ARDS/Severe Sepsis: Do's, Don'ts, and Maybes for the New Age

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Introduction

The acute respiratory distress syndrome (ARDS) was first described in 1967 by Ashbaugh (1) as an entity comprising acute respiratory failure, refractory hypoxemia, poorly compliant (i.e. stiff) lungs, and diffuse bilateral infiltrates on chest radiograph (CXR). Since that time ARDS has been widely recognized in both medical and surgical patients and ARDS accounts for a significant number of intensive care unit (ICU) days in most major hospitals. The incidence of ARDS, using the current definition of the syndrome, is thought to range between 13.5 – 75 per 100,000 population (2).

Multiple clinical risk factors have been identified for the development of ARDS (2) (Table 1).

Table 1

Clinical Disorders Associated with the Development Of the Acute Respiratory Distress Syndrome

Direct Lung Injury	**Indirect Lung Injury**
Common causes	*Common causes*
Pneumonia	Sepsis
Aspiration of gastric contents	Severe trauma with shock and multiple Transfusions
Less common causes	*Less common causes*
Pulmonary contusion	Cardiopulmonary bypass
Fat emboli	Drug overdose
Near-drowning	Acute pancreatitis
Inhalational injury	Transfusions of blood products
Reperfusion pulmonary edema after lung transplantation or pulmonary embolectomy	

However chief amongst these risks, particularly in patients in medical ICUs, is infection. Patients with pneumonia or sepsis from an extrapulmonary site accounted for greater than 60% of individuals with ARDS enrolled in a recent NIH sponsored multi-center trial (Table 2). It is thus reasonable to explore ARDS and sepsis together though it is important to realize that overlap between these entities is incomplete.

Table 2

Causes of ARDS in 902 Patients Participating in ARDS Network Trials (3)

Risk	n	
Sepsis	236	(26%)
Pneumonia	320	(35%)
Aspiration	134	(15%)
Trauma	96	(11%)
Other	116	(13%)

This can be best appreciated by reviewing (Table 3) the definitions for ARDS and the three categories of sepsis related illness (SIRS, sepsis-SIRS, severe sepsis). Many patients with SIRS or sepsis-SIRS lack the requisite pulmonary disease to qualify for a diagnosis of ARDS. In a large recent trial of activated protein C for severe sepsis (4), which will be discussed in a latter section, 53% of patients enrolled had pneumonia and approximately 75% of patients required mechanical ventilation. It would thus be reasonable to assume that a significant number of patients with severe sepsis would also meet criteria for ARDS. This review will focus primarily on patients with ARDS, many of whom would also fit the criteria for severe sepsis. Patients with ARDS/severe sepsis are amongst the most gravely ill individuals in a hospital and are often cared for by specialists trained in either pulmonary/critical care medicine or critical care medicine alone. As such a valid question is whether knowledge of this topic is important for general internists.

Table 3

Definitions

ARDS
- Acute onset
- Bilateral infiltrates on CXR
- PcW ≤18mm or absence of clinical evidence of left atrial hypertension
- PaO_2/F_IO_2 ≤200

Systemic Inflammatory Response (SIRS)
- T >38°C or <36°C
- Heart rate > 90/min
- Respiratory rate >20
- WBC >12,000, <4,000 or with >10% bands

Sepsis-SIRS
- Documented infection

Severe Sepsis
- Sepsis plus at least one organ dysfunction: hypotension, lactic acidosis, oliguria, DIC, hypoxemia

Why is ARDS/Severe Sepsis Management Important to Internists?

A recent survey (5) found that intensivists (predominantly those trained in pulmonary/critical care medicine) provided care to approximately 37% of ICU patients. In another study (6) however care provided in a "closed" ICU setting, where intensivists would play a pre-eminent role was estimated to occur in only 15% of ICU patients. Thus the majority of patients in ICU's nationwide are cared for by non-critical care trained physicians.

There is considerable evidence that care provided by specialists in critical care medicine is associated with improved patient survival when compared to care provided by non-specialists (7-14). A recent analysis of these differences in survival (6) suggested that an excess mortality of between 53,850 – 126,000 lives per year occurs as a result of critically ill patients being cared for by physicians not trained in critical care medicine (Figure 1). Although these figures can clearly be challenged there is no doubt that purchasers of healthcare have recognized that important improvements in outcome occur in ICU settings where trained intensivists are responsible for the management of patients. Indeed intensivists were found to be much more likely to provide care in ICU's with a high proportion of patients (>30%) covered by managed care.

Figure 1

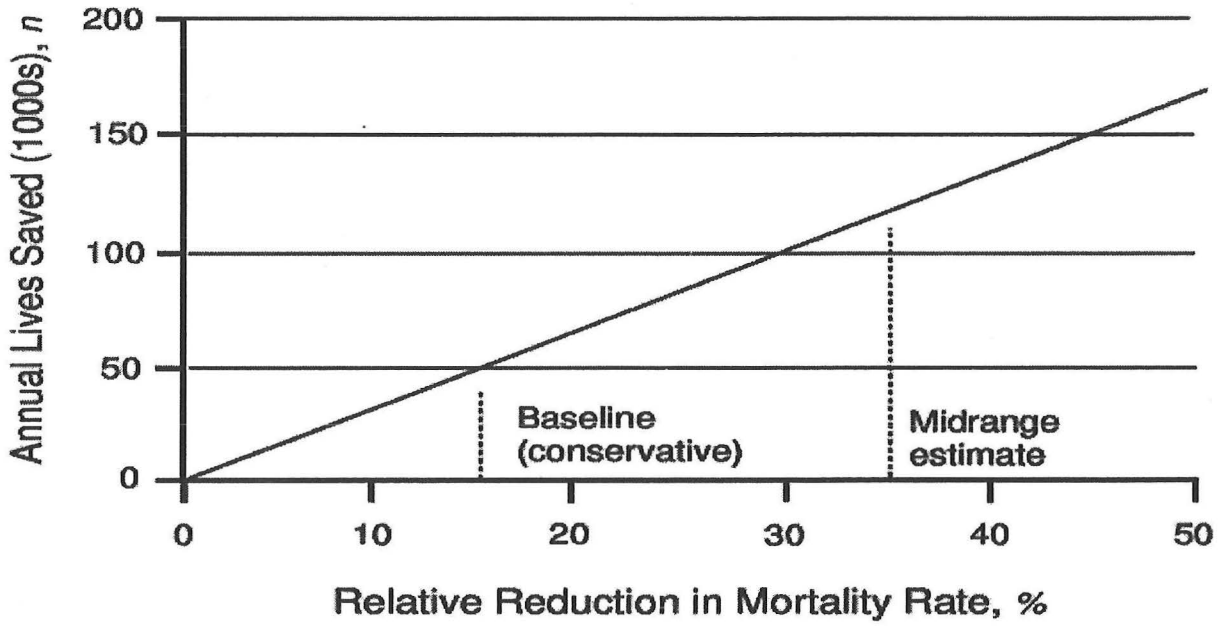

Fig. 1. Lives saved each year in the United States using staffing by trained intensivists. A relative reduction in mortality rate of 35% suggested by 9 separate studies would reduce mortality by 126,000; using a conservative estimate of a 15% reduction in mortality, 53,850 lives/year would be saved (6).

The Leapfrog Group, a consortium of large U.S. healthcare purchasers comprised primarily of Fortune 500 companies, has developed purchasing principles designed to promote safety and healthcare value (15). The Leapfrog Group has identified three "safety" issues and transformed them into essential standards for the purchase of healthcare services from a hospital.

These include a) computerized physician order entry to reduce the risk of adverse drug events, b) minimum requirements in terms of the number of surgical/invasive procedures performed at a hospital given data demonstrating superior outcome at Centers with high volume, and c) that hospital care in the ICU is managed by physicians who are board certified (or eligible) in critical care medicine. It is noteworthy that the Leapfrog Group has specifically indicated that hospitalists are not acceptable as a substitute for board certified critical care physicians (16).

Despite the evidence-based demand for care by trained critical care physicians it is clear that the manpower to provide these trained specialists does not exist. A recent study (17) suggested a growing shortage of specialists trained in pulmonary and critical care medicine (Figure 2). Although manpower surveys are notoriously difficult (18) anecdotal experience, including offers from private practice pulmonary/critical care groups to actually fund additional fellowship slots in return for new associates, suggests that a shortage of trained critical care physicians already exists.

Figure 2

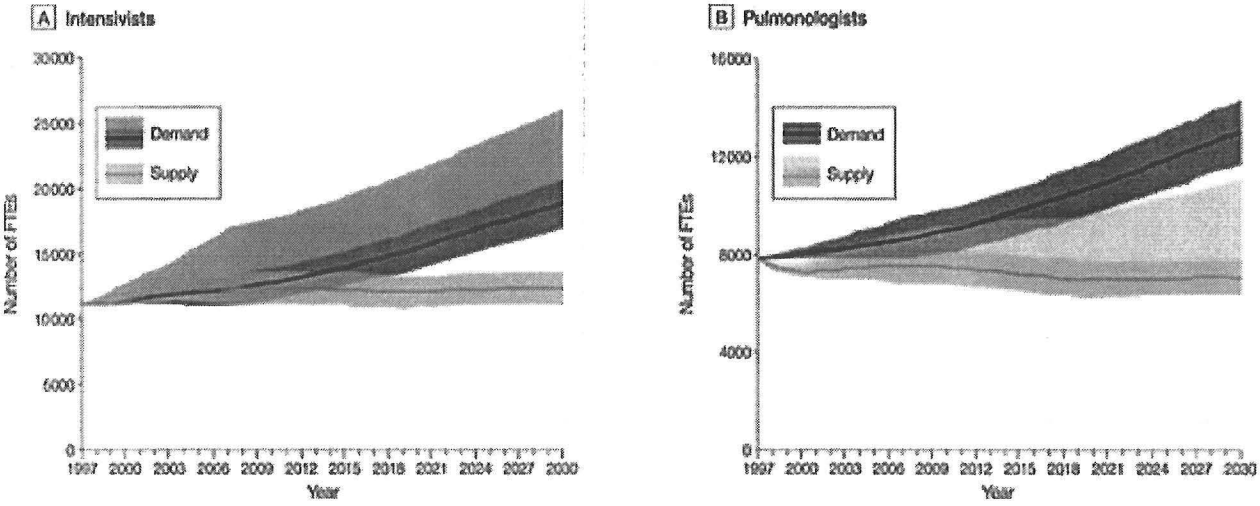

Fig. 2. Balance of supply (lighter shade) and demand (darker shade) for intensivists (A) and pulmonologists (B) in the years 1997-2030. A significant shortage is forecast by 2012 for both groups (17).

Given the improved outcomes associated with ICU care delivered by critical care trained physicians and the likely inability to significantly expand the number of these physicians it is apparent that other types of physicians will have to "pick up the slack". Improving the training of internists in critical care medicine would therefore seem to be a major challenge for American medicine in the years to come. This review will therefore concentrate on three areas of ARDS management where data has suggested that mortality may be altered: ventilator management, use of hemodynamic monitoring to optimize oxygen delivery to tissues, and the use of activated protein C in patients with severe sepsis.

ARDS – Overview of Pathogenesis, Abnormalities of Gas Exchange, Mortality Trends

ARDS is characterized by two distinct phases (2). In the acute or exudative phase patients experience injury to microvascular endothelium and alveolar epithelium resulting in flooding of the air spaces with protein-rich edema fluid. In addition to the deleterious effect of fluid in the air spaces on diffusion of oxygen, proteins such as albumin are capable of inactivating surfactant thus promoting collapse of alveolar units. Recruitment of inflammatory cells promotes further injury to alveolar epithelial cells, which limits the production of surfactant and can lead to transmigration of bacteria from the air space into the bloodstream (19). Marked abnormalities of the coagulation system lead to platelet-fibrin thrombi in the distal vessels of the lung and other organs, and may play a crucial role in the development of multi-organ failure (see below), which is thought to be the major cause of mortality in ARDS. Radiographically the patient develops rapidly progressive infiltrates similar to any form of pulmonary edema.

During the acute phase of ARDS severe hypoxemia, usually refractory to high concentrations of inspired oxygen (F_IO_2) occurs. Two major mechanisms responsible for severe hypoxemia in patients with ARDS have been identified. The first is release of vasomodulatory substances by inflammatory cells. Chief amongst these substances appears to be nitric oxide. Studies utilizing animals where the inducible form of nitric oxide synthase (the enzyme responsible for NO production by inflammatory cells) has been knocked-out has shown a marked attenuation of hypoxemia in experimental models of lung injury (20). This data suggests that inflammatory cells promote increased perfusion at the site of inflamed and presumably poorly ventilated alveolar units, resulting in severe ventilation-perfusion mismatch. The other major contributor to the difficulty in oxygenation is the loss/inactivation of surfactant promoting microatelectasis in alveolar units. This in turn leads to alveolar units which are perfused but not ventilated, resulting in the development of a severe shunt (i.e. a mixture of deoxygenated and oxygenated blood). Physiologically the hallmark of this microatelectasis is a shift of the normal pressure-volume relationship (i.e. the compliance) of the lung (Figure 3). In patients on mechanical ventilators atelectasis occurs in normal lungs at low lung volumes. In order to "pop open" the collapsed units a threshold amount of pressure must be applied. Below this threshold increasing amounts of pressure result in little change in lung volume. Once the threshold has been reached the collapsed units open and lung volume rapidly increases with small increments of pressure. The point at which the slope of the compliance curve of the lung first begins to rapidly increase is referred to as the **lower inflection point**.

Figure 3

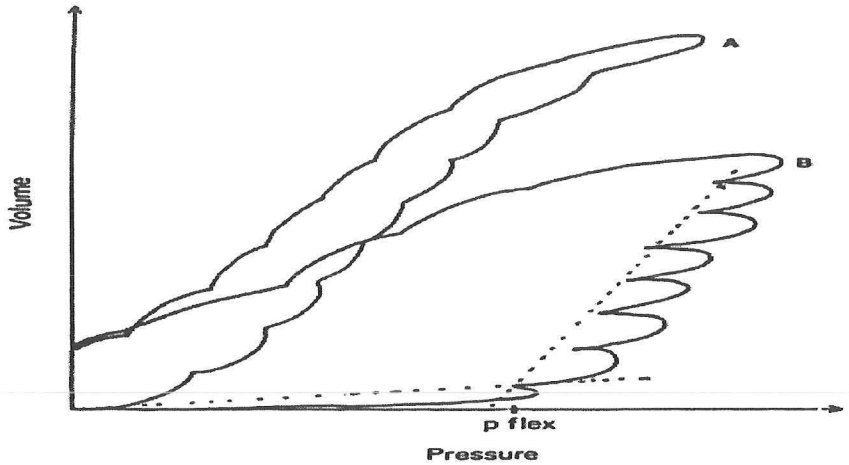

Fig. 3. Compliance curves of normal (A) and experimental, surfactant depleted animals (B). The lower part of each curve is during inspiration and the upper part of each curve is during expiration (the difference is referred to as hysteresis). The lower inflection point (p flex) is shifted to the right in B indicating severe microatelectasis (21).

In patients with ARDS the lower inflection point is shifted to the right. A cornerstone of management is to prevent microatelectasis by causing a higher volume of air to be left in the lung at the end of expiration. This is accomplished by using PEEP (positive end expiratory pressure), a valve which closes and blocks further exhalation when airway pressure drops to the mandated level of PEEP. Use of PEEP results in a marked improvement in oxygenation and a decrease in shunt. Because the limitation to diffusion of carbon dioxide is much less than that of oxygen it is rare for patients in this phase of ARDS to demonstrate marked CO_2 retention, unless it is the result of circulatory collapse or intentional hypo-ventilation (permissive hypercapnea).

The second phase of ARDS, usually beginning 3-4 days into the illness involves the development of fibrosing alveolitis followed by repair. Pulmonary edema resolves and is replaced by an influx of inflammatory and mesenchymal cells, continued pro-coagulant activity, fibrosis and ultimately repair. During this phase hypoxemia may be persistent but is usually less difficult to manage then during the acute phase. Lung compliance may worsen and ventilated areas of the lung may not be perfused owing to thrombi in pulmonary capillaries (i.e. dead space rises) with resultant hypercarbia. It is during this phase of ARDS that pneumothorax may occur in roughly 10% of patients.

Overall there is considerable data to suggest that survival in ARDS has improved over what was observed in major medical centers 10 - 20 years ago. Mortality rates ranging between 40-60% were commonly reported in series from 1980 – 1992 (22-26). Patients with sepsis consistently had mortalities in excess of 50%. In the recent ARDS Net Study (Table 4) mortality was significantly below 50% regardless of risk factor for developing ARDS. A series from Seattle reported that mortality for ARDS was 36% in 1993 compared to 53-68% in the years 1983 – 1987 (27). Similarly data from the United Kingdom disclosed a decline in the mortality rate from 66% in 1990 – 1993 to 34% in the years 1994 – 1997 (28).

Table 4

Mortality Among Patients With Different Clinical Risk Factors for ARDS (2)

Risk Factor	Mortality
Sepsis	102/236 (43%)
Pneumonia	116/320 (37%)
Aspiration	49/134 (11%)
Trauma	11/96 (11%)
Other	41/116 (35%)
Total	319/902 (35%)

Although the reasons for improved survival are likely multiple one major contributor to the improved mortality is thought to be an improved understanding of the uses of mechanical ventilation in ARDS. As will be detailed in the next section this primarily has resulted from a) reappraisal of oxygenation as the primary endpoint in ventilator management, b) refinement of the understanding of ventilator induced lung injury, and c) clinical trials which have demonstrated major benefits in limiting tidal volumes utilized for patients with ARDS.

Ventilator Management of ARDS

Titrating Therapy to Oxygenation

Marked difficulty in oxygenation is a central criteria for diagnosing ARDS. Many, if not all, interventions which have been studied in ARDS have utilized improvement in oxygenation as a primary outcome in measuring benefit. However there is significant data to suggest that oxygenation, at least as determined by the arterial PO_2 or the ratio of PO_2/F_IO_2, has little impact on overall survival.

One study attempted to evaluate the PaO_2/F_IO_2 ratio and mortality in 101 original papers from 1967 – 1994 and found no relationship (Figure 4) between oxygenation and outcome (29).

Figure 4

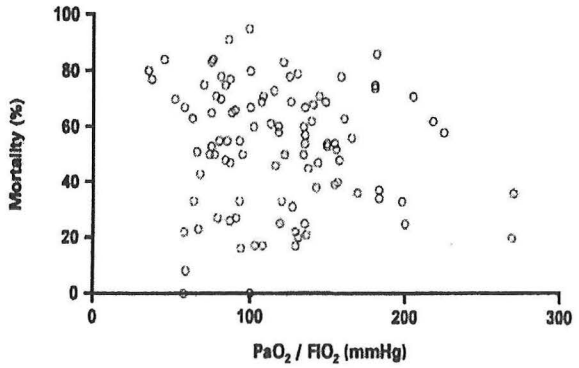

Fig. 4. Correlation between mortality rates and PaO_2/F_IO_2 ratio from data in 101 original papers.

More recently a randomized trial demonstrated a significant improvement in oxygenation when patients were ventilated in the prone position (30), but no benefit in survival. The authors did note in a post-hoc analysis a reduced 10 day mortality in the quartile of patients with the most severe hypoxemia who received prone ventilation, however this benefit did not persist to discharge. Clearly there are patients who succumb as a result of severe, refractory hypoxemia in the early stages of ARDS. Some of these may benefit from a variety of strategies, which are outside the scope of this review, aimed at improving oxygenation to some minimal acceptable level. It is noteworthy that in the ARDS Net trial (31) oxygenation was worse over the first three days utilizing a ventilator strategy which ultimately lead to significantly reduced mortality (see below). As a recent editorial (32) commented "these results highlight the importance of focusing on important clinical outcomes such as mortality rather than on intermediate physiological markers such as hypoxemia".

Ventilator Induced Lung Injury

For most clinicians the term ventilator induced lung injury (VILI) conjures up either oxygen toxicity or barotrauma, such as a pneumothorax. However recent data suggests that barotrauma, while certainly not desirable, does not impact survival in ARDS (33) and there is little prospective data to support the concept that oxygen toxicity plays a major role in modifying the outcome of ARDS. On the other hand significant experimental data has accumulated to suggest that more subtle forms of VILI dramatically impact survival. Abnormalities of lung fluid balance, changes in epithelial and endothelial permeability, and severe ultrastructural changes in alveolar cells, all of which closely resemble that produced by other forms of acute lung injury, have been induced following mechanical ventilation in animals (34).

For the purposes of this review VILI will be divided into two types, low lung volume injury and high lung volume injury, based on the normal lung compliance curve (Figure 5). As previously described there is a lower inflection point, below which microatelectasis occurs. In addition there is an **upper inflection point**, where at higher lung volumes the lung becomes over distended.

Figure 5

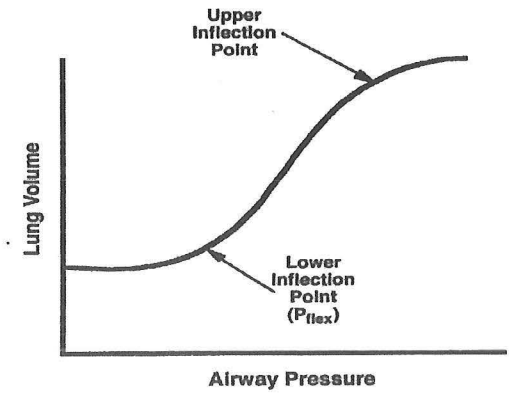

Fig. 5. Static pressure-volume curve. Constructed by administering increasing volumes and measuring corresponding airway pressure in an apneic sedated patient.

In patients on mechanical ventilators a compliance curve can be generated by incrementally increasing the patient's tidal volume and then pausing the ventilator after the breath has been fully delivered but before the patient is allowed to exhale (an inspiratory hold). The resulting pressure that is measured at any given tidal volume is the **plateau pressure**, which reflects both the compliance of the lung and the chest wall. It is very difficult to generate a compliance curve which plots plateau pressure vs. tidal volumes at low tidal volumes unless the patient is paralyzed. Thus finding the lower inflection point is difficult. One method of performing a compliance curve to detect the lower inflection point is called the "super-syringe" method, the patient is paralyzed and hooked up to a large syringe with a pressure transducer rather than a ventilator and a compliance curve generated. Conversely the upper inflection point can be approximated in most patients without resorting to extreme measures. It should be noted that the compliance curve is essentially a mean value; it cannot fully reflect the broad heterogeneity of individual alveolar units.

Low Lung Volume Injury

Normal lungs tolerate mechanical ventilation with physiologic tidal volumes and low PEEP for extended periods of time with no apparent damage. In animals with experimental forms of acute lung injury however repetitive collapse and opening of surfactant depleted alveolar units by using tidal volumes below the lower inflection point lead to marked bronchiolar epithelial necrosis, hyaline membrane formation, decreased compliance and worsening hypoxemia (35). In other models utilizing PEEP to keep the compliance curve above the lower inflection point in surfactant-depleted animals reduced the severity of hyaline membrane formation (21). Some experimental studies have suggested that a high PEEP provided benefits which were greater than the deleterious effects of high PEEP related to over-distending the lung (36).

The use of PEEP in ARDS likely diminishes some of the concern about low lung volume injury. Whether the majority of these patients are actually above the lower inflection point is unclear. In a randomized trial (Table 5) of 53 patients (37) with ARDS who received low tidal volumes there was a suggestion that a ventilator strategy which involved setting PEEP above the lower inflection point (LIP) was associated with an improved survival at 28 days compared to a higher tidal volume lower PEEP group. The mean level of PEEP needed to keep patients 2 cm above the LIP was 16.4 cm over the first 36 hours; patients receiving conventional ventilation had a mean PEEP of 8.7 cm during this time period. Plateau pressures were significantly lower in the high PEEP/low tidal volume group (30 cm) than the conventionally managed group (36.8 cm). A prospective randomized trial is now underway where the super-syringe method is utilized to measure a lower inflection point and PEEP is adjusted accordingly in patients who are also receiving low tidal volumes.

Table 5

Respiratory Values During the First Week Of Mechanical Ventilation (37)

PEEP (cm)	Control	First Hour	36 Hours	Day 2-7
Protective vent	6.2	16.3*	16.4*	13.2*
Conventional vent	6.2	6.9	8.7	9.7
Plateau pressure (cm)				
Protective	32.5	31.8	30.1*	23.9*
Conventional	29.5	34.4	36.8	37.8
Tidal volume				
Protective	661	362*	348*	387*
Conventional	646	763	768	738

*p<0.01

High Lung Volume Injury

A large body of data exists to demonstrate that utilizing a combination of tidal volumes and PEEP which result in lung volumes above the upper inflection point leads to significant lung damage and increased mortality in ARDS (34). Although high volumes are often accompanied by high plateau pressures, experimental data has demonstrated that alveolar over-distension is independently associated with lung injury (Figure 6).

Figure 6

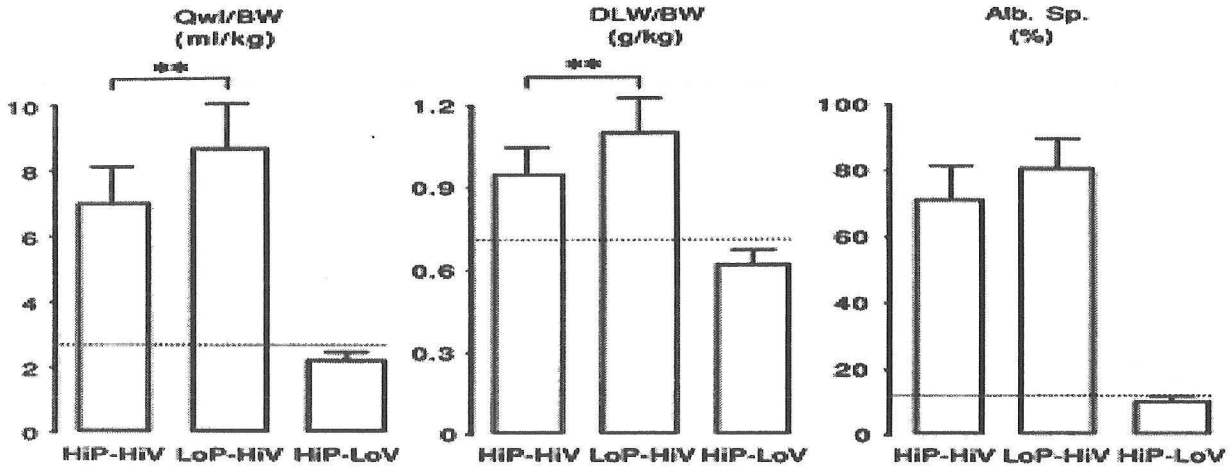

Fig. 6. Comparison of pulmonary edema (extravascular lung water content=Qwl/BW); increasing permeability of pulmonary capillaries (dry lung weight/body weight=DLW/BW); and amount of albumin transuded into the alveolar space (Alb space %) in animals receiving different ventilation strategies. Hip-Hiv=high pressure/high tidal volume; Lop-Hiv=low pressure/high tidal volume; Hip-Lov=high pressure/low tidal volume. The dotted line indicates upper limit of normal. High tidal volumes were independently associated with lung injury (38).

This is of particular importance clinically in terms of the use of PEEP. When tidal volumes are kept constant ventilator induced lung injury resulting in pulmonary edema in an animal model was significantly worsened by higher levels of PEEP (Figure 7), though oxygenation was improved. As discussed in a prior section utilizing oxygenation as a primary endpoint for ventilator management appears to be unjustified. Indeed in some instances maneuvers to improve oxygenation may be deleterious.

Figure 7

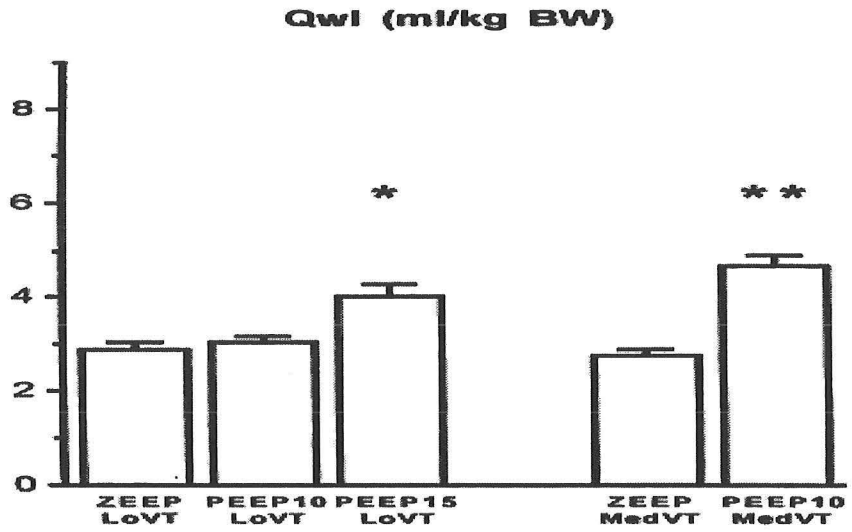

Fig. 7. Effect of increasing PEEP at low tidal volume (7 cc/kg) or medium tidal volume (14 cc/kg) on pulmonary edema (Qwl/BW) in an animal model of lung injury. For any given tidal volume at some level PEEP becomes injurious and can induce pulmonary edema from over-distension (39).

The best determinant of oxygenation in ARDS is mean alveolar pressure (40). Mean alveolar pressure can be increased in patients on mechanical ventilators by three mechanisms: a) increasing the driving pressure delivered by the ventilator (this may be done directly using pressure control ventilation where the patient receives a predetermined amount of pressure (Pset)), b) increasing the duration of the delivered positive-pressure breath (increasing the ratio of inspiratory time/expiratory time) or c) by increasing total PEEP. As can be appreciated from the lung compliance curve, at some point an increased alveolar pressure will result in the patient being above the upper inflection point. Oxygenation may be improved but the risk of lung injury is magnified.

The use of high tidal volumes has been demonstrated to result in significantly elevated local production of many pro-inflammatory cytokines including IL-6, TNF and IL-1 (41, 42). Although these cytokines may not directly impact survival their increased production demonstrates that the changes induced by high tidal volumes are not inert. Furthermore, production of TNF may be responsible for the evidence of an acute increase in epithelial cell apoptosis in ARDS, a situation which would be expected to exacerbate alveolar integrity (43, 44). High tidal volumes in experimental models has also been demonstrated to lead to bacterial transmigration from lung into the blood stream (45).

Clinical Trials of "Lung Protective" Ventilator Strategies

Several important studies have now demonstrated that ventilator strategies designed to limit hyperinflation have a profound impact on survival in ARDS (2, 31, 37, 46). It is noteworthy that the added monetary cost of these strategies is essentially zero. Studies have utilized either limited tidal volumes or have adjusted ventilator settings to keep plateau pressures below pre-determined levels, presumably to avoid surpassing the upper inflection point.

A landmark study in ARDS patients in 1995 (47) titrated PEEP to the lower inflection point and then adjusted tidal volumes in a stepwise fashion (Figure 8a). This study revealed that the percentage of patients exceeding the upper inflection point (UIP) increased exponentially over a narrow range of tidal volumes; at 5.5 ml/kg all patients were below the UIP while 50% and 75% exceeded it at tidal volumes of 8 and 8.5 ml/kg respectively (Figure 8b).

Figure 8

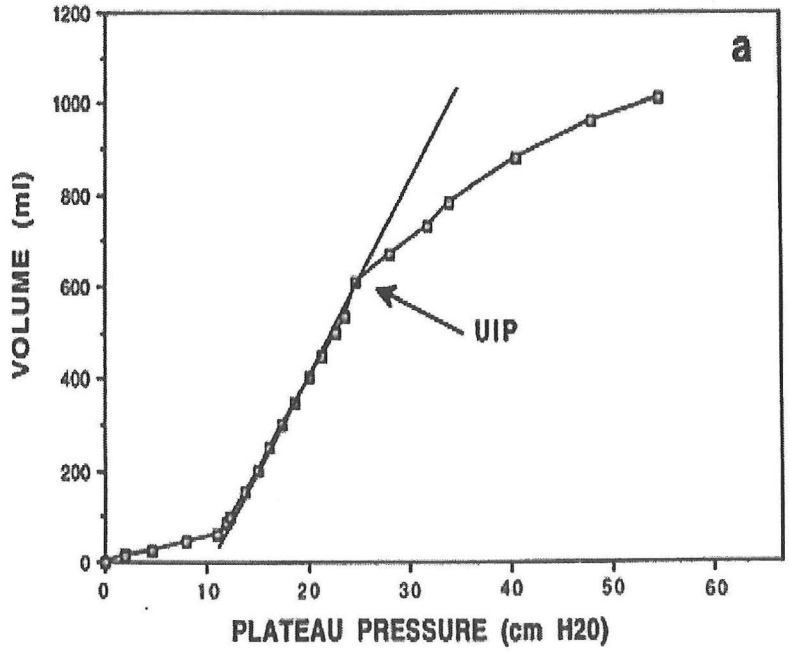

Fig. 8. **a)** Pressure-volume curve defining both the lower and upper inflection point (UIP) in an individual patient with ARDS.

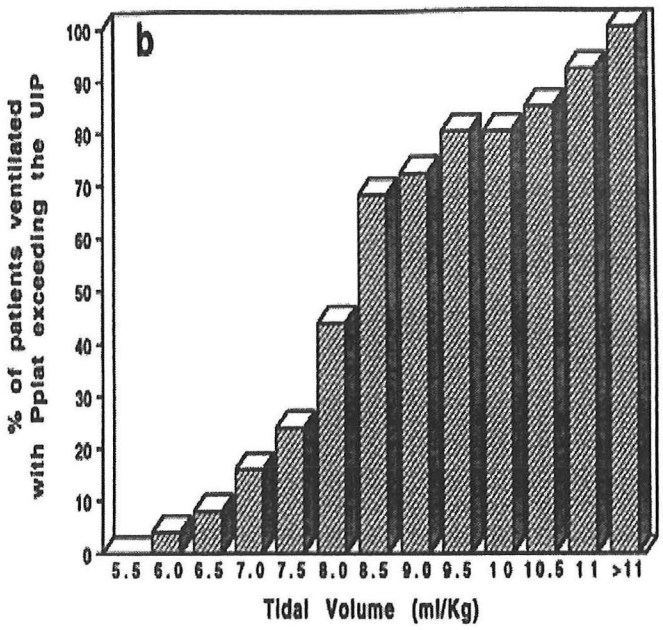

Fig. 8. **b)** Percentage of ARDS patients exceeding the UIP at any given tidal volume. PEEP was set to keep patients above the lower inflection point (47).

These observations were utilized in the design of several controlled trials of lung protective ventilation in ARDS (2, 31, 37, 48-50), the most prominent of which is the ARDS Net Study (31). Before discussing this trial it is important to realize that the concept of lung protective ventilation has only recently gained acceptance. A prominent editorial in 1998 (51) stated "The routine use of tidal volumes of less than 10 ml/kg is not necessary or warranted in the great majority of patients with acute lung injury".

The ARDS Net Study randomized patients to two groups. The first received an initial tidal volume of 12 cc/kg of **predicted body weight**[1] and required plateau pressures to be lower than 50 cm. The second group received an initial tidal volume of 6 cc/kg of predicted body weight and required plateau pressures to be <30 cm. It should be noted that using this formula for predicted body weight, measured weight usually exceeded predicted weight by 20%.

The trial was stopped after the enrollment of 861 patients because mortality was significantly (P<0.007) decreased in the low tidal volume group (31%) compared to the high tidal volume group (39.8%) (Figure 9). A subsequent analysis revealed that regardless of clinical risk factor (sepsis, pneumonia, aspiration, trauma, other) total mortality was reduced in the low tidal volume (LTV) group.

[1]*Predicted body weight:

Men	50+	0.91 (height (cm) – 152.4)
Women	45.5+	0.91 (height (cm) – 152.4)

Figure 9

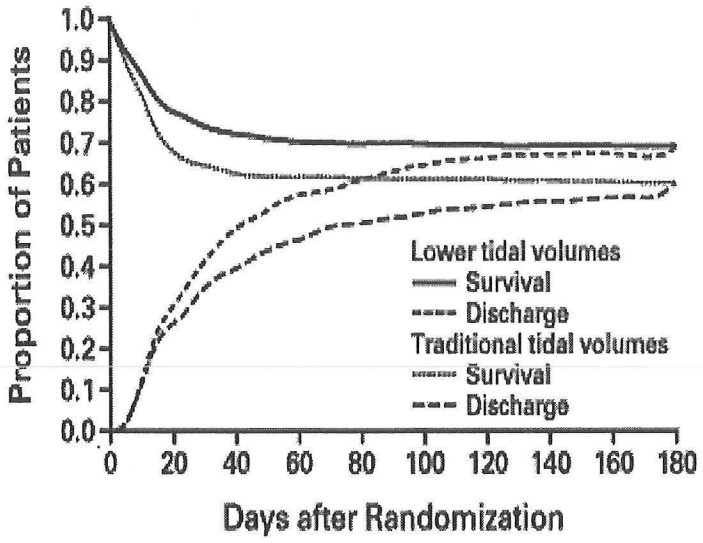

Fig. 9. Comparison of survival and hospital discharge in patients receiving low tidal volumes or traditional tidal volumes in the ARDS Net Study. A significant survival benefit was found in the low tidal volume group (31).

Several important pieces of data emerged from analysis of this trial (Table 6). First, plateau pressures were markedly lower in the LTV group. Second, a vigorous attempt to maintain a normal pH and PCO_2 in the LTV group required a respiratory rate of nearly 30 breaths/minute. Third oxygenation, as measured by the pO_2/F_IO_2 was worse in the LTV group. Fourth the level of PEEP utilized in both groups (8.6 – 9.4 cm) was lower than commonly used in such patients, and likely resulted in some patients being below the lower inflection point.

Table 6

RESPIRATORY VALUES DURING THE FIRST SEVEN DAYS OF TREATMENT IN PATIENTS WITH ACUTE LUNG INJURY AND THE ACUTE RESPIRATORY DISTRESS SYNDROME.*

VARIABLE	DAY 1		DAY 3		DAY 7	
	GROUP RECEIVING LOWER TIDAL VOLUMES	GROUP RECEIVING TRADITIONAL TIDAL VOLUMES	GROUP RECEIVING LOWER TIDAL VOLUMES	GROUP RECEIVING TRADITIONAL TIDAL VOLUMES	GROUP RECEIVING LOWER TIDAL VOLUMES	GROUP RECEIVING TRADITIONAL TIDAL VOLUMES
Tidal volume (ml/kg of predicted body weight)	6.2±0.9	11.8±0.8	6.2±1.1	11.8±0.8	6.5±1.4	11.4±1.4
No. of patients	387	405	294	307	181	179
Plateau pressure (cm of water)	25±7	33±9	26±7	34±9	26±7	37±9
No. of patients	384	399	294	307	168	173
Peak inspiratory pressure (cm of water)	32±8	39±10	33±9	40±10	33±9	44±10
No. of patients	382	401	295	308	178	177
Mean airway pressure (cm of water)	17±13	17±12	17±14	19±17	17±14	20±10
No. of patients	369	385	288	301	176	173
Respiratory rate (breaths/min)	29±7	16±6	30±7	17±7	30±7	20±7
No. of patients	389	406	296	308	185	181
Minute ventilation (liters/min)	12.9±3.6	12.6±4.5	13.4±3.5	13.4±4.8	13.7±3.8	14.9±5.3
No. of patients	387	401	296	307	182	177
FiO_2	0.56±0.19	0.51±0.17	0.54±0.18	0.51±0.18	0.50±0.17	0.54±0.20
No. of patients	390	406	296	308	185	181
PEEP (cm of water)	9.4±3.6	8.6±3.6	9.2±3.6	8.6±4.2	8.1±3.4	9.1±4.2
No. of patients	390	406	296	308	185	181
PaO_2:FiO_2	158±73	176±76	160±68	177±81	165±71	164±88
No. of patients	350	369	284	297	148	160
PaO_2 (mm Hg)	76±23	77±19	74±22	76±23	73±17	75±21
No. of patients	350	369	284	297	148	160
$PaCO_2$ (mm Hg)	40±10	35±8	43±12	36±9	44±12	40±10
No. of patients	351	369	285	297	147	160
Arterial pH	7.38±0.08	7.41±0.07	7.38±0.08	7.41±0.07	7.40±0.07	7.41±0.08
No. of patients	351	369	285	297	148	160

*Plus–minus values are means (±SD) of the values recorded between 6 and 10 a.m. on days 1, 3, and 7 after enrollment. The numbers of patients refers to those who were receiving ventilation and for whom data were available. FiO_2 denotes fraction of inspired oxygen, PEEP positive end-expiratory pressure, PaO_2 partial pressure of arterial oxygen, and $PaCO_2$ partial pressure of arterial carbon dioxide. All differences between study groups were significant on each day ($P<0.05$) except for mean airway pressure on days 1, 3, and 7; the PaO_2:FiO_2 on day 7; minute ventilation on days 1 and 3; pH on day 7; and PaO_2 on days 1, 3, and 7.

The emerging consensus that VILI may contribute to multi-organ failure (32) and death in patients with ARDS has raised interest anew in strategies of gas exchange which would avoid the use of mechanical ventilators. The use of extracorporeal membrane oxygenators (ECMO) has been studied in several series (52-55), most of which lacked adequate controls. A randomized trial (56) in the United States found no benefit in survival when ECMO was utilized with a strategy of extremely low tidal volumes (~3 ml/kg) and high PEEP (~24 cm). Given the lack of practicality and expense it is unlikely that further large trials of ECMO will be performed.

From the preceding section it is possible to compile a brief list of Do's, Don'ts, and Maybes relating to ventilator management in ARDS:

DO
Keep tidal volumes between 6-7 cc/kg
Keep plateau pressure <32 cm
Use moderate levels of PEEP

DON'T
Overly titrate therapy to indices of oxygenation;
sats of 88% or more are sufficient

MAYBE
Set PEEP at the lower inflection point
Keep pH normal

These recommendations are not based on improving gas exchange but on the improved survival demonstrated in ARDS patients with lung protective strategies.

Use of Hemodynamic Monitoring to Optimize Oxygen Delivery to Tissues

The level of arterial pO_2 is only one index of oxygenation. Indeed oxygen dissolves poorly into blood and delivery of oxygen to tissues is largely dependent on binding of O_2 to hemoglobin and the delivery of blood to peripheral tissues by the cardiovascular system. As such indices of oxygen delivery might correlate better with survival in ARDS than a simple measurement of arterial pO_2 or the pO_2/F_IO_2 ratio.

Systemic oxygen delivery (SOD) is dependent on the cardiac output x the arterial O_2 content (where arterial O_2 content/100 ml = (1.39 x Hgb (gm/dl) x % Hgb saturation). The desire to determine whether SOD is appropriate in individual patients with ARDS or severe sepsis has been a major theme over the past two decades and has been referred to as "the holy grail of critical care medicine" (57).

Although many tools have been utilized to assess the adequacy of oxygen delivery to tissues (58-61), the most practical tool has been the placement of a thermodilution right heart catheter (RHC). This allows measurement of cardiac output, intravascular pressures, and mixed venous oxygen saturation; all of these in theory might provide useful information concerning the adequacy of cardiac function, intravascular volume status, and the balance between oxygen delivery and the demand of peripheral tissues for oxygen.

There are several theoretical reasons why utilizing a RHC to follow some index of SOD might be appropriate in ARDS. First, positive pressure ventilation with PEEP has been shown to reduce cardiac output in some patients while simultaneously improving arterial pO_2 (2). Second, altered myocardial contractility is well described in severe sepsis (62). Third, assessment of hemodynamic variables has been shown to improve outcomes in patients with severe heart failure (63).

Relationship of Systemic Oxygen Delivery and O_2 Utilization (Consumption)

Significant data generated during the 1980's suggested that SOD in patients with ARDS/severe sepsis might be too low (64). In normal individuals (Figure 10) for any given physiological state (rest, exercise, etc.) there is a critical level of oxygen delivery below which oxygen consumption is limited. In this setting tissues must respire anaerobically, usually resulting in a lactic acidosis. Above this level of SOD further O_2 consumption does not occur. Thus in normals a plateau occurs where further increases in SOD do not result in further utilization of oxygen.

Figure 10

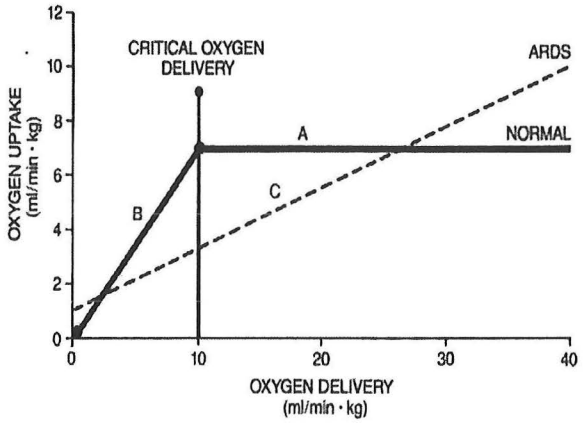

Fig. 10. Oxygen uptake-oxygen delivery relationships in normal subjects and in patients with ARDS (64).

In some patients with ARDS however a plateau is never seen. Oxygen consumption continues to be driven by increases in SOD, perhaps suggesting that SOD is limiting the ability of cells to respire aerobically. Curiously a lactic acidosis is not reliably present in these patients (65). Some investigators actually theorized that an "oxygen debt" existed in ARDS patients (66) and that if SOD could be increased the patients would have enhanced clinical outcomes. However the relationship between SOD and O2 consumption in ARDS is far more complicated than suggested by Figure 10. First, these relationships occur on an individual cellular level and are likely heterogeneous; measurements by RHC cannot adequately reflect these events. Secondly, patients with ARDS demonstrate a heterogeneous relationship between SOD and O_2 consumption.

A classic investigation by Danek and colleagues in 1980 (67) demonstrated that two groups of patients with ARDS were defined based on the response to increased SOD. In one group of patients relationships were similar to that seen in normal individuals (Figure 11); above some crucial level of SOD no correlation existed between SOD and oxygen consumption. Analysis of mixed venous oxygenation revealed a relationship observed in normal individuals as well. As cardiac output (and thus SOD) increased mixed venous pO_2 increased, reflecting that O_2 consumption was not driven by providing more oxygen. This is a relationship seen not only in normal individuals but in those with cardiogenic or hypovolemic shock.

Figure 11

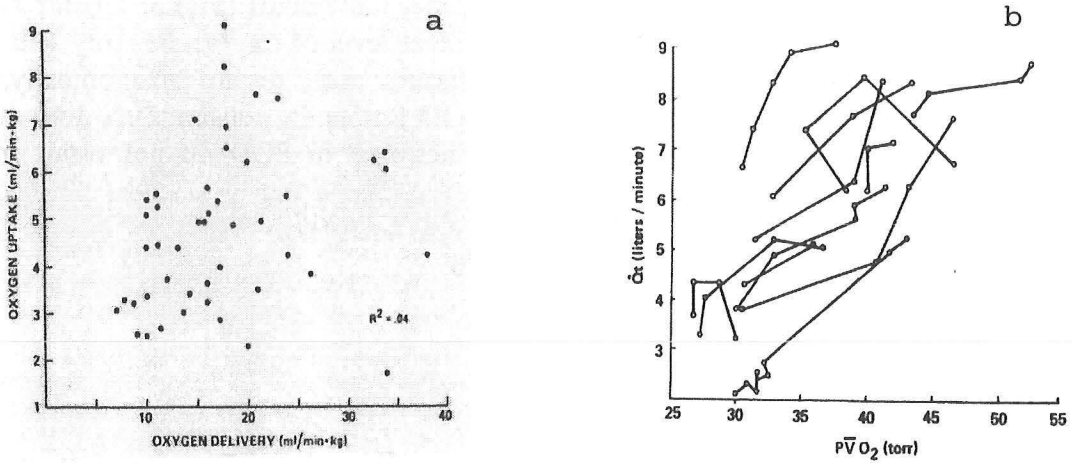

Fig. 11. **a)** Above a critical level of oxygen delivery one group of patients with ARDS demonstrated no relationship between increasing SOD and increasing oxygen uptake (consumption), similar to that seen in normals/cardiogenic/hypovolemic shock **b)** Mixed venous pO_2 in these patients directly reflected changes in cardiac output. Data for individual patients is shown by each line (67).

In contrast (Figure 12) another group of patients with ARDS demonstrated a direct correlation between SOD and oxygen uptake, never reaching a plateau value. In these patients multiple relationships were observed between cardiac output and mixed venous pO_2. In some patients the normal direct relationship was seen. In others oxygen consumption driven by SOD resulted in a decline in mixed venous pO_2 as cardiac output increased. In still others no discernible change in mixed venous pO_2 was observed with changes in cardiac output, implying that oxygen was extracted down to the same level regardless of delivery.

Figure 12

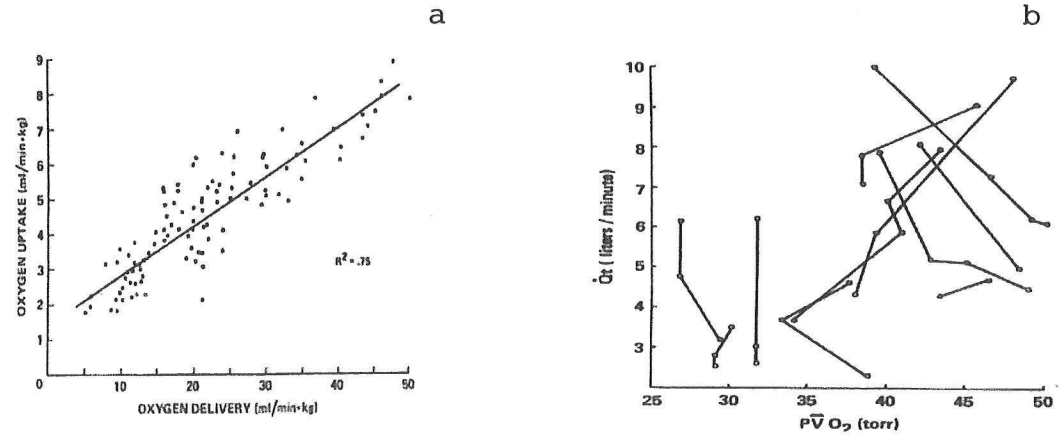

Fig. 12. **a)** A second group of patients with ARDS demonstrated that oxygen consumption was driven by increasing oxygen delivery. Each point represents a data set in an individual patient. **b)** In this group the mixed venous pO2 did not reliably reflect changes in cardiac output (or SOD). Individual patients are represented by each line (67).

Taken together these observations demonstrate that **in patients with ARDS** as opposed to normal individuals or patients with cardiogenic/hypovolemic shock **mixed venous O_2 does not reliably reflect the adequacy of oxygen delivery**.

Clinical Trials of Increased SOD in ARDS/Sepsis

The concept of "oxygen debt" has lead to several clinical trials where maneuvers were undertaken to increase SOD by either increasing cardiac output or arterial oxygen content (usually by increasing hemoglobin). These studies were designed with the hypothesis that increasing SOD would be beneficial. As will be reviewed below these studies are largely consistent and suggest that increasing SOD in ARDS may be deleterious to survival.

Vasodilation with prostacyclin (PGI_2) effectively increased cardiac index in all patients with ARDS (66). Two groups of patients were identified in this trial similar to that observed by Danek. In one group increasing SOD had an insignificant impact on oxygen consumption. All of these patients survived. In the other group oxygen consumption was markedly increased following administration of prostacyclin. All of these patients died. Although the authors concluded that evidence of an "oxygen debt" portended a poor outcome in ARDS they could not exclude the possibility that increasing SOD actually contributed to the patient's demise.

A second study (68) utilized PGE_1 in a randomized double blind study in patients with ARDS. This study was supported by the manufacturer of the drug and was terminated prematurely when it was clear that no benefit would be seen. In fact an analysis of the data clearly shows a worse outcome in the 50 patients "unloaded" with PGE_1 compared to controls which almost certainly would have been significant if the original enrollment goals of the study were reached (Figure 13). Patients receiving PGE_1 demonstrated a significant increase in SOD and a smaller increase in oxygen consumption, likely reflecting the presence of the two different subsets of ARDS patients seen in the two prior studies.

Figure 13

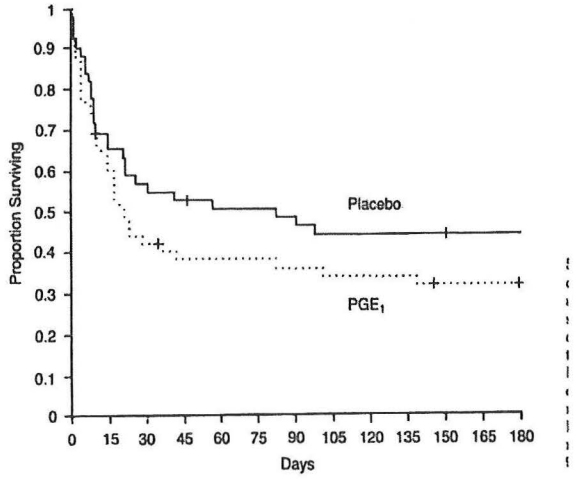

Fig. 13. Survival curve for the 50 PGE_1-treated patients and 50 placebo-treated patients.

A third study (69) utilized dobutamine to boost SOD in a heterogeneous group of critically ill patients. Importantly upon entry into this trial patients received an attempt at volume expansion. If cardiac index, SOD, and oxygen consumption were increased by volume expansion alone the patients were not entered into the trial. Of the 109 patients screened 9 improved with fluid alone, all survived. For the remaining patients who received Dopamine, therapy was titrated to achieve a cardiac index >4.5 L/minute/m^2SOD>600 ml/min/m^2, or oxygen consumption >170 ml per minute. Fifty patients were enrolled in the treatment or control groups (Figure 14), change in survival was significantly better in the control group. Indeed in the subset of patients with septic shock the control mortality was 52%; in the treatment group it was 71%. In the group with ARDS mortality was 67% in the control group and 81% in the treatment group.

Figure 14

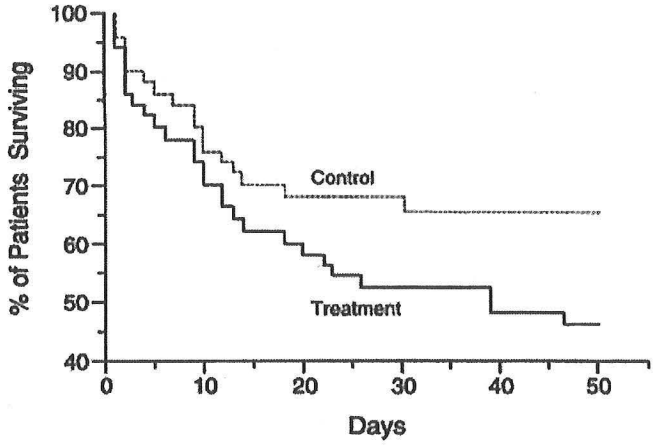

Fig. 14. In-hospital survival of critically ill patients (a majority with ARDS or severe sepsis) who received treatment designed to increase SOD (treatment) or control. Both in-hospital and in-ICU mortality was greater in the treatment group (p=0.04). Excess mortality occurred late and was attributed to multi-organ failure (69).

One other study (70) utilized a variety of therapeutic interventions with pressors/vasodilations to achieve either a supranormal cardiac index or a normal mixed venous O_2 saturation in a heterogeneous group of critically ill patients. No survival benefit was seen when either a supranormal cardiac index or a normal mixed venous O_2 sat was achieved.

To summarize these trials it is clear that no benefit is derived from increasing SOD or trying to keep mixed venous oxygenation normal in patients with ARDS. Indeed as stated by the authors of one of these reports (69) "contrary to what might have been expected, our results suggest that in some cases aggressive efforts to increase oxygen consumption may have been detrimental".

Further data to support this concern may be provided by a large study of transfusion strategies (71) in a diverse group of critically ill patients. Improved outcomes were observed in patients with hemoglobins kept between 7-9 gm/dl compared to those transfused to hemoglobins between 10-12 gm/dl, though the mechanisms for this benefit are likely multiple.

The mechanisms by which increasing O_2 delivery or consumption could contribute to reduced survival are unclear. Certainly increasing cardiac output may have an associated cardiac morbidity though the observation that patients who increased cardiac output without increasing O_2 consumption survived (66) suggests that it is the increased consumption of oxygen which is deleterious. A variety of toxic oxygen species produced in sepsis including peroxynitrite, which is capable of poisoning mitochondria and uncoupling oxidative phosphoylation, may be increased as more oxygen is consumed in this setting (72).

Use of Right Heart Catheters in ARDS

Multiple studies have tried to address whether the use of RHC in critically ill patients is associated with an increase in mortality (73-76). Truly randomized studies have been difficult, indeed one attempt at a controlled study in Canada was halted when only a third of eligible patients were entered.

Perhaps the best study addressing this issue (77) utilized complicated mathematical strategies to equilibrate the severity of illness between patients who received RHC and those who did not. The results demonstrated a significant increase in mortality for patients receiving RHC, which was particularly seen in patients with acute respiratory failure (Figure 15). Although earlier studies were concerned with procedural complications related to RHC (78, 79) there is little data to suggest that this significantly impacts mortality (80).

Figure 15

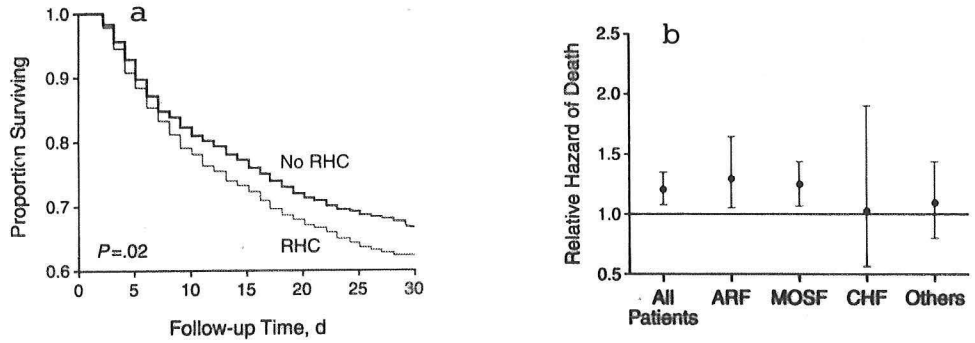

Fig. 15. **a)** Thirty-day survival curves for 2016 patients matched for disease category and propensity score (a multivariate index of severity of illness) who either received right heart catheters (RHC) or did not (No RHC). Survival was significantly better in the population without RHC. **b)** The 95% confidence intervals for relative hazard of death associated with RHC in 5735 patients (all patients); 1789 patients with acute respiratory failure (ARF), 2480 patients with multiorgan system failure (MOSF), 456 patients with congestive heart failure (CHF) and 1010 patients with other conditions (77).

Utilization of a RHC may lead to significant changes in therapy. In one recent study (80) of patients with acute lung injury use of RHC was associated with a change in one or more therapeutic interventions (fluids, vasopressors/vasodilators, diuretics) in 78% of patients. Given the data presented in the preceding section it could be argued that changes in therapy which lead to increased SOD might contribute to increased mortality. In any event there is no data to

suggest that such maneuvers are beneficial. Furthermore it is apparent from several studies that use of the pulmonary capillary wedge pressure (PCWP) to assess volume status in patients with ARDS is seriously flawed. For multiple reasons, including reflection of alveolar rather than vascular pressures and compression of the microvasculature by interstitial edema (81) (Figure 16) the PCWP frequently over-estimates true left atrial pressure. Use of diuretics based on an elevated PCWP in this setting may be unwise.

Figure 16

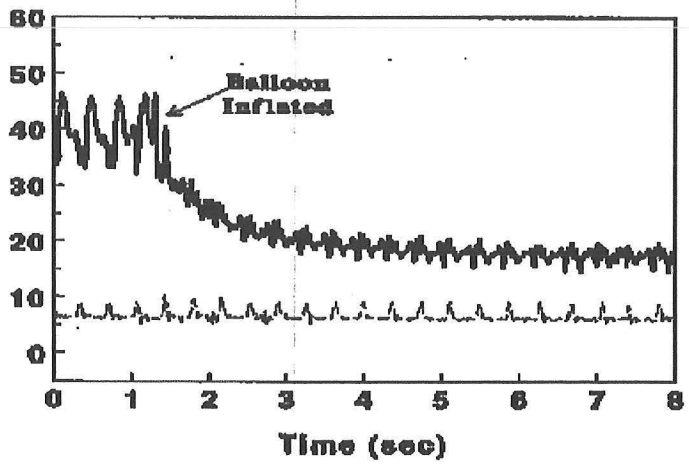

Fig. 16. Discrepancy between left atrial pressure (lower curve) and pulmonary capillary wedge (PcW) pressure (top curve) in an animal model of sepsis-induced ARDS. In control animals (not shown) the PcW and left atrial pressure were identical 3 seconds after catheter balloon inflation (81).

From the preceding data another set of Do's, Don'ts and Maybes in ARDS/Severe Sepsis can be generated:

DO

Use common sense in assessing adequacy of oxygen delivery and using pressors

DON'T

Titrate therapy to obtain a "satisfactory" mixed venous pO_2

Increase cardiac output or SOD unnecessarily

MAYBE

Leave the RHC in its package

Activated Protein C in ARDS/Sepsis

A variety of procoagulant mechanisms have been implicated in the pathogenesis of ARDS and severe sepsis. Most pro-inflammatory cytokines such as TNF, IL-1 and IL-6 are capable of activating the coagulation pathway and inhibit fibrinolysis (82). Deposition of fibrin and evidence of increased fibrin turnover have been demonstrated in the lungs in ARDS (83). Extravascular fibrin deposition is marked in alveolar and interstitial compartments during the evolution of ARDS (84) and can also occur in both lung microvasculature and larger pulmonary arteries (85). Similarly endotoxin promotes coagulation and fibrin deposition by increasing the expression of tissue factor, which is capable of directly activating the extrinsic coagulation pathway. Recently considerable attention has focused on the use of activated protein C (APC) to promote fibrinolysis in patients with severe sepsis, many of whom have ARDS. Clinical trials have also been conducted with recombinant tissue factor inhibitor, though the results are preliminary (86) and will not be covered at present.

Function of APC

Activated protein C is converted from its precursor protein, protein C, by thrombin coupled to thrombomodulin (87). Once activated APC inhibits coagulation factors V_a and $VIII_a$, thus blunting coagulation. In addition APC inhibits two proteins (plasminogen activator inhibitor 1 and thrombin-activatable fibrinolysis inhibitor) which block fibrinolysis. Thus APC both inhibits coagulation and promotes fibrinolysis.

During sepsis conversion of protein C to APC is impaired as thrombomodulin is down regulated by a range of pro-inflammatory cytokines (88). Reduced APC levels have been reported in several series of septic patients (Figure 17) (89). Serial measurements of APC have been shown (90-93) to have prognostic significance in septic patients with survivors exhibiting a progressive normalization of levels. Animal models of gram-negative sepsis have suggested that administration of APC improved survival in gram-negative sepsis (94) and a recent report in humans demonstrated that APC improved outcomes in severe meningococcemia (95).

Figure 17

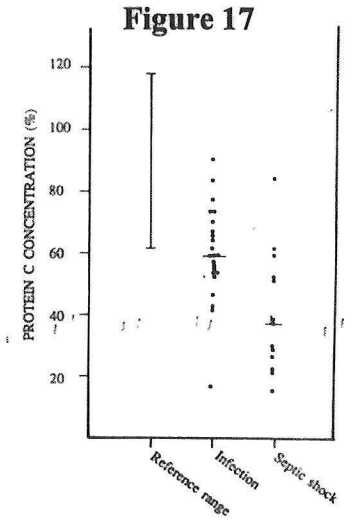

Fig. 17. Concentration of protein C in patients with severe infection (n=24)

and septic shock (n-13). Reference ranges and median values are indicated.

Other effects of APC have also been demonstrated including inhibition of pro-inflammatory cytokines, decreased expression of adhesion proteins, and inhibition of NFκB.

The transcription factor nuclear factor Kappa-B (NFκB) is an important second messenger for many pro-inflammatory cytokines and may play an integral role in the mortality of sepsis. Enhanced NFκB expression was associated with decreased survival in a small series of septic patients (96). Gene transfer of the inhibitor of NFκB (IκBalpha) in a murine model of endotoxic shock reduced NFκB activity, decreased tissue factor production and increased survival (96). APC directly suppressed expression of the p50 and p52 subunits of NFκB in endothelial cells (97), resulting in the blockade of NFκB activity and a dose dependent suppression of numerous adhesion molecules. In addition APC affected several proteins involved in apoptosis, including Bcl-2 homologue protein and inhibitor of apoptosis protein. APC ameliorated both TNF and staurosporine-induced apoptosis in endothelial cells. Thus in addition to direct effects on procoagulant/anticoagulant balance APC has important properties in down-regulating inflammation and promoting cell survival.

Use of APC in Severe Sepsis

The PROWESS Study (4) randomized 1690 patients with severe sepsis to receive either placebo or recombinant APC (drotrecogin alfa activated) by intravenous infusion for 96 hours. The primary and point was death from any cause and was assessed at 28 days after the start of the infusion (Figure 18). The trial was terminated prematurely because of a highly significant survival benefit during the second interim analysis.

Figure 18

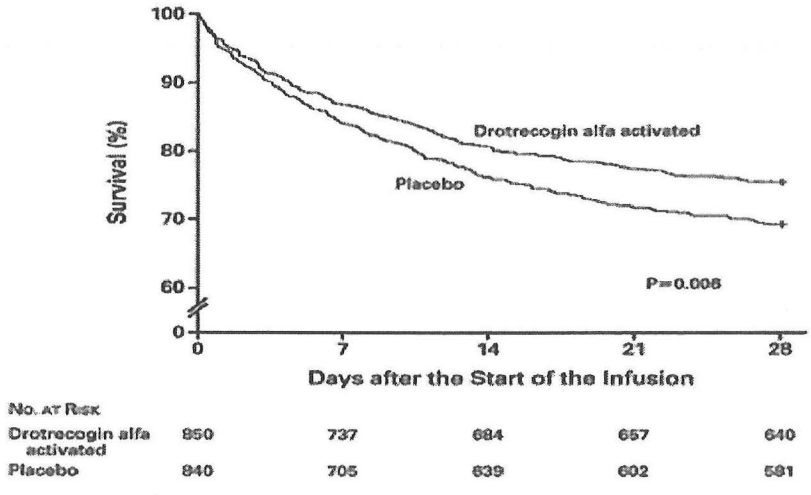

Fig. 18. Survival in patients with severe sepsis receiving activated protein C (Drotrecogin alfa activated) or placebo (4).

Between 79-83% of patients had protein C deficiency at entry into the trial. A highly significant (P<0.009) reduction in mortality was observed in the group of patients with protein C deficiency who received APC. In contrast, though a trend towards improved mortality was observed in patients who did not have protein C deficiency, this did not reach statistical significance (p=0.06).

Patients with marked thrombocytopenia (<30,000), HIV-AIDS (CD4<50), chronic renal failure requiring hemodialysis, recent GI hemorrhage, severe trauma, or severe liver disease were excluded from the trial. Plasma D-dimer levels dropped significantly during the four day infusion of APC, but then began to rise again (Figure 19). It is noteworthy that a mean of 18 hours transpired before the clinical onset of first organ dysfunction and the time of initial infusion of APC. This would suggest that time exists to gather data, perhaps regarding the level of protein C, prior to administering the drug. Overall, the rate of complications was similar in the control and treatment groups though the incidence of serious bleeding (3.5%) was higher in the APC group than controls (2.0%).

Figure 19

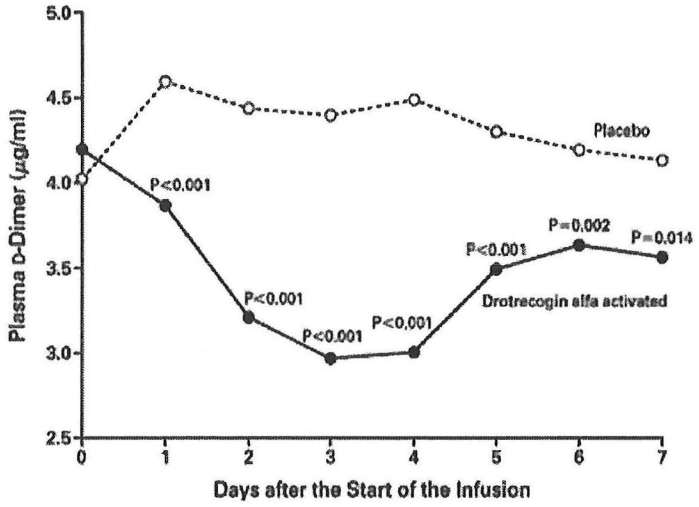

Figure 19. Plasma D-dimer levels in patients receiving APC or placebo. Infusion of APC occurred over the first 4 days (4).

From the PROWESS Study it is possible to classify APC therapy as both a DO and a MAYBE. Clearly this will be an expensive therapy, though the cost is unknown. The drug will be manufactured under the trade name Xigris, and a decision about FDA approval is imminent. It will be important to have rigid criteria, both inclusion and exclusion, for using this drug. However the experimental basis for using APC is sound and the clinical data for using APC in severe sepsis encouraging. Whether APC will be useful in ARDS from etiologies other than sepsis remains to be seen (98, 99).

Conclusion

Significant reductions in mortality have been observed over the last decade in patients with ARDS. Enhanced understanding of VILI, the relationship between oxygen delivery, oxygen consumption and mortality in ARDS and the role of APC have led to clinical trials that provide firm evidence on which to base management of patients in the ICU. The progress seen in this disease has demonstrated that successful clinical trials can be performed in critically ill patients, whose mortality might be expected to be significant regardless of management. Although considerable mortality remains, proper management can clearly improve survival. As such physicians caring for critically ill patients with ARDS/severe sepsis would be wise to remember the words of John Adams:

"We cannot insure success, but we can deserve it".

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