**Full Case:**

**A 20-YEAR-OLD FULL-TERM PREGNANT WOMAN** was rushed to the operating room for emergency cesarean section because of fetal distress. During emergence from general anesthesia, the patient vomited and aspirated.

**Questions:**

**Delineate the risk factors for aspiration pneumonitis.**

Aspiration pneumonitis arises most often from aspiration of gastric content that is both acidic and voluminous. It can also occur from aspiration of oropharyngeal content. Several patient characteristics lead to the development of aspiration.

These include:
- Neurologic dysphagia
- Disruption of gastroesophageal junction
- Anatomic abnormalities of the upper aerodigestive tract
- General anesthesia
- Pharmacologic agents that alter consciousness (e.g., sedatives, antipsychotics, antidepressants, narcotics)
- Extremes of age (elderly, neonates)

The risk of aspiration pneumonitis is approximately 10% in patients presenting to the hospital after a drug overdose. This condition used to be very common in general anesthesia and accounted for most obstetric morbidity and mortality. The most recent report suggests an incidence of 1 in 3,000 patients receiving general anesthetics; however, the mortality remains very high and accounts for 10% to 30% of all deaths related to anesthesia. The elderly, particularly the nursing home population, is at increased risk of aspiration secondary to both an increased incidence of pharyngeal dysmotility and gastroesophageal reflux. Aspiration pneumonia and pneumonitis are the most common causes of death in patients with dysphagia caused by neurologic disorders, a condition that affects approximately 300,000 to 600,000 people yearly in the United States.
What is Mendelson syndrome?

Mendelson first described acute chemical aspiration pneumonitis in 1946. The triphasic sequence beginning with immediate respiratory distress, bronchospasm, cyanosis, tachycardia, and dyspnea, following with partial recovery, and concluding with a final phase of gradual respiratory recovery is characteristic of Mendelson syndrome. No signs of mediastinal shift are seen, but chest x-ray films usually show irregular mottled densities. This syndrome is due to the irritation of bronchioles by gastric hydrochloric acid, producing bronchiolar spasm, a peribronchiolar exudates, and congestion.

You suspect the patient has aspirated; what is your initial management strategy?

Rapidly tilt the operating table to a 30-degree head-down position to have the larynx at a higher level than the pharynx and to allow gastric content to drain to the outside. While an assistant maintains cricoid pressure, succion the mouth and pharynx as rapidly as possible.
Next, endotracheal intubation should be performed (if the patient had been extubated) with immediate inflation of the endotracheal cuff to prevent further aspiration. Quickly suction through the endotracheal tube before administering 100% oxygen by PPV. This is to prevent pushing aspirated material beyond your reach. Suction should be brief to avoid cardiac arrest from hypoxia. Give 100% oxygen before and after suctioning.

An orogastric tube should be inserted to empty the stomach. The pH value of the gastric content should be determined. Tracheobronchial aspirate is collected for culture and sensitivity tests. Auscultation of the chest will determine whether diminished breathing sounds, wheezing, rales, and rhonchi are present. If bronchospasm is noted, B2-agonists such as albuterol or terbutaline may be administered through metered-dose inhaler adapters to the anesthetic circuit.

The earliest and most reliable sign of aspiration is hypoxemia, which follows aspiration of even the mildest and most benign aspirate. Therefore, analysis of arterial blood gases should be performed to determine the severity of hypoxemia. Early application of PEEP is recommended to improve pulmonary function.


Would you give prophylactic antibiotics?

The initial aspirate, excluding feculent aspirate, is usually sterile and remains so for the first 24 hours. Thereafter, the aspiration pneumonitis can become aspiration pneumonia either from
contamination of the initial aspirate or secondarily from aspiration of a colonized oropharyngeal secretion in a host that now has tracheobronchial and alveolar damage. Colonization cultures may demonstrate gram-positive or gram-negative superinfection or both, usually with Escherichia, Klebsiella, Staphylococcus, Pseudomonas, and Bacteroides or with anaerobes. Prophylactic antibiotic has not been shown to improve mortality or reduce secondary infection rates. Cultures must be taken as soon as possible after aspiration and thereafter as clinically indicated. The antibiotic therapy is given according to the sensitivity test result. Prophylactic use of broad-spectrum antibiotics may lead to drug-resistant bacterial and fungal superinfection. However, if intestinal obstruction is a possibility, antimicrobial therapy for the possibility of anaerobic and gram-negative infection may be warranted. Although data supporting the use of prophylactic antibiotics are lacking, it is not unusual for clinicians to prescribe such therapy in settings in which the host is considered immunocompromised (e.g., elderly and critically ill patients). If one or several antibiotics have been administered, prompt withdrawal should occur with laboratory or clinical evidence of no infection. In contrast, the use of antibiotics in aspiration pneumonia is unequivocally indicated (e.g., third-generation cephalosporins, fluoroquinolones, or piperacillin).


Would you give steroid therapy?
The value of systemic corticosteroids is controversial. The rationale for immediate use of corticosteroids is to reduce inflammation and stabilize lysosomal membranes. In addition, they have been shown to prevent pulmonary cellular damage by protecting type n alveolar pneumocytes and to attenuate agglutination of leukocytes and platelets.

In experimental studies, the effectiveness of corticosteroid therapy appeared to be related to the pH value of aspirates. When the pH value of the aspirate was in the narrow range of 1.5 to 2.5, corticosteroid therapy was beneficial in treating acid-aspiration pneumonitis. Dexamethasone, given 0.08 mg per kg every 6 hours, decreased pulmonary water content significantly starting at 24 hours, with return to the normal range by 72 hours. When the pH value of the aspirate was less than 1.5, the pulmonary parenchymal damage was maximal. Therefore, the steroid therapy was not effective. When the pH value of the aspirate was higher than 2.5, the response was similar to that of water.

Wolfe, Bone, and Ruth found that pneumonia caused by gram-negative bacteria was more frequent after aspiration in patients treated with corticosteroids than in those who were not. Similarly, studies in animals have failed to demonstrate a beneficial effect of corticosteroids on pulmonary function, lung injury, alveolar-capillary permeability, or outcome after acid aspiration. Furthermore, because of the failure of two multicenter, randomized, controlled trials to demonstrate a benefit of high-dose corticosteroids in patients with ARDS, the administration of corticosteroids cannot be recommended.


Define acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).

ARDS is the most severe form of ALI. To standardize definitions, a consensus panel of experts developed a set of criteria characterizing ARDS and ALI. The criteria include onset that is acute, bilateral infiltrates on chest radiography, hypoxemia, and no evidence of cardiogenic failure (i.e., pulmonary artery occlusion pressure, <18 mmHg). Additionally, this group defined hypoxemia in ALI as a Pao2/FIo2 ratio of less than 300 mm Hg and selected a threshold ratio of Pao2/FIo2 of less than 200 mm Hg for ARDS, reflecting the more severe nature of the disease.

Describe the pathogenesis of ALI.

The histopathology reveals areas of hyaline membrane, alveolar hemorrhage, increased endothelial and epithelial permeability, and neutrophilic infiltration. Increased permeability allows passage of protein-rich plasma both in the alveolar and in the interstitial spaces, resulting in poor lung compliance and ineffective gas exchange. As the injury process progresses, dependent lung regions beneath the diseased and edematous lung become collapsed, worsening oxygenation. Additionally, alveolar surfactant content diminishes, and its space becomes filled with fibrin and other cellular materials. Ultimately, a fibroproliferative phase is entered whereby further destruction of the lungs occurs with varying degrees of collagen deposition and pulmonary fibrosis.

Complement activation may also play a major role in the pathogenesis of ARDS. Activation of the complement cascade through the alternative pathway by endotoxin or lipopolysaccharides results in the production of C5a complement. C5a complement causes microvascular occlusion and pulmonary granulocyte aggregation and embolization. The resultant damage to the endothelium leads to capillary leakage and pulmonary interstitial edema, ultimately producing terminal airway and alveolar edema and collapse. However, studies have shown limitations of the complement-neutrophil theory. Complement activation does not necessarily correlate with the development or severity of ARDS. ARDS can develop in patients with neutropenia, and pulmonary sequestration of neutrophils may not produce lung injury. As a result, the complement-neutrophil theory of ARDS has been expanded to include central roles for additional humoral mediators (such as endotoxin,
tumor necrosis factor, interleukins, and thromboxane) and cellular mediators (e.g., the macrophage-monocyte system). The lung in patients with ARDS is now viewed as one of the organs involved in the multiorgan system dysfunction that occurs as a result of the systemic inflammatory response syndrome. Increased mediator levels are found in bronchoalveolar lavage fluid from patients with ARDS.


**Describe the basic modes of mechanical ventilation. Discuss the advantages and disadvantages of pressure-controlled and volume-controlled modes.**

Fundamentally, the various modes of mechanical ventilation, both new and old, share the following variables: trigger, control, limit, cycle, and baseline.

**Trigger mode**
The trigger is the first and most important component of the inspiratory phase, marking the end of exhalation. Examples of triggering mechanisms include time, flow, and pressure. In the nonparalyzed and nonanesthetized state, the patient triggers a mechanical or assisted breath by generating negative transpulmonary pressure that is sensed by the ventilator as a pressure change in the airway (the ventilator circuit including the endotracheal tube). The threshold for triggering a breath (i.e., the set sensitivity) can be altered depending on the clinical setting; however, the greatest challenge in mechanical ventilation is determining the level at which
sensitivity pressure should be set (usually at 1 to 2 cm H2O). If the threshold is set too low, the ventilator will be triggered by any process that causes the airway pressure to surpass the set threshold. These include patient motion, external compression, gastric suctioning, and air leaks in the circuit or in the chest tubes. Conversely, if the threshold is set too high, the work of breathing increases; that is, to trigger every breath, the patient must make a significant effort to overcome the threshold limit for inspiratory flow to occur. At high levels of ventilatory assistance, as much as one third of the patient's inspiratory efforts may be insufficient to trigger the ventilator. In a 2001 review, Tobin explained that "breaths that do not reach the threshold for triggering the ventilator have higher tidal volumes and shorter expiratory times than do breaths that do trigger the ventilator." In the setting of acute respiratory failure, the inspiratory effort exhausted by the patient is approximately four to six times the normal value. This level of respiratory work frequently causes breath stacking, generating intrinsic PEEP, which in turn imposes a tremendous burden on inspiratory muscle and if sustained can result in muscle fatigue and cardiopulmonary collapse.

**Control mode**
The delivered breath can be either pressure regulated (pressure control) or volume targeted (volume control). In the pressure-controlled mode, the amount of volume delivered is inversely related to the resistance encountered. When the resistive forces are low (i.e., normal compliance), the tidal volume for a given pressure will be relatively larger than if compliance were poor. For adults, the recommended upper limit of pressure control is 35 cm H2O. Higher pressures may directly cause ALI or delay healing of the already injured lung. When the resistive forces are high, the resultant tidal volume may be inadequate for ventilation or oxygenation, even at high levels of inspiratory pressures. Typically, these patients have ARDS, and lower levels of arterial oxygen tension (Pao2) are tolerated along with higher levels of arterial carbon dioxide tension (permissive hypercapnia).

Volume-controlled mode is the most common control mode used to ventilate patients mechanically. Examples include assist-control ventilation and synchronous intermittent mandatory ventilation (SIMV). The ventilator will attempt to deliver a preset volume
regardless of the pressure generated. For patients with poorly compliant lungs, volume-controlled mode may promote barotrauma and acute lung injury (ALI).

**Limit mode**
The limit is an essential feature in mechanical ventilation. Its variables include volume, pressure, and flow. The upper and lower limits of these variables should be preselected for each patient and adjusted in a manner consistent with the goals of the protective lung strategy employed.

**Cycle mode**
As discussed in the previous section, cycling has several variables: time, flow, and pressure. As such, the inspiratory phase and the expiratory phase becomes controlled. The challenge faced is in synchronizing the machine's cycling of inspiration and exhalation with the patient's "neural" respiratory cycle. Although pressure, flow, and time can be used to affect cycling, the manipulation of one or all three variables, both intrabreath and interbreath, to coincide precisely with the demands of the patient is virtually impossible.

**Baseline mode**
The baseline variable is the function that is controlled during exhalation and generally indicates the level of PEEP.


**What are the major factors governing oxygen toxicity? What is the mechanism of oxygen toxicity?**

Oxygen toxicity is governed by the duration of exposure, the partial pressure of oxygen, and the susceptibility of the individual to pulmonary oxygen injury. The degree of toxicity is related to the
partial pressure, but not to the percentage of oxygen inspired, as demonstrated during U.S. space flights, where astronauts tolerate 100% oxygen for 2 to 4 weeks at a tension of 250 mm Hg. Systemic oxygen toxicity is related to arterial oxygen tension, whereas pulmonary oxygen toxicity depends on alveolar oxygen tension. Retrolental fibroplasia (retinopathy of prematurity) in the premature neonate has been reported after exposure to Pao2 at more than 80 to 150 mm Hg for a few hours. Pulmonary toxicity can develop after prolonged exposure to oxygen at concentrations between 0.5 and 1.0 atmospheres. It must be emphasized that the adult patient can generally tolerate 1 atmosphere of oxygen partial pressure for at least 24 hours. Moreover, there is no evidence that clinically relevant pulmonary oxygen toxicity occurs in humans at inspired partial pressures less than 0.5 atmosphere. Lastly, no patients should ever experience life-threatening levels of hypoxemia to avoid possible oxygen toxicity.


The so-called free-radical theory of oxygen toxicity proposed in the early 1960s has garnered a great deal of recent experimental support and is now accepted as the most probable molecular-level explanation for oxygen toxicity. Various highly reactive and potentially cytotoxic free-radical products of oxygen are generated metabolically in the cell. These short-lived O2 metabolites, including superoxide anion (O2-), hydroxyl radical (OH), hydrogen peroxide (H2O2), and singlet oxygen (O-), have been shown to be capable of effects such as inactivation of sulfhydryl enzymes, interaction with and disruption of DNA, and peroxidation of unsaturated membrane lipids with resultant loss of membrane integrity. The cell is also equipped with an array of antioxidant defenses, including the enzymes superoxide dismutase (SOD), catalase, glutathione peroxidase, vitamin E, and ascorbate. Under hyperoxia, the intracellular generation and influx of free radicals is believed to increase markedly and may overwhelm the detoxifying
capacity of the normal complement of antioxidant defenses, with resultant cytotoxicity.

The pathology of oxygen toxicity is nonspecific and consists of atelectasis, edema, alveolar hemorrhage, inflammation, fibrin deposition, and thickening and hyalinization of alveolar membranes. There are exudative and proliferative phases. Capillary endothelium is damaged early and plasma leaks into interstitial and alveolar spaces. Pulmonary surfactant may be altered. Type I alveolar lining cells are injured early, and bronchiolar and tracheal ciliated cells can be damaged by 80% to 100% oxygen. Resolution of exudative changes, hyperplasia of alveolar type II cells, fibroplastic proliferation, and interstitial fibrosis occur with recovery or with the development of tolerance to oxygen. Total resolution is possible if the initial hyperoxia is not overwhelming.


**How would you determine the best PEEP and the optimal PEEP? What are the cardiopulmonary effects of PEEP?**

Fairley, and Isenberg described best conventional PEEP in 1975. The best PEEP is defined as the level of PEEP with the highest oxygen transport, which is the product of cardiac output and oxygen content. This PEEP correlates with the highest total respiratory compliance, the highest mixed venous oxygen tension, and the lowest VDNT. Arterial oxygen tension and intrapulmonary shunt are not good indicators of the best conventional PEEP. They continue to improve even after this level has been reached. Oxygen transport decreases after the best PEEP is reached, because the cardiac output decreases. Civetta, Barnes, and Smith described optimal high PEEP in 1975. It is defined as the level of PEEP with the lowest intrapulmonary shunt and
without compromising cardiac output. The PEEP used in this report is so-called high or super PEEP, more than 25 cm H2O, whereas the PEEP in the article by Suter, Fairley, and Isenberg is conventional PEEP, ranging from 5 to 20 cm H2O. However, the concept of best or optimal PEEP has evolved over the years. More recently, the endpoint for PEEP application is the lowest level of PEEP that provides an adequate Pao2 at an PI02 of less than 0.5. Increasing PEEP beyond this level to obtain optimum values for various other endpoints, such as the production of maximum oxygen transport, maximum static pulmonary compliance, shunt less than 15% to 20%, minimal arterial end-tidal C02 gradient, decreased mixed venous oxygen tension, and minimum FI02 will not be clinically helpful and may be harmful.


The cardiovascular effects of PEEP depend on the severity of respiratory failure, the level of PEEP, the intravascular volume, the contractility of the heart, and the pulmonary vasculature. In healthy subjects without respiratory failure, PEEP decreases cardiac output mainly because of increased intrathoracic pressure resulting in decreased venous return. PEEP also causes pulmonary parenchymal
overdistention, which makes the lung come in close contact with the left ventricle, changing compliance and interfering with ventricular function. In addition, PEEP increases pulmonary pressure and resistance, resulting in right ventricular dilation, which causes an intraventricular septum shift toward the left ventricle. The leftward septal shift decreases ventricular diastolic filling, resulting in decreased stroke volume and cardiac output. The aforementioned deleterious effect of PEEP is more apparent in individuals with limited cardiovascular reserve. Although PEEP is applied only at the end of expiration, in actuality, the alveolar and transpulmonary pressures are highest during inspiration (driving pressures exceeding 20 to 30 cm H2O in some patients) and are associated with the greatest negative hemodynamic effects.

In persons with respiratory failure, PEEP, up to optimum levels, usually increases or does not change cardiac output because of an increase in oxygenation with resultant improvement of cardiac performance. Cardiac output decreases when PEEP exceeds the individual's optimum PEEP. Hypotension during PEEP therapy may be exacerbated by hypovolemia.

In patients with underlying left ventricular failure and filling pressure more than 18 mm Hg, PEEP may increase cardiac output by increasing coronary arterial oxygen content, augmenting, systolic function, or reducing venous return. The decreased venous return may produce a shift in the Starling curve to filling pressures associated with better myocardial function.


**What are the indications and contraindications for extracorporeal membrane oxygenation? How many ways can it be used? What are its results?**
Extracorporeal membrane oxygenation (ECMO) should be used for patients in severe acute respiratory failure with reversible lung disease, who are dying of severe hypoxemia despite maximal conventional ventilatory care (e.g., tracheal intubation, mechanical ventilation with 10 to 15 cm H2O PEEP, diuresis, chest physical therapy, antibiotics, normothermia or mild hypothermia, sedation, paralysis, and increased oxygen concentration). Indications for ECMO by the NIH are as follows: PaO2 less than 50 mm Hg for more than 2 hours with FiO2 of 1.0 and conventional PEEP; and a PaO2 less than 50 mmHg for more than 12 hours with FiO2 of more than 0.6 and conventional PEEP. Active bleeding is the only absolute contraindication to use of the artificial lung. The three routes for ECMO are as follows: venovenous perfusion from the inferior vena cava by way of the femoral vein to the oxygenator and then to the superior vena cava; venoarterial perfusion from the femoral vein to the oxygenator and then to the femoral artery; and venovenous arterial perfusion from the femoral vein to the oxygenator and then to both the internal jugular vein and the femoral artery.

A collaborative study on ECMO has been completed under the auspices of the National Heart, Lung, and Blood Institute of the NIH. The results of this controlled study are as follows:
. Compared with the control group of conventional respiratory therapy, ECMO did not improve mortality (90%), and the predominant cause of death was still progressive respiratory failure.
. ECMO did not affect the progress of disease (or lung pathology in those patients who died) any differently from conventional respiratory therapy.
. Although ECMO is an effective means of short-term life support, its clinical application for the treatment of ARDS is not appropriate or economically justified.

However, data analyzed from a national registry series of 715 neonatal ECMO patients (1980 to 1987) demonstrated an overall survival of 81%, which in earlier series had been the overall mortality rate with conventional therapy. As neonatal ECMO has evolved, entry criteria have been used, and experience with ECMO technology has been shown to improve survival. ECMO is now a proven support modality for neonatal respiratory failure that is due to several causes, such as meconium aspiration syndrome, persistent pulmonary hypertension of
the newborn, congenital diaphragmatic hernia, and infant respiratory distress syndrome.


What is nitric oxide (NO)? What is the role of inhaled NO in the treatment of ARDS?

1987, endothelium-derived relaxing factor was identified as NO. NO produced by the endothelium diffuses into vascular smooth muscle where NO activates soluble guanylate cyclase. The subsequent increase in intracellular cyclic guanosine monophosphate (cGMP) causes smooth muscle vasodilation. Endothelium-independent nitrovasodilators such as nitroglycerin and nitroprusside also act through guanylate cyclase activation to directly release NO.

Inhaled NO is a selective pulmonary vasodilator. NO is not effective during systemic administration because it is rapidly inactivated by hemoglobin. Therefore, inhaled NO may diffuse from the alveoli to pulmonary vascular smooth muscle and produce pulmonary vasodilation without systemic vasodilation because any NO that diffuses into blood will be inactivated by hemoglobin. Inhaled NO has been shown to be effective in treating primary pulmonary hypertension, as well as decreasing pulmonary hypertension and
improving oxygenation after mitral valve replacement and in the newborn with persistent pulmonary hypertension.

Pulmonary hypertension and hypoxemia universally occur in ARDS. Pulmonary hypertension in ARDS may be due to active vasoconstriction from local alveolar hypoxic pulmonary vasoconstriction and other vasoconstrictor mediators. Hypoxemia in ARDS is due to ventilation/perfusion mismatch, intrapulmonary shunting, or anatomic shunting. Intravenous pulmonary vasodilator therapy with agents such as nitroglycerin, nitroprusside, prostaglandin E, prostacyclin, adenosine, and nifedipine produces small reduction in pulmonary artery pressure but large reduction in systemic blood pressure and arterial oxygenation. The adverse effect on oxygenation is primarily due to reversal of hypoxic pulmonary vasoconstriction. On the contrary, inhaled NO may decrease pulmonary hypertension and improve oxygenation in patients with ARDS because inhaled NO may be distributed according to ventilation so the associated vasodilation increases blood flow to well-ventilated alveoli.

Rossaint et al. published the first major report of the use of inhaled NO in patients with ARDS. They found that inhaled NO (5 to 20 parts per million [ppm]) effectively decreased pulmonary hypertension and improved oxygenation. In a subsequent study, they showed that inhaled concentrations of only 60 to 250 parts per billion could increase Pao2 by 30%. These concentrations had little or no effect on pulmonary artery pressure. The other major study by Bigatello et al. demonstrated that inhaled NO produced dose-related decreases in pulmonary artery pressure with 50% of the maximal effect occurring at 5 ppm. Inhaled NO also increased oxygenation, but dose-response effects could not be demonstrated.

Inhaled NO has been effective on ARDS in combination with other therapies. The combination of inhaled NO (5 to 10 ppm) and almitrine bismesylate, a potentiator of hypoxic pulmonary vasoconstrictor, had additive effects on improving oxygenation in ARDS and simultaneously decreased pulmonary hypertension. Dcerring et al. studied intravenous phenylephrine, 50 to 200 /Lg per minute, titrated to a 20% increase in mean arterial pressure; inhaled NO, 40 ppm; and the combination of phenylephrine and NO. They found that phenylephrine alone can improve Pao2 in patients with ARDS. In phenylephrine-responsive
patients, phenylephrine augments the improvement in Pao2 seen with inhaled NO. These results may reflect selective enhancement of hypoxic pulmonary vasoconstriction by phenylephrine, which complements selective vasodilation by inhaled NO. However, an important unsolved issue is the potential pulmonary toxicity of inhaled NO. Toxicity may be due to NO itself, or to its reactive metabolite, N02. NO can combine with superoxide anion to produce peroxynitrite anion, which is a powerful oxidizing agent. The effects of NO and N02 on repair versus fibrosis in injured lung and on pulmonary host defenses are unknown. Therefore, the effects of inhaled NO on outcome in patients with ARDS are not predictable.

Overall, the data on NO therapy in the setting of ARDS demonstrate that it can improve oxygenation in some patients, but this is limited over time and it does not improve survival. Currently, NO is not recommended for use in the setting of ARDS.


Describe weaning by synchronized intermittent mandatory ventilation (IMV), pressure support, continuous positive airway pressure (CPAP), and T-piece.

Mechanical ventilatory assistance is often an obligatory step during management of critically ill patients; however, complete withdrawal from this support represents a significant clinical problem in approximately 25% of intubated patients. Frequently employed weaning techniques have included PSV, T-piece, CPAP, and SIMV. Several studies have compared these various weaning approaches, but the results have been conflicting. Brochard et al. compared weaning by PSV, T-piece, and SIMV and found weaning by PSV to be superior to weaning by T-piece and by SIMV. In contrast, in a large multicenter trial of nonsurgical patients with diverse medical problems, Esteban et al. demonstrated that the duration of weaning by T-piece once a day was significantly less than weaning by PSV, which in turn was less than weaning by SIMV. Recently, Kollef et al. showed that a protocol-guided weaning by nurses and respiratory therapists was safe and led to extubation more rapidly than physician-directed weaning. Therefore, in addition to differences in study design, weaning modalities, and
weaning techniques, there are selection and physician biases that interfere with the process of weaning. Although employment of protocol-driven weaning may control for physician bias, it is also data driven, time consuming, and costly.

**Conventional T-piece technique**

When the patient meets the criteria for weaning, a T-piece adapter and heated nebulizer are connected to the patient's endotracheal tube. The patient should be in a semisitting or sitting position. The inspired oxygen concentration is set at a level 5% to 10% higher than what the patient was receiving during mechanical ventilation. The vital signs and cardiac rhythm are monitored carefully every 5 to 10 minutes. Arterial blood gases are determined 15 minutes after weaning is begun and then every hour. The patient who tolerates the T-piece very well is extubated 2 to 4 hours. Oxygen is then administered through a face mask with a heated nebulizer, at the same inspired oxygen concentration as during the T-piece trial.

The high success associated with T-piece weaning is related primarily to the fact that the clinician biases are removed from the process. In other words, the patient becomes the sole controller of his or her weaning and readiness for extubation. No guessing is involved. One is either ready or not for weaning, and the best way to determine this is to apply no support. The weaning process is very difficult because the patient's need varies on a breath-by-breath basis, such that the clinician is incapable of predicting such changes. The common error is to be too conservative, thereby prolonging the weaning process.

**Synchronized intermittent mandatory ventilation technique**

Weaning is accomplished by a gradual decrease in the SIMV rate that the ventilator delivers, allowing the patient slowly to take over spontaneous ventilation. This system allows the patient to breathe spontaneously between the preset mechanical ventilation. This system ensures intermittent hyperinflation of the lung.

Weaning by SIMV is the least effective approach in terms of weaning time. It promotes dependence on the ventilator and can be "confusing" to the respiratory center. The delivery of the mechanical breath must coincide with the central inspiratory time. The same rule applies during
exhalation. Prolonging the mechanical breath will overlap with the neural start of exhalation; that is, although the neural input is telling the patient to exhale, the ventilator continues to inflate the lungs. This is frequently seen in patients with COPD whose airway flow changes more slowly and the expiratory muscle becomes active during ventilator-induced inflation. A mismatch can also occur if the patient's inspiratory drive occurs before exhalation is complete, leading to "breath stacking."

Another important aspect of synchronization during PPV is the flow rate that changes on an intra breath and an interbreath basis. Frequently, patients will show signs of "air hunger" and tachypnea if the inspiratory flow rate is inadequate. In most ventilators, the flow rate is set at 60 L per minute. Too much flow is also problematic. Occasionally, the flow rate is increased to lower the inspiratory time while increasing the exhalation time. Unfortunately, the patient may respond adversely by becoming tachypneic, resulting in shortened expiratory times, which then potentiates dynamic hyperinflation (intrinsic PEEP). Several studies have shown a flow-related inspiratory termination reflex. Activating such reflexes can result in curtailing the neural inspiration producing shallow inspiratory efforts. Overall, the consequences of poor synchronization include increase in work of breathing, anxiety, patient discomfort, ineffective ventilation, and increased morbidity and mortality.

**Pressure-support weaning**
Pressure-support weaning can be combined with IMV and with CPAP weaning. Its proposed advantages include reducing the work of breathing, improving synchronization between the patient and the ventilator, reducing inspiratory pressures, and facilitating weaning. While on IMV, once the patient has been weaned to a minimum rate (i.e., IMV of 4 to 6 breaths per minute), the level of pressure support is gradually reduced (2 to 3 cm H2O at a time). In some cases, this level of change is performed only once a day, whereas in other cases, the changes may be made several times a day. When the pressure-support level is at a minimum «8 cm H2O, weaning parameters are obtained in preparation for complete withdrawal from the mechanical ventilation. Attention to the pressure-volume and flow waveforms, which are available in most mechanical ventilators, can facilitate the
weaning process and help determine other important aspects of respiratory mechanics.
As with IMV, the inherent problem with pressure-support weaning is the clinical biases that exist. Once again, the technology and the knowledge that allow for minute-to-minute assessment and adjustment of the dynamic environment of the patient's physiology needs are lacking. Consequently, we make predictions about the level of support the patient needs and await clinical and laboratory signs of problems or success.

Overall, difficulties with weaning can be ascribed in part to the heterogeneity of underlying pulmonary diseases and to inconsistencies in clinical practice. Data-driven approaches to weaning are often nonpredictive of outcome and may fail to provide clinicians with signs of impending respiratory muscle fatigue. The patient's respiratory demand can vary considerably, requiring appropriate and timely ventilatory adjustments. A potential solution to this labor-intensive and costly task is to employ a computer-driven automated weaning process.


**Full Case:**

A 20-YEAR-OLD FULL-TERM PREGNANT WOMAN was rushed to the operating room for emergency cesarean section because of fetal distress. During emergence from general anesthesia, the patient vomited and aspirated.
Questions:

Delineate the risk factors for aspiration pneumonitis.

Aspiration pneumonitis arises most often from aspiration of gastric content that is both acidic and voluminous. It can also occur from aspiration of oropharyngeal content. Several patient characteristics lead to the development of aspiration. These include:

- Neurologic dysphagia
- Disruption of gastroesophageal junction
- Anatomic abnormalities of the upper aerodigestive tract
- General anesthesia
- Pharmacologic agents that alter consciousness (e.g., sedatives, antipsychotics, antidepressants, narcotics)
- Extremes of age (elderly, neonates)

The risk of aspiration pneumonitis is approximately 10% in patients presenting to the hospital after a drug overdose. This condition used to be very common in general anesthesia and accounted for most obstetric morbidity and mortality. The most recent report suggests an incidence of 1 in 3,000 patients receiving general anesthetics; however, the mortality remains very high and accounts for 10% to 30% of all deaths related to anesthesia. The elderly, particularly the nursing home population, is at increased risk of aspiration secondary to both an increased incidence of pharyngeal dysmotility and gastroesophageal reflux. Aspiration pneumonia and pneumonitis are the most common causes of death in patients with dysphagia caused by neurologic disorders, a condition that affects approximately 300,000 to 600,000 people yearly in the United States.


What is Mendelson syndrome?

Mendelson first described acute chemical aspiration pneumonitis in 1946. The triphasic sequence beginning with immediate respiratory distress, bronchospasm, cyanosis, tachycardia, and dyspnea, following with partial recovery, and concluding with a final phase of gradual respiratory recovery is characteristic of Mendelson syndrome. No signs of mediastinal shift are seen, but chest x-ray films usually show irregular mottled densities. This syndrome is due to the irritation of bronchioles by gastric hydrochloric acid, producing bronchiolar spasm, a peribronchiolar exudates, and congestion.

You suspect the patient has aspirated; what is your initial management strategy?

Rapidly tilt the operating table to a 30-degree head-down position to have the larynx at a higher level than the pharynx and to allow gastric content to drain to the outside. While an assistant maintains cricoid pressure, suction the mouth and pharynx as rapidly as possible.

Next, endotracheal intubation should be performed (if the patient had been extubated) with immediate inflation of the endotracheal cuff to prevent further aspiration. Quickly suction through the endotracheal tube before administering 100% oxygen by PPV. This is to prevent pushing aspirated material beyond your reach. Suction should be brief to avoid cardiac arrest from hypoxia. Give 100% oxygen before and after suctioning.
An orogastric tube should be inserted to empty the stomach. The pH value of the gastric content should be determined. Tracheobronchial aspirate is collected for culture and sensitivity tests. Auscultation of the chest will determine whether diminished breathing sounds, wheezing, rales, and rhonchi are present. If bronchospasm is noted, B2-agonists such as albuterol or terbutaline may be administered through metered-dose inhaler adapters to the anesthetic circuit.

The earliest and most reliable sign of aspiration is hypoxemia, which follows aspiration of even the mildest and most benign aspirate. Therefore, analysis of arterial blood gases should be performed to determine the severity of hypoxemia. Early application of PEEP is recommended to improve pulmonary function.


**Would you give prophylactic antibiotics?**

The initial aspirate, excluding feculent aspirate, is usually sterile and remains so for the first 24 hours. Thereafter, the aspiration pneumonitis can become aspiration pneumonia either from contamination of the initial aspirate or secondarily from aspiration of a colonized oropharyngeal secretion in a host that now has tracheobronchial and alveolar damage. Colonization cultures may demonstrate gram-positive or gram-negative superinfection or both, usually with Escherichia, Klebsiella, Staphylococcus, Pseudomonas, and Bacteroides or with anaerobes. Prophylactic antibiotic has not been shown to improve mortality or reduce secondary infection rates.
Cultures must be taken as soon as possible after aspiration and thereafter as clinically indicated. The antibiotic therapy is given according to the sensitivity test result. Prophylactic use of broad-spectrum antibiotics may lead to drug-resistant bacterial and fungal superinfection. However, if intestinal obstruction is a possibility, antimicrobial therapy for the possibility of anaerobic and gram-negative infection may be warranted. Although data supporting the use of prophylactic antibiotics are lacking, it is not unusual for clinicians to prescribe such therapy in settings in which the host is considered immunocompromised (e.g., elderly and critically ill patients). If one or several antibiotics have been administered, prompt withdrawal should occur with laboratory or clinical evidence of no infection. In contrast, the use of antibiotics in aspiration pneumonia is unequivocally indicated (e.g., third-generation cephalosporins, fluoroquinolones, or piperacillin).


**Would you give steroid therapy?**

The value of systemic corticosteroids is controversial. The rationale for immediate use of corticosteroids is to reduce inflammation and stabilize lysosomal membranes. In addition, they have been shown to prevent pulmonary cellular damage by protecting type n alveolar pneumocytes and to attenuate agglutination of leukocytes and platelets.
In experimental studies, the effectiveness of corticosteroid therapy appeared to be related to the pH value of aspirates. When the pH value of the aspirate was in the narrow range of 1.5 to 2.5, corticosteroid therapy was beneficial in treating acid-aspiration pneumonitis. Dexamethasone, given 0.08 mg per kg every 6 hours, decreased pulmonary water content significantly starting at 24 hours, with return to the normal range by 72 hours. When the pH value of the aspirate was less than 1.5, the pulmonary parenchymal damage was maximal. Therefore, the steroid therapy was not effective. When the pH value of the aspirate was higher than 2.5, the response was similar to that of water.

Wolfe, Bone, and Ruth found that pneumonia caused by gram-negative bacteria was more frequent after aspiration in patients treated with corticosteroids than in those who were not. Similarly, studies in animals have failed to demonstrate a beneficial effect of corticosteroids on pulmonary function, lung injury, alveolar-capillary permeability, or outcome after acid aspiration. Furthermore, because of the failure of two multicenter, randomized, controlled trials to demonstrate a benefit of high-dose corticosteroids in patients with ARDS, the administration of corticosteroids cannot be recommended.


**Define acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).**

ARDS is the most severe form of ALI. To standardize definitions, a consensus panel of experts developed a set of criteria characterizing ARDS and ALI. The criteria include onset that is acute, bilateral infiltrates on chest radiography, hypoxemia, and no evidence of cardiogenic failure (i.e., pulmonary artery occlusion pressure, <18 mmHg). Additionally, this group defined hypoxemia in ALI as a Pao2/FIo2 ratio of less than 300 mm Hg and selected a threshold ratio of Pao2/FIo2 of less than 200 mm Hg for ARDS, reflecting the more severe nature of the disease.


Describe the pathogenesis of ALI.

The histopathology reveals areas of hyaline membrane, alveolar hemorrhage, increased endothelial and epithelial permeability, and neutrophilic infiltration. Increased permeability allows passage of protein-rich plasma both in the alveolar and in the interstitial spaces, resulting in poor lung compliance and ineffective gas exchange. As the injury process progresses, dependent lung regions beneath the diseased and edematous lung become collapsed, worsening oxygenation. Additionally, alveolar surfactant content diminishes, and its space becomes filled with fibrin and other cellular materials. Ultimately, a fibroproliferative phase is entered whereby further destruction of the lungs occurs with varying degrees of collagen deposition and pulmonary fibrosis.

Complement activation may also play a major role in the pathogenesis of ARDS. Activation of the complement cascade through the alternative pathway by endotoxin or lipopolysaccharides results in the production of C5a complement. C5a complement causes microvascular occlusion and pulmonary granulocyte aggregation and embolization. The resultant damage to the endothelium leads to capillary leakage and pulmonary interstitial edema, ultimately producing terminal airway and alveolar edema and collapse. However, studies have shown limitations of the complement-neutrophil theory. Complement activation does not necessarily correlate with the development or severity of ARDS. ARDS can develop in patients with neutropenia, and pulmonary sequestration of neutrophils may not produce lung injury. As a result, the complement-neutrophil theory of ARDS has been expanded to include central roles for additional humoral mediators (such as endotoxin, tumor necrosis factor, interleukins, and thromboxane) and cellular mediators (e.g., the macrophage-monocyte system). The lung in patients with ARDS is now viewed as one of the organs involved in the multiorgan system dysfunction that occurs as a result of the systemic inflammatory response syndrome. Increased mediator levels are found in bronchoalveolar lavage fluid from patients with ARDS.
Describe the basic modes of mechanical ventilation. Discuss the advantages and disadvantages of pressure-controlled and volume-controlled modes.

Fundamentally, the various modes of mechanical ventilation, both new and old, share the following variables: trigger, control. limit, cycle, and baseline.

**Trigger mode**
The trigger is the first and most important component of the inspiratory phase, marking the end of exhalation. Examples of triggering mechanisms include time, flow, and pressure. In the nonparalyzed and nonanesthetized state, the patient triggers a mechanical or assisted breath by generating negative transpulmonary pressure that is sensed by the ventilator as a pressure change in the airway (the ventilator circuit including the endotracheal tube). The threshold for triggering a breath (i.e., the set sensitivity) can be altered depending on the clinical setting; however, the greatest challenge in mechanical ventilation is determining the level at which sensitivity pressure should be set (usually at 1 to 2 cm H20). If the threshold is set too low, the ventilator will be triggered by any process that causes the airway pressure to surpass the set threshold. These include patient motion, external compression, gastric suctioning, and air leaks in the circuit or in the chest tubes. Conversely, if the threshold is set too high, the work of breathing increases; that is, to trigger every breath, the patient must make a significant effort to
overcome the threshold limit for inspiratory flow to occur. At high levels of ventilatory assistance, as much as one third of the patient's inspiratory efforts may be insufficient to trigger the ventilator. In a 2001 review, Tobin explained that "breaths that do not reach the threshold for triggering the ventilator have higher tidal volumes and shorter expiratory times than do breaths that do trigger the ventilator." In the setting of acute respiratory failure, the inspiratory effort exhausted by the patient is approximately four to six times the normal value. This level of respiratory work frequently causes breath stacking, generating intrinsic PEEP, which in turn imposes a tremendous burden on inspiratory muscle and if sustained can result in muscle fatigue and cardiopulmonary collapse.

**Control mode**
The delivered breath can be either pressure regulated (pressure control) or volume targeted (volume control). In the pressure-controlled mode, the amount of volume delivered is inversely related to the resistance encountered. When the resistive forces are low (i.e., normal compliance), the tidal volume for a given pressure will be relatively larger than if compliance were poor. For adults, the recommended upper limit of pressure control is 35 cm H2O. Higher pressures may directly cause ALI or delay healing of the already injured lung. When the resistive forces are high, the resultant tidal volume may be inadequate for ventilation or oxygenation, even at high levels of inspiratory pressures. Typically, these patients have ARDS, and lower levels of arterial oxygen tension (Pao2) are tolerated along with higher levels of arterial carbon dioxide tension (permissive hypercapnia).

Volume-controlled mode is the most common control mode used to ventilate patients mechanically. Examples include assist-control ventilation and synchronous intermittent mandatory ventilation (SIMV). The ventilator will attempt to deliver a preset volume regardless of the pressure generated. For patients with poorly compliant lungs, volume-controlled mode may promote barotrauma and acute lung injury (ALI).

**Limit mode**
The limit is an essential feature in mechanical ventilation. Its variables include volume, pressure, and flow. The upper and lower limits of
these variables should be preselected for each patient and adjusted in a manner consistent with the goals of the protective lung strategy employed.

**Cycle mode**  
As discussed in the previous section, cycling has several variables: time, flow, and pressure. As such, the inspiratory phase and the expiratory phase becomes controlled. The challenge faced is in synchronizing the machine's cycling of inspiration and exhalation with the patient's "neural" respiratory cycle. Although pressure, flow, and time can be used to affect cycling, the manipulation of one or all three variables, both intrabreath and interbreath, to coincide precisely with the demands of the patient is virtually impossible.

**Baseline mode**  
The baseline variable is the function that is controlled during exhalation and generally indicates the level of PEEP.


**What are the major factors governing oxygen toxicity? What is the mechanism of oxygen toxicity?**

Oxygen toxicity is governed by the duration of exposure, the partial pressure of oxygen, and the susceptibility of the individual to pulmonary oxygen injury. The degree of toxicity is related to the partial pressure, but not to the percentage of oxygen inspired, as demonstrated during u.s. space flights, where astronauts tolerate 100% oxygen for 2 to 4 weeks at a tension of 250 mm Hg. Systemic oxygen toxicity is related to arterial oxygen tension, whereas pulmonary oxygen toxicity depends on alveolar oxygen tension. Retrolental fibroplasia (retinopathy of prematurity) in the premature neonate has been reported after exposure to Pao2 at more than 80 to
150 mm Hg for a few hours. Pulmonary toxicity can develop after prolonged exposure to oxygen at concentrations between 0.5 and 1.0 atmospheres. It must be emphasized that the adult patient can generally tolerate 1 atmosphere of oxygen partial pressure for at least 24 hours. Moreover, there is no evidence that clinically relevant pulmonary oxygen toxicity occurs in humans at inspired partial pressures less than 0.5 atmosphere. Lastly, no patients should ever experience life-threatening levels of hypoxemia to avoid possible oxygen toxicity.


The so-called free-radical theory of oxygen toxicity proposed in the early 1960s has garnered a great deal of recent experimental support and is now accepted as the most probable molecular-level explanation for oxygen toxicity. Various highly reactive and potentially cytotoxic free-radical products of oxygen are generated metabolically in the cell. These short-lived O2 metabolites, including superoxide anion (O2), hydroxyl radical (OH), hydrogen peroxide (H2O2), and singlet oxygen (O-), have been shown to be capable of effects such as inactivation of sulfhydryl enzymes, interaction with and disruption of DNA, and peroxidation of unsaturated membrane lipids with resultant loss of membrane integrity. The cell is also equipped with an array of antioxidant defenses, including the enzymes superoxide dismutase (SOD), catalase, glutathione peroxidase, vitamin E, and ascorbate. Under hyperoxia, the intracellular generation and influx of free radicals is believed to increase markedly and may overwhelm the detoxifying capacity of the normal complement of antioxidant defenses, with resultant cytotoxicity.

The pathology of oxygen toxicity is nonspecific and consists of atelectasis, edema, alveolar hemorrhage, inflammation, fibrin deposition, and thickening and hyalinization of alveolar membranes. There are exudative and proliferative phases. Capillary endothelium is damaged early and plasma leaks into interstitial and alveolar spaces.
Pulmonary surfactant may be altered. Type I alveolar lining cells are injured early, and bronchiolar and tracheal ciliated cells can be damaged by 80% to 100% oxygen. Resolution of exudative changes, hyperplasia of alveolar type II cells, fibroplastic proliferation, and interstitial fibrosis occur with recovery or with the development of tolerance to oxygen. Total resolution is possible if the initial hyperoxia is not overwhelming.


**How would you determine the best PEEP and the optimal PEEP? What are the cardiopulmonary effects of PEEP?**

Fairley, and Isenberg described best conventional PEEP in 1975. The best PEEP is defined as the level of PEEP with the highest oxygen transport, which is the product of cardiac output and oxygen content. This PEEP correlates with the highest total respiratory compliance, the highest mixed venous oxygen tension, and the lowest VDNT. Arterial oxygen tension and intrapulmonary shunt are not good indicators of the best conventional PEEP. They continue to improve even after this level has been reached. Oxygen transport decreases after the best PEEP is reached, because the cardiac output decreases.

Civetta, Barnes, and Smith described optimal high PEEP in 1975. It is defined as the level of PEEP with the lowest intrapulmonary shunt and without compromising cardiac output. The PEEP used in this report is so-called high or super PEEP, more than 25 cm H2O, whereas the PEEP in the article by Suter, Fairley, and Isenberg is conventional PEEP, ranging from 5 to 20 cm H2O. However, the concept of best or optimal PEEP has evolved over the years. More recently, the endpoint for PEEP application is the lowest level of PEEP that provides an adequate Pao2 at an PI02 of less than 0.5. Increasing PEEP beyond this level to obtain optimum values for various other endpoints, such as the production of
maximum oxygen transport, maximum static pulmonary compliance, shunt less than 15% to 20%, minimal arterial end-tidal CO2 gradient, decreased mixed venous oxygen tension, and minimum FI02 will not be clinically helpful and may be harmful.


The cardiovascular effects of PEEP depend on the severity of respiratory failure, the level of PEEP, the intravascular volume, the contractility of the heart, and the pulmonary vasculature. In healthy subjects without respiratory failure, PEEP decreases cardiac output mainly because of increased intrathoracic pressure resulting in decreased venous return. PEEP also causes pulmonary parenchymal overdistention, which makes the lung come in close contact with the left ventricle, changing compliance and interfering with ventricular function. In addition, PEEP increases pulmonary pressure and resistance, resulting in right ventricular dilation, which causes an intraventricular septum shift toward the left ventricle. The leftward septal shift decreases ventricular diastolic filling, resulting in decreased stroke volume and cardiac output. The aforementioned deleterious effect of PEEP is more apparent in individuals with limited
cardiovascular reserve. Although PEEP is applied only at the end of expiration, in actuality, the alveolar and transpulmonary pressures are highest during inspiration (driving pressures exceeding 20 to 30 cm H2O in some patients) and are associated with the greatest negative hemodynamic effects.

In persons with respiratory failure, PEEP, up to optimum levels, usually increases or does not change cardiac output because of an increase in oxygenation with resultant improvement of cardiac performance. Cardiac output decreases when PEEP exceeds the individual's optimum PEEP. Hypotension during PEEP therapy may be exacerbated by hypovolemia.

In patients with underlying left ventricular failure and filling pressure more than 18 mm Hg, PEEP may increase cardiac output by increasing coronary arterial oxygen content, augmenting, systolic function, or reducing venous return. The decreased venous return may produce a shift in the Starling curve to filling pressures associated with better myocardial function.


**What are the indications and contraindications for extracorporeal membrane oxygenation? How many ways can it be used? What are its results?**

Extracorporeal membrane oxygenation (ECMO) should be used for patients in severe acute respiratory failure with reversible lung disease, who are dying of severe hypoxemia despite maximal conventional ventilatory care (e.g., tracheal intubation, mechanical ventilation with 10 to 15 cm H2O PEEP, diuresis, chest physical therapy, antibiotics, normothermia or mild hypothermia, sedation, paralysis, and increased oxygen concentration). Indications for ECMO by the NIH are as follows: $P_{aO2}$ less than 50 mm Hg for more than 2 hours with $FI_{O2}$ of 1.0 and conventional PEEP; and a $Pao2$ less than 50
mmHg for more than 12 hours with F102 of more than 0.6 and conventional PEEP. Active bleeding is the only absolute contraindication to use of the artificial lung. The three routes for ECMO are as follows: venovenous perfusion from the inferior vena cava by way of the femoral vein to the oxygenator and then to the superior vena cava; venoarterial perfusion from the femoral vein to the oxygenator and then to the femoral artery; and venovenous arterial perfusion from the femoral vein to the oxygenator and then to both the internal jugular vein and the femoral artery.

A collaborative study on ECMO has been completed under the auspices of the National Heart, Lung, and Blood Institute of the NIH. The results of this controlled study are as follows:
. Compared with the control group of conventional respiratory therapy, ECMO did not improve mortality (90%), and the predominant cause of death was still progressive respiratory failure.
. ECMO did not affect the progress of disease (or lung pathology in those patients who died) any differently from conventional respiratory therapy.
. Although ECMO is an effective means of short-term life support, its clinical application for the treatment of ARDS is not appropriate or economically justified.

However, data analyzed from a national registry series of 715 neonatal ECMO patients (1980 to 1987) demonstrated an overall survival of 81%, which in earlier series had been the overall mortality rate with conventional therapy. As neonatal ECMO has evolved, entry criteria have been used, and experience with ECMO technology has been shown to improve survival. ECMO is now a proven support modality for neonatal respiratory failure that is due to several causes, such as meconium aspiration syndrome, persistent pulmonary hypertension of the newborn, congenital diaphragmatic hernia, and infant respiratory distress syndrome.


What is nitric oxide (NO)? What is the role of inhaled NO in the treatment of ARDS?

1987, endothelium-derived relaxing factor was identified as NO. NO produced by the endothelium diffuses into vascular smooth muscle where NO activates soluble guanylate cyclase. The subsequent increase in intracellular cyclic guanosine monophosphate (cGMP) causes smooth muscle vasodilation. Endothelium-independent nitrovasodilators such as nitroglycerin and nitroprusside also act through guanylate cyclase activation to directly release NO.

Inhaled NO is a selective pulmonary vasodilator. NO is not effective during systemic administration because it is rapidly inactivated by hemoglobin. Therefore, inhaled NO may diffuse from the alveoli to pulmonary vascular smooth muscle and produce pulmonary vasodilation without systemic vasodilation because any NO that diffuses into blood will be inactivated by hemoglobin. Inhaled NO has been shown to be effective in treating primary pulmonary hypertension, as well as decreasing pulmonary hypertension and improving oxygenation after mitral valve replacement and in the newborn with persistent pulmonary hypertension.

Pulmonary hypertension and hypoxemia universally occur in ARDS. Pulmonary hypertension in ARDS may be due to active vasoconstriction from local alveolar hypoxic pulmonary vasoconstriction and other vasoconstrictor mediators. Hypoxemia in ARDS is due to ventilation/perfusion mismatch, intrapulmonary shunting, or anatomic shunting. Intravenous pulmonary vasodilator
therapy with agents such as nitroglycerin, nitroprusside, prostaglandin E, prostacyclin, adenosine, and nifedipine produces small reduction in pulmonary artery pressure but large reduction in systemic blood pressure and arterial oxygenation. The adverse effect on oxygenation is primarily due to reversal of hypoxic pulmonary vasoconstriction. On the contrary, inhaled NO may decrease pulmonary hypertension and improve oxygenation in patients with ARDS because inhaled NO may be distributed according to ventilation so the associated vasodilation increases blood flow to well-ventilated alveoli.

Rossaint et al. published the first major report of the use of inhaled NO in patients with ARDS. They found that inhaled NO (5 to 20 parts per million [ppm]) effectively decreased pulmonary hypertension and improved oxygenation. In a subsequent study, they showed that inhaled concentrations of only 60 to 250 parts per billion could increase Pao2 by 30%. These concentrations had little or no effect on pulmonary artery pressure. The other major study by Bigatello et al. demonstrated that inhaled NO produced dose-related decreases in pulmonary artery pressure with 50% of the maximal effect occurring at 5 ppm. Inhaled NO also increased oxygenation, but dose-response effects could not be demonstrated.

Inhaled NO has been effective on ARDS in combination with other therapies. The combination of inhaled NO (5 to 10 ppm) and almitrine bismesylate, a potentiator of hypoxic pulmonary vasoconstrictor, had additive effects on improving oxygenation in ARDS and simultaneously decreased pulmonary hypertension. Dcering et al. studied intravenous phenylephrine, 50 to 200 /Lg per minute, titrated to a 20% increase in mean arterial pressure; inhaled NO, 40 ppm; and the combination of phenylephrine and NO. They found that phenylephrine alone can improve Pao2 in patients with ARDS. In phenylephrine-responsive patients, phenylephrine augments the improvement in Pao2 seen with inhaled NO. These results may reflect selective enhancement of hypoxic pulmonary vasoconstriction by phenylephrine, which complements selective vasodilation by inhaled NO. However, an important unsolved issue is the potential pulmonary toxicity of inhaled NO. Toxicity may be due to NO itself, or to its reactive metabolite, NO2. NO can combine with superoxide anion to produce peroxynitrite anion, which is a powerful oxidizing agent. The effects of NO and NO2 on repair versus fibrosis in injured lung and on pulmonary host defenses
are unknown. Therefore, the effects of inhaled NO on outcome in patients with ARDS are not predictable.

Overall, the data on NO therapy in the setting of ARDS demonstrate that it can improve oxygenation in some patients, but this is limited over time and it does not improve survival. Currently, NO is not recommended for use in the setting of ARDS.


Describe weaning by synchronized intermittent mandatory ventilation (IMV), pressure support, continuous positive airway pressure (CPAP), and T-piece.

Mechanical ventilatory assistance is often an obligatory step during management of critically ill patients; however, complete withdrawal from this support represents a significant clinical problem in approximately 25% of intubated patients. Frequently employed weaning techniques have included PSV, T-piece, CPAP, and SIMV. Several studies have compared these various weaning approaches, but the results have been conflicting. Brochard et al. compared weaning by PSV, T-piece, and SIMV and found weaning by PSV to be superior to weaning by T-piece and by SIMV. In contrast, in a large multicenter trial of nonsurgical patients with diverse medical problems, Esteban et al. demonstrated that the duration of weaning by T-piece once a day was significantly less than weaning by PSV, which in turn was less than weaning by SIMV. Recently, Kollef et al. showed that a protocol-guided weaning by nurses and respiratory therapists was safe and led to extubation more rapidly than physician-directed weaning. Therefore, in addition to differences in study design, weaning modalities, and weaning techniques, there are selection and physician biases that interfere with the process of weaning. Although employment of protocol-driven weaning may control for physician bias, it is also data driven, time consuming, and costly.

Conventional T-piece technique

When the patient meets the criteria for weaning, a T-piece adapter and heated nebulizer are connected to the patient’s endotracheal tube. The patient should be in a semisitting or sitting position. The inspired
oxygen concentration is set at a level 5% to 10% higher than what the patient was receiving during mechanical ventilation. The vital signs and cardiac rhythm are monitored carefully every 5 to 10 minutes. Arterial blood gases are determined 15 minutes after weaning is begun and then every hour. The patient who tolerates the T-piece very well is extubated 2 to 4 hours. Oxygen is then administered through a face mask with a heated nebulizer, at the same inspired oxygen concentration as during the T-piece trial.

The high success associated with T-piece weaning is related primarily to the fact that the clinician biases are removed from the process. In other words, the patient becomes the sole controller of his or her weaning and readiness for extubation. No guessing is involved. One is either ready or not for weaning, and the best way to determine this is to apply no support. The weaning process is very difficult because the patient's need varies on a breath-by-breath basis, such that the clinician is incapable of predicting such changes. The common error is to be too conservative, thereby prolonging the weaning process.

Synchronized intermittent mandatory ventilation technique
Weaning is accomplished by a gradual decrease in the SIMV rate that the ventilator delivers, allowing the patient slowly to take over spontaneous ventilation. This system allows the patient to breathe spontaneously between the preset mechanical ventilation. This system ensures intermittent hyperinflation of the lung.

Weaning by SIMV is the least effective approach in terms of weaning time. It promotes dependence on the ventilator and can be "confusing" to the respiratory center. The delivery of the mechanical breath must coincide with the central inspiratory time. The same rule applies during exhalation. Prolonging the mechanical breath will overlap with the neural start of exhalation; that is, although the neural input is telling the patient to exhale, the ventilator continues to inflate the lungs. This is frequently seen in patients with COPD whose airway flow changes more slowly and the expiratory muscle becomes active during ventilator-induced inflation. A mismatch can also occur if the patient's inspiratory drive occurs before exhalation is complete, leading to "breath stacking."
Another important aspect of synchronization during PPV is the flow rate that changes on an intra breath and an interbreath basis. Frequently, patients will show signs of "air hunger" and tachypnea if the inspiratory flow rate is inadequate. In most ventilators, the flow rate is set at 60 L per minute. Too much flow is also problematic. Occasionally, the flow rate is increased to lower the inspiratory time while increasing the exhalation time. Unfortunately, the patient may respond adversely by becoming tachypneic, resulting in shortened expiratory times, which then potentiates dynamic hyperinflation (intrinsic PEEP). Several studies have shown a flow-related inspiratory termination reflex. Activating such reflexes can result in curtailing the neural inspiration producing shallow inspiratory efforts. Overall, the consequences of poor synchronization include increase in work of breathing, anxiety, patient discomfort, ineffective ventilation, and increased morbidity and mortality.

**Pressure-support weaning**
Pressure-support weaning can be combined with IMV and with CPAP weaning. Its proposed advantages include reducing the work of breathing, improving synchronization between the patient and the ventilator, reducing inspiratory pressures, and facilitating weaning. While on IMV, once the patient has been weaned to a minimum rate (i.e., IMV of 4 to 6 breaths per minute), the level of pressure support is gradually reduced (2 to 3 cm H2O at a time). In some cases, this level of change is performed only once a day, whereas in other cases, the changes may be made several times a day. When the pressure-support level is at a minimum <8 cm H2O, weaning parameters are obtained in preparation for complete withdrawal from the mechanical ventilation. Attention to the pressure-volume and flow waveforms, which are available in most mechanical ventilators, can facilitate the weaning process and help determine other important aspects of respiratory mechanics. As with IMV, the inherent problem with pressure-support weaning is the clinical biases that exist. Once again, the technology and the knowledge that allow for minute-to-minute assessment and adjustment of the dynamic environment of the patient's physiology needs are lacking. Consequently, we make predictions about the level of support the patient needs and await clinical and laboratory signs of problems or success.
Overall, difficulties with weaning can be ascribed in part to the heterogeneity of underlying pulmonary diseases and to inconsistencies in clinical practice. Data-driven approaches to weaning are often nonpredictive of outcome and may fail to provide clinicians with signs of impending respiratory muscle fatigue. The patient's respiratory demand can vary considerably, requiring appropriate and timely ventilatory adjustments. A potential solution to this labor-intensive and costly task is to employ a computer-driven automated weaning process.


