

## The Adult Respiratory Distress Syndrome

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The adult respiratory distress syndrome (ARDS) represents a common denominator of acute lung injury leading to alveolar flooding, decreased lung compliance, and altered gas transport. In the absence of specific etiology and therapy, the management of ARDS remains largely supportive. Ubiquitous use of intermittent positive-pressure ventilation with positive end-expiratory pressure (PEEP) improves arterial oxygenation but with some risk of pulmonary barotrauma and decreased cardiac output. The recent understanding of lung inflation as a modulator of right heart afterload and the effect of the right ventricle on global cardiac performance continues to redefine optimal patterns of ventilatory and hemodynamic intervention in ARDS.

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### INTRODUCTION

Diffuse lung injury associated with shock or trauma has been recognized since the early part of this century. The term, the adult respiratory distress syndrome (ARDS), was defined by Petty and Ashbaugh [1] as acute, life-threatening respiratory failure after widely diverse insults in patients with no prior history of cardiopulmonary dysfunction. Although predisposing factors are usually multiple and diverse (Table 1) [2-16], the pulmonary response to insult is stereotypic. While the precise pathogenic mechanisms remain unknown, the common denominator of injury is damage to the alveolar endothelium and epithelium, leading to increased permeability to protein, interstitial and alveolar edema, and resultant impairment of gas transport [17,18]. This review will emphasize ventilatory and hemodynamic management of patients with ARDS. The pathophysiology of this syndrome is also discussed.

### DEFINITION

The diagnosis of ARDS should be made in accordance with criteria (Table 2) that distinguish it from cardiogenic pulmonary edema or other forms of less severe non-cardiogenic edema [19]. The syndrome is characterized by tachypnea, dyspnea, and cyanosis in the context of an antecedent catastrophic traumatic or systemic insult. Chest radiographic features usually include an initial pattern of interstitial edema followed by a later phase of diffuse alveolar infiltration and consolidation. Since it is difficult to differentiate clinically between cardiogenic and noncardiogenic pulmonary

TABLE 1  
Predisposing Conditions for the Adult  
Respiratory Distress Syndrome

Aspiration	Head injury
pH > 2.5	Hemodialysis
pH < 2.5	High altitude
Blood transfusion	Lung contusion
Leukoagglutinin reaction	Myocardial failure (?)
Microemboli	Myocardial infarction (?)
Burns (body surface)	Oxygen toxicity
Cardiopulmonary bypass	Pancreatitis
DIC	Pneumonia
Drugs (idiosyncratic)	Gram-positive
Thiazides	Gram-negative
Drowning	Legionella
Drug overdoses	Mycoplasma
Aspirin	Pneumocystis
Heroin	Tuberculosis
Methadone	Viral
Paraquat	Radiation
Embolism	Re-expansion (lung)
Fat	Shock
Pulmonary	Hemorrhagic
Gas inhalation	Sepsis
Cl <sub>2</sub>	Smoke inhalation
NH <sub>3</sub>	TTP
NO <sub>2</sub>	Tumor lysis syndrome
SO <sub>2</sub>	(lymphoblastic leukemia)
	Venous air embolism

edema, a Swan Ganz catheter is usually necessary. Physiologic manifestations of ARDS include ventilation/perfusion ( $V_A/Q$ ) mismatch, right to left intrapulmonary shunting, reduced functional residual capacity, and decreased total lung compliance, resulting in arterial hypoxemia and altered gas transport across alveolar-capillary membranes. The pulmonary edema and atelectasis result in pulmonary venous admixture that may approach 50 percent of total cardiac output. Total ventilated dead space increases and dead space to tidal volume ( $V_D/V_T$ ) ratios may approach .6 or greater.

In the early phases, the histology of ARDS consists of non-homogeneous areas of atelectasis, alveolar flooding, hemorrhage, congestion, and inflammation [2]. The lungs are wet and have an increased density, with the cut surface approaching the texture of liver (Fig. 1). The gravity-dependent areas of the lung tend to be most affected, but the lesions are spotty owing to the maldistribution of pulmonary blood flow at the level of the microcirculation. After three to four days from the onset of the clinical syndrome, hyaline membranes form in the air spaces from protein-rich fluid, fibrin, and fibrinogen, and, after five to seven days, collagen deposition and fibrosis of the lung occur [2].

Despite maximal pharmacological and mechanical support, including hemodynamic and extracorporeal methods [20] to optimize systemic oxygen transport, mortality rates in patients with ARDS remain greater than 50 percent. Data from the National

TABLE 2  
Criteria for the Diagnosis of the Adult  
Respiratory Distress Syndrome

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A. Clinical setting
1. Catastrophic event
a. Pulmonary
b. Non-pulmonary, e.g., shock
2. Exclusions
a. Chronic pulmonary disease
b. Left heart dysfunction
3. Respiratory distress
a. Tachypnea 20 (b/m)
b. Labored breathing
B. X-ray: Diffuse pulmonary infiltration
1. Interstitial (early)
2. Alveolar (late)
C. Physiologic
1. $\text{PaO}_2 < 50$ mm Hg with $\text{FIO}_2 > .6$
2. Overall compliance, $< 50$ cc/cm $\text{H}_2\text{O}$ (usually 20–30 cc/cm $\text{H}_2\text{O}$ )
3. Increased shunt function ( $Q_s/Q_t$ )
4. Increased dead space ventilation ( $V_D/V_T$ )
D. Pathologic
1. Heavy lungs, usually greater than 1,000 g
2. Congestive atelectasis
3. Hyaline membranes
4. Fibrosis

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Heart, Lung, and Blood Institute [21] demonstrated a mortality rate of 41 percent among patients less than 65 years. Among those patients with acute respiratory failure and age greater than 65 years, the mortality rate was 68 percent. Further increases in mortality were observed in patients with ARDS in association with multi-organ system failure (Fig. 2).

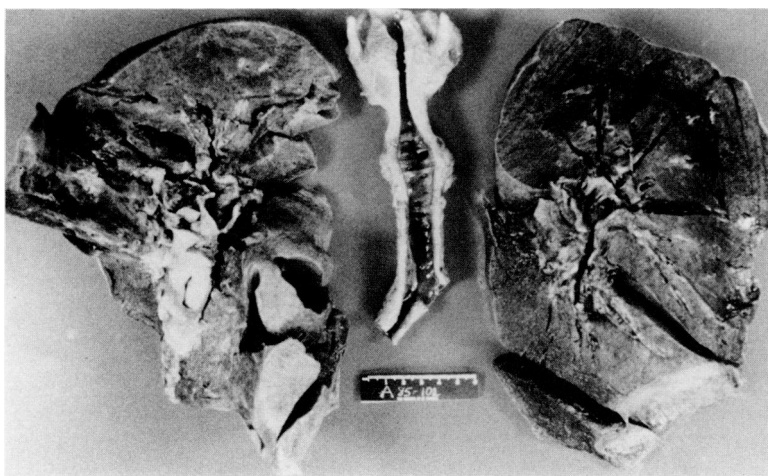


FIG. 1. Cut surface of post-mortem ARDS lung. Note extensive consolidation, with cut surface approaching the texture of liver.

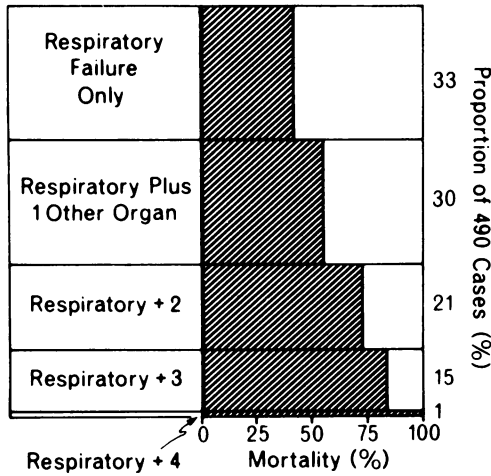


FIG. 2. Mortality of ARDS related to organ failure (age 12–65). Reproduced with permission from [123].

PATHOPHYSIOLOGY OF ARDS

Alveolar-Capillary Permeability

The basic features of ARDS involve the development of excess fluid in the lungs in the presence of low or normal pulmonary capillary wedge pressures (PCWP). Principal factors governing fluid ( $Q_f$ ) and solute ( $Q_s$ ) transfer from the alveolar capillary to the pulmonary interstitium are net transmembrane hydrostatic pressure and net transmembrane oncotic pressure. Starling’s equation [22] for transcapillary equilibrium may be applied to the pulmonary microcirculation:

$$Q_t = k[(P_{pc} - P_{pi}) - \delta(\pi_{pc} - \pi_{pi})]$$

- where  $Q_t$  = net flow rate across pulmonary capillary membrane
- $k$  = filtration coefficient
- $\delta$  = reflection coefficient
- $P_{pc}$  = hydrostatic forces in pulmonary capillary
- $P_{pi}$  = hydrostatic forces in pulmonary interstitium
- $\pi_{pc}$  = colloid osmotic pressure in pulmonary capillary
- $\pi_{pi}$  = colloid osmotic pressure in pulmonary interstitium

In the case of high-pressure, cardiogenic pulmonary edema,  $Q_t$  into the pulmonary interstitium is a function of increased pulmonary artery and venous hydrostatic forces. In the case of low-pressure, non-cardiogenic pulmonary edema, endothelial damage decreases the protein reflection coefficient,  $\delta$ , and fluid and protein flow along a positive pressure gradient into the pulmonary interstitium (interstitial pressure =  $-2$  cm  $H_2O$ ) [23,24] initially in a peribronchial and perivascular distribution.

The alveolar epithelium, in the normal lung with an intact basement membrane, has high fluid ( $k$ ) and solute ( $\delta$ ) reflection coefficients [25–28]. This accounts for the relative impermeability of the alveolus to extravascular lung water and the preservation of alveolar-capillary oxygen diffusion until alveolar flooding occurs. Pulmonary edema does not usually occur unless the rate of fluid transfer into the pulmonary interstitium exceeds maximal lung lymph clearance rates of 20 ml/hour [14]. This rate of edema formation correlates with PCWP greater than 26 mm Hg in normals. Interstitial edema alone causes minimal gas exchange abnormalities, but with

progressive alveolar flooding, oxygenation deteriorates. In fact, one recent experimental study showed a good correlation between worsening shunt fraction and a progressive increase in extravascular lung water [28].

Clinical studies have confirmed that extravascular lung water is higher in patients with ARDS than patients with cardiogenic pulmonary edema, presumably because of an abnormal increase in endothelial and epithelial permeability (Fig. 3) [27].

### *Alveolar Gas Exchange*

The mechanisms by which gas exchange abnormalities develop in ARDS are complex. Increased lung endothelial permeability leads first to interstitial edema in a peribronchial and perivascular distribution, followed by alveolar flooding. In terms of lung mechanics, this process leads to increases in airway resistance, due to peribronchial edema, and decreased lung elastic properties, due to interstitial and alveolar edema. This effect is manifested in practical terms as decreased lung compliance, which is the change in volume per unit change in distending airway pressure of the lung. As a result of the changes in the mechanical properties of the lung, a higher work of breathing is required to generate adequate transpulmonary pressure to inflate the lung. If this increased work of breathing cannot be maintained, lung volume is reduced as transpulmonary distending pressures do not exceed elastic recoil forces of the alveoli. The volume at which alveolar forces favor airway closure is called the critical closing volume, and similarly the pressure at which intra-alveolar pressure exactly equals the pressure caused by the elastic recoil forces is called the critical closing pressure. ARDS, therefore, results in a restrictive ventilatory pattern with a reduction of total lung capacity (Fig. 4). Since alveolar collapse is most likely to occur at end tidal breathing, ARDS produces a net reduction in functional residual capacity.

Early in the progression of altered membrane permeability in ARDS, the distribution of interstitial and alveolar lung water is not homogeneous. As a result, there is a maldistribution of whole lung ventilation with inspired gas flow favoring alveoli with normal compliance as opposed to those with collapse and decreased compliance. Gas distribution throughout the lung is governed by airway time constants, which are a product of airway resistance and segmental lung compliance.

Alveolar gas tensions, therefore, represent a balance between inspired gas distribution, alveolar-capillary membrane transfer, and uptake by the pulmonary circulation. Under normal conditions, ventilation/perfusion ratios ( $V_A/Q$ ) are matched except for gravitational differences in pulmonary blood flow (increasing from apex to base in the upright position).  $V_A/Q$  ratios can, however, range from zero in cases in which lung is perfused but not ventilated (basilar lung) to infinity in segments of lung which are ventilated and not perfused (apical lung). To take extreme conditions, a segment of lung with a  $V_A/Q = 0$  would imply that blood flow is entering at mixed venous oxygen and carbon dioxide contents and exits from the alveolar capillary unit without alteration. This would represent shunted blood, and the ratio of shunted blood ( $Q_s$ ) to total blood flow ( $Q_t$ ) would be the intrapulmonary shunt fraction ( $Q_s/Q_t$ ). Alternatively, there may be ventilation but no perfusion, and in such an instance inspired gas concentrations equal expired gas concentrations; this is referred to as dead space ventilation, and the fraction of dead space ventilation ( $V_D$ ) to total ventilation ( $V_T$ ) would be the dead space to tidal volume ratio ( $V_D/V_T$ ). In one recent study of ARDS patients, 32 percent of pulmonary blood flow was shunt, 17 percent was to low  $V_A/Q$  areas, and 40 percent to normal lung [29].

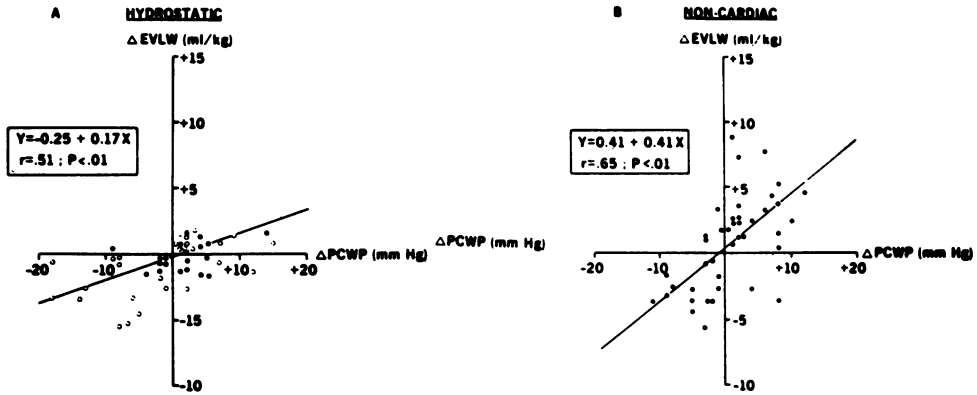


FIG. 3. A. Analysis of repeated studies of patients demonstrated linear correlation between changes in both PCWP and EXTLW in patients with, potentially, only hydrostatic influence on EXTLW formation. Patients without radiographically determined edema (*solid circles*) and cardiogenic pulmonary edema (*open circles*) were assumed to reflect combined hydrostatic group. B. Analysis of repeated studies of patients also demonstrated linear correlation between changes in both PCWP and EXTLW in patients with non-cardiogenic pulmonary edema; importantly, the slope of this relationship was greater than found in the hydrostatic group, A, indicating that changes in PCWP were accompanied by greater change in EXTLW content in patients with non-cardiogenic pulmonary edema than occurred in patients classified in the hydrostatic group. Reproduced with permission from [27].

**Bronchoalveolar Lavage Characteristics**

Analysis of bronchoscopic alveolar lavage specimens from ARDS patients yields a variety of inflammatory, vasoactive, and proteolytic mediators [2,30]. Lavage samples are exudative, with protein concentrations equal to that of plasma. There is a rich fraction of polymorphonuclear leukocytes (PMNs), oxidants, and proteases with the ability to cleave complement [31], fibrinogen, fibronectin, plasma kallikrein [32], and

COMPARATIVE SPIROMETRICS IN NORMAL AND ARDS LUNG

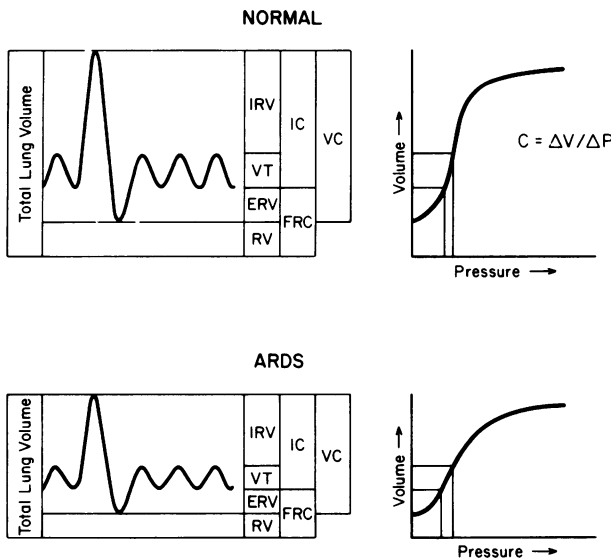


FIG. 4. A restrictive ventilatory defect is associated with ARDS, with a reduction in total lung capacity (TLC).

generate vasoactive peptides (bradykinin, vasopressin, angiotensin, serotonin, and prostaglandins) [33]. Many cleavage products are chemotactic for PMNs, fibroblasts, and smooth muscle cells, thereby perpetuating the injury.

Additional characteristic features of bronchoalveolar lavage specimens from patients with ARDS include increased amounts of inactivated, aggregated surfactant. Studies by VonWichert and Kohl [34] have shown decreased dipalmitoylphosphatidylcholine (major surface-active component of pulmonary surfactant)/phosphatidylcholine ratios among patients who died of ARDS. The extent to which this finding accounts for alterations in lung elastic properties, increased critical airway closure, and surface tension abnormalities favoring alveolar collapse is difficult to quantitate. Compounding the problem of abnormal surfactant is the replacement of thin alveolar epithelial Type I cells responsible for gas exchange by hyperplasia of thicker Type II cells [35].

### *Pulmonary Vascular Resistance*

The magnitude of impairment of oxygen ( $O_2$ ) and carbon dioxide ( $CO_2$ ) transfer across alveolar-capillary membranes in ARDS, however, is not purely a function of alterations in lung mechanics and shunt fraction alone. Shoemaker et al. [36] have recently shown that patients with acute respiratory insufficiency display alterations in direct and derived cardiovascular variables that may precede the clinical onset of ARDS by as much as 36 hours. In the face of decreased arterial  $O_2$  content, cardiac performance is increased as determined by thermodilution cardiac output and indices of right and left ventricular stroke work. Mean pulmonary artery pressure and pulmonary vascular resistance are usually markedly elevated. Peripheral oxygenation is impaired, as a function of decreased blood hemoglobin and maldistribution of microcirculatory perfusion causing increased tissue shunting. If mixed venous blood has an oxygen tension below 30 mm Hg, this condition will compound arterial hypoxemia [37].

The pulmonary hypertension seen in acute lung injury occurs on a multifactorial basis. Pulmonary vascular resistance (PVR) may be altered passively, with the length and radius of pulmonary blood vessels changing as a function of the mechanical and elastic properties of the lung, or directly by the action of neurohumoral or chemical mediators on vasomotor tone of the vascular smooth muscle [38]. Total PVR is increased when lung volume is either decreased or increased from a normal functional residual capacity [39]. At low lung volume, elastic recoil and relatively increased interstitial fluid pressures shorten large (extra-alveolar) vessels in the lung and increase resistance to flow through them. As lung volume increases, extra-alveolar vessels lengthen and resistance decreases. At high lung volumes, extra-alveolar resistance is minimal, but the resistance across the alveolar capillary bed increases exponentially as alveolar capillaries are mechanically compressed and lengthened. PVR, which is the net sum of the series resistances of extra-alveolar and alveolar circulation, increases with increasing total lung capacity (Fig. 5).

The modulation of the pulmonary microcirculation by alveolar hypoxia may contribute significantly to the onset of pulmonary hypertension during acute respiratory failure. Altering the distribution and the flow of blood toward alveolar units which are well ventilated and away from those that are not well ventilated maximizes  $V_A/Q$  matching and minimizes  $Q_s/Q_r$ . Benumof et al. [40,41] have recently shown that alveolar hypoxia increases pulmonary vascular resistance in the extra-alveolar circula-

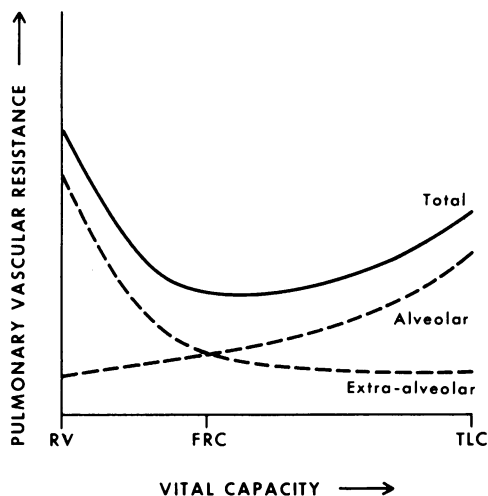


FIG. 5. The effect of increasing lung volume on extra-alveolar, intra-alveolar, and mean pulmonary vascular resistance. Reproduced with permission from Benumof JL: Respiratory physiology and function during anesthesia. In Anesthesia. Edited by RD Miller. New York, Churchill Livingstone, 1986, p 1122.

tion primarily and have postulated hypoxic pulmonary vasoconstriction (HPV) [42] as a mechanism for increased PVR during ventilation at low lung volumes. Other studies indicate that this effect occurs in both isolated lung [43] and intact animal models [44], suggesting that HPV is primarily a response to local chemical stimuli,  $O_2$  and pH, which are modulated by sympathetic vasomotor tone.

The autoregulation of the pulmonary microcirculation by HPV is impaired by various factors, many of which also may have profound effects on arterial oxygenation [45] (Table 3). Acid-base disturbances can inhibit HPV. Metabolic and respiratory alkalosis cause pulmonary vascular smooth muscle dilatation, whereas metabolic and respiratory acidosis cause pulmonary vascular smooth muscle constriction. Mixed venous oxygen tension may affect HPV, with a low mixed venous oxygen tension causing pulmonary vascular vasodilation in acinar units. Furthermore, vasoactive drugs that act directly on the pulmonary circulation may facilitate  $V_A/Q$  mismatch by inhibition of HPV. Vasodilators which inhibit HPV include sodium nitroprusside [46,47], nitroglycerin [48], calcium channel blockers (diltiazem [49] and nifedipine [50]), aminophylline, and aerosolized (alupent and terbutaline) and non-aerosolized (isoproterenol and dobutamine)  $B_2$  agonists.

Anesthetic agents have variable effects on the pulmonary circulation. Inhalation agents reported to inhibit HPV include nitrous oxide [51], isoflurane [52], and halothane [53]. Intravenous induction and maintenance agents, by contrast, have negligible effects on alveolar capillary microcirculation.

Clinical conditions of acute and chronic left ventricular dysfunction such as dilated cardiomyopathy, mitral insufficiency, or stenosis may inhibit HPV due to the inability of the pulmonary microcirculation to constrict against pulmonary artery pressures greater than 18 mm Hg [54].

#### *Mediators of Lung Injury [2]*

One major substrate for proteolytic, chemotactic, and vasoactive mediators in ARDS is arachidonic acid (Fig. 6). In its natural state, arachidonic acid is bound to membrane phospholipids of endothelial cells. In conditions of gram-negative sepsis and endotoxic shock, granulocytes in the presence of complement-activated plasma and superoxide radicals ( $O_2^-$ ) stimulate membrane phospholipase to produce free arachi-



TABLE 3  
Inhibitors of Hypoxic  
Vasoconstriction (HPV)

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Anesthetics
Halothane
Isoflurane
Nitrous oxide
Bronchodilators (B <sub>2</sub> )
Alupent
Aminophylline
Terbutaline
Calcium antagonists
Diltiazem
Nifedipine
Verapamil <sup>a</sup>
Inotropes (B <sub>1</sub> and B <sub>2</sub> )
Amirinone <sup>a</sup>
Dobutamine
Isoproterenol
Mechanics
Cardiomyopathy
LV dysfunction
Mitral stenosis
Pulmonary hypertension
Metabolic states
Decreased PvO <sub>2</sub>
Hypoxemia
Metabolic alkalosis
Respiratory alkalosis
Vasodilators
Nitroglycerin
Sodium nitroprusside

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<sup>a</sup>Probable

donic acid [55]. Arachidonic acid is metabolized via the lipoxygenase pathway to produce leukotrienes, the slow-reacting substance of anaphylaxis (SRS-A), and 5- and 11-hydroxyeicosatetraenoic acid (5-HETE and 11-HETE), which are potent effectors of increased lung vascular permeability and smooth muscle vascular resistance. Matthay et al. [56] have identified very high levels of leukotriene D<sub>4</sub>(LTD<sub>4</sub>) in the pulmonary edema fluid of patients with ARDS.

Alternatively, by the cyclo-oxygenase pathway, arachidonic acid is metabolized to prostacyclin (PgI<sub>2</sub>) and thromboxane B<sub>2</sub>(TxB<sub>2</sub>), potent vascular smooth muscle vasodilators, and to thromboxane A<sub>2</sub>(TxA<sub>2</sub>), which produces both potent bronchoconstriction and pulmonary artery vasoconstriction. Frolich et al. [57] have shown that the pulmonary hypertension and increased airway resistance noted during endotoxemia is a direct function of the endogenous production of TxA<sub>2</sub>. Furthermore, Gerber et al. [58] have suggested that the loss of HPV and subsequent pulmonary venous admixture ( $Q_s/Q_t$ ) are secondary to the vasodilating action of prostacyclin.

Some evidence supports the role of platelet aggregation and degranulation along with fibrin deposition as a causative factor for lung microvascular injury and small-vessel capillary occlusion [59]. In ARDS, the activation of the alternate complement pathway is associated with increased circulating levels of C5a [60–62], which has been shown to produce leukocyte and thrombocyte aggregation and fibrin

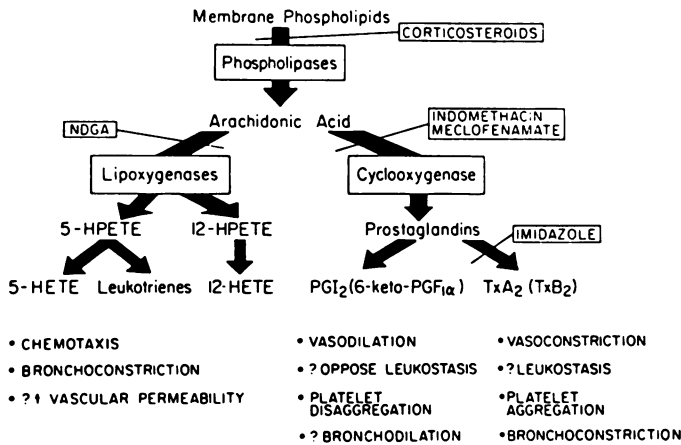


FIG. 6. Arachidonate metabolism showing some products of both the cyclooxygenase and lipoxygenase pathways and some effects of arachidonate metabolites which are important in lung injury. Reproduced with permission from Brigham KL: Mechanisms of lung injury. Clin Chest Med 3:13, 1982.

deposition. The current concept is that activated PMNs aggregate, attach to the pulmonary capillary endothelium, and release proteases and oxidants, thereby causing endothelial damage [2]. Platelet degranulation results in the release of histamine and serotonin, which produce smooth muscle vasoconstriction in pulmonary arterioles and bronchioles [63]. In addition, platelet degranulation can activate the kallikrein system. There is diffuse microthrombosis, reflecting increased local intravascular coagulation.

Saba and Jafta [64] have shown low levels of plasma fibronectin (opsonic  $\alpha_2$  endothelial surface binding protein) in sepsis and multiple organ failure. There is some recent evidence to suggest that fibronectin may also be important in the repair of vascular endothelial injury and may influence the clearance of vasoactive mediators through the reticuloendothelial system.

## MANAGEMENT OF ARDS

### *Mechanical Ventilation*

The treatment of ARDS is largely supportive. Increases in extravascular lung water decrease the elastic recoil properties of the lung due to increased alveolar and interstitial pressures and altered alveolar surface tension forces. Thus, decreases in lung compliance lead to marked alterations in pulmonary mechanics with an increased work of breathing, to the extent that 20 percent of the total cardiac output may be necessary for the energy requirements of the diaphragm and intercostal muscles during spontaneous ventilation [65,66]. The tidal volumes of normal spontaneous ventilation are well above critical closing volumes. In patients with ARDS, progressively greater transpulmonary pressures are required to maintain alveolar ventilation. Total lung volume is decreased. FRC and expiratory lung volume decrease and fall below critical closing volumes, resulting in alveolar collapse. Because critical closing pressures in the lung are usually significantly less than critical opening pressures, it takes more work to re-expand collapsed alveoli than to maintain their patency, especially in the presence of abnormal surfactant. In ARDS, decreased lung compliance favors progressive atelectasis with resultant increases in  $Q_s/Q_r$ . Since the basic abnormalities are both alveolar flooding and alveolar collapse, increasing the inspired oxygen concentration ( $FIO_2$ ) does little to increase the oxygen content of shunted pulmonary arterial blood through non-ventilated alveoli.

Reasonable guidelines for the institution of mechanical ventilation may be based on arterial blood gas measurements. The following determinants [67] indicate cardiorepiratory failure which, under most circumstances, is unable to meet systemic metabolic demands:

1.  $\text{PaO}_2 \leq 55$  mm Hg on  $\text{FIO}_2, \geq .5$
2.  $\text{PaCO}_2 \geq 50$  mm Hg
3.  $\text{pH} \leq 7.30$

Intermittent positive-pressure ventilation has been employed successfully to reduce the work of breathing and to improve arterial oxygenation since 1909 [68]. The current practice of employing large tidal volumes (10–15 cc/kg) over long inspiratory times (1.0–2.0 seconds) has afforded the re-expansion of collapsed alveoli and increased functional residual capacity at modest inspiratory pressures [69]. The importance of a large tidal volume administration over a long inspiratory time is of key importance in the ARDS lung, which has an average compliance of 20–30 cc/cm  $\text{H}_2\text{O}$  (normal ventilated lung is 50–100 cc/cm  $\text{H}_2\text{O}$ ) and minimal risk of alveolar gas trapping. Prolonged inspiratory times or inspiratory hold modes allow time for gas distribution and pressure equalization in the lung and improve alveolar ventilation when airway resistance is increased. The optimal inflation hold period for ARDS lung is about .5–1.0 second and should be used in conjunction with inspiratory/expiratory ratios (I:E) of 1:2 to 1:3 [70,71].

Additionally, some data support the use of a sine-wave pattern over a square-wave flow pattern for optimal ventilation in patients with ARDS [70]. Studies by Dammann and McAshlan [71] have shown optimal inert (argon) gas distribution and minimal  $V_A/Q$  mismatching in ARDS patients during sine-wave-generated patterns of ventilation. Noncompliant, inelastic lung produces high impedance to inspiratory gas flow [72]. Lung inflation, therefore, is associated with nonhomogeneous gas distribution, owing to differences in pulmonary time constants ( $T = R \times C$ ) in the alveolar subunits [73]. Consequently, convective gas flow is stratified into fast space (low resistance) [74] and slow space (high resistance) [75] distribution throughout alveolar subunits. The inhomogeneity of alveolar gas distribution is further stratified with increasing rates of inspiratory flow. Positive-pressure ventilation at high frequency and short inspiratory phase produces great differences between fast and slow space ventilation and is the primary mechanism for mechanical ventilation-induced  $V_A/Q$  mismatch [76].

The inspiratory plateau of the ventilatory cycle is designed as an equilibrium, non-dynamic state during which pressure and flow become constant within the alveoli. By allowing the distribution of inspired gas from fast to slow spaces, a penduluft effect is created which improves ventilation to the low compliance subunits [77]. Pressure redistribution in the lung results in an alveolar recruitment phase during the end-inspiratory plateau [78]. Because pressure becomes constant during the inspiratory hold, total chest compliance ( $C_T$ ) may be approximated from the change in exhaled lung volume and the change in airway pressure:

$$C_T = V_T (P_{EI} - P_B)$$

where  $V_T$  = exhaled tidal volume

$P_{EI}$  = end-inspiratory pressure

$P_B$  = baseline airway pressure

The expiratory phase of a mechanically ventilated breath for a patient with ARDS is generally a passive return to baseline (atmospheric) pressure. The rate of this decline in pressure is determined by the elastic recoil forces of the lung. Expiratory resistance may be applied to retard flow and splint small airways to prevent premature alveolar closure. This might best be done in the setting of patients receiving low-rate, large tidal volume ventilation to minimize problems with gas trapping in the lung and pulmonary barotrauma.

In ARDS, therefore, there is a rationale for the use of large volume (15 cc/kg) and low-frequency ventilation with an emphasis toward increased I:E ratios (slow inspiratory flow rates) to facilitate maximal inspired gas distribution at lower peak airway pressures.

#### *Positive End-Expiratory Pressure*

Despite modifications of inspiratory and expiratory flow patterns, alveolar collapse following mechanical inspiration occurs as end-expiratory pressure falls below critical closing pressure, creating respiratory-phasic increases in  $Q_s/Q_t$ . The application of positive end-expiratory pressure (PEEP) [79–82] at a pressure which exceeds critical closing pressure minimizes atelectasis, increases FRC, and decreases  $Q_s/Q_t$ . In ideal terms, the inspiratory phase of mechanical ventilation should inflate atelectatic lung while PEEP should prevent the re-establishment of  $Q_s/Q_t$ .

The physiologic goal of PEEP therapy is to increase functional residual capacity so that alveoli remain open throughout all phases of the respiratory cycle to participate continually in gas exchange. This state allows optimization of systemic oxygen transport at relatively lower inspired oxygen concentrations in an effort to minimize the risk of oxygen toxicity. PEEP increases functional residual capacity in a linear relationship in normal lungs [83], usually at a rate of 400 cc/5 cm H<sub>2</sub>O positive end-expiratory pressure [84]. The usual therapeutic range for PEEP is 0–15 cm H<sub>2</sub>O; some investigators have used higher levels of PEEP (25–42 cm H<sub>2</sub>O) [85]. Controversy has surrounded the definition of optimal PEEP. Suter et al. [86] defined “best PEEP” as the point of maximal static lung compliance, whereas “optimal PEEP” refers to the PEEP level which reduces  $Q_s/Q_t$  to 15 percent while maintaining satisfactory cardiovascular function [87].

In general, there are no specific guidelines for PEEP administration. Under most conditions, PEEP in 3–5 cm H<sub>2</sub>O increments will significantly reduce  $Q_s/Q_t$  and improve systemic oxygen transport. Under optimal conditions, the inspired fraction of oxygen should be decreased to .5 or less on PEEP settings of up to 15–18 cm H<sub>2</sub>O. Civetta et al. [88] have shown recently that a significant number of patients with ARDS require PEEP at levels above 15 cm H<sub>2</sub>O and have advocated the use of PEEP at levels only to be limited by decreased systemic oxygen transport. Since PEEP may profoundly depress cardiac function and overdistend normal alveoli, hence decreasing alveolar blood flow, too much PEEP will decrease overall systemic oxygen transport. Furthermore, PEEP has been shown to increase pulmonary artery pressure at about one-third to one-half the rate of increase in transpulmonary pressure [89]. Some of the extravascular lung water is redistributed from the airspaces to the lung interstitium, but PEEP does not reduce the overall lung water. Actually, data support an increase in extravascular lung water with PEEP therapy, probably on the basis of altered effluent lymphatic flow [90]. Because of the redistribution and net increase in extravascular lung water, the abrupt discontinuation of PEEP may lead to rebound alveolar flooding

and acute increases in  $Q_s/Q_t$ . Guidelines for PEEP discontinuation, therefore, should favor a gradual wean of positive end-expiratory pressure at a rate not to exceed 3–5 cm H<sub>2</sub>O per 12 hours when discontinuing mechanical ventilatory support [91].

A recent prospective study by Pepe et al. [92] established that PEEP does not have prophylactic value in preventing ARDS in high-risk patients.

### *Oxygen Therapy and Oxygen Toxicity*

Increases in inspired oxygen concentration (FIO<sub>2</sub>) will usually improve arterial oxygenation. Arterial hypoxemia is often secondary to low but finite  $V_A/Q$  ratios in the lung. The arterial hypoxemia produced by low  $V_A/Q$  is worsened by low FIO<sub>2</sub> and improved by increasing FIO<sub>2</sub>. In ARDS, the cause for arterial hypoxemia is increased  $Q_s/Q_t$  primarily, and only to a small extent caused by low  $V_A/Q$  ratios. The application of hyperoxic therapy, therefore, is often of very little value in fixed shunt conditions. Despite significant evidence to the contrary, high inspired oxygen is still commonly used in the treatment of acute respiratory failure.

Although in the immediate term hyperoxic therapy is partially effective in altering arterial hypoxemia, prolonged exposure to elevated partial pressures of oxygen is associated with lung microvascular and cellular injury. The histopathology of oxygen toxicity is indistinguishable from that of ARDS, making the limitations of oxygen therapy difficult to define. The final outcome is progressive interstitial fibrosis and destruction of pulmonary architecture.

The mechanisms of oxygen toxicity involve single electron transfers to molecular oxygen which produce three major cytotoxic molecules: superoxide anion, hydrogen peroxide, and hydroxyl radicals. Superoxide (O<sub>2</sub><sup>-</sup>) is reactive in cellular pathways and may function both as an oxidant by obtaining electrons or as a reductant by giving up its unpaired electron to produce molecular oxygen (O<sub>2</sub>) in a more stable low-energy state. The hydroxyl radical (OH<sup>-</sup>) is the most reactive and cytotoxic intermediate. It is largely generated from O<sub>2</sub><sup>-</sup> by the Fenton reaction with iron.

The biochemical pathways of oxygen toxicity remain to be fully elucidated [93–98]. Significant data link the activity of these oxygen intermediates to the breakdown of cellular membrane lipids, a process which is called lipid peroxidation. Lipid peroxides produced by this process are inhibitors of cellular enzyme function. Nucleic acid and cellular protein destruction occur via sulfhydryl oxidation mediated by these high-energy oxygen moieties.

In normal lung, sufficient protective mechanisms exist to maintain a constant clearance of these free oxygen radicals. Cytochrome oxidase plays a major role in the multivalent reduction of oxygen radicals and compartmentalizes free electrons within the mitochondria so that they cannot interact with cellular proteins. Further specific enzymatic pathways break down these intermediates. Superoxide dismutase converts superoxide anion to hydrogen peroxide, which is then catalyzed to water and oxygen. Additionally, glutathione peroxidases will directly reduce hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>). Lastly, glutathione by itself is an effective free radical scavenger.

The antioxidant pathways are very effective at normal fractions of inspired oxygen at normal atmospheric pressure. Kinetic studies show that the rate of oxygen radical production equals the rate of clearance. In ARDS, activated granulocytes in the presence of increased FIO<sub>2</sub> enhance superoxide radical formation [93]. Flick and others [94] have shown decreased superoxide dismutase activity in sepsis and microembolic states. Reversible functional changes have also been observed in alveolar

macrophagic function with a 60 percent decrease in foreign particle clearance in lung exposed to 100 percent oxygen for 48 hours [95]. Furthermore, increased oxygen tensions (90–95 percent) have been shown to reduce mucociliary transport during lung injury from mean rates of 23 mm/minute to 10 mm/minute after a six-hour exposure [96].

Certain conditions may predispose to oxygen toxicity. Both paraquat [97] and bleomycin [2] enhance the rate of free oxygen radical generation in injured lung and increase the development of pulmonary interstitial fibrosis.

A spectrum of clinical observations has been made in normal volunteers breathing 100 percent oxygen. During the first six hours, respiratory function and ventilation remain normal, and tracheobronchitis is found to occur [99]. Between six and 24 hours of exposure, ventilatory mechanics are impaired, marked by increased splinting and reduction in vital capacity [100]. After 24 to 30 hours of exposure, increases in extravascular lung water and decreases in total thoracic compliance are noted, along with gas exchange abnormalities of low PaO<sub>2</sub> and increased A-aO<sub>2</sub> difference [101]. After 72 hours, a gradual decrease in diffusion capacity is demonstrated. This clinical spectrum is reversible over a two-week period.

#### *Absorption Atelectasis*

High fractional inspired oxygen concentrations lead to absorption atelectasis. At an FIO<sub>2</sub> of .5 or less, nitrogen comprises much of the total alveolar gas pressure. Since nitrogen exists fully saturated in body fluids and tissues, only oxygen is transferred from the alveolus to blood, and a net transfer of nitrogen does not occur. Nitrogen is therefore retained in the alveolus and serves as a “splint” as the entire gas volume of oxygen diffuses into blood. At increasing inspired concentrations of oxygen, decreasing amounts of residual gas remain in alveoli, and progressive atelectasis may occur in mechanically ventilated patients at an FIO<sub>2</sub> of 1.0 after 24 hours (Fig. 7) [102]. In general, the magnitude of absorption atelectasis is directly proportional to the blood solubility of the inspired gas mixture [103]. Under general anesthesia with 75:25 percent nitrous oxide (N<sub>2</sub>O):oxygen mixture of inspired gas, atelectasis is likely to occur as N<sub>2</sub>O diffuses into the blood at a rate which is 34-fold that of nitrogen:oxygen mixtures at normal atmospheric pressure [104].

#### *Pulmonary Barotrauma*

Pulmonary barotrauma refers to the development of pneumothorax, pneumomediastinum, or subcutaneous emphysema due to the rupture of alveoli with gas dissection along blood vessels and fascial planes. The overall incidence of pulmonary barotrauma in ARDS patients being mechanically ventilated is about 7 percent. Highest incidences have been reported among patients with chronic obstructive bronchitis and emphysema with an increased tendency to gas trapping. Special procedures such as bronchoscopy and central line placement further increase this risk. The addition of PEEP up to 15 cm H<sub>2</sub>O does not alter this incidence significantly. In patients who require PEEP levels of 25–40 cm H<sub>2</sub>O the incidence of pulmonary barotrauma increases to about 14 percent, but what remains difficult to determine is to what degree this effect is due to PEEP and mechanical ventilation or to the intrinsic lung disease itself.

To summarize, arterial hypoxemia requires aggressive positive-pressure ventilation directed to minimize  $Q_s/Q_t$  in order to achieve an arterial oxygen saturation of 90 percent on an FIO<sub>2</sub> of .5 or less. Most often this can be achieved with PEEP levels of 15

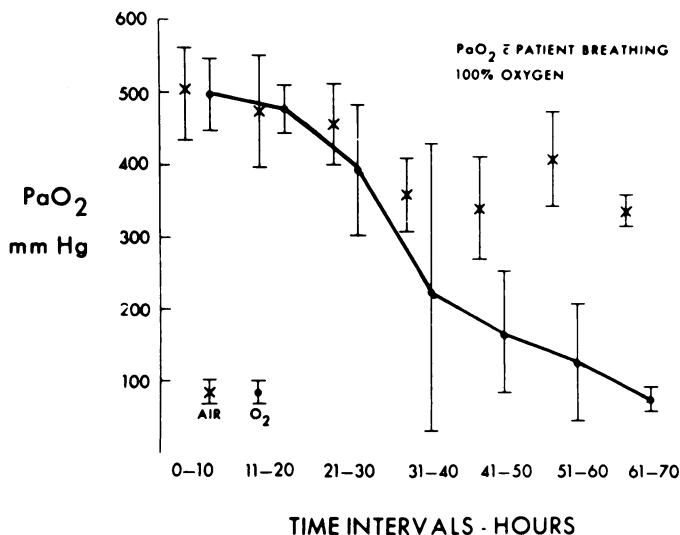


FIG. 7. Changes in arterial oxygen tension ( $\text{PaO}_2$ ) during intermittent positive-pressure ventilation with air vs. 100 percent oxygen in patients over 72 hours. Note the significant reduction in  $\text{PaO}_2$  in the group ventilated with 100 percent oxygen after 40 hours. Reproduced with permission from [102].

cm  $\text{H}_2\text{O}$  or less, but there are no arbitrary limits, and selected patients may require very high-level PEEP (20–40 cm  $\text{H}_2\text{O}$ ) to achieve oxygenation in spite of the attendant risks of alveolar rupture and pulmonary barotrauma. In all instances, the effect of PEEP should be determined so that tissue oxygen delivery remains optimal.

### *Heart-Lung Interaction*

As early as 1947, Cournand et al. [105] demonstrated that intermittent positive-pressure ventilation with PEEP decreases cardiac output in man. Braunwald [106] subsequently has shown the relationship between transthoracic and transpulmonary pressure gradients developed during mechanical ventilation and the translocation of central blood volume peripherally leading to decreased venous return [106]. Furthermore, this effect was reversed by aramine infusions and pronounced by conditions of hypovolemia and decreased systemic vascular resistance [107]. Right and left ventricular chamber studies [108–110] suggested that decreases in cardiac output had a multifactorial basis which included:

1. Decreased venous return
2. Increased right heart afterload and right heart dysfunction
3. Decreased biventricular preload
4. Altered cardiac geometry and contractile symmetry
5. Altered right and left ventricular interdependence
6. Decreased contractility

The output of the right ventricle is significantly afterload-dependent [111]. Principal ventilatory factors determining right heart afterload include airway pressure and resting lung volume. Total pulmonary vascular resistance is increased when lung volume is either decreased or increased from a normal functional residual capacity. Increases in transpulmonary pressure during mechanical ventilation increase lung volume and may exponentially increase pulmonary vascular resistance. Changes in ventilatory phase or mode may modulate right heart hemodynamics by increasing right

ventricular afterload. Right ventricular failure in combination with decreased venous return may synergistically depress cardiac output.

The relationship between pulmonary vascular resistance and total cardiac blood flow is a hyperbolic function with cardiac output decreasing exponentially with increased pulmonary vascular resistance [112]. Jardin et al. [113] have shown that mechanical ventilation with PEEP (30 cm H<sub>2</sub>O) and volume loading (10 cc/kg) can result in a shift of the interventricular septum with paradoxical motion due to right heart dilatation, and decreased left ventricular chamber size. In pericardiectomized patients, this septal interaction may be minimized, as the free wall of the right ventricle may be displaced laterally, and left ventricular function may be less impaired by changes in right heart mechanics [114]. Right ventricular impairment and leftward septal displacement also cause alterations in left ventricular pressure-volume relationships in dogs and support a theoretical basis for ventilation and PEEP effects on left ventricular filling and diastolic function [115]. Augmented right ventricular loading can significantly affect left ventricular performance.

Because the right ventricle is a low-pressure chamber with systolic function primarily afterload-dependent, changes in right ventricular hemodynamics may be a marker for the potential impairment of left ventricular function during mechanical ventilation. Until recently, methods of evaluating right ventricular function were limited to angiographic, radionuclide (Technetium 99M, both first-pass and gated studies), and echocardiographic techniques. Inherent in these techniques were problems in imaging the right ventricle due to its crescent-shaped geometry, coaxial shortening, and location under the sternum.

Recent advances in the design of thermistors for pulmonary artery catheters allow for the continuous and repeated measurement of right ventricular ejection fraction in a simple and accurate manner. The response time of the thermistor has been modified to 50 msec, which is rapid enough to measure beat-to-beat temperature variations and allow for calculation of right ventricular ejection fraction via thermal indicator dilution methods [116].

Right ventricular ejection fraction is defined as right ventricular stroke volume divided by right ventricular end-diastolic volume. The normal value for right ventricular ejection fraction obtained via this thermal technique is approximately 40 percent [117].

The reproducibility, accuracy, and clinical applicability of this technique were demonstrated in both a canine model and humans following cardiac surgery. Injection of the thermal indicator just above the tricuspid valve was associated with a high reproducibility ( $r = 0.90$ ) as well as accuracy ( $r = 0.90$ ) [117].

New data have shown that in post-operative ventilated patients thermal right ventricular ejection fraction deteriorates (45 percent to 27 percent) with PEEP levels greater than 15 cm H<sub>2</sub>O. This is associated with a concomitant increase in right ventricular end-diastolic volume and right ventricular end-systolic volume (Fig. 8) [118]. Changes in ventilatory phase or mode may modulate right heart function, as right ventricular ejection fraction is most reduced with assist control ventilation (29 percent) and increased with increasing levels of negative inspiration during intermittent mandatory (42 percent) and spontaneous (49 percent) ventilation (Fig. 9). This is supported by observations that cardiac output in mechanically ventilated ARDS patients was affected by an average PEEP of 22 cm H<sub>2</sub>O during intermittent



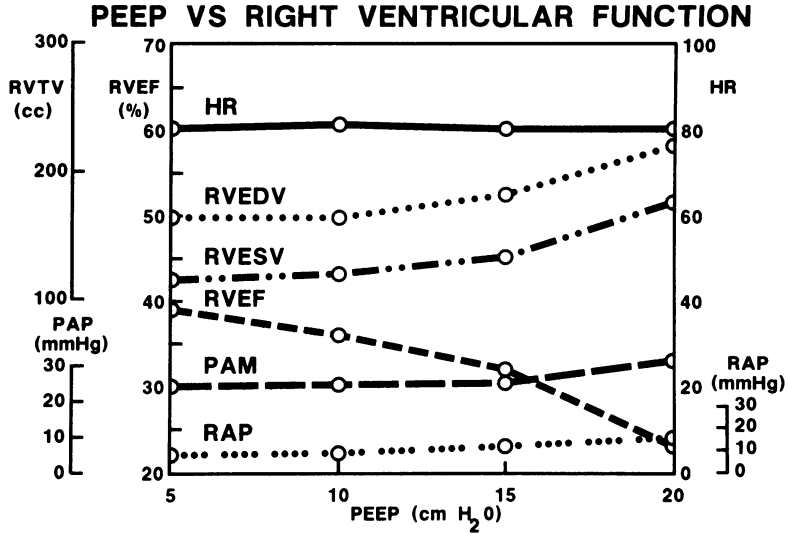


FIG. 8. Data showing the effect of PEEP on thermal right ventricular ejection fraction (RVEF), right ventricular end-diastolic volume (RVEDV), and right ventricular end-systolic volume (RVESV).

mandatory versus an average PEEP of 11 cm during assist control ventilation, which directly correlated with changes in intrathoracic pressure between modes [119].

The interdependence of cardiopulmonary function during acute respiratory distress provides an important indication for the use of pulmonary artery catheterization for the analysis of direct and derived hemodynamic indices (Table 4). Packman and Rackow [120] have suggested an optimal PCWP range of 8–12 cm H<sub>2</sub>O in patients in shock with acute respiratory failure to maintain both cardiac output and to minimize extravascular lung water. Barash [121] has advocated the use of the left ventricular stroke work index and pulmonary capillary wedge pressure to assess overall cardiac performance during mechanical ventilation. By plotting left ventricular stroke work

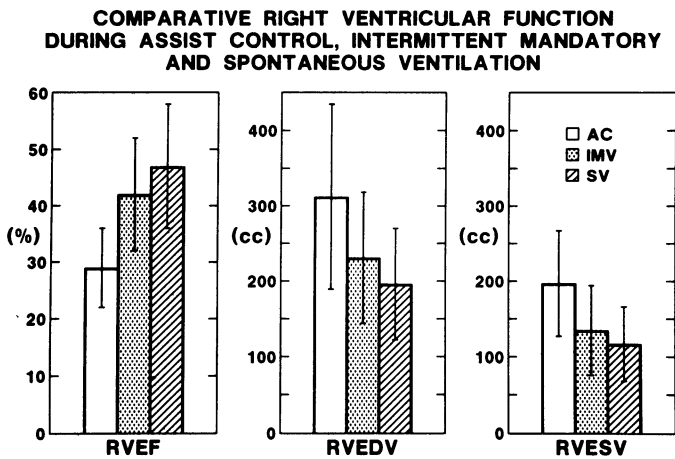


FIG. 9. The modulation of right ventricular function during assist control (AC), intermittent mandatory (IMV) and spontaneous ventilation (SV), as illustrated by changes in right ventricular ejection fraction (RVEF), right ventricular end-diastolic volume (RVEDV), and right ventricular end-systolic volume (RVESV).

TABLE 4  
Hemodynamic Variables

Variable	Circulation	Normal Range
Cardiac index (CI)	$CI = CO/BSA$	2.5–4.0 l/minute/m <sup>2</sup>
Stroke volume index (SVI)	$SVI = CI/HR$	30–50 ml/beat/m <sup>2</sup>
Systemic vascular resistance index (SVRI)	$SVRI = 80 (MAP - RAP)/CI$	1,800–2,500 dynes/second cm <sup>5</sup> /m <sup>2</sup>
Pulmonary vascular resistance index (PVRI)	$PVRI = 80 (MPAP - PCWP)/CI$	50–220 dynes/second cm <sup>5</sup> /m <sup>2</sup>
Left ventricular stroke work index (LVSWI)	$LVSWI = 0.0136 (MAP - CVP)SVI$	44–68 g/m/beat/m <sup>2</sup>
Right ventricular stroke work index (RVSWI)	$RVSWI = 0.0136 (MPAP - PCWP)SVI$	4–8 g/m/beat/m <sup>2</sup>
Right ventricular ejection fraction (RVEF)	$RVEF = SV/EDV$	40–50%
Right ventricular end-diastolic volume index (RVEDVI)	$RVEDVI = SVI/EF$	80–120 cc/m <sup>2</sup>
Right ventricular end-systolic volume index (RVESVI)	$RVESVI = RVEDVI - SVI$	50–70 cc/m <sup>2</sup>
Arterial O <sub>2</sub> content (CaO <sub>2</sub> )	$CaO_2 = (1.39 \cdot Hb \cdot O_2Sat) + (PaO_2 \cdot 0.0031)$	18–20 vol%
Mixed venous O <sub>2</sub> content (CvO <sub>2</sub> )	$CvO_2 = (1.39 \cdot Hb \cdot O_2VSat) + (PvO_2 \cdot 0.0031)$	13–16 vol%
Pulmonary capillary O <sub>2</sub> content (CcO <sub>2</sub> )	$CcO_2 = (1.39 \cdot Hb \cdot 1) + (PAO_2 \cdot 0.0031)$	21 vol%
Oxygen transport (SOT)	$SOT = CO \cdot CaO_2 \cdot 10$	800–1,200 ml/minute
Oxygen consumption (VO <sub>2</sub> )	$VO_2 = (CaO_2 - CvO_2) \cdot CO \cdot 10$	180–320 ml/minute
A-V O <sub>2</sub> difference (A-V O <sub>2</sub> D)	$A-V O_2D = CaO_2 - CvO_2$	4–6 vol%
Intrapulmonary shunt (Q <sub>s</sub> /Q <sub>t</sub> )	$Q_s/Q_t = (CcO_2 - CaO_2) / (CaO_2 - CvO_2)$	≤8%

Abbreviations: CO = cardiac output, BSA = body surface area, O<sub>2</sub> = oxygen, PaO<sub>2</sub> = alveolar oxygen tension

index as a function of pulmonary capillary wedge pressure, it is possible to construct a ventricular function curve. This curve represents the total work within a given cardiac cycle. An upward shift of the curve (as with volume loading) denotes improved ventricular performance, and a downward shift of the curve (as with increased PEEP) denotes impaired ventricular performance.

Optimizing systemic oxygen transport in acute hypoxic respiratory failure requires diligent use of direct and derived hemodynamic data. Recent work by Malloy et al. [122] suggested that systemic oxygen delivery might best be optimized by inotropic agents such as dobutamine, which increase cardiac output and concomitantly decrease pulmonary capillary wedge pressure, instead of more classically utilized dopamine. In eight patients, dobutamine increased indices of cardiac function as noted by increased left ventricular ejection fraction, decreased left ventricular volume, and increased cardiac output, and favorably influenced respiratory function as noted by increased arterial oxygen tension and decreased Q<sub>s</sub>/Q<sub>t</sub> during PEEP.

The interfaced physiology of the heart and lungs in patients with ARDS requires the use of derived respiratory indices (refer to Table 4), specifically systemic oxygen transport, to define optimal levels of artificial respiratory support. Mixed venous oxygen tension (PvO<sub>2</sub>), likewise, represents the final balance between tissue oxygen

supply and demand and makes possible the determination of overall oxygen uptake and utilization.

### SUMMARY

Despite the ubiquitous use of advanced hemodynamic and ventilatory support, it is estimated that 40,000 patients with ARDS will die annually. Overall mortality rates approach 60–70 percent, with a significantly worse prognosis for ARDS combined with multi-organ systems failure. Although one might expect physiological parameters, such as arterial oxygen tension, A-a gradient, and lung compliance, to be somewhat predictive of outcome, there are no statistical differences in outcome between survivors and non-survivors in these parameters [123]. Therapeutic interventions, including extracorporeal support of the circulation, have similarly failed to influence these statistics. With recent advances in cardiopulmonary supportive care, we remain hopeful for a better understanding of the basic mechanisms of lung injury and repair, the better to guide therapeutic options.

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