFOV systems in which expiration is assisted. The shorter the expiratory period and the greater the respiratory time constants, the lower the frequency at which gas trapping becomes a problem.

A modest degree of gas trapping is not always undesirable, and the term "auto-PEEP" may give a more balanced view of this effect. The proximal airway pressure is not a real indicator of true intrathoracic pressure during HFOV, and esophageal pressure may be a better index for clinical use.

Humidification During HFOV. The need for good humidification (90% relative humidity) in HFOV is essential to avoid severe irreversible damage to the trachea. On one hand, viscous secretions can obstruct alveoli and one bronchi, deteriorating ventilation; on the other hand, excessive humidification can lead to condensation in the child's circuit, the endotracheal tube, and the airways, reducing the effect of HFOV. At present, the most advanced humidifiers available (e.g., Fischer Paykel) are able to solve the majority of HFOV-related humidification problems, avoiding those difficulties that were seen with high-frequency jet ventilation use.

Cooling Effects of High-Frequency Ventilation. There is no documented evidence for such a claim, provided that adequate humidification is provided. The gas flows used in HFOV may be high, but the thermal capacity of gases is very low. In contrast, the latent heat of vaporization of water is considerable. In high-frequency jet ventilation, for example, at typical clinically used minute volumes, the cooling effect from the gas alone is the equivalent of about 250 $kcal^{-1}$ (about 7% to 10%) of the daily calorie requirement. The cooling effect that would result from the use of dry gas, with the consequent latent heat losses from evaporation, would be approximately 3000–3500 $kcal/day^{-1}$. Thus, simple warming of the inspired gas would produce little clinical benefit.

Prevention of Aspiration. In paralyzed, deeply sedated children, HFOV can prevent aspiration of pharyngeal contents by its auto-PEEP effect, so described for high-frequency ventilation (47). Patients who are capable of voluntary inspiration or coughing can generate a negative tracheal pressure, which could favor aspiration of regurgitated gastric material.

The theoretical *advantages* of HFOV include maintaining open airways, smaller phasic volume and pressure change, gas exchange at significantly lower airway pressures, less involvement of the cardiovascular system, and less depression of endogenous surfactant production. HFOV is recommended to reduce lung barotrauma and the consequent lung injury in nonhomogeneous lung pathology, in air leaks, in persistent pulmonary hypertension of the newborn (PPHN), and in ventilation of premature babies (41, 48–50).

Contraindications of HFOV are in cases of pulmonary obstruction from fresh meconium aspiration (danger of overinflating the more compliant lung units), bronchopulmonary dysplasia with clinical evidence of increased expiratory resistance and respiratory syncytial virus bronchiolitis, and intracranial hemorrhage.

There are a limited number of published large clinical trials on the use of HFOV in pediatric patients (41, 46, 50), but from them, the benefits deriving from the reopening of the closed alveoli and maintaining them open, as well as reduction of airleak, have still to be fully demonstrated. Even though in several studies bronchiolitis is excluded from possible treatment (51), recently published cases have shown a reasonable possibility of successful treatment (52, 53).

The described *complications* of HFOV are connected with overinflation in obstructive lung diseases, intracranial hemorrhages, reduction in heart rate attributed to increased vagal activity, bronchopulmonary dysplasia, necrotizing tracheobronchitis, increased permeability of lung epithelium, and insufficient humidification of tracheobronchial secretions (48, 54–56). Adverse neurologic events have been demonstrated to be con-

nected with ventilatory strategies more than with high-frequency devices (57).

Although HFOV can maintain adequate gas exchange for prolonged periods in many situations, there is as yet no clearly defined clinical role for this mode of ventilation. Recent studies in premature babies with hyaline-membrane disease and in term or near-term hypoxemic newborns have demonstrated an important improvement in oxygenation and a reduced incidence of airleak with HFOV.

There are no data from randomized, controlled trials supporting the routine use of rescue HFOV in term or near-term infants with severe pulmonary dysfunction. Cochrane Review (58) shows no evidence of a reduction in mortality at 28 days, in the number of patients requiring extracorporeal membrane oxygenation, days on a ventilator, days receiving oxygen, or days in the hospital.

Until a large-scale trial demonstrates the certain benefits deriving from HFOV compared with conventional ventilation and excludes a greater possible incidence of pulmonary airleak caused by the continuous expansion of the lung, the use of HFOV must be considered an interesting but not confirmed new mode of ventilation for specific types of respiratory failure in pediatric patients (59), including respiratory distress syndrome (RDS) of premature babies in which more experience has been gained and better results have been described.

Independent Lung Ventilation (ILV)

The possibility of independent ventilation of the two lungs of newborn and young children by means of selective intubation was first reported in 1984, using two single tubes (60). Despite favorable results, the method itself was complicated and difficult to apply. In newborns and infants, a notable change occurred with the testing and clinical use of a prototype double-lumen tube, later manufactured by Portex as special equipment. The arrival of this tube, in addition to simplifying the intubation maneuver and facilitating nursing, has made it possible to apply independent lung ventilation to the treatment of unilateral lung disease in pediatric patients (60–62).

Selective Bronchial Intubation. Older than 6–8 yrs of age, selective bronchial intubation is possible using a cuffed double-lumen tube similar to that used in adults (26- to 28-Fr Bronchocath Mallinckrodt, Bronchoport Rusch). The Marraro Paediatric Endobronchial Bilumen Tube, produced by SIMS-Portex, may be used in neonates and children 2–3 yrs of age. It is uncuffed to maximize the internal diameter of the tube and has no carinal hook, thus minimizing tracheal trauma (62–64).

Ventilators. ILV requires two ventilators that permit the application of different modes of ventilation and different PEEP levels for each lung. Synchronization of the beginning of the inspiratory phase can avoid mediastinal shifts that impede venous return and reduce cardiac output (61, 65). Nonsynchronous ventilation of the lungs, tested essentially in animals and adult patients, may create serious ventilation disorders (66, 67). These complications occur in pediatric patients mainly at respiratory frequencies <30 breaths per minute (68).

Hemodynamic Impact of ILV. The hemodynamic changes with ILV are similar to those encountered with intermittent positive-pressure ventilation with 5 cm H_2O PEEP. If the levels of PEEP are too high or the tidal volume is too great, central venous pressure rises and cardiac output and arterial blood pressure fall. Higher levels of PEEP may be maintained without hemodynamic changes in the more affected lung than the normal lung (61, 69, 70).

Gas Exchange. Application of ILV leads to a rapid improvement in Pao_2, because of the recruitment of lung areas to ventilation. This improvement is enhanced when better PEEP is applied independent of each lung.

Elimination of CO_2 in the more pathologic lung is lower than in the less pathologic lung because of the smaller ventilating lung volume. Applying ILV and using a selective PEEP for each lung, a progressive increase in the elimination of CO_2 is noted because of the recruitment to ventilation of new lung areas.

Indications for ILV. At present, ILV can be generally indicated in the treatment of unilateral lung pathology, such as monolateral atelectasis, emphysema, pneumonia, pneumothorax, and bronchopulmonary fistula. In postoperative care, ILV can be used for lung reexpansion after thoracic surgery, for correction of V/Q mismatch in the lung remaining dependent during surgery, and for the treatment of pulmonary complications arising during anesthesia and surgery, e.g., pneumothorax or aspiration syndrome (69, 71, 72).

A new possible indication for ILV can be the selective administration of drugs to one lung, such as antibiotics or surfactant (73). Unsolved problems with ILV application are as follows: large air leaks with the use of the uncuffed double-lumen tube (possible hypoventilation); the lumens of the double tube can be easily blocked by secretions deriving from insufficient humidification and warming of inspired gases; high costs of treatment because two ventilators are required.

SUPPORTED SPONTANEOUS BREATHING

Pressure Support Ventilation

Pressure support ventilation is designed to support spontaneous ventilation during the inspiratory phase (74, 75). The patient triggers each breath by opening the demand valve of the ventilator. There are different types of triggers that reduce the work of breathing in the patient. The oldest is the pressure trigger. By using this trigger, the patient must create intrapulmonary negative pressure to activate ventilatory support. Obtaining this negative pressure requires demanding work of breathing from the patient, inversely proportional to the sensitivity of the preset trigger.

In the volume trigger, the patient must inspire a volume equivalent to the preset trigger sensitivity to activate breathing. It is necessary to create a flow and to maintain it until a preset volume is inspired.

In the flow trigger, without bias flow, the work of breathing is required from the patient. To activate the system, it is necessary that the patient inspire all the gas present in the inspiratory circuit and create a flow equal to the preset sensitivity. Recently, in more technically advanced ventilators, a flow trigger with "bias flow" highly sensitive to minimal flow variations in the circuit is incorporated and requires a minimal work of breathing to activate the beginning of the inspiratory phase. In all types of flow trigger, sensitivity must be correctly assessed to avoid auto-trigger activation. A supplementary gas flow is delivered to the inspiratory circuit to produce a positive inspiratory pressure at a preset value. The cycles are pressure limited, and there is no preset tidal volume. The patient triggers the assisted breathing according to the trigger mode and regulates the respi-

ratory rate, inspiratory and expiratory time, and tidal volume.

Advantages of this method of ventilation are that it reduces the work of breathing and reduces respiratory muscle fatigue and oxygen consumption (76–78). Hemodynamic stability is favored because breathing is triggered spontaneously (79).

There are some disadvantages to pressure support ventilation. If the pressure support is high, the patient tends to reduce the respiratory rate and tidal volume. The risk of barotrauma is increased, and accordingly, gases of large tidal volume may not be adequately warmed and humidified. If the pressure support is low, patients tend to increase their respiratory rate and to reduce the tidal volume. Oxygen consumption and the work of breathing are increased. In the presence of inhomogeneous lung pathology, pressure support ventilation tends to favor ventilation of better aerated areas without affecting the collapsed lung areas.

Volume Support Ventilation

Volume support ventilation is a new means of assisting spontaneous breathing that can be correctly applied when lung pathology is improved and the ventilatory setting is near the normal value for the specific patient under normal conditions. The ventilator, breath by breath, adapts the inspiratory pressure support to the changes in the mechanical properties of the lung and the thorax to ensure that the lowest possible pressure is used to deliver the preset tidal and minute volume that remain constant. The inspiratory pressure is constant, and the flow is decelerated. The initial values for expected tidal and minute volume should be set, as should all parameters to be used in PRVC that can be activated in the presence of apnea. When the patient is able to ventilate at the preset tidal volume, the ventilator does not support the single breath. At this stage, extubation may be performed with safety (31, 33, 79–82).

This method avoids the pressure support ventilation disadvantages of continuous manual adaptation of pressure to the improving lung pathology and of volutrauma connected with high preset inspiratory pressure and nullifies the risk of apnea. In this case, the new ventilators, e.g., Siemens Servo 300, Servo 300A, and Servo I, automatically switch to PRVC.

Pressure support ventilation and volume support ventilation are indicated when weaning from ventilation (33, 83) and in patients with chronic obstructive pulmonary disease. It is useful to promote respiratory muscle training and to compensate for the high resistance of endotracheal tubes during spontaneous respiration with continuous positive airway pressure. During postoperative care, pressure support ventilation may preserve or reactivate spontaneous breathing and reinflate areas of atelectasis after surgery. Both methods are contraindicated using deep sedation and muscle relaxants in central neurologic disorders and in hypoventilation syndromes (83–85).

SUPPORTIVE TREATMENTS

Permissive Hypercapnia

A lung protective strategy may lead to CO_2 retention. Tidal volume can be limited so that the physiologic deadspace fraction for each breath rises to the point at which frequency cannot be increased to normalize effective alveolar minute volume. Moderate CO_2 retention, if compensated for and allowed to develop gradually, can be well tolerated. It has been suggested that hypercapnia be limited to a degree that allows arterial pH to be maintained at >7.2 (86, 87). Hypercapnia is generally regarded as an undesirable consequence of limiting alveolar stress, and it has been suggested to avoid hypercapnic acidosis because acidosis can be associated with decreased myocardial contractility, cerebral vasodilation, decreased seizure threshold, and hyperkalemia.

In recent studies in animals (88), hypercapnic acidosis per se has been discussed because it may contribute to the benefits of lung-protective ventilation. Respiratory acidosis can protect the lung from ischemia-reperfusion injury (89), whereas respiratory alkalosis potentiated lung injury (90).

The protective effect of respiratory acidosis has been associated with the inhibition of xanthine oxidase and was prevented by buffering the acidosis. If "lung protective ventilation" does reduce pulmonary and systemic inflammation (91) and perhaps multiple organ dysfunction (92, 93), hypercapnic acidosis per se could be partly responsible, perhaps by down-regulating inflammatory cells (94, 95) and possible other mechanisms, as well as by inhibition of xanthine oxidase. Permissive hypercapnia is contraindicated in intracranial hypertension, in pulmonary hypertension, and in severe cardiac disease because acidosis can induce myocardial depression (96–98).

Acute hypercapnia causes complex physiologic changes, probably affecting all cells and organ systems. Although these are poorly understood, some (including possible down-regulation of inflammatory cells) could be detrimental, and the degree of harm or benefit could vary in different clinical circumstances. A clinical trial intentionally elevating $Paco_2$ can be considered when we have a better understanding of the cellular and systemic effects of hypercapnia and acidosis (99). Further definition of patient groups in whom hypercapnia is poorly tolerated will be important in the formulation of general recommendations regarding the use of these ventilatory strategies, particularly in neonates and premature babies (96, 100–103).

Prone Positioning

In acute lung injury, a gradient in regional compliance develops, favoring nondependent lung. In addition, because of an increase in lung mass, there is an accentuation of the normal gradient in pleural pressure that increases as one approaches dependent lung.

In the supine position, the lowest regional end-expiratory volumes and the greatest frequency of cyclic airspace collapse and recruitment are found in the dorsal lung. By rotating the patient to the prone position, the least compliant lung with the most favorable transalveolar pressure excursion and limited tidal transalveolar pressure change are present in ventral lung regions (104–106).

The increased dorsal lung recruitment and ventilation, rather than a significant redistribution of regional blood flow, improve oxygenation and ventilation/perfusion matching and reduce shunt in patients with lung injury in several uncontrolled studies (107–111). The improvement in compliance that occurs in the prone position may allow reductions in Fio_2 and PEEP and augment drainage of secretions from the dependent lung. Safety concerns, including accidental extubation and catheter removal, hemodynamic instability, and pressure necrosis can limit the application of the prone position.

DRUGS FOR SUPPORTING VENTILATION TREATMENTS

Surfactant

The utility of surfactant treatment was demonstrated in premature animal models by Enhorning and Robertson (112) and confirmed in the premature infant by Fujiwara and his colleagues in 1980 (113). These reports resulted in an explosion in interest in surfactant for the treatment of RDS and possibly for other lung diseases in which surfactant deficiency can be suspected.

Natural and Artificial Surfactant. Pulmonary surfactant is a complex mixture of lipids and specific apoproteins, 80% phospholipid, 8% neutral lipids, and 10% to 12% proteins. The phospholipid component consists of 60% saturated phosphatidylcholine, 20% unsaturated phosphatidylcholine, anionic phospholipids, phosphatidylglycerol, and phosphatidylinositol. The main active component is dipalmitoyl phosphatidylcholine, which is responsible for reducing surface tension and maintaining alveolar stability.

The protein part of the surfactant system includes two major categories differing in structure and hydrophobicity. Natural SP-A is a collagen-like, hydrophilic glycoprotein. This protein has no direct surface tension-lowering capability but interacts with phospholipids, carbohydrates, calcium, and cell membrane receptors. It accelerates adsorption of phospholipids to an air-liquid interface, regulates secretion and reuptake of surfactant by alveolar type II pneumocytes as well as the extracellular transformation of lamellar bodies to tubular myelin (this latter process also requires calcium and SP-B), stimulates phagocytosis of bacteria and viruses by alveolar macrophages, and increases the resistance of surfactant to inhibition by serum proteins. SP-D is another collagen-like hydrophilic protein present in the airspaces, which stimulates the production of free oxygen radicals by alveolar macrophages, but its biophysical role in the surfactant system has not been defined. SP-B and SP-C are two hydrophobic proteins and enhance the adsorption of surfactant phospholipids to an air-liquid interface. SP-B is an essential constituent of tubular myelin, the extracellular reservoir of surfactant generating the surface film in terminal airspaces. Surfactant is synthesized by type II pneumocytes and by Clara cells in the bronchiolar epithelium.

Both animal and artificial surfactants are available on the market. The former, derived from bovine and porcine lungs, contains surfactant proteins B and C. It is more effective than artificial surfactant, which lacks these surfactant proteins.

Administration of Surfactant. There are two different modes of administration of surfactant, either direct instillation into the distal end of the tracheal tube via a suctioning catheter or via a nebulizer in the ventilated gases. The most uniform distribution of surfactant after instillation is obtained during a brief period of manual ventilation (2–3 mins), with respiratory physiotherapy and postural drainage. Administration of surfactant in two to four divided doses avoids early deterioration in gas exchange and unwanted vagal reflexes. The airways should not be suctioned for the first hour after surfactant administration to avoid the elimination of surfactant.

Aerosol enables continuous uniform administration of surfactant over a long period, reducing possible barotrauma on the lung. The aerosolized microparticles must be <5 micron in diameter to reach the alveoli. Larger particles remain in the tubes and in trachea and bronchi (114, 115). In inhomogeneous lung pathology, aerosolized surfactant reaches the better ventilated areas, without benefiting pathologic areas (116).

Several disadvantages are connected with aerosol administration. First, the reduced dose delivered can be rapidly inactivated by proteinaceous edema in the lung. Furthermore, an insufficient quantity of surfactant reaches the lung because of excessive dispersion in the ventilator circuit and tracheal tube. Finally, the aerosolization process can alter the structure of surfactant, inactivating it. Special equipment has been created to administer the drug directly close to the main bronchi, thereby solving to some extent the first two problems.

Selective bronchial instillation of surfactant has been suggested using a conventional tube introduced in one main bronchus, using a double-lumen tube (73), or via a bronchoscope (117, 118). The advantages deriving from this method are the delivery of large doses to distal regions of the lung and the reduction of the instilled dose (lowered costs). The disadvantages are connected with the complexity of procedures and long-time treatment.

Several studies are being performed using surfactant bronchoalveolar lavage to remove the extraneous material from the lung and to enable a more uniform distribution of the surfactant (119–122). The disadvantage of this procedure is connected with its complexity.

Adverse Effects of Surfactant. Transient airway obstruction (correlated with transient hypoxemia and hypotension) has been demonstrated in premature babies and in newborns, and the risk of pulmonary trauma and hemorrhage from dramatically increased tidal volumes from improved compliance has been suggested immediately after surfactant supplementation. Changes in cerebral perfusion from rapid redistribution of pulmonary blood flow into cerebral circulation can be present in very premature babies but have not been demonstrated in children and adults.

After impressive results in the treatment of neonatal RDS (123–126), the use of surfactant has been proposed in several forms of lung pathology in infants and children, such as congenital diaphragmatic hernia (73, 127, 128), meconium aspiration syndrome, inhalation syndrome, pneumonia (129–134), ARDS from different origins, and bronchiolitis.

Exogenous surfactant may be beneficial, and bronchoalveolar lavage using diluted doses of surfactant has been very promising in meconium aspiration syndrome and inhalation syndrome (135, 136). The place of surfactant in relation to other interventions, such as extracorporeal membrane oxygenation, high-frequency oscillatory ventilation, and inhaled nitric oxide, remains unclear. In particular, the real efficacy of surfactant supplementation compared with the successful treatment with the combined use of nitric oxide and high-frequency oscillatory ventilation in severe, persistent pulmonary hypertension of the newborn must be assessed (137).

Response to surfactant treatment is unpredictable and ranges from no response to a variable response or a good response in ARDS (138–141). A poor response may be caused by rapid inhibition and inactivation of administered surfactant by plasma components filling the alveolar space, to reduced doses, and to delay in supplementation (lung pathology that has become untreatable). Good results have been obtained using higher or multiple doses of surfactant.

Surfactant has also been used with success in the treatment of severe bronchiolitis (142–144) because of stabilizing surface tension into alveoli and terminal

bronchioles. Surfactant instillation was generally well tolerated, and no safety concerns were identified in the abovementioned studies. More rapid improvement in oxygenation and moderation of ventilatory support was demonstrated in two studies (142, 143), probably because the surfactant was instilled after open-lung strategies and a high PEEP level to keep the lung open were applied. The studies also showed that surfactant supplementation allows reduction of the duration of intubation and the length of PICU stay.

Surfactant instillation has been proposed in the treatment of pediatric acute hypoxemic respiratory failure (145) and subsequently positive preliminary results have been confirmed from members of the Mid-Atlantic Pediatric Critical Care Network (146). Children who received surfactant demonstrated rapid improvement in oxygenation and, on average, were extubated sooner and spent fewer days in the PICU than control patients.

Several questions on its use remain unsolved. Given that the efficacy of the surfactant appears closely related to the dose used as well as the severity of the lung pathology, a definition of optimal dosage is probably required for each specific pathology. The effect of surfactant can diminish over time in some lung pathologies; therefore, the frequency and the necessity of supplementary doses and quantities need to be defined. Two important aspects of surfactant efficacy appear connected with ventilatory strategy applied before and after treatment and the possibility of removing from the lung inhibiting and inactivating factors using bronchoalveolar lavage before surfactant supplementation. Finally, the possible immunologic response should be investigated because of the presence of specific proteins in the natural surfactant, even though no adverse reactions have been noted to date.

Nitric Oxide

Pulmonary hypertension and severe hypoxemia are the common end points of many conditions, including ARDS, meconium aspiration, and PPHN. Various pulmonary vasodilator therapies have been tested but are limited by systemic vasodilation, hypotension, worsening right-to-left shunt, or cardiac dysrhythmias.

Nitric oxide (NO) was described in 1987 as the "endothelium-derived relaxing factor" that acted exclusively on vascular smooth muscle of the lung and did not have any systemic effects (147). NO is produced by the endothelium from arginine and acts as a local vasodilator, diffusing into subjacent vascular smooth muscle and combining intracellularly with the heme present in guanylate cyclase. The resulting nitrosyl-heme activates guanylate cyclase, stimulating the production of cyclic guanosine 3'5'-monophosphate and subsequently relaxing vascular smooth muscle. When NO diffuses into the intravascular space, its biological activity is limited by rapid and avid binding to hemoglobin. Several vasodilators, such as nitroglycerine and nitroprusside, act by releasing NO (148–150). A large quantity of research has been dedicated to the selective effect on pulmonary vessels, but the use of inhaled NO should be tempered by concerns over its possible toxicity (151). In fact, NO may form several toxic products and is oxidized to nitrogen dioxide (NO_2) in oxygen mixtures. The rate of oxidation is dependent on oxygen concentration and the square of the NO concentration. Other highly cytotoxic compounds may be produced, and the combination of NO with hemoglobin forms nitrosyl Fe-hemoglobin and then methemoglobin. The following recommendations have been made for the safe use of inhaled NO (151–153): a) specific circuits must be used to ensure accurate continuous delivery of NO, while minimizing levels of NO_2; b) calibrated tanks of NO in nitrogen should be used, and concentrations of the undiluted gas should be limited to 1000 ppm to reduce any effects of leakage or overdose; c) the smallest effective dose of NO should be used because the long-term toxicity of NO is not known; d) exhaust gases from the breathing circuit must be scavenged to minimize environmental pollution; e) NO and NO_2 concentrations must be monitored, either continuously or intermittently; f) the blood methemoglobin concentration should be measured regularly in every patient; g) lesions of the skin and gastrointestinal tract can be demonstrated in zinc deficiency (154).

The dose of NO varies, but in general, as low a dose as possible is used (6–20 ppm) (151, 153). Higher doses are used initially and reduced to maintenance doses of between 5 and 10 ppm after 4–6 hrs.

Use of NO in Persistent Pulmonary Hypertension of the Newborn. NO has been used successfully in term neonates with PPHN, including in specific conditions such a congenital diaphragmatic hernia, meconium aspiration syndrome, and sepsis (155–158). Neonates who do not have echocardiographic confirmation of PPHN tend not to respond as well to inhaled NO as those with a definite diagnosis of PPHN. High-frequency oscillatory ventilation is a useful adjunct to inhaled NO. However, the response to NO in PPHN may be incomplete or only transient.

NO has been shown to be useful in ARDS (159, 160). It acts primarily by reducing pulmonary vascular resistance and improving oxygenation. It also reduces right ventricular afterload and improves right ventricular contractility and thus cardiac output. It reduces microvascular pressure to attenuate fluid filtration. Multicenter studies are required to assess the place of NO in the treatment of ARDS.

NO is used in the assessment of pulmonary reactivity during cardiac catheterization and the treatment of pulmonary hypertension after cardiac surgery with controversial results (161). It is useful to determine operability before heart or heart-lung transplantation (162, 163). Several multicenter studies are in progress to investigate which patients are likely to benefit from NO, the role of NO in relation to other therapy, and optimal delivery approaches to improve safety and efficacy (164, 165).

Perfluorocarbons

The possibilities of using liquid instead of air in the exchange of gases became a reality with the discovery of the properties of perfluorocarbons (PFC). In 1966, Clark and Gollan (166) demonstrated that mice, rats, and other animals can survive after immersion in oxygenated PFC and thus opened the way to current clinical research and applications.

Characteristics of Perfluorocarbons. PFCs are derived from common organic compounds, such as benzene. They are colorless and odorless and can be stored indefinitely at room temperature. They are resistant to autoclaving. They are insoluble in water or in lipids, and water or lipids do not dissolve in them. Oxygen, carbon dioxide, and many other gases are very easily dissolved in them. All PFCs have a low surface tension and rapidly evaporate at body temperature from the lung and the skin. The mechanisms for uptake, distribution, and elimination in the body are not clearly defined but are

correlated to lipid tissue composition, organ perfusion, and the ventilation-perfusion ratio in the lung. The physiochemical characteristics of the PFC, i.e., molecular structure and vapor pressure, and lung pathophysiology play an important role. Small quantities of PFC can be absorbed in the blood and distributed to the tissues with preference for lipids and fats. The absorbed PFC can remain in the tissues for long periods but do not seem to exert any toxic effects. The persistence in the body and the predilection for fatty tissue warrant further investigation, particularly with respect to the developing central nervous system of neonates and premature babies (167).

At present, there are two methods of administration of PFCs under research. Total liquid ventilation, developed by Shaffer et al. (168–171), and partial liquid ventilation or perfluorocarbon-associated gas exchange proposed by Fuhrman et al. (172) and Lachmann et al (173).

Total liquid ventilation is a ventilatory technique using PFCs instead of gas to obtain gas exchange. It requires complex equipment (pump, membrane oxygenator, CO_2 removal) and is applied after a short period of partial liquid ventilation. Partial liquid ventilation is a ventilatory technique using PFCs to fill the functional residual capacity of the lungs, while gas tidal volumes are delivered by a conventional volume-regulated ventilator.

Indications for Liquid Ventilation. It has been supposed that liquid ventilation eliminates the air-liquid interface and reduces surface tension. For this reason, liquid ventilation has been tested in RDS in premature babies. It has been shown that partial liquid ventilation leads to clinical improvement and survival in infants who are not predicted to survive (174). Partial liquid ventilation has been tested in uncontrolled clinical studies and in case reports of ARDS in children and adults.

Unfortunately, despite encouraging initial results in uncontrolled clinical studies, a preliminary large clinical trial of infants and children affected by life-threatening respiratory failure and outside extracorporeal membrane oxygenation criteria was interrupted because of an incorrect protocol of treatment (patients presented with severe advanced pathology and were probably untreatable in any case) and disappointing initial results. A clinical trial conducted in the United States and Europe, involving 56 centers, on 311 adult patients affected by ARDS from different origins was disappointing on the beneficial effects of partial liquid ventilation vs. conventional ventilation. Two different dosages of PFC were tested. Mortality was higher in patients treated with partial liquid ventilation. Moreover, severe hypoxemia developed in the presence of inhomogeneous lung pathology because of the compression of pathologic areas and normal aerated lung units. The incidence of pneumothorax was higher and return to conventional ventilation was more difficult than previously supposed. However, the PFC used was demonstrated to be safe (175).

Even though the results of a previous study of ARDS were disappointing, probably largely due to incorrect protocol and criteria of access to treatment, other fields of research remain open and are being thoroughly investigated. For example, PFC-bronchoalveolar lavage may be useful in meconium aspiration and inhalation syndromes in which it facilitates the removal of the meconium or other material present in the lung, supports gas exchanges, and eliminates inhomogeneous lung ventilation (176–178). Future applications could be in the treatment of cystic fibrosis and proteinosis. In both cases, PFC could remove the material present in the lungs, improve gas exchange, reduce the tendency to atelectasis, and prevent the loss of surface activity, should the aforementioned be confirmed by large clinical trials.

PFC has also been investigated for the study of the lung structure, in radiology (179), for topical administration of drugs (e.g., antibiotics and chemotherapies (180–183)), for heating pulmonary lobi to increase blood flow in the treatment of lung cancer, and as a ventilatory support for unusual types of treatment (184).

Several problems remain to be solved regarding optimal clinical use of partial liquid breathing: a) physical chemical properties of the ideal perfluorochemical compounds and proper dose to use; b) the management of ventilation during partial liquid ventilation, particularly regarding PEEP and tidal volume and the return to conventional gas ventilation over prolonged periods of time; c) the hemodynamic effects in the presence of pulmonary hypertension; d) the significant degree of lactic acidosis and the increase in hypoxemia in inhomogeneous lung pathology; e) the uptake and metabolism of PFC with regard to damage from long-term persistence in the tissues.

PFC use remains a fascinating and stimulating area requiring further study. To avoid disappointment after the initial enthusiasm, widespread clinical trials must confirm its applicability and positive results in humans.

SUMMARY

The recognition that alveolar overdistension rather than peak inspiratory airway pressure is the primary determinant of lung injury (i.e., volutrauma rather than barotrauma) has constituted a substantial shift in the understanding of the pathogenesis of ventilator-induced side effects and has led to new research of possible innovative ventilatory treatment.

The necessity of protecting the lung appeared more clearly when independent lung ventilation began to be more deeply studied and widely used. In cases of lung pathology with unilateral prevalence, in conventional mechanical ventilation, the less pathologic lung supports all ventilation to maintain adequate gas exchange leading to possible overdistention and barotrauma, whereas independent lung ventilation enables more aggressive ventilation of the more pathologic lung, protecting the less damaged lung at the same time.

A strategy combining recruitment maneuvers, low tidal volume, and higher PEEP has been demonstrated to decrease the incidence of barotrauma and volutrauma. Given that appropriate tidal volumes are critical in determining adequate alveolar ventilation and also in avoiding lung injury, volume-control ventilation with high PEEP levels has been proposed as the preferable protective ventilatory mode.

PRVC ventilation and HFOV have taken on an important role as protective lung strategies. The former delivers a controlled tidal and minute volume in a pressure-limited manner using the lowest possible inspiratory pressure. It appears particularly useful in patients with normal ventilated lung and in homogeneous lung pathology. Moreover, the method appears suitable in cases of rapid changes in lung compliance and airway resistance (e.g., surfactant supplementation, nitric oxide, aminophylline) avoiding manual adaptation of ventilation.

HFOV presents theoretical advantages that include maintaining open airways, smaller phasic volume and pressure

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change, gas exchange at significantly lower airway pressures, less involvement of the cardiovascular system, and less depression of endogenous surfactant production. The method is widely used in neonatal RDS but does not appear to find an application in inhomogeneous lung pathology. Further data are required for the treatment of children, confirming the encouraging preliminary results in specific lung pathologies.

Spontaneous breathing ventilation supported artificially in the inspiratory phase (pressure support ventilation) has been widely used to maintain or reactivate spontaneous breathing and to avoid hemodynamic variations connected with controlled ventilation. Pressure support ventilation uses preset inspiratory pressure support but is not able to control tidal volume spontaneously. Depending on resistance and compliance, use of a cuffed or uncuffed tube, an involuntary increase or reduction in tidal volume can create hypo- or hyperventilation. Volume support ventilation reduces the need for manual adaptation to maintain a stable tidal and minute volume. When the patient is able to ventilate a prefixed tidal volume, the ventilator does not support any pressure, and therefore, the patient can be extubated without risk. Both methods are useful in weaning the patient from a ventilator but need the cooperation of the patient and sufficient respiratory drive.

Supportive treatments (e.g., prone positioning and permissive hypercapnia) have taken on an important role in the treatment of patients undergoing artificial ventilation. Prone positioning is used to recruit dependent lung areas and permissive hypercapnia to limit tidal volume.

Beneficial effects deriving from permissive hypercapnia are not limited only to the reduction of tidal volume but also to the probable protective effects of acidosis on the lung (animal studies). Surfactant and nitric oxide have been proposed in specific lung pathologies to make the lung easier to ventilate, to reduce oxygen concentration in ventilated gases, and to facilitate gas exchange.

More recently, the investigation of the possibility of ventilating the lung using a liquid instead of gas to effectuate gas exchange has opened new vistas on several lung pathologies with high mortality rates requiring elimination of air-liquid interface and reduction in surface tension. This method could lead to the creation of an ideal ventilatory mode in which lung opening forces would be reduced or eliminated, thus reducing lung trauma significantly.

From an analysis of the various methods proposed, the conviction emerges that the best ventilatory treatment may be obtained by applying a combination of types of treatment, including the factors outlined above. The literature and acquired experience show that early treatment is extremely important for the overall positive final result. Lung recruitment maneuvers followed by maintaining an open lung after reopening not only favor more rapid resolution of the lung pathology but also reduce the side effects of ventilation (volutrauma, barotrauma, biotrauma).

All the methods proposed still require further confirmation through large controlled clinical trials that can assess the real efficacy demonstrated by pilot studies and case reports and define specifically the most suitable method or associated methods to treat individual pathologies in the various pediatric age groups.

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