Mechanical Ventilation

Conventional Approaches

To characterize the pattern of sleep in critically ill patients, and particularly the effect of noise, Freedman and colleagues (1) did continuous polysomnography for 24 to 48 hours in 22 patients (20 were receiving mechanical ventilation). The EEG could not be scored in five patients because of septic encephalopathy. Total sleep time was 8.8 hours (range, 1.7 to 19.4 hours) over a day. All patients had abnormal sleep architecture, each bout of sleep averaged 15 (range 6–40) minutes, and stage 1 sleep predominated (59%). Total sleep time was longer during the day than at night (57 versus 43%). Environmental noise was responsible for only 12% of arousals. The authors conclude that mechanically ventilated patients are qualitatively, but not quantitatively, sleep deprived, and that environmental noise accounts for a smaller proportion of the sleep–wake abnormalities than is generally imagined.

Patient–Ventilator Interaction

In 13 ventilator-supported patients, Beck and coworkers (2) compared electrical activity in the crura of the diaphragm, using a multiple array electromyographic electrode in the esophagus, and global pressure-generating activity of the diaphragm, as reflected by transdiaphragmatic pressure. To induce changes in respiratory drive, pressure support was varied between 2 and 20 cm H₂O. Adding pressure support produced equivalent decreases in the mean values of electrical activity and transdiaphragmatic pressure (r = 0.84), and equivalent decreases in the peak values of the two signals (r = 0.90). Between the lowest and highest level of pressure support, the inspiratory volume at which electrical activity achieved its peak did not differ (276 versus 277 ml). The authors conclude that sampling a limited number of activated motor units in the crura of the diaphragm with an esophageal electrode is sufficient to obtain a measure of overall diaphragmatic activation in mechanically ventilated patients.

Shortening the time of inflation during mechanical ventilation causes tachypnea in healthy subjects, but the response might be different in patients with chronic obstructive pulmonary disease (COPD) because of time-constant inhomogeneities in their lungs. To investigate this issue, Laghi and colleagues (3) studied 10 patients with COPD during assist-control ventilation. Decreasing the time of mechanical inflation, achieved through an increase in inspiratory flow from 30 to 90 liters per minute, caused a 29% increase in respiratory frequency, a 10% increase in expiratory time, and a 9% decrease in intrinsic
PEEP (positive end-expiratory pressure). Decreasing the time of mechanical ventilation, achieved through shortening of an applied inspiratory pause from 2 to 0 seconds, caused a 40% increase in frequency, a 30% increase in expiratory time, and a 14% decrease in intrinsic PEEP. In both experiments, decreases in the time of mechanical inflation caused a decrease in inspiratory effort. The authors conclude that strategies that shorten the time of mechanical inflation cause tachypnea in patients with COPD, but that intrinsic PEEP does not increase because the time for exhalation is also prolonged.

Studies of patient–ventilator interaction in patients are hampered by the difficulty in obtaining a precise measure of neural inspiratory time. Stell and coworkers (4) obtained a direct measure of neural inspiratory time using a test lung, and then assessed the coordination between mechanical timing and neural timing of 13 ventilators used for noninvasive ventilation under conditions that mimic an acute exacerbation of COPD. Increasing airway resistance, from 3.6 to 20 cm H₂O per liter per second, and increasing the end-expiratory lung volume, from 3.3 to 6.3 liter, had a variable, but generally small, effect on the timing of coordination. Triggering at both the start and end of inspiration was delayed by less than 120 milliseconds with three of the ventilators, whereas delays of 120 to 300 milliseconds occurred with the other ventilators. Delays of as much as 500 milliseconds occurred with some ventilators. Delays in triggering were slightly aggravated by a leak. The authors conclude that many ventilators used for noninvasive ventilation in patients with an acute exacerbation of COPD have considerable delays in triggering, and that the delays result primarily from the physical properties of the ventilator, rather than from the degree of airway obstruction and hyperinflation occurring in the patient.

In sleeping humans and dogs, controlled ventilation at high volumes and frequencies eliminates respiratory motor output. To determine the factors causing the respiratory inhibition, Satoh and colleagues (5) studied six dogs during non-REM (rapid eye movement) sleep. A single tidal volume (75 to 200% of control value) caused apnea when applied during the initial 25 to 65% of expiration. Increasing the frequency of normocapnic mechanical ventilation by as little as 1 breath per minute above eupnic frequency caused silence of the diaphragm and tonic activation of the expiratory triangularis sterni muscle. The silencing occurred within a few ventilator cycles, was sustained for several minutes of controlled ventilation, and persisted after cessation of controlled ventilation (despite P₆O₂ being above the normocapnic level). Once the higher frequency had eliminated inspiratory motor output, the duration of mechanical ventilation and the size of the tidal volume determined the length of the apneas that followed the cessation of mechanical ventilation. The authors conclude that an increase in the frequency of controlled ventilation is critical in causing silence of the inspiratory muscles and tonic activity of the expiratory muscles, and that the duration of mechanical ventilation and the size of delivered volume determine the length of the apnea that follows the cessation of mechanical ventilation.

The role of nonchemical neuromechanical influences in causing apnea following mechanical ventilation is debated by Dempsey and Skatrud (6) and Younes (7), with rebuttals from each (8, 9).

In a critical care perspective, Tobin and colleagues (10) discuss patient–ventilator interactions.

Nonconventional Modes

Proportional-assist ventilation delivers inspiratory assistance in proportion to a patient’s respiratory resistance. Because resistance is measured on a one-time basis under passive conditions, assistance does not match changes in patient demands over time. Younes and colleagues (11) developed a method for detecting changes in resistance over time in actively breathing patients. By inducing a transient fall in flow and then measuring the resulting changes in airway pressure, volume, and flow, the investigators computed pulse resistance. In 67 critically ill patients, pulse resistance during active breathing showed good agreement with the standard measurement under passive conditions (the difference was about 5%). Two-thirds of patients showed biologically significant changes in resistance (2 cm H₂O per liter per second) over a period of 90 minutes. The authors conclude that pulse resistance provides a reliable measure of inspiratory resistance, and its incorporation into proportional assist ventilation should enable mechanical assistance to keep pace with changes in patient effort. An editorial commentary by Tobin (12) accompanies this article.

Measurement of respiratory elastance requires the absence of patient effort, and this confines the measurement to controlled passive ventilation. By using proportional-assist ventilation, Younes and coworkers (13) reasoned that respiratory muscle activity would approach zero at 0.25 seconds after the onset of an end-inspiratory occlusion, and that the airway pressure at this point would reflect passive elastic recoil pressure. Brief occlusions were randomly applied in 74 ventilator-dependent patients. At high levels of assistance, respiratory muscle activity approached zero at the onset of an occlusion. At lower levels of assistance, airway pressure increased exponentially during the occlusion with an average time constant of 0.21 seconds; by 0.25 seconds after the beginning of the occlusion, patient effort was minimal. The new method yielded elastance values within 1% of values measured during controlled passive ventilation. The authors conclude that measurement of airway pressure at 0.25 seconds after the onset of an end-inspiratory occlusion during proportional assist ventilation provides a reliable estimate of passive elastic recoil.

Proportional assist ventilation delivers positive pressure in proportion to a patient’s respiratory resistance and elastance. To achieve maximum benefit, it is necessary to repeatedly measure resistance and elastance. In 14 patients receiving proportional assist via a mask, Farre and coworkers (14) determined whether the forced oscillation technique would provide accurate measurements of resistance. Resistance was measured by superimposing a pressure oscillation of 5 Hz on the airway pressure and by Fourier analysis of the pressure and flow signals. The values obtained were within 3% of resistances measured with an esophageal balloon. The authors conclude that the forced oscillation technique provides a reliable measure of respiratory resistance during proportional assist ventilation, and that the measurements should make it possible to continuously adjust ventilator settings in proportion to change in patient resistance.

The reason for the wide variation in the severity of obstructive sleep apnea is not known. To determine the role of ventilatory stability and controller gain, Younes and colleagues (15) studied 12 patients with severe disease (apnea-hypopnea index 88) and 20 patients with mild-to-moderate disease (apnea-hypopnea index 27) during sleep. To remove the confounding influence of upper airway resistance, the upper airway was first stabilized with continuous positive airway pressure (CPAP). Controller gain in a patient was measured by gradually increasing levels of proportional assist ventilation. The gain was taken as the ratio of the tidal volume during assisted breathing to the tidal volume of the first reloaded (unassisted) breath. Periodic breathing with central apneas occurred in 75% of patients with severe sleep apnea and in 30% of patients with mild-to-moderate sleep apnea, despite the level of assistance.
Bryan (21) recalls an early study of high-frequency ventilation.

Protective Ventilation

In eight patients with the acute respiratory distress syndrome (ARDS), Mancini and coworkers (22) used the multiple inert gas elimination technique to study the effect of a protective strategy of mechanical ventilation (tidal volume of 5 to 7 ml per kilogram and PEEP set at 2 cm H₂O above the lower inflection point on a pressure–volume curve) on gas exchange. Compared with conventional ventilation (tidal volume of 10 to 12 ml per kilogram and PEEP of 8 to 10 cm H₂O), the protective strategy produced a decrease in minute ventilation from 9.9 to 6.3 liters per minute, an increase in PCO₂ from 39 to 57 mm Hg, an increase in PO₂ from 93 to 166 mm Hg, an increase in cardiac output from 7.9 to 9.1 liters per minute, and a decrease in intrapulmonary shunt from 39 to 31%. The protective strategy resulted in a redistribution of pulmonary blood flow from nonventilated alveoli to normal lung units. The decrease in shunt was proportional to lung recruitment, as measured on a pressure–volume curve (r² = 0.79). The authors conclude that the combination of a low tidal volume and a high PEEP improves oxygenation in patients with ARDS as a result of a decrease in intrapulmonary shunt caused by lung recruitment.

Both a decrease in tidal volume and strategies for recruiting alveoli may minimize the risk of ventilator-induced lung injury. In 15 patients with ARDS, Richard and colleagues (23) examined whether a lower tidal volume causes derecruitment. Pressure–volume curves were performed and PEEP was set at each patient’s lower inflection point. For an elastic pressure of 30 cm H₂O, recruitment was 41% less with a low versus conventional tidal volume (6 versus 10 ml/kg). While patients were being ventilated with a low tidal volume, a re-expansion maneuver (two sustained inflations at 45 cm H₂O) produced a 45% increase in lung recruitment at an elastic pressure of 20 cm H₂O. Under the same conditions, an increase in PEEP of 4 cm H₂O produced a 90% increase in recruitment. The authors conclude that lowering tidal volume from 10 to 6 ml per kilogram causes a significant loss of lung volume and that this derecruitment can be transiently reversed by a re-expansion maneuver or by PEEP.

A low tidal volume has been shown to decrease mortality in patients with ARDS. To assess whether this benefit depends on the underlying disease state, Eisner and coworkers (24) analyzed data from 902 patients participating in a clinical trial. Mortality varied with the underlying risk factor: sepsis 43%; pneumonia 36%; aspiration 37%; and trauma 11%. The benefit of using a low rather than a conventional tidal volume did not vary among disease states. The authors conclude that low tidal volume should be used broadly in patients with acute lung injury or ARDS.

Fairley (25) recalls early attempts to protect the acutely injured lung during mechanical ventilation.

Liquid Ventilation

When used for partial liquid ventilation, the high density of perfluorocarbon causes it to be distributed largely to dependent regions of the lung. To circumvent this problem, Kandler and coworkers (26) delivered the substance as an aerosol, that is small droplets of perfluorocarbon in the gas phase. In piglets with lung injury resulting from surfactant depletion, two hours of administering aerosolized perfluorocarbon at a tidal volume of 10 ml per kg caused oxygenation to improve by 82%. In contrast, oxygenation improved by 6% with partial liquid ventilation at a tidal volume of 10 ml per kg, by 32% with
partial liquid ventilation at a tidal volume of 30 ml per kg, and by 18% with intermittent mandatory ventilation (IMV). After two hours, therapy was stopped and the animals were ventilated with IMV for the next six hours. After six hours, maximum values of $P_{CO_2}$ were: 406 mm Hg for piglets that received aerosolized perfluorocarbon; 96 mm Hg for piglets that received partial liquid ventilation at a tidal volume of 10 ml per kg; 217 mm Hg for piglets that received partial liquid ventilation at a tidal volume of 30 ml per kg; and 68 mm Hg for piglets that received IMV. Aerosolized perfluorocarbon also achieved the lowest $P_{CO_2}$ and the highest compliance. The authors conclude that aerosolized perfluorocarbon produces a greater improvement in oxygenation as compared with an equal volume of non-aerosolized perfluorocarbon delivered by partial liquid ventilation. This article is accompanied by an editorial commentary by Hlastala and Souders (27).

Partial liquid ventilation is usually used in combination with controlled ventilation and neuromuscular blockade. Franz and coworkers (28) assessed the effect of combining partial liquid ventilation with proportional-assist ventilation, a mode that allows active respiratory efforts. Compared with combining liquid ventilation with controlled ventilation and muscle paralysis, delivering it with proportional-assist ventilation achieved a 13% higher cardiac output and 11% higher oxygen transport in healthy rabbits, and a 32% higher cardiac output and 36% higher oxygen transport in rabbits with lung injury (secondary to surfactant depletion). The authors conclude that the combination of partial liquid ventilation and proportional-assist ventilation achieves a greater improvement in oxygen transport as compared with the combination of partial liquid ventilation and controlled ventilation.

To determine whether mixing antibiotics with the solution used for partial liquid ventilation increases their tissue concentration, Franz and coworkers (29) studied 19 healthy rabbits and 18 surfactant-depleted rabbits. When antibiotics were delivered as an emulsion in combination with perfluorodecaline, the pulmonary tissue concentration of gentamicin was 24-fold higher in the healthy animals than in the animals with lung injury as compared with administration of the same dosages intravenously. The pattern with vancomycin was similar. Lung histology, lung mechanics, and gas exchange did not differ between the treatment groups. The authors conclude that delivering gentamicin or vancomycin in conjunction with partial liquid ventilation achieves higher pulmonary tissue concentrations as compared with administering the agents intravenously. This article is accompanied by an editorial commentary by Brun-Buisson and Lemaire (30).

**Ventilator-Induced Lung Injury**

Held and colleagues (31) determined whether the early inflammatory response caused by ventilator-induced lung injury is similar to that caused by endotoxin. In isolated perfused lungs of BALB/c mice, both lipopolysaccharide and overventilation (end-inspiratory pressure of $-25$ cm H$_2$O during negative pressure ventilation) caused translocation of nuclear factor-κB, which was abolished by pretreatment with dexamethasone. Both of the challenges caused similar increases in $\alpha$-chemokines (macrophage inflammatory protein-$\alpha$), $\beta$-chemokines (macrophage chemotactic protein-1), and cytokines (tumor necrosis factor-$\alpha$, interleukin-6), which were largely prevented by pretreatment with dexamethasone. C57/HeJ mice have a mutation of Toll-like receptor-4, which makes them insensitive to endotoxin. (The *Toll* gene encodes a receptor that binds to surface ligands/epitopes on bacteria to effect signaling from the cell membrane to the nucleus.) In these mutant mice, overventilation, but not endotoxin, caused translocation of nuclear factor-κB and the release of macrophage inflammatory protein-$\alpha$, thus excluding contamination by endotoxin as the cause of the inflammatory response to overventilation. The authors conclude that overventilation triggers the activation of nuclear factor-κB and elicits the release of $\alpha$-chemokines, $\beta$-chemokines, and cytokines from perfused lungs in a manner qualitatively and quantitatively similar to that seen with endotoxin, and that glucocorticoids diminish this response. An editorial commentary by Slutsky (32) accompanies this article.

Ventilator-induced lung injury has been reported to cause the release of inflammatory cytokines. Because the previous studies were done on isolated, unperfused lungs that were already damaged by surfactant depletion or hypoxia, Ricard and colleagues (33) investigated the phenomenon in an *in vivo* model. Compared with the delivery of a tidal volume of 7 ml per kg, a tidal volume of 42 ml per kg caused severe pulmonary edema. The lavage fluid, however, did not contain tumor necrosis factor-$\alpha$ or macrophage inflammatory protein-2, and it contained only a slight increase in interleukin-1β. Cytokines were not detected in plasma. Experiments were also conducted in isolated, unperfused rat lungs under three conditions: static inflation; a tidal volume of 7 ml per kg; and a tidal volume of 42 ml per kg. Tumor necrosis factor-$\alpha$ was negligible for all conditions, and the high tidal volume caused a slight increase in interleukin-1β and a moderate increase in macrophage inflammatory protein-2 in the lavage fluid. The authors conclude that ventilator-induced injury does not necessarily cause the primary production of proinflammatory cytokines in the lung. An editorial commentary by Simon (34) accompanies this article.

To investigate the mechanisms of airspace enlargement caused by mechanical ventilation, Goldstein and colleagues (35) developed a model of multifocal bronchopneumonia by instilling *E. coli* into the bronchi of nine piglets. The animals were ventilated with a tidal volume of 15 ml per kilogram. After three days, the lungs had both nonventilated infected regions and normally ventilated noninfected regions. The normally ventilated noninfected regions had emphysema-like lesions, and the degree of alveolar distension correlated with the decrease in compliance. The nonventilated bronchopneumonic regions had frequent pseudocysts and bronchiolectasis, and edema was rare. The degree of bronchiolar distension correlated with the plateau pressure, suggesting a link between ventilator-induced airspace enlargement and extension of alveolar damage. The authors conclude that mechanical ventilation causes airspace enlargement, rather than edema, in piglets with bronchopneumonia, and that the lesions resemble those reported in patients with ARDS. An editorial commentary by Marini (36) accompanies this article.

The heat stress or heat shock response can protect against an otherwise lethal injury. To determine whether heat stress attenuates ventilator-induced lung injury, Ribeiro and colleagues (37) exposed rats to 15 minutes of heat (rectal temperature $41^\circ$C), and 18 hours later ventilated their isolated lungs with a tidal volume of 40 ml per kilogram for two hours. In animals not exposed to heat, mechanical ventilation produced a decrease in compliance (47%), an increase in cytokines, and no change in the fraction of surfactant large aggregates. Compared with control animals, animals exposed to heat stress had a smaller decrease in compliance (17%), a relative increase in the fraction of surfactant large aggregates, and relative decreases in tumor necrosis factor-$\alpha$ (70%), interleukin-1β (86%), and macrophage inflammatory protein-2 (80%). The authors conclude that exposing animals to heat stress confers protection against ventilator-induced lung injury.
To determine whether respiratory acidosis modulates ventilator-induced lung injury, Broccard and coworkers (38) studied isolated rabbit lungs. While maintaining normocapnia, an increase in peak alveolar pressure from 15 to 30 cm H$_2$O caused lung weight to increase 21-fold, the ultrafiltration coefficient to increase 140-fold, and the level of protein in bronchoalveolar fluid to increase 4-fold. When PCO$_2$ was increased to 105 mm Hg, the same alveolar pressure (30 cm H$_2$O) caused lung weight to increase 7.5-fold, the ultrafiltration coefficient to increase 25-fold, and the level of protein in bronchoalveolar fluid to increase 2-fold. The authors conclude that hypercapnic acidosis decreases ventilator-induced injury of isolated rabbit lungs.

**Weaning**

In patients with COPD requiring mechanical ventilation for more than 15 days, Vitacca and coworkers (39) compared two methods of weaning: pressure support versus trials of spontaneous breathing. Of 75 eligible patients, 23 (31%) tolerated an initial spontaneous-breathing trial and were excluded. Among 26 patients weaned by pressure support, pressure was initially set at 19 cm H$_2$O and was then lowered by 2 cm H$_2$O twice a day until the patients tolerated a level of 8 cm H$_2$O for eight hours. Among 26 patients weaned by spontaneous-breathing trials, the trials were done twice a day and the duration was progressively doubled until the patients sustained spontaneous breathing for eight hours. Pressure support and spontaneous breathing trials achieved equivalent rates of weaning success (73 versus 77%), durations of ventilator support (181 versus 130 hours), and unit stays (33 versus 35 days). The patients in the study were also compared with 55 patients managed without a protocol. Compared with the nonprotocol group, the study patients had a higher 30-day rate of weaning success (87 versus 70%), shorter ventilator time (103 versus 170 days), and shorter unit stay (27 versus 38 days). The authors conclude that pressure support and trials of spontaneous breathing are equally effective in the weaning of patients receiving prolonged mechanical ventilation, and that use of an explicit protocol achieves more effective weaning than does conventional clinical practice. An editorial commentary by Hill (40) accompanies this article.

In medical patients, a two-step protocol consisting of daily measurement of weaning predictors followed by a trial of spontaneous breathing has been shown to achieve better outcome as compared with conventional weaning practice. Naaman and colleagues (41) did a randomized controlled comparison of these two approaches in 100 neurosurgical patients. Of 49 patients managed by the two-step protocol, 86% satisfied weaning predictors, and 82% passed a trial of spontaneous breathing. Only 25% of patients in this group were extubated on the day of passing the trial; a neurosurgeon’s concern over a patient’s sensorium was the commonest explanation (84%) for declining to extubate. The duration of mechanical ventilation and clinical outcome were the same in the two groups. The authors conclude that a protocol previously shown to expedite weaning in medical patients did not influence the clinical practice of neurosurgeons.

Because some patients develop airway obstruction following removal of an endotracheal tube, Jaber and coworkers (42) determined whether breathing a helium–oxygen mixture would decrease inspiratory effort in 18 patients after extubation. Excursions in transdiaphragmatic pressure were 10.2 cm H$_2$O while the patients breathed supplemental oxygen (concentrations of 25 to 40%), and fell to 8.6 cm H$_2$O when they breathed helium–oxygen. A measure of inspiratory effort decreased by 16% after 15 minutes of breathing the helium–oxygen mixture via a face mask. Comfort improved in 69% of the patients when breathing a helium–oxygen mixture, and gas exchange did not change. The authors conclude that breathing a helium–oxygen mixture after extubation decreases inspiratory effort and makes breathing more comfortable.

**Patient Posture**

The pathophysiology of ARDS is believed to differ depending on whether the inciting cause is pulmonary or nonpulmonary in nature. Rialp and coworkers (43) assessed the influence of the underlying cause on the response to prone positioning and inhaled nitric oxide. On turning a patient from the supine to the prone position, the increase in P$_{O_2}$/F$_{O_2}$ did not differ between eight patients with a pulmonary cause of ARDS and seven patients with a nonpulmonary cause of ARDS (106 versus 184 mm Hg for the overall group). Inhaled nitric oxide improved oxygenation only in the patients with a pulmonary cause of ARDS: oxygenation improved by 23% in the supine position and by 35% in the prone position. The authors conclude that prone positioning improves oxygenation in patients with either a pulmonary or a nonpulmonary cause of ARDS, but that inhaled nitric oxide improves oxygenation only in patients with a pulmonary cause of ARDS.

**Noninvasive Ventilation**

In a prospective study over three weeks in 42 ICUs in France, Carlucci and colleagues (44) assessed the use of noninvasive ventilation. Of 689 patients, 581 were ventilated through an endotracheal tube and 108 (16%) were ventilated noninvasively. Of patients admitted without an endotracheal tube, 35% were ventilated noninvasively. Noninvasive ventilation was used in 50% of the patients with hypercapnic respiratory failure, in 27% of the patients with pulmonary edema, in 14% of the patients with hypoxemic respiratory failure, and in no patient with coma. Forty percent of patients initially ventilated noninvasively were later intubated. Patients ventilated noninvasively had a lower incidence of pneumonia (10 versus 19%) and mortality (22 versus 41%). The authors conclude that noninvasive ventilation is successful in selected patients and is associated with a lower risk of mortality and death as compared with ventilation through an endotracheal tube.

A mortality rate of as much as 80% has been reported in patients who require the reinsertion of an endotracheal tube during the recovery period immediately after the surgical resection of lung tissue. To determine the effectiveness of noninvasive ventilation in this setting, Auriant and coworkers (45) did a prospective randomized trial on 48 patients admitted to the intensive care unit with acute hypoxemic respiratory failure after resection of a lung carcinoma. Of 24 patients managed with pressure support of 8.5 cm H$_2$O (delivered for an average of 14 hours a day over two days), 21% required endotracheal intubation, as compared with 50% of the 24 patients in the conventional management group. Mortality was 12.5% in the patients assigned to noninvasive ventilation and 37.5% in the conventional management group. The study was stopped after interim analysis of the data. The authors conclude that noninvasive ventilation decreases the need for endotracheal intubation and improves survival in patients who develop acute hypoxemic respiratory failure after surgical resection of lung tissue.

In 44 patients with acute respiratory failure, Gay and coworkers (46) did a randomized controlled comparison of proportional-assist ventilation versus pressure support. The two modes were delivered noninvasively through a nasal mask, and the settings were gradually increased to improve gas exchange and relieve dyspnea. Mortality and intubation rates
were equivalent for the two modes. Proportional-assist ventilation achieved a lower rate of refusal, a greater reduction in respiratory rate, fewer complications (mainly ulceration of the nasal bridge), and a smaller difference between inspiratory and expiratory pressure (6 versus 9 cm H₂O at two hours) for equivalent tidal volumes. The authors conclude that proportional assist ventilation can be delivered noninvasively to treat acute respiratory failure, and that it achieves a greater improvement in some respiratory variables as compared with pressure support.

In 12 patients with chronic respiratory disorders, Vitacca and coworkers (47) compared the effect of pressure support delivered via an endotracheal tube to delivery via a facemask. Compared with spontaneous breathing, delivering pressure support via a mask or via an endotracheal tube produced equivalent decreases in inspiratory effort (50 versus 48%). Tidal volume, normalized to inspiratory effort, was 30% higher when pressure support was delivered via a mask as compared with delivery via an endotracheal tube. The patients also had less dyspnea with the mask system. Resistance, compliance, and arterial blood gases were equivalent with the two routes of delivery. The authors conclude that delivery of pressure support via a facemask decreases patient effort at least as effectively as delivery via an endotracheal tube, and that the mask system is better tolerated by patients.

In 13 adult patients with cystic fibrosis (mean age 26 years), Milross and colleagues (48) compared the effects of low-flow oxygen, noninvasive positive-pressure ventilation (inspiratory pressure 12 cm H₂O, expiratory pressure 5 cm H₂O), and air breathing during three nights of sleep. Minute ventilation did not change between wakefulness and non-REM sleep on any night. Minute ventilation decreased between non-REM and REM sleep on the nights with air breathing (by 1.43 liters per minute) and low-flow oxygen (by 1.88 liters per minute). Noninvasive ventilation prevented the fall in minute ventilation between non-REM and REM sleep. Oxygen saturation was improved by both low-flow oxygen and noninvasive ventilation, and noninvasive ventilation prevented the increase in PSCO₂ seen on the other two nights. The authors conclude that noninvasive ventilation improves alveolar ventilation in patients with cystic fibrosis during sleep.

During pressure support, the inspiratory phase of mechanical assistance ends when flow falls to a predetermined fraction of peak inspiratory flow. Because pressure support is commonly delivered noninvasively by facemasks that are subject to leaks, Hotchkiss and colleagues (49) explored the effect of leakage on ventilator performance. A mathematical model was used to investigate the dynamic behavior of pressure support, and the derived predictions were then tested in a mechanical lung model. An inspiratory leak proximal to the airway opening produced marked variation in both the duration and expiratory pressure (6 versus 9 cm H₂O), and maximal workload during exercise (72 versus 59 watts). The sexually active patients were also younger and more likely to be married or have a partner. After initiating ventilation, 36% of patients became less sexually active and 46% reported no change. Sexually active patients had intercourse five times a month. The authors conclude that more than one third of patients receiving noninvasive ventilation are sexually active.

In a state of the art review article, Mehta and Hill (51) discuss noninvasive ventilation.

The report of an international consensus conference on noninvasive ventilation that was sponsored by the American Thoracic Society, the European Respiratory Society, the European Society of Intensive Care Medicine, and the Societe de Reanimation de Langue Francaise is presented (52).

**Adjunctive Therapy**

Helium–oxygen mixtures have a low gas density and they decrease airway resistance and improve ventilation in mechanically ventilated patients, but their effect on delivery of bronchodilator aerosols is not known. In an *in vitro* model of a mechanically ventilated tracheobronchial tree, Goode and colleagues (53) found that aerosol delivery from a metered-dose inhaler was 30% of the nominal dose when the ventilator circuit contained oxygen and 47% when the circuit contained 80% helium and 20% oxygen. The improved delivery resulted primarily from less deposition in the spacer chamber (39 versus 55%). When a nebulizer was operated with the helium–oxygen mixture, the efficiency of the nebulizer was decreased to one fifth of that seen with oxygen; to achieve efficiency comparable to that seen with oxygen, gas flow needed to be increased 2.5 times in the nebulizer. Maximal efficiency was achieved when the nebulizer was operated with oxygen and the emitted aerosol was entrained into a ventilator circuit containing helium and oxygen. The authors conclude that use of helium–oxygen mixtures in a ventilator circuit can increase delivery of aerosolized bronchodilators from both metered-dose inhalers and nebulizers by as much as 50%.

**ACUTE LUNG INJURY AND ACUTE RESPIRATORY DISTRESS SYNDROME**

**Classification**

In controlled trials, patients with ARDS are usually classified either by the American-European consensus criteria or by the lung injury score (a more complex calculation). To examine the agreement between the two methods, Meade and colleagues (54) analyzed data on 118 patients included in a controlled trial. The incidence of ARDS was 55% using the American-European criteria and 62% using the lung injury score. Chance-corrected agreement (kappa) was 0.73 and chance-independent agreement (phi) was 0.63. Disagreement did not arise from any single component. Clinical outcomes were similar with both classifications. The authors conclude that the choice of these two definitions of ARDS is unlikely to explain different outcomes among study populations, and that investigators may safely use the definitions interchangeably.

**Prediction**

Surfactant protein-B, secreted by type II pulmonary epithelial cells, leaks into the bloodstream of patients with ARDS. To determine whether the plasma level of surfactant protein-B predicts the development of ARDS, Bersten and coworkers (55) obtained plasma from 54 patients at risk of ARDS within...
8 hours of admission to the ICU. Twenty patients (41%) developed ARDS. The initial level of surfactant protein-B predicted the development of ARDS: the area under a receiver operating characteristic (ROC) curve was 0.77 for the protein as compared with an area of 0.65 for lung injury score. In 22 patients with a direct lung insult, the area under the ROC curve was 0.87. The authors conclude that plasma surfactant protein-B helps predict the occurrence of ARDS, especially in patients with a direct lung insult.

**Physiologic and Radiologic Studies**

The use of computed tomography for studying alveolar recruitment has traditionally consisted of measuring the decrease in nonaerated parenchyma on a single section. In 16 patients with ARDS, Malbouisson and colleagues (56) compared the traditional approach with spiral computed tomography. Recruitment was measured as the change in gas penetration of poorly and nonaerated lung regions. With the new technique, PEEP 15 cm H₂O was shown to produce a 119% increase in functional residual capacity, alveolar recruitment of 449 ml, distension of previously aerated areas of 395 ml, and overdistension of 28 ml. Improvement in PO₂ with PEEP was correlated with recruitment measured with the new method \((r = 0.76)\) but not with the old method. Recruitment measured with the new and old methods did not correlate. The authors conclude that the new method for measuring alveolar recruitment with PEEP takes into account recruitment occurring in poorly and nonaerated lung regions, quantifies distension of normally aerated regions, and is correlated with the improvement in oxygenation. This article is accompanied by an editorial commentary by Brochard (57).

In a state of the art review article,Gattinoni and colleagues (58) discuss the knowledge gained from the use of computed tomography as a research tool in ARDS.

**Animal Models**

In sheep subjected to a third-degree burn (40% of total body surface) and smoke inhalation injury, Soejima and colleagues (59) determined whether increased production of nitric oxide is responsible for edema formation. At 24 hours after the injuries, the sheep had cardiac depression, increases in total amount of nitric oxide metabolites \((NO_2^-)\) in plasma or lymph, and the airway epithelium was stained for nitrotyrosine. One hour after the injuries, administration of mercaptoethylguanidine, a selective inhibitor of inducible nitric oxide synthase and a scavenger of peroxynitrite, prevented the increase in nitric oxide metabolites in lymph or serum, the nitrotyrosine staining, the hemodynamic depression, and the changes in permeability of the pulmonary microvasculature. The microvascular permeability of the burned skin did not change. The authors conclude that nitric oxide generated by inducible nitric oxide synthase plays an important role in the systemic and pulmonary microvascular permeability that follows cutaneous burns and smoke inhalation.

The role of endogenous nitric oxide in contributing to the pulmonary edema that results with ischemia-reperfusion injury is controversial. To better understand the process, Schütte and coworkers (60) caused ischemia in isolated rabbit lungs for 210 minutes and then reperfused the lungs. When the ischemia was combined with normoxic ventilation and measures taken to avoid vascular collapse, the synthesis of nitric oxide was decreased moderately during the ischemia. During reperfusion, synthesis was fully restored and was accompanied by moderate leakage. Pretreatment with \(^{N^o}\)-monomethyl-L-arginine \((L-NMMA)\), an inhibitor of nitric oxide synthase, suppressed the synthesis of nitric oxide but did not affect the leakage. When the ischemia was combined with anoxic ventilation, the endogenous formation of nitric oxide was completely lost, but it was promptly restored on reperfusion. This protocol produced the most severe vascular leakage, which was markedly reduced by the nitric oxide synthase inhibitor or by superoxide dismutase. The authors conclude that endogenous nitric oxide is not involved in initiating or mitigating lung injury caused by ischemia-reperfusion under normoxic ischemic conditions, but that the return of nitric oxide synthesis upon reperfusion after anoxic ischemia contributes to initiating the vascular leak, possibly through interaction with superoxide.

The family of superoxide dismutases (intracellular, mitochondrial, and extracellular) reduces superoxide into hydrogen peroxide and oxygen. To determine the role of extracellular superoxide dismutase in attenuating lung injury, Bowler and coworkers (61) used a transgenic mouse that overexpresses the enzyme. Lung injury was caused by removing 30% of an animal's blood volume. Lung water increased by 17% in the wild-type mice and by 2% in the transgenic mice. Lipid peroxidation, as assessed by lung \(F_2\) isoprostanes, increased by 35% in the wild-type mice, but did not increase in the transgenic mice. Hemorrhage produced a 2.5-fold increase in nuclear factor-κB in the wild-type mice, which was almost completely prevented in the transgenic mice. Hemorrhage caused an 11-fold increase in myeloperoxidase in the wild-type mice, which was attenuated in the transgenic mice. The authors conclude that extracellular superoxide dismutase attenuates the lung injury caused by hemorrhage.

The sequestration of neutrophils in the pulmonary microvasculature is an important initiator of acute lung injury. Suwa and colleagues (62) investigated the role of interleukin-6 in this process. Neutrophil precursors in the bone marrow of rabbits were labeled with a thymidine analog, 5'-bromo-2'-deoxyuridine, and 24 hours later the animals received an injection of interleukin-6. The injection caused the accelerated release of immature neutrophils from the marrow and the preferential sequestration of these cells in lung capillaries. The excess sequestration was associated with an increase in F-actin content of the neutrophils and a decrease in their deformability. The changes were not due to activation of peripheral neutrophils. The authors conclude that administration of interleukin-6 causes accelerated release of neutrophils from the bone marrow, and that the neutrophils have high levels of F-actin, are less deformable, and sequester preferentially in lung microvessels.

To determine the relative changes in mechanics and structural remodeling of the lungs during the early phase of acute injury, Rocco and coworkers (63) studied mice with differing degrees of lung injury caused by paraquat. In strips of lung parenchyma, tissue resistance, dynamic elastance and hysteresivity increased in proportion to the dose of paraquat. The content of collagen fibers increased exponentially with the severity of the injury. Of three types of elastic fibers, elaunin and fully developed elastic fibers did not change, whereas oxylan fibers increased only with the high doses of paraquat. The authors conclude that the mild structural abnormalities during the early phase of acute lung injury secondary to paraquat are accompanied by pronounced changes in the mechanical properties of lung tissue.

**Cellular and Molecular Mechanisms**

Vascular endothelial growth factor acts on endothelial cells to increase permeability via alterations in both the paracellular (tight junctions) and transcellular (caveolae) pathways. Thousand and coworkers (64) studied the involvement of vascular endothelial growth factor in patients with ARDS. The levels of the growth factor in the plasma of 40 patients with ARDS...
were at least twice as high as compared with the levels in three other groups: 28 patients at risk of ARDS, 9 ventilated control patients, and 14 healthy subjects. The levels on Day 4 were 2.7 times higher in patients with ARDS who subsequently died as compared with the survivors. In vitro cultures of peripheral blood mononuclear cells from the patients with ARDS produced 3.4 times more vascular endothelial growth factor as compared with the patients at risk. The addition of plasma from the patients with ARDS produced a greater increase in endothelial permeability as compared with plasma from the control subjects. The addition of an inhibitor of the growth factor produced a 48% decrease in permeability. The authors conclude the patients with ARDS have increased plasma levels of vascular endothelial growth factor and that this growth factor increases the permeability of endothelial cells.

Geiser and colleagues (65) asked, “Does pulmonary edema from patients with acute lung injury inhibit the repair of the alveolar epithelium?” Edema fluid from 21 patients with acute lung injury or ARDS caused a 33% increase in wound repair of a human alveolar epithelial-like cell line (A549) as compared with pooled plasma from healthy donors. In contrast, edema fluid from patients with hydrostatic pulmonary edema and plasma from patients with either ARDS or hydrostatic edema had an effect on epithelial repair similar to that seen with pooled plasma from healthy subjects. The benefit of the alveolar fluid on epithelial repair was decreased by 46% when interleukin-1β was inhibited. The authors conclude that pulmonary edema fluid collected early in the course of acute lung injury or ARDS increases the repair of alveolar epithelium by a mechanism involving interleukin-1β.

Reactive oxygen and reactive nitrogen species cause damage to macromolecules by oxidation or nitrination of critical residues in proteins. In 19 patients at risk for ARDS and 41 patients with established ARDS, Sittipunt and colleagues (66) measured end-products of nitric oxide (nitrate and nitrite) in bronchoalveolar fluid. Nitrate plus nitrite were detected in the patients at risk of ARDS, and also for as long as 21 days after the ARDS had become established. Nitrotyrosine was detected in the patients with ARDS for as long as 14 days after its onset, but it was not present in healthy controls. Alveolar macrophages of patients with ARDS were positive for inducible nitric oxide synthase and nitrotyrosine, and remained positive for as long as 14 days after the onset of ARDS. Nitrate plus nitrite did not predict the onset of ARDS, although the concentrations were higher in the patients with ARDS who died. The authors conclude that nitric oxide-dependent pathways are important in the lungs of patients before and after the onset of ARDS. An editorial commentary by Baldus and colleagues (67) accompanies this article.

To assess the balance between proinflammatory and anti-inflammatory mediators in the lungs of patients with ARDS, Park and coworkers (68) did serial bronchoalveolar lavages in 46 patients with established ARDS and in 23 patients who were at risk for ARDS. The levels of tumor necrosis factor-α, interleukin-1β, and interleukin-6 were increased both before and during the early period after the onset of ARDS. The anti-inflammatory response (in terms of the cognate receptors and/or antagonists) was greater as compared with the proinflammatory response. The anti-inflammatory mediators included: soluble tumor necrosis factor-α receptors I and II; interleukin-1 receptor antagonist and soluble interleukin-1 receptor II; soluble interleukin-6 receptor; and interleukin-10. The molar ratios of inflammatory agonists to antagonists declined by one to two orders of magnitude after the onset of ARDS, limiting the activity of tumor necrosis factor-α and soluble interleukin-1β in the lungs at the onset of ARDS. The authors conclude that a prominent anti-inflammatory response provides a mechanism for limiting the intensity of the inflammatory response both before and during the early stage of ARDS.

To determine the relationship between complexes of interleukin-8 and its autoantibody on the clinical course of ARDS, Kurdowska and colleagues (69) did bronchoalveolar lavage in 19 patients who were at risk of ARDS and 45 patients with established ARDS. The concentration of complexes of interleukin-8 with its autoantibody was higher at the onset of established ARDS than in the patients who were at risk for ARDS, and it was also higher at the onset of ARDS in the patients who subsequently died. The authors conclude that complexes of interleukin-8 with its autoantibody are an important prognostic indicator for the development and outcome of ARDS.

To determine whether patients with acute lung injury have increased levels of nitrite and nitrate, Zhu and colleagues (70) studied edema fluid and plasma from 34 patients with early acute lung injury and 29 patients with hydrostatic pulmonary edema. Edema fluid from the patients with acute lung injury had 64% higher levels of nitrite and nitrate as compared with the patients with hydrostatic edema. The levels were 49% higher in patients with shock as compared with the patients without shock. Increased levels of nitrite and nitrate were associated with slower clearance of alveolar fluid. Patients with acute lung injury experienced nitrination of surfactant protein A (an effect that is known to impair its host defense properties). The authors conclude that reactive nitrogen species may play a role in the pathogenesis of acute lung injury.

In a state of the art review article, Lee and Downey (71) discuss the role of leukocyte elastase in acute lung injury.

In a report from an NHLBI/NCI Workshop, Idell and colleagues (72) discuss fibrin turnover in lung inflammation and neoplasia.

**Fluid Biology**

In 79 patients with acute lung injury or ARDS, Ware and Matthay (73) measured net alveolar fluid clearance. The clearance of alveolar fluid was calculated from serial sampling of edema fluid over the first four hours after intubation. The mean clearance of alveolar fluid was estimated as 6% per hour. Net clearance was impaired (less than 3% per hour) in 56% of patients, submaximal in 32%, and maximal (at least 14% per hour) in only 13% of patients. In a previous study of 65 patients with hydrostatic pulmonary edema, 75% had maximal or submaximal clearance. Maximal clearance was more likely in women, nonsmokers, and patients without sepsis. Hospital mortality was 20% in patients with maximal clearance, and 62% in patients with impaired or submaximal clearance. Clearance of alveolar fluid did not correlate with endogenous or exogenous catecholamines. The authors conclude that clearance of alveolar fluid is impaired in most patients with acute lung injury or ARDS and that maximal clearance is associated with a lower mortality. An editorial commentary by Sznejder (74) accompanies this article.

In a report from an NHLBI workshop, Crandall and Matthay (75) discuss bench-to-bedside research on alveolar epithelial transport.

**Outcome**

In a critical care perspective, Idell (76) discusses the potential role of anticoagulants in the treatment of ARDS.

**Treatment**

To determine the quality-adjusted survival in the first year after ARDS, Angus and colleagues (77) studied 200 patients (excluding those with sepsis or with acute nonpulmonary dysfunction
at presentation). Survival was 70% at one month, but fell to 56% at six months and was unchanged at one year. Quality of well-being was low at 6 (0.59) and 12 months (0.60) (perfect is 1 and death is 0). Quality-adjusted life-years were 36 per 100 patients. The authors conclude that short-term mortality underestimates long-term mortality in patients with ARDS, and that survivors have a low quality of life.

Petty (78) recalls the discovery of ARDS and writing the first description of the condition.

**SEPSIS AND SHOCK**

**Mechanisms in Patients and Volunteers**

The inflammatory response to intravenous endotoxin has been well characterized. To determine the effect of the same dose on the lung, O’Grady and colleagues (79) instilled endotoxin into a lung segment of 34 healthy subjects. The local response occurred in two phases. An early phase (2 to 6 hours) consisted of neutrophil influx with increased levels of cytokines (tumor necrosis factor-α, tumor necrosis factor receptors, interleukin-1β, interleukin-1 antagonist, interleukin-6, and granulocyte-colony-stimulating factor) and chemokines (interleukin-8, epithelial activating protein-78, monocyte chemotactic protein-1, macrophage inflammatory protein-1α, and macrophage inflammatory protein-1β). A later phase (24 to 48 hours) was manifested by persistence of the neutrophilia and increased numbers of macrophages, monocytes, and lymphocytes. During the later phase, most of the cytokines and chemokines had returned to basal levels but some (tumor necrosis factor receptors, 1-selectin, lactoferrin, and myeloperoxidase) persisted. Increased permeability to albumin occurred in both phases. The authors conclude that the local pulmonary response to endotoxin has a unique qualitative and temporal inflammatory response that differs from that seen with an intravenous challenge. An editorial commentary by Blackwell and Christman (80) accompanies this article.

To determine the effect of endotoxin on control of breathing, Preas and coworkers (81) measured breathing pattern nonobtrusively in 12 healthy subjects who received endotoxin or placebo intravenously. Endotoxin produced an increase in body temperature of 2°C, an increase in respiratory frequency of 8 breaths per minute, and an increase in the alveolar to arterial oxygen gradient. These responses were blocked by the cyclooxygenase inhibitor, ibuprofen. Endotoxin produced increases in respiratory drive and dyspnea, which were not suppressed by ibuprofen. Endotoxin produced an increase in the relationship between the value of respiratory frequency in a breath with the values of respiratory frequency in neighboring breaths. This relationship was related to the change in arterial \(P_{O2}\) (\(r = 0.86\)) and was blocked by ibuprofen. The authors conclude that endotoxemia causes increases in respiratory motor output and dyspnea, independently of fever and symptoms, and that it curtails the freedom to vary respiratory timing—an effect that is mediated by the cyclooxygenase pathway.

To determine whether sepsis alters the function of mitochondria, Adrie and coworkers (82) studied peripheral blood monocytes of 18 patients with sepsis and 17 healthy subjects. Compared with the control group, the patients with sepsis displayed a 2.2-fold increase in the percentage of monocytes with depolarized mitochondria (considered an initial and irreversible step toward apoptosis) within three days. The increase was still present 7 to 10 days later, and it returned to control values by discharge. The combination of apoptotic and necrotic cells was two-fold higher in the patients with sepsis. Proteins that regulate cell death differed little between the patients with sepsis and control subjects: Bel-2, an anti-apoptotic molecule, was equivalent in the two groups; soluble Fas ligand was undetectable in most patients; and heat shock protein 70 was increased in the patients with sepsis, but only in the first three days. Patients who died had a 2.2-fold greater number of monocytes with depolarized mitochondria within the first three days, and the expression of Bel-2 was less than one-third of that in the survivors. The authors conclude that mitochondrial dysfunction is common in the circulating monocytes of septic patients and is associated with increased mortality.

Because of reports of endothelial damage in sepsis, Mutunga and colleagues (83) asked “Do patients with sepsis experience increased shedding of endothelial cells”? Endothelial cells, identified by antibodies to von Willebrand factor, were about 8 times higher in 8 patients with sepsis (but not in shock) and about 15 times higher in 15 patients with septic shock as compared with 9 mechanically ventilated patients without sepsis or in 11 healthy subjects. A similar pattern was seen when the vascular endothelial growth factor receptor KDR was used to identify endothelial cells. Endothelial cell counts were 69% higher in patients who died of septic shock as compared with the survivors. The authors conclude that patients with sepsis and septic shock have an increase in circulating endothelial cells, adding support to the hypothesis that widespread endothelial damage occurs in sepsis.

The presence of the A allele at the +250 site within the gene for lymphotoxin-α (also known as tumor necrosis factor-β) is associated with increased mortality from septic shock, and the AA homozygotes have the greatest risk. Similar but less universal findings have been reported for polymorphism at the −308 site in the promoter region of the gene for tumor necrosis factor-α. To determine whether gene polymorphisms at these two sites influence the clinical presentation of pneumonia, Waterer and colleagues (84) genotyped 280 patients with community acquired pneumonia: 31 had septic shock, 80 had hypoxic respiratory failure, and 25 (9%) died. The lymphotoxin-α +250 genotype was associated with an increased risk of septic shock. The AA homozygotes were 2.5 times more likely to develop septic shock as compared with the non-AA homozygotes. This genotype was not associated with the development of hypoxic respiratory failure. Carriage of the 250A: 308G haplotype was associated with an increased risk of septic shock, suggesting that lymphotoxin-α +250 is a marker and not a causative polymorphism. The authors conclude that the different genotype associations for septic shock and hypoxic respiratory failure have important implications for immunotherapy in patients with community acquired pneumonia and sepsis.

Harbarth and coworkers (85) attempted to find a marker that discriminates between sepsis and noninfectious causes of the systemic inflammatory response syndrome. Of 78 consecutive patients admitted with suspected infection, the final diagnoses were sepsis in 14, severe sepsis in 21, septic shock in 25, and systemic inflammatory response syndrome in 18 patients. Discrimination, measured as the area under a receiver-operating characteristic curve, was 0.92 for procalcitonin, 0.75 for interleukin-6, and 0.71 for interleukin-8. A threshold concentration of procalcitonin, at 1.1 ng per ml, yielded a sensitivity of 97% and a specificity of 78% in differentiating patients with the systemic inflammatory response syndrome from patients with sepsis-related conditions. The authors conclude that an elevated level of procalcitonin provides the best indication of sepsis in patients admitted to an ICU with suspected infection.

In a state of the art review article, Wang and colleagues (86) discuss the role of HMGB1 as a late mediator of systemic inflammation.

In a critical care perspective, Munford and Pugin (87) discuss how the normal responses to injury may prevent systemic inflammation and cause immunosuppression.
Endotoxia in Animals

To compare the effects of hemorrhagic shock and endotoxic shock on microcirculation, Nakajima and coworkers (88) measured the velocity of erythrocytes and the density of perfused villi in the small intestine of mice using intravital microscopy. One hour after endotoxia or bleeding, the mean arterial pressure was 71 mm Hg in a low endotoxin group, 43 mm Hg in a high endotoxin group, and 43 mm Hg in a hemorrhagic group as compared with 73 mm Hg in a control group. Compared with the control group, erythrocyte velocity was decreased in the capillaries of the villus tip by 31% in the low endotoxin group and by 82% in the high endotoxin group, but it did not change in the hemorrhagic group. The density of erythrocyte-perfused villi was decreased by 5% in the low endotoxin group, by 67% in the high endotoxin group, and by 13% in the hemorrhagic group. The authors conclude that small amounts of endotoxin decreases mucosal perfusion of intestinal villi even in the absence of systemic hypotension, and that larger doses of endotoxin induce greater abnormalities in mucosal perfusion as compared with equivalent hypotension induced by hemorrhage.

Cytotoxic T lymphocytes induce apoptosis by two independent pathways: the binding of Fas ligand (a membrane protein of the tumor necrosis factor family) to Fas (the receptor antigen); and granzymes and perforin (pore-forming protein) of cytotoxic T lymphocytes. After instilling endotoxin into the trachea of mice, Kitamura and colleagues (89) found dose-dependent upregulation of messenger RNA of the proapoptosis molecules. Fas was upregulated in alveolar and inflammatory cells. Inflammatory cells positive for Fas ligand migrated into the air spaces. Administration of P2, an antibody that blocks the Fas–Fas ligand system, attenuated the lung injury, without attenuating messenger RNA expression of the proapoptosis molecules and the accumulation of neutrophils in the lung. Concanamycin A, which blocks the perforin–granzyme system, did not alter the effects of endotoxin. The authors conclude that two independent pathways of apoptosis are involved in the lung injury caused by endotoxin, and that inhibition of the Fas–Fas ligand system, but not of the perforin–granzyme system, attenuates the injury.

Caspases, a family of proteases, are involved in the initiation and execution of apoptosis. To investigate the role of caspases in heart failure caused by sepsis, Neriere and colleagues (90) studied isolated hearts of rats exposed to intravenous endotoxin. The hearts showed multiple caspase activities and a typical apoptosis pattern. A broad-spectrum caspase inhibitor (z-VAD.fmk), administered in conjunction with endotoxin, completely prevented the myocardial dysfunction, and it also reduced the caspase activities and nuclear apoptosis. The authors conclude that caspase activation has a central role in myocardial dysfunction and cell death resulting from endotoxin.

Activity of the transcription factor, nuclear factor-κB, can be assessed in vivo through the use of a line of transgenic mice that express photinus luciferase. After treating the mice with lipopolysaccharide, Sadikot and coworkers (91) assessed the effect of dexamethasone on nuclear factor-κB in this in vivo model. Luciferin, the substrate for luciferase, was injected into the peritoneal cavity of the mice, and emission of light over the lungs was closely correlated with the direct measurement of luciferase activity in homogenates of lung tissue ($r^2 = 0.84$) — with both reflecting activity of nuclear factor-κB. Compared with animals treated with lipopolysaccharide alone, administering dexamethasone intraperitoneally did not inhibit luciferase activity in the lungs, but, instead, it increased its activity. In a separate in vitro study of macrophages derived from these mice, dexamethasone inhibited the induction of nuclear factor-κB after treatment with lipopolysaccharide. The authors conclude that measurement of bioluminescence in this transgenic strain of mice provides a reliable method for studying activity of nuclear factor-κB in vivo, and that extrapolating from in vitro findings to the inflammatory processes that occur in vivo can be misleading.

To determine the role of the neuronal isoform of nitric oxide synthase in the diaphragmatic injury of sepsis, Comtois and colleagues (92) injected lipopolysaccharide into wild-type mice and knockout mice deficient in the gene for neuronal nitric oxide synthase. Lipopolysaccharide decreased maximum force of the diaphragm by about 25% in the wild-type mice and by about 40% in the knockout mice. Total nitric oxide synthase activity increased in the wild-type mice due to the inducible nitric oxide synthase isoform. In the knockout mice, activity of nitric oxide synthase reached about 10% of that in wild-type mice, and inducible nitric oxide synthase protein level reached about 60%. Stopping isolated muscle strips for three minutes produces a sarcolemmal injury, and lipopolysaccharide increased this injury by about 50% in both the wild-type and knockout mice. The protein level of the endothelial isoform of nitric oxide synthase was not altered by lipopolysaccharide in either group of mice. The authors conclude that the neuronal isoform of nitric oxide synthase protects against the negative effect of endotoxin on diaphragmatic contractility, but it is not involved in the associated sarcolemmal injury.

To determine whether monocyte chemotactic protein 1, a C-C chemokine, has a synergistic action with endotoxin in causing alveolar inflammation, Maus and coworkers (93) studied BALB/c mice. Instilling the chemokine into the trachea produced a delayed monocyte influx into the alveolar compartment, peaking after 48 hours, without enhanced neutrophil traffic or upregulation of proinflammatory cytokines. Instilling endotoxin into the trachea elicited an early neutrophilic response, peaking after 6 hours, accompanied by modest elevations of tumor necrosis factor-α, interleukin-6, and macrophage inflammatory protein-2. Instilling both monocyte chemotactic protein-1 and endotoxin into the trachea produced a 22-fold increase in neutrophils (peaking at 12 hours), an eight-fold increase in alveolar monocytes (peaking at 48 hours), and large increases in the proinflammatory cytokines and lung vascular leakage. When the same combination was administered via the peritoneum, the synergistic response did not occur. Blocking neutrophil recruitment with anti-CD 18 did not affect the cytokine response to the combination. The authors conclude that the combination of monocyte chemotactic protein-1 and endotoxin in the alveolar compartment have a synergistic action, producing an early inflammatory response with increased cytokine synthesis and neutrophil recruitment, and a late phase of enhanced monocyte traffic and expansion of the alveolar macrophage pool.

Tacrolimus (FK506) is a macrolide immunosuppressant that inhibits lymphocytes and the production of interleukin-2. Koshika and colleagues (94) determined whether pretreatment with tacrolimus protects against acute lung injury caused by lipopolysaccharide and phosphor myristate acetate. Contrasted with a mortality of 67% in dogs receiving lipopolysaccharide alone, treatment with medium and high doses of tacrolimus decreased mortality to 20 and 0%, respectively. Tacrolimus attenuated the hypoxemia, systemic hypotension, pulmonary hypertension, and pulmonary edema associated with the acute lung injury. Treatment with the methylprednisolone had no effect. The authors conclude that tacrolimus (FK506) could have prophylactic benefit against acute lung injury caused by endotoxic shock.

Inhibitors of protein tyrosine kinase decrease lung injury, but the mechanism of action is obscure. In rats with acute lung
injury caused by the intratracheal instillation of lipopolysaccharide. Kang and coworkers (95) assessed the effect of genistein, a specific inhibitor of protein tyrosine kinase, on the transcription factor, nuclear factor-κB, and on a number of proinflammatory gene products. The control animals developed increased levels of protein in bronchoalveolar fluid and activation of DNA-binding activity of nuclear factor-κB in alveolar macrophages and lung tissue. Treatment with genistein two hours before administration of lipopolysaccharide inhibited the features of lung injury and the activation of nuclear factor-κB, which correlated with depression in the phosphorylation of protein tyrosine and the phosphorylation of Jun N-terminal kinase (JNK) in lung tissue. Genistein also suppressed neutrophil recruitment, and the production of cytokine-inducible neutrophil chemoattractant (CINC) and matrix metalloproteinase-9 (MMP-9). The authors conclude that genistein, an inhibitor of protein tyrosine kinase, attenuates endotoxin-induced lung injury by inhibiting the activation of nuclear factor-κB and, in turn, decreasing the production of proinflammatory gene products that cause neutrophil recruitment.

In a nonlethal model of endotoxemia in rabbits, Tavernier and colleagues (96) studied the subcellular mechanisms that are responsible for the myocardial depression caused by sepsis. At 36 hours after injection of lipopolysaccharide (a time when papillary muscle contractility was consistently decreased), the endotoxemic and control animals had equivalent mitochondrial respiration, coupling between oxidation and phosphorylation, creatine kinase function, and maximal calcium-activated force. Skinned fibers from the left ventricle of the endotoxemic animals were more sensitive to calcium; this decreased sensitivity was abolished by treatment with protein kinase A or alkaline phosphatase. Pretreatment of control fibers with isoproterenol, but not with S-nitroso-N-acetylpenicillamine (SNAP; a nitric oxide donor), decreased the sensitivity of fibers to calcium to that found in endotoxemic animals. The authors conclude that myocardial depression during sepsis may be secondary to a phosphorylation-dependent decrease in the sensitivity of myofibers to calcium, and that it can occur without any impairment in cellular energy generation or transport.

Sepsis in Animals

Matuschak and colleagues (97) investigated whether lung inflammation secondary to sepsis is exacerbated by an ischemia-reperfusion injury of the liver. E. coli was injected intravenously into rats, some of which then had their hepatic vessels clamped for 90 minutes, followed by reperfusion for 1 or 24 hours. Infected animals that experienced ischemia followed by 24 hours of reperfusion had higher serum levels of endotoxin, tumor necrosis factor-α, alanine aminotransferase, interleukin-6, and neutrophil influx into the liver as compared with infected animals not experiencing ischemia. Pulmonary edema and influx of neutrophils into the lungs were more severe in infected animals with an ischemia–reperfusion injury as compared with infected animals without ischemia–reperfusion injury or noninfected animals with ischemia–reperfusion injury. A leukotriene inhibitor attenuated the levels of tumor necrosis factor-α and the ischemic liver injury, but did not affect mortality. The authors conclude that a local decrease in hepatic blood flow predisposes to lung inflammation by augmenting circulating levels of endotoxin and tumor necrosis factor-α.

Sepsis induces the expression of tissue factor, which activates the coagulation cascade. In baboons, Welty-Wolf and coworkers (98) determined whether blocking the complex of tissue factor and Factor VIIa would decrease the organ injury caused by sepsis. The baboons were first primed with killed Escherichia coli, and bacteremic sepsis was then induced by an infusion of live E. coli. Control animals developed 2- to 10-fold increases in inflammatory mediators, alveolar edema, hemorrhage, and inflammatory cell infiltration, accompanied by prominent deposition of fibrin in the lung and kidney. Administration of the tissue factor inhibitor at the time of infusing E. coli prevented the pulmonary edema, pulmonary hypertension and renal dysfunction, decreased the proinflammatory cytokine response, and diminished the fibrin deposition in the lung and kidney. The authors conclude that intervening proximally in the coagulation cascade, at the level of the complex between tissue factor and Factor VIIa, decreases the pulmonary and renal injury caused by bacteremic sepsis.

Intercellular adhesion molecule 1 (ICAM-1, CD54) mediates the adhesion of neutrophils to endothelial cells. Welty-Wolf and colleagues (99) determined whether an antibody against this adhesion molecule would decrease the sequestration and transmigration of neutrophils into the lung and decrease lung injury caused by sepsis. Sepsis was induced in 12 baboons by priming them with heat-killed E. coli and infusing live bacteria 12 hours later. At the time of receiving the live bacteria, six animals were treated with a monoclonal antibody to intercellular adhesion molecule 1. Survival time was decreased in animals treated with the antibody, and these animals had greater hypotension and metabolic acidosis. Therapeutic levels of the antibody did not decrease sequestration or migration of neutrophils into the lungs. The authors conclude that an antibody to intercellular adhesion molecule 1 does not ameliorate acute lung injury caused by E. coli sepsis, and that the antibody worsens metabolic variables and survival.

The microsomal enzyme, heme-oxygenase, catalyzes the oxidation of heme to biliverdin and carbon monoxide, providing a powerful protection against oxidative stress. Two isoforms have been identified: heme–oxygenase-1, the inducible form (also known as heat shock protein 32), and heme–oxygenase-2, the constitutive form. Taille and colleagues (100) determined whether this system protects against diaphragmatic dysfunction caused by endotoxin. Rats inoculated with endotoxin experienced a decrease in diaphragmatic contractility, and the diaphragmatic myocytes had enhanced expression of heme–oxygenase-1. Expression was also enhanced in the rectus abdominis, the soleus muscle, and the left ventricle. Endotoxin did not modify expression of heme–oxygenase-2. Administration of an inhibitor of heme-oxygenase activity, zinc protoporphyrin IX, further impaired the contractile failure and oxidative stress. Pretreatment with hemin, an inducer of heme–oxygenase-1, completely prevented the oxidative stress and contractile failure. The authors conclude that the heme-oxygenase pathway is a major cellular system for protecting the diaphragm against oxidative stress during sepsis.

Inosine is a naturally occurring purine that is formed from the breakdown of adenosine by adenosine deaminase. Liaudet and coworkers (101) studied the anti-inflammatory effect of inosine in a murine model of sepsis caused by cecal ligation and puncture. Twelve hours after the injury, mice treated with two doses of inosine (one hour before and six hours after the injury) had lower plasma levels of tumor necrosis factor-α, interleukin-6, and interleukin-10, as compared with mice treated with a vehicle. Inosine reduced organ damage, as reflected by an increase in the ratio of NADH to NADPH (an indicator of the mitochondrial redox state) in the liver, a decrease in myeloperoxidase in the lung, decreased formation of malondialdehyde in the gut and liver, and decreases in macrophage inflammatory protein-1α and -2 in the lung and liver. Inosine also improved endothelium-dependent relaxant responses of
aortic rings. Survival at 120 hours was 5% in mice treated with vehicle and 23% in mice treated with inosine. The authors conclude that inosine reduced systemic inflammation and organ damage and improved survival in mice with septic shock secondary to peritonitis.

L’Her and Sebert (102) studied the rate of glycolysis and maximal activity of the mitochondria in monocytes taken from septic rats. Four hours after inducing sepsis by ligating and perforating the cecum, the rats developed a 2.8-fold increase in plasma lactate. The rate of glycolysis was increased by 150% in aerobic fluxes and by 140% in anaerobic fluxes in the septic rats. Mitochondrial function, as reflected by oxygen consumption dependent on pyruvate–malate, was decreased by 22%. The authors conclude that an alteration in mitochondrial function contributes to the hyperlactemia of sepsis, which is mainly a consequence of an increased rate of glycolysis.

To investigate the role of a host’s response to a local peritoneal infection in the development of sepsis and lung injury, Matute-Bello and colleagues (103) inoculated the peritoneal cavity of rabbits with fibrin clots containing \textit{E. coli} at $10^8$, $10^9$, or $10^{10}$ colony-forming units per clot. The lowest dose caused a resolving infection, the medium dose caused a persistent infection with minimal systemic manifestations, and the highest dose caused a rapidly lethal infection with septic shock and lung injury. The onset of septic shock was associated with the lack of neutrophils in the peritoneal cavity, secondary to their lysis by free myeloperoxidase. Most animals became bacteremic, but only those with severe systemic inflammation developed lung injury. The authors conclude that the failure of the host to recruit and maintain adequate numbers of neutrophils at the primary site of infection appears to be a key mechanism in determining whether an infection is controlled locally or causes severe systemic effects.

Hollenberg and coworkers (104) attempted to replicate in mice the features of human septic shock–vasodilation, hypotension, and increased cardiac output. Cecal ligation and puncture resulted in gram-negative bacteremia, and all of the untreated mice died. Survival increased to 24% with fluid resuscitation, to 30% with antibiotics, and to 46% with a combination of fluid and antibiotics. Blood pressure was monitored continuously with micromanometers and echocardiography was done every six hours. The septic mice developed a 36% fall in arterial pressure, accompanied by a 28% increase in heart rate and a 47% increase in cardiac output. The authors conclude that inducing peritonitis in mice and then treating them with fluid and antibiotics replicates the mortality, hypotension, and hyperdynamic state of human sepsis.

Nonseptic Causes of Shock

The degradation products generated by the action of heme–oxygenase on heme provide protection against oxidative stress. To determine whether the inducible isoform, heme–oxygenase-1, plays a protective role in hemorrhagic shock, Tamion and coworkers (105) bled different groups of rats. Pretreatment with hemoglobin 16 hours before the bleeding produced an increase in messenger RNA for heme–oxygenase-1 in peritoneal macrophages. The pretreatment with hemoglobin led to a marked decrease in the synthesis of tumor necrosis factor–alpha after resuscitation, it prevented pulmonary edema, and it increased mesenteric blood flow. An inhibitor of heme–oxygenase-1, tin–protoporphyrin (Sn-PP), abolished the beneficial effects induced by pretreatment with hemoglobin. The authors conclude that induction of heme–oxygenase-1 plays a protective role against the inflammatory response caused by hemorrhagic shock.

VENTILATOR-ASSOCIATED PNEUMONIA

Diagnosis

To determine whether exhaled nitric oxide might serve as a marker of pneumonia, Adrie and colleagues (106) studied 49 mechanically ventilated patients, 21 of whom were diagnosed with pneumonia. The concentration of exhaled nitric oxide at end-exhalation was 5.9 ppb in patients with pneumonia and 3.2 ppb in patients without pneumonia. Mean nasal nitric oxide was 1.039 ppb in patients with pneumonia and 367 ppb in patients without pneumonia. Plasma levels of nitric oxide did not differ between the groups. In another 60 patients, a threshold concentration of nitric oxide of 5 ppb at end exhalation had a positive predictive value for pneumonia of 74% and a negative predictive value of 89%. The authors conclude that tracheal and nasal levels of nitric oxide help in discriminating between patients with and without pneumonia, and that pneumonia does not increase the systemic production of nitric oxide.

The frequency of colonization of the lower respiratory tract with nontypeable \textit{Haemophilus influenzae} is not well defined. In washes or brush specimens on bronchoscopy, Bandi and coworkers (107) found nontypeable \textit{H. influenzae} in 6 of 23 (26%) patients with stable chronic bronchitis, in 1 of 15 (7%) patients with an acute exacerbation of chronic bronchitis, and in 0 of 26 healthy subjects undergoing elective surgery. The low recovery in the patients with an acute exacerbation probably resulted from the use of parenteral antibiotics. In five of the nine patients with stable chronic bronchitis, molecular typing revealed different strains of nontypeable \textit{H. influenzae} in the upper and lower respiratory tract. Intracellular nontypeable \textit{H. influenzae} were found in bronchial biopsy specimens from 13 of the 15 (87%) patients with an exacerbation, 8 of the 24 (33%) stable patients, and 0 of 7 healthy subjects. The authors conclude that the lower airways of patients with stable chronic bronchitis is molecular typing revealed different strains of nontypeable \textit{Haemophilus influenzae}, that cultures obtained from the upper airways differ from cultures from the lower airways, and that intracellular infection with \textit{H. influenzae} contributes to the pathogenesis of acute exacerbations of chronic bronchitis.

Treatment

Selective decontamination of the digestive tract consists of administering nonabsorbable antibiotics to the oropharynx and stomach, usually combined with parenteral antibiotics. Because the relative impact of each component on the rate of ventilator-associated pneumonia has not been defined, Bergmans and coworkers (108) investigated the effect of decontaminating the oropharynx alone. In a randomized double-blind study, 87 patients had an Orabase paste containing gentamicin, colistin, and vancomycin applied to their buccal cavity. Blind study, 87 patients had an Orabase paste containing gentamicin, colistin, and vancomycin applied to their buccal cavity. In another 60 patients, a threshold concentration of nitric oxide of 5 ppb at end-exhalation was 5.9 ppb in patients with pneumonia and 3.2 ppb in patients without pneumonia. Mean nasal nitric oxide was 1.039 ppb in patients with pneumonia and 367 ppb in patients without pneumonia. Plasma levels of nitric oxide did not differ between the groups. In another 60 patients, a threshold concentration of nitric oxide of 5 ppb at end exhalation had a positive predictive value for pneumonia of 74% and a negative predictive value of 89%. The authors conclude that tracheal and nasal levels of nitric oxide help in discriminating between patients with and without pneumonia, and that pneumonia does not increase the systemic production of nitric oxide.

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or ICU stay were not affected. The authors conclude that oropharyngeal colonization is of pivotal importance in the pathogenesis of ventilator-associated pneumonia. An editorial commentary by Pittet and colleagues (109) accompanies this article.

In 27 patients with confirmed pneumonia (including quantitative cultures of lavage) who received appropriate antimicrobial therapy, Dennesen and colleagues (110) described the resolution of clinical and microbiological findings. Resolution of clinical parameters was slow, being most evident during the first six days and most apparent for oxygenation. Appropriate antimicrobial therapy rapidly eradicated colonization with *S. pneumoniae* and *H. influenzae*, but Enterobacteriaceae, *P. aeruginosa* and *S. aureus* persisted despite in vitro susceptibility to the agents given. Newly acquired colonization, especially with *P. aeruginosa* and Enterobacteriaceae, occurred in the second week. The authors conclude that clinical responses to treatment for ventilator-associated pneumonia occur within six days, and speculate that shorter courses of therapy may be effective.

**NOSOCOMIAL INFECTIONS**

To determine the incidence of primary and catheter-related bacteremia, Renaud and colleagues (111) studied 2,201 patients in 15 French ICUs. Bacteremia occurred in 5% of patients who had a more than 48-hour stay. Of these bacteremias, secondary bacteremia (recovers from the same organism from the bloodstream and from an infection at another site) accounted for 45%, catheter-related bacteremia (inflammation at the exit site of the catheter plus recovery of the same organism from the bloodstream and catheter tip) for 26%, and primary bacteremia (absence of an identified source growing the same organism as found in the bloodstream) for 29%. Secondary bacteremia was associated with a 4.6-fold increase in mortality, and an attributable mortality (the difference in crude mortality between the affected population and an unaffacted population) of 35%. In a case-control study of 96 pairs, attributable mortality was 21% in the patients with primary and catheter-related bacteremia and 55% in the patients with secondary bacteremia. The median excess length of stay in the ICU for survivors was 9.5 days, and it was similar irrespective of the source of the bacteremia. The authors conclude that the risk of mortality associated with primary and catheter-related bacteremia is much lower than that of secondary bacteremia. An editorial commentary by Trick and Weinstein (112) accompanies this article.

In an occasional essay, Brun-Buisson (113) comments on the new guidelines for preventing infections associated with intravascular catheters.

**MONITORING**

**Pressure–Volume Curves**

It has been suggested that the lower inflection point on a pressure–volume curve indicates the range of pressure and volume over which recruitment of previously collapsed lung units occurs and that further recruitment does not occur over the linear portion of the curve. To study the relationship between effective compliance (the mean tidal slope of the pressure–volume relationship) and the level of PEEP needed to prevent alveolar collapse at end expiration, Hickling (114) developed a mathematical model of the lungs affected by ARDS. As PEEP was increased progressively, no relationship was seen between effective compliance and the level of PEEP preventing collapse at end expiration. The best compliance was achieved with PEEP ranging between 11 and 20 cm H2O, and it varied greatly with tidal volume and lung mechanics. Applying PEEP at an initial high level and then lowering it progressively achieved a more consistent relationship between PEEP and effective compliance; the level of PEEP achieving maximum effective compliance was about 3 cm H2O lower than that needed to prevent end-expiratory collapse. Effective compliance was always higher using an approach of progressively decreasing PEEP, as opposed to progressively increasing PEEP. The author concludes that monitoring effective compliance as PEEP is decreased progressively from an initial high value may help in estimating the level of PEEP that prevents alveolar collapse at end expiration.

In 16 patients with acute lung injury, Maggiore and coworkers (115) determined whether the loss of lung volume on decreasing PEEP from a high level provides a useful way of identifying the optimal level of PEEP for patient management. PEEP was lowered in decrements of 5 cm H2O from either 20 cm H2O (seven patients) or 15 cm H2O (nine patients), and pressure–volume curves were repeated at each new setting. Derecruitment was measured as the loss of volume between a given level of PEEP and ZEEP (at a fixed elastic pressure of 20 cm H2O). Of the total volume lost between the highest and lowest level of PEEP, 34% was lost with the first 5 cm H2O decrement in PEEP. The losses of volume were evenly spread over the entire range of PEEP, and they bore no relationship to the lower inflection point. Compliance of the linear portion of the pressure–volume curve, when measured on ZEEP, was positively correlated with derecruitment at a PEEP of 15 cm H2O (r = 0.90). Oxygenation was correlated with derecruitment (r = 0.60). The authors conclude that the losses of lung volume over a wide range of decrements in PEEP imply that alveoli close down over a wide range of pressures, and that the lower inflection point may be of little value in finding a level of PEEP that will prevent alveolar closure.

In five patients with acute lung injury, Crotti and coworkers (116) tried to better define the factors that influence recruitment and derecruitment. Recruitment continued to occur over the entire range of the pressure–volume curve, even beyond the upper inflection point. The threshold opening pressure at which new recruitment occurred ranged from 0 to 45 cm H2O, and 20 cm H2O was the most common value. Recruitment varied among regions of the lung. In the nondependent region, no recruitment occurred. In the middle region, most of the recruitment was complete on reaching a plateau pressure of 30 cm H2O at end-inspiration. And in the dependent region, recruitment continued at pressures of 45 cm H2O. Most derecruitment occurred at PEEP values spanning 0 to 15 cm H2O. For a given airway pressure of 10 cm H2O, only 15% of collapsed tissue had become opened on the inspiratory limb whereas 50% was still open on the deflation limb. Noneaerated tissue at end-expiration was correlated with nonaerated tissue at end-inspiration (r = 0.97). The authors conclude that recruitment occurs over the entire range of the pressure–volume curve and that collapse at end-expiration is related to the extent of collapse at end-inspiration.

In dogs with oleic-acid injury, Pelosi and coworkers (117) studied the mechanism of recruitment and derecruitment, and also tested the reliability of esophageal pressure as an indicator of pleural pressure. The absolute value of esophageal pressure provided a good estimate of pleural pressure only in the mid lung region, although changes in esophageal pressure reflected changes in pleural pressure in all regions (r = 0.86). Recruitment continued to occur over the entire inspiratory limb of the pressure–volume curve. On reaching the lower inflection point, only 20% of eventual recruitment had been accomplished. For a given PEEP and transpulmonary pressure, increasing tidal volume produced decreases in tissue collapse...
at end-inspiration. Nonaerated tissue at end-inspiration was correlated with nonaerated tissue at end-inspiration (r = 0.86), suggesting that recruiting more tissue at end-inspiration caused more tissue to stay recruited at end-expiration. The authors conclude that lung recruitment continues to occur over the entire pressure–volume curve, and that collapse at end-expiration occurs when the gravitational pressure of the lung superimposed on a unit exceeds the positive pressure applied by the ventilator.

Because the significance of changes in the shape of the pressure–volume curve is poorly understood, Martin-Lefèvre and coworkers (118) undertook a series of experiments in ventilated rats. An upper inflection point on the curve was easily seen in normal rats. Viscous liquid was instilled to produce distal airway obstruction: it caused an increase in end-inspiratory pressure (indicating a decrease in aerated lung volume), a decrease in compliance, and a decrease in the upper inflection point. Similar changes were seen with pulmonary edema caused by high volume ventilation. The volumes at which the upper inflection points became apparent were correlated with changes in compliance (r = 0.93), and each was correlated with the severity of pulmonary edema (r = 0.95 for both). When edema was profuse, a lower inflection point was clearly evident. The authors conclude that most of the changes in the pressure–volume curve produced by pulmonary edema are caused by airway obstruction.

To determine whether the size of the tidal volume before performing pressure–volume curves and the magnitude of peak pressure as the curves are being performed have an influence on the variables calculated from the curve, Takeuchi and coworkers (119) induced lung injury in nine sheep by lung lavage. Pressure–volume curves were measured at peak pressures of 40, 50 and 60 cm H2O, and the animals were ventilated with the same peak pressure for one minute before each curve. A lower inflection point was absent in two animals at a peak pressure of 40 cm H2O, but an inflection point developed when these animals were ventilated with higher pressures. A higher pressure before and during the pressure–volume curve resulted in a higher value for the upper inflection point, a higher compliance for the linear portion of the inflation limb (between the lower and upper inflection points), a higher point of maximum curvature on the deflation limb, and a higher compliance for the linear portion of the deflation limb. The peak pressure during the pressure-volume curve had no influence on the lower inflection point, the compliance at the start of the curve, and the compliance at the end of the inflation limb. The authors conclude that the volume history and peak pressure during a pressure–volume curve affect the variables calculated from the inflation and deflation limbs of the curve, and that a single curve provides limited insight into lung mechanics.

**Intrinsic PEEP and Respiratory Muscles**

Ninane and coworkers (120) developed a new approach for detecting airflow limitation. They reasoned that manual compression of the abdomen during expiration would not produce an increase in airflow in a patient with flow limitation. In seven healthy seated subjects, manual compression caused a 27% decrease in the anteroposterior dimension of the abdomen, a 15 cm H2O increase in gastric pressure, and a 6 cm H2O increase in esophageal pressure. Expiratory flow was increased over the entire range of expiration, as compared with the preceding spontaneous expiration. In 12 seated patients with COPD, compression caused similar changes in abdominal dimensions and pressures but half of the patients showed no increase in expiratory flow. In the supine posture, abdomino-nal compression failed to increase expiratory flow in 10 of the 12 patients with COPD. In another seven patients with obstructive sleep apnea who had collapsible upper airways, applying negative pressure to the upper airway produced a pattern of airflow limitation in three patients, whereas compressing the abdomen elicited a normal response. The authors conclude that measuring the change in expiratory flow after manually compressing the abdomen is a simple method for detecting airflow limitation.

**Tissue Oxygenation**

Regional PCO2 of the gastric lumen has been used to monitor gut perfusion and cellular energy balance. Brinkmann and colleagues (121) investigated the influence of gastric pH on regional P CO2 in 17 healthy subjects. Intravenous pentagastrin caused gastric pH to decrease from 1.2 to 0.6 and regional P CO2 to increase by 26%. Intravenous omeprazole caused gastric pH to increase to 4.4, regional P CO2 to fall by 8%, and interindividual variability in regional P CO2 to decrease. The authors conclude that changes in gastric pH confound the interpretation of gastric P CO2 tonometry.

**Procedures**

To determine the relative accuracy of ultrasonography performed by an ICU physician versus radiography in detecting complications after central venous catheterization, Maury and coworkers (122) studied 85 catheter insertions (70 subclavian and 15 internal jugular). All but one of the ultrasonographic examinations was interpretable. Ultrasonography detected the single pneumothorax that occurred and all but one of the 10 catheter misplacements. No false positive results occurred. The mean time for the entire ultrasonographic examination was 7 minutes, whereas it took 80 minutes from the time of contacting radiology until receiving the film. The authors conclude that ultrasonography performed by an ICU physician is accurate in detecting pneumothorax and catheter misplacement after inserting a central venous catheter.

**inhaled Nitric Oxide**

Because the coagulation system is involved in acute lung injury, and because nitric oxide is used to treat lung injury, Kobayashi and colleagues (123) investigated the effect of inhaled nitric oxide on the coagulation system in the intra-alveolar space of mice. Compared with animals breathing air, animals receiving nitric oxide 40 ppm (with or without oxygen) for three weeks had increased concentrations of total protein, thrombin, and soluble tissue factor (assessed as activation of factor X by factor VIIIa/tissue factor complex) in lavage fluid, and increased nitrotyrosine in lung tissue (a marker of peroxynitrite formation). These changes were not seen in mice exposed to nitric oxide 2 ppm (with or without oxygen). Expression of messenger RNA of tissue factor was greater in the lungs of animals receiving the high dose of nitric oxide. The authors conclude that a high dose of inhaled nitric oxide over three weeks triggered substantial increases in tissue factor expression and thrombin generation in the lung.

**TOXICOLOGY**

Isocapnic hyperpnea increases the elimination of carbon monoxide, but using mechanical ventilation for this purpose may also decrease cardiac output and oxygen delivery. In five mechanically ventilated sheep exposed to severe carbon monoxide poisoning, Kreck and coworkers (124) compared five patterns of mechanical ventilation. The mean half-time for carboxyhemoglobin washout was 14.3 minutes for baseline minute
ventilation. The half-time fell by 34% for a two-fold increase in respiratory rate, by 44% for a two-fold increase in tidal volume, by 57% for a four-fold increase in respiratory rate, and by 64% for a four-fold increase in tidal volume. Oxygen transport was increased by the two-fold and four-fold increases in tidal volume, and by the four-fold increase in respiratory rate. The authors conclude that isocapnic hyperpnea increases carbon monoxide elimination and oxygen delivery in an animal model of severe carbon monoxide poisoning.

ETHICAL ISSUES
A major task of ICU physicians is to provide family members with appropriate, clear, and compassionate information. In a prospective study in 43 French ICUs involving 637 patients and 920 family members, Azoulay and colleagues (125) measured the ability of staff to meet family needs and identified factors that might improve family satisfaction. Seven predictors of family satisfaction were found. One factor was family related, namely the family being of French descent (relative ratio of satisfaction, 26%). The other six factors were related to the caregivers: patient-to-nurse ratio of 3 or less (relative ratio of satisfaction, 13%), information provided by junior physicians (relative ratio, 30%), help from the family’s usual doctor (relative ratio, 9%), perceived contradictions in information given (relative ratio, −21%), not knowing the specific role of each caregiver (relative ratio, −14%), and insufficient time spent giving information (relative ratio, −3%). The authors conclude that family satisfaction with efforts of ICU staff to meet their needs depends mostly on factors related to caregivers and that these factors are amenable to modification.

In a critical care perspective, Luce and Lemaire (126) discuss transatlantic differences and similarities on the approach to withdrawing life support.

In a critical care perspective, Freeman and colleagues (127) discuss the factors involved in the safeguarding of patients enrolled in clinical trials.

NONPULMONARY CRITICAL CARE
Pharmacotherapy
Because critically ill patients are susceptible to oxidative stress, Tsujiya and colleagues (128) compared the antioxidant properties of two sedatives, propofol and midazolam. In a homogenous solution, propofol efficiently scavenged hydrophilic peroxyl radicals and midazolam efficiently scavenged lipophilic radicals. In the presence of erythrocyte membranes, propofol inhibited the oxidative damage induced by either hydrophilic or lipophilic radicals, whereas midazolam had little effect. Application of peroxyl radicals to aortic rings normally blocks the endothelium-dependent relaxation achieved by acetylcholine; this effect was greatly attenuated when pre-treated with propofol (much more so than with midazolam). The authors conclude that propofol has a greater potential for reducing oxidative stress as compared with midazolam.

Trauma
To determine the prevalence of psychiatric morbidity in survivors of life-threatening accidents, Schnyder and coworkers (129) did a 1-year follow-up study of 106 consecutive patients (initial score on a Glasgow coma scale of 14.4). Twenty-seven patients (22.5%) had some form of psychiatric morbidity: 18 had symptoms of anxiety, nine were depressed, two met criteria of post-traumatic stress syndrome, and 13 met subsyndromal criteria of this disorder. On logistic regression analysis, psychiatric morbidity at one year was predicted by a sense of death during the incident and by biographical risk factors for the development of psychological and psychosomatic disorders. The authors conclude that the prevalence of psychiatric morbidity in survivors of a severe traumatic injury is less than previously reported, and that a combination of psychosocial variables predicts the individuals at greatest risk.

In an update in nonpulmonary critical care, Gentililoro and Pierson (130) discuss the implications of trauma for the critically ill patient.

Renal Disorders
To determine whether nitric oxide has beneficial or detrimental effects on renal function in sepsis, Cohen and coworkers (131) studied pigs with endotoxemic shock. Administration of lipopolysaccharide caused a decrease in mean arterial pressure, an increase in cardiac output and renal blood flow, and a diversion of blood flow to the renal medulla. An inhibitor of both constitutive and inducible nitric oxide synthase, Nω-

G-L-arginine methyl ester (l-NAME), increased mean arterial pressure, decreased renal blood flow, decreased glomerular filtration rate, and increased sodium excretion. A selective inhibitor of inducible nitric oxide synthase, S-methylisothiourea (SMT), also increased mean arterial pressure and decreased renal blood flow, but it did not decrease glomerular filtration rate or increase sodium excretion. The authors conclude that nitric oxide has a beneficial action on the kidneys of endotoxemic animals because it maintains renal blood flow and glomerular filtration rate.

Gastroenterologic Disorders
In a critical care perspective, Frossard and colleagues (132) discuss the role of new serum markers for the diagnosis of acute pancreatitis.

Cardiac Disorders
To determine whether the underlying cause of a cardiac arrest has an influence on myocardial function after resuscitation, Kamohara and coworkers (133) induced cardiac arrest in different groups of rats. All the rats were successfully resuscitated by precordial compression with mechanical ventilation. With cardiac arrest induced by asphyxia secondary to neuromuscular blockade, myocardial function was depressed similarly whether or not the asphyxia was associated with airway obstruction. With cardiac arrest induced by electrical fibrillation of the ventricles, myocardial function was more severely depressed after resuscitation, as compared with cardiac arrest caused by asphyxia, despite an equivalent duration of asphyxia in the two groups. The authors conclude that myocardial function is more impaired after cardiac arrest caused by ventricular fibrillation, as compared with cardiac arrest caused by asphyxia.

In an update in nonpulmonary critical care, Schulman and Fessler (134) discuss the management of acute coronary syndromes in critically ill patients.

Hematological Disorders
The major indication for transfusing red blood cells is to improve oxygen delivery, but the effect on tissue oxygenation may be less predictable than efforts made to increase cardiac output. Van der Linden and colleagues (135) investigated this issue in a model of oxygen uptake–oxygen supply dependency during cardiopulmonary bypass in dogs. A target increase in oxygen delivery of 40% was achieved by two methods: increasing the flow of blood in the pump or a transfusion of red blood cells. Increasing blood flow by 69% produced a 17%
increase in oxygen uptake. A transfusion that increased hemoglobin from 6.4 to 11.1 g per dl produced a 14% increase in oxygen uptake. The authors conclude that under conditions of oxygen supply dependency, a transfusion of red blood cells and an increase in blood flow are equally effective in restoring tissue oxygenation.

Endocrinological Disorders
In an update in nonpulmonary critical care, Shenker and Skatrud (136) discuss adrenal insufficiency in critically ill patients.

In an update in nonpulmonary critical care, Campbell and Skatrud (139) discuss the implications of pregnancy for the critically ill patient.

Neurological Disorders
In an update in nonpulmonary critical care, Provençol and colleagues (138) discuss neurological problems in critically ill patients.

Pregnancy
In an update in nonpulmonary critical care, Campbell and Klocke (139) discuss the implications of pregnancy for the critically ill patient.

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