

ARDS – A Brief Overview

Lucas Pitts, M.D.

Assistant Professor of Medicine

Pulmonary and Critical Care Medicine

University of Kansas School of Medicine

Outline

- Definition of ARDS
- Epidemiology of ARDS
- Pathophysiology of ARDS
- Ventilator management strategies
 - Low tidal volume ventilation
 - Permissive hypercapnia
 - Open lung ventilation
 - Recruitment maneuvers
 - Prone ventilation
 - High frequency ventilation
- Non ventilatory and novel therapies

Introduction

- Condition first described in 1960s
 - Described by military clinicians in Vietnam as “shock lung”
 - Simultaneously described as “adult respiratory distress syndrome”
- Terminology changed when it was discovered that persons of any age could be affected
 - “acute respiratory distress syndrome”

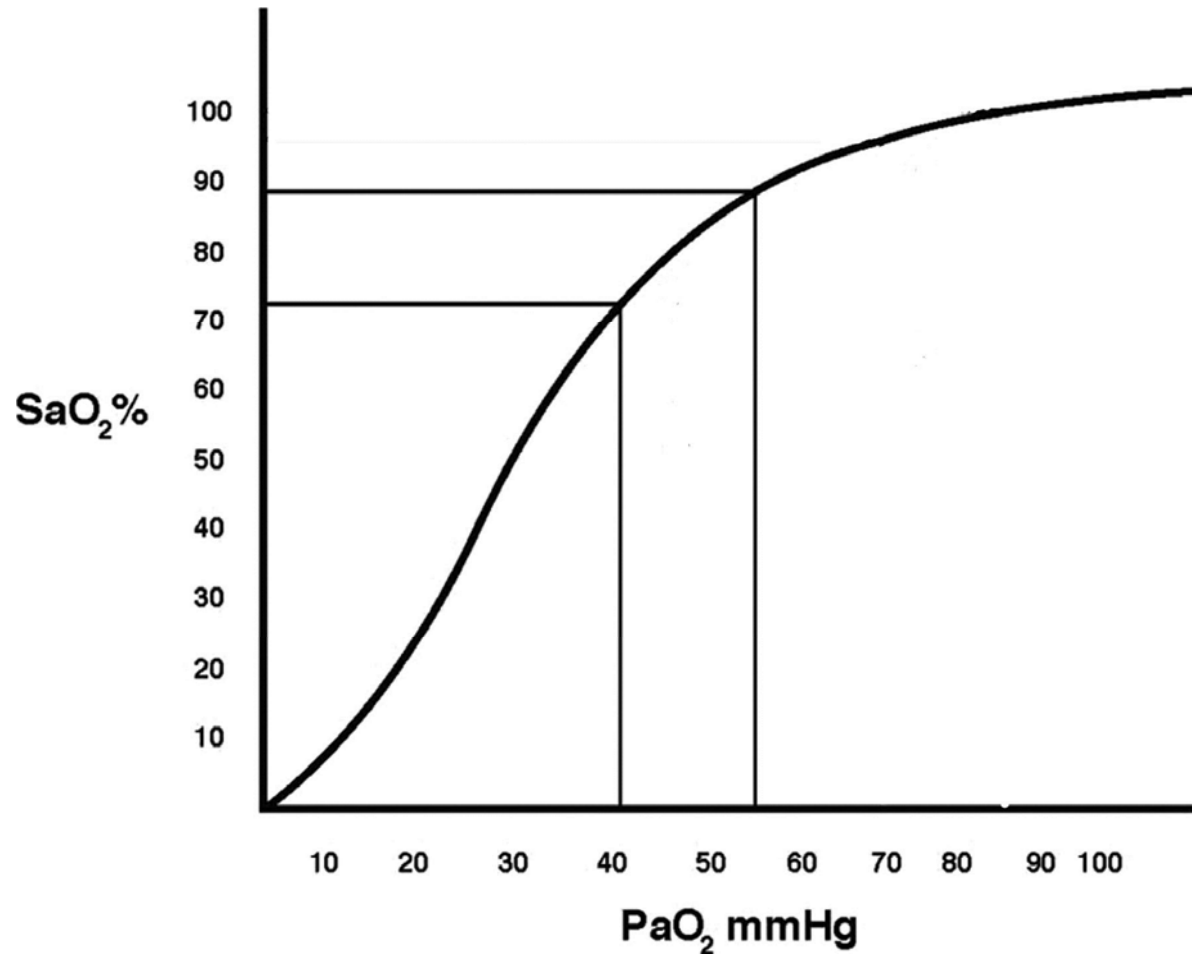
Definitions

- Acute onset of bilateral pulmonary infiltrates consistent with pulmonary edema
 - Without evidence of elevated left atrial pressure
 - PCWP \leq 18 mmHg
- ALI (acute lung injury) and ARDS are differentiated by degree of hypoxemia
 - ALI – P/F ratio of 201 to 300 mmHg
 - ARDS – P/F ratio of \leq 200 mmHg

P/F Ratio

- PaO₂ requires ABG analysis to determine
 - Can be difficult to obtain in some patients
- SpO₂ is a reasonable substitute (Rice, 2007)
 - SpO₂/FiO₂ 235 predicted P/F 200
 - SpO₂/FiO₂ 315 predicted P/F 300
- ALI/ARDS is an arbitrary definition

Oxyhemoglobin Dissociation Curve



Epidemiology

- Incidence (Rubenfeld, 2012)
 - ALI
 - 86 per 100k person-years
 - ARDS
 - 64 per 100k person-years
 - Increases dramatically with patient age
 - 16/100k person-years (15-19y/o)
 - 306/100k person-years (75-84y/o)
 - Approximately 190,000 cases of ALI in the U.S each year

Epidemiology

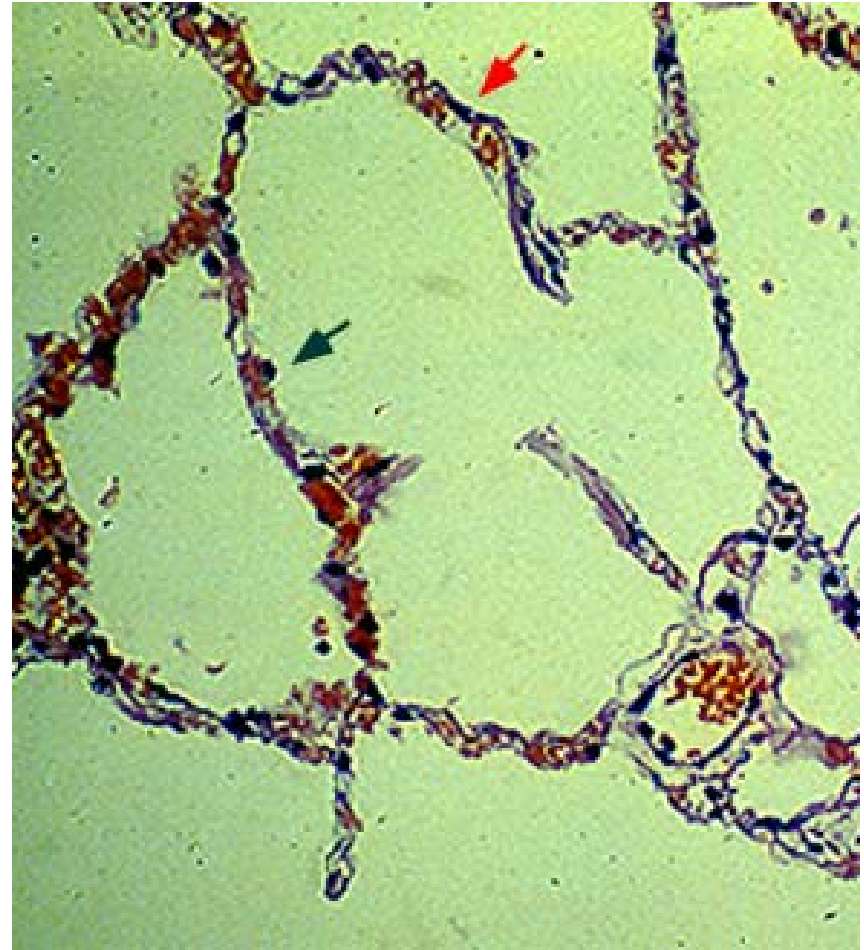
- 10-15% of ICU patients meet criteria for ALI or ARDS
 - 20% of those mechanically ventilated
- Incidence appears to be decreasing (Li, 2010)
 - Decline in hospital-acquired ARDS
 - Those with ARDS tend to be much sicker than they used to be

Epidemiology

- Previously had a mortality rate greater than 50% (Ashbaugh, 1967)
- Mortality decreased to 29-38% during the 1990s
- Mortality appears to be continuing to decline, now approaching 25%
- A minority of patients with ARDS die exclusively from respiratory failure
- Most patients succumb to secondary complications or their primary illness

Pathophysiology

- ARDS is characterized by accumulation of fluid and proteinaceous debris in the alveoli and interstitium of the lung
- Normal lung function requires dry, patent alveoli to be closely approximated to perfused capillaries



Pathophysiology

- Fluid crosses pulmonary capillary membranes under control of hydrostatic and oncotic forces
- Serum protein remains intravascular
- Small quantities of fluid are normally allowed into the interstitium
- Three mechanisms normally prevent alveolar edema
 - Retained intravascular protein
 - Interstitial lymphatic return
 - Capillary epithelial tight junctions

Pathophysiology

- ALI/ARDS are consequences of alveolar injury leading to diffuse alveolar damage
- Lung injury leads to release of pro-inflammatory cytokines
 - Neutrophils are recruited to the lungs
 - Toxic mediators are released damaging capillary and alveolar endothelium
- Protein escapes from the vascular space
- Fluid overwhelms lymphatics and fills air spaces
 - Alveolar collapse ensues

Consequences of Injury

- Impairment of gas exchange
 - V/Q mismatching
 - Shunting leads to hypoxemia
 - Increased dead space impairs CO₂ elimination
- Decreased lung compliance
 - Stiffness of nonaerated lung
 - Smaller tidal volumes can lead to markedly elevated airway pressures
- Pulmonary hypertension

Three Stages of ARDS

- Exudative stage
 - Diffuse alveolar damage
- Proliferative stage
 - Resolution of pulmonary edema
 - Proliferation of type II pneumocytes
 - Squamous metaplasia
 - Interstitial infiltration
 - Collagen deposition
- Fibrotic stage
 - Obliteration of lung architecture
 - Cyst formation
 - Fibrosis

Etiologies

- Many different potential etiologies
 - More than 60 possible causes have been identified
- Sepsis
 - Most common cause of ALI/ARDS
 - Concurrent alcoholism markedly increases risk
 - 70% vs. 30%
- Aspiration
 - ALI/ARDS develops in approximately 33% of hospitalized patients with witnessed aspiration

Etiologies

- Pneumonia
 - CAP is most common cause of out-of-hospital development of ALI/ARDS¹
 - Nosocomial pneumonia well-recognized to progress to ALI/ARDS
- Severe trauma
 - Bilateral lung contusion
 - Fat embolism following long bone fractures
 - Delayed onset – 12 to 48 hours following trauma
 - Many patients predisposed to sepsis
 - Trauma-related ALI/ARDS carries more favorable prognosis than ALI/ARDS from other causes²

1. Baumann WR. Incidence and mortality of adult respiratory distress syndrome: a prospective analysis from a large metropolitan hospital. Crit Care Med 1986;14(1):1-4.

2. Calfee CS, Eisner MD, Ware LB, et al. Trauma-associated lung injury differs clinically and biologically from acute lung injury due to other clinical disorders. Crit Care Med 2007;35(10):2243-2250.

Etiologies

- Massive transfusion
 - >15 units of PRBC is a risk factor for the development of ALI/ARDS¹
 - Selection bias?
- TRALI
 - Development within 6 hours of transfusion
- Lung and HSCT
 - Primary graft failure in lung transplant recipients
 - Poor preservation of donor organ
 - DAH, engraftment syndrome, infections in HSCT recipients

1. Hudson LD. Clinical risks for development of the acute respiratory distress syndrome. American Journal of Respiratory and Critical Care Medicine 1995;151(2):293–301.

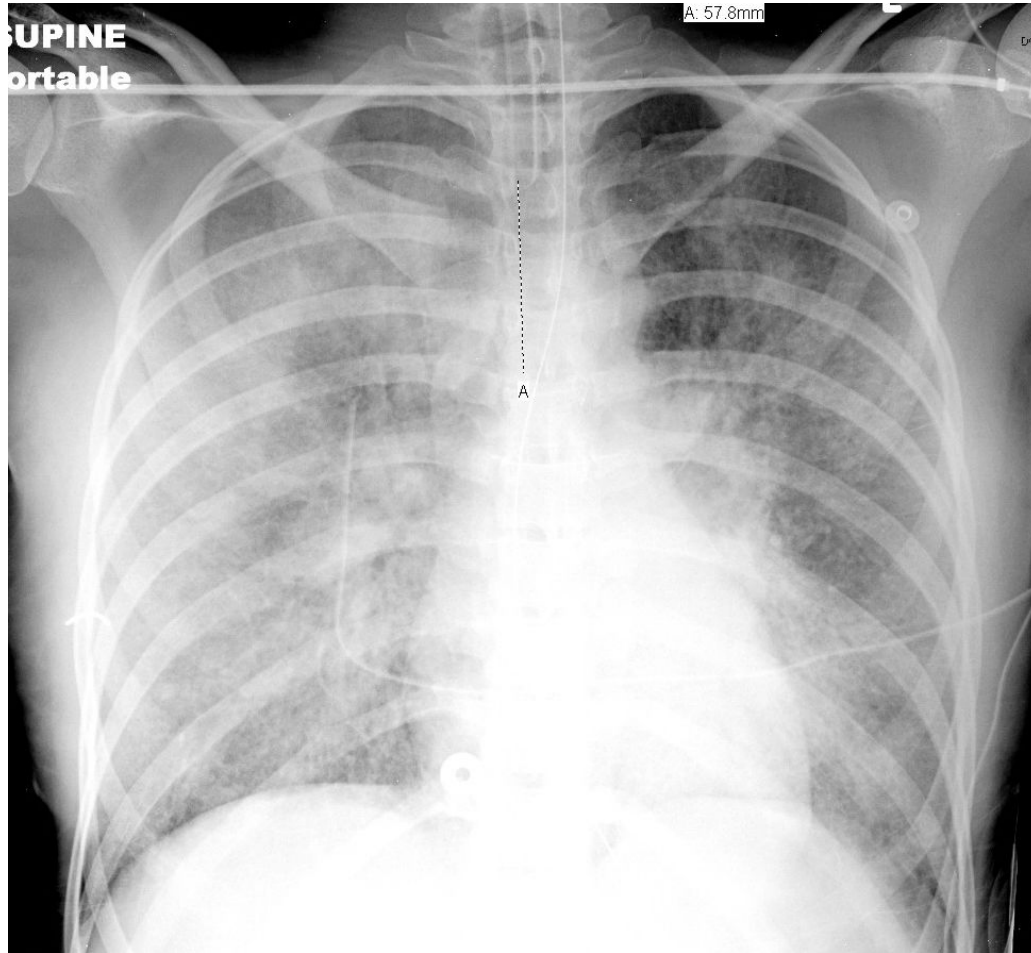
Etiologies

- Overdose and toxicity (Reed, et al.)
 - Aspirin, cocaine, opioids, phenothiazines, tricyclic antidepressants
 - Protamine, nitrofurantoin, systemic chemotherapy (at therapeutic dosages)

Initial Course

- Pulmonary abnormalities develop within 48 to 72 hours following the inciting event
 - Rapid worsening of clinical status common
- ABG generally indicates respiratory alkalosis, hypoxemia
 - Hypoxemia due to physiologic shunting

ARDS Initial CXR



Subsequent Course

- Following the initial acute phase of disease, patients may take one of two courses:
 - Improvement in ventilatory requirements accompanied by radiographic improvement
 - Entrance into the organizing/fibrotic phase of ARDS with persistent ventilator dependence and radiographic abnormality

Complications

- ALI/ARDS is associated with many complications generally seen in states of critical illness
- Complications specific to ALI/ARDS
 - Barotrauma
 - Sedation/paralysis

Barotrauma

- A result of pulmonary parenchymal tissue breakdown and a generally uniform need for positive pressure ventilation
- Incidence appears to be 13% among patients using low-tidal volume ventilation strategies
- Highest levels of barotrauma found among patients receiving high PEEP
 - Mean airway pressure, plateau pressure, and driving pressure did not predict barotrauma

Consequences of Sedation and Paralysis

- Prolonged depression of mental status
- Persistent neuromuscular weakness
 - Critical illness myopathy
 - Most prominent when neuromuscular blocking agents are used in conjunction with corticosteroids

Ventilatory Strategies

- Low Tidal Volume Ventilation
- Permissive hypercapnia
- Open-lung ventilation
- Recruitment maneuvers
- Prone ventilation
- High frequency ventilation

Low Tidal Volume Ventilation

The New England Journal of Medicine

© Copyright, 2000, by the Massachusetts Medical Society

VOLUME 342

MAY 4, 2000

NUMBER 18



**VENTILATION WITH LOWER TIDAL VOLUMES AS COMPARED WITH
TRADITIONAL TIDAL VOLUMES FOR ACUTE LUNG INJURY
AND THE ACUTE RESPIRATORY DISTRESS SYNDROME**

THE ACUTE RESPIRATORY DISTRESS SYNDROME NETWORK*

Low Tidal Volume Ventilation

- Randomized 861 patients with ALI/ARDS to traditional ventilation versus lower tidal volume ventilation
 - Traditional ventilation: initial V_t 12 mL/kg; plateau pressure ≤ 50 cm H₂O
 - Lower tidal volume ventilation: initial V_t 6 mL/kg; plateau pressure ≤ 30 cm H₂O
- Study aborted because mortality was significantly lower in the lower-tidal volume group (31.0% vs. 39.8%)
- Number of days without ventilator increased in lower-tidal volume group (12 vs. 10)

Low Tidal Volume Ventilation

- Preponderance of quality evidence has shown LTVV improves mortality and other outcomes in ARDS
- Reduction in mortality and increases in ventilator-free days

Potential Harm of LTVV

- Was not associated with any clinically important adverse outcomes in the ARMA trial
- Auto-PEEP
 - Higher respiratory rates are required for LTVV to maintain the same minute ventilation
 - May lead to hemodynamic instability
- Sedation
 - WOB and ventilator asynchrony may increase with LTVV
 - Initial need for increased sedation when ventilation initiated, but does not appear to persist
 - Post-hoc analysis of ARMA trial did not find any differences in sedation duration among patient groups

Breath Stacking

- Can occur despite sedation
- Causes episodic delivery of higher V_t which may undermine benefits of LTVV
- Can be ameliorated by delivering slightly higher V_t
 - P_{plat} should remain ≤ 30 cm H₂O

Breath Stacking

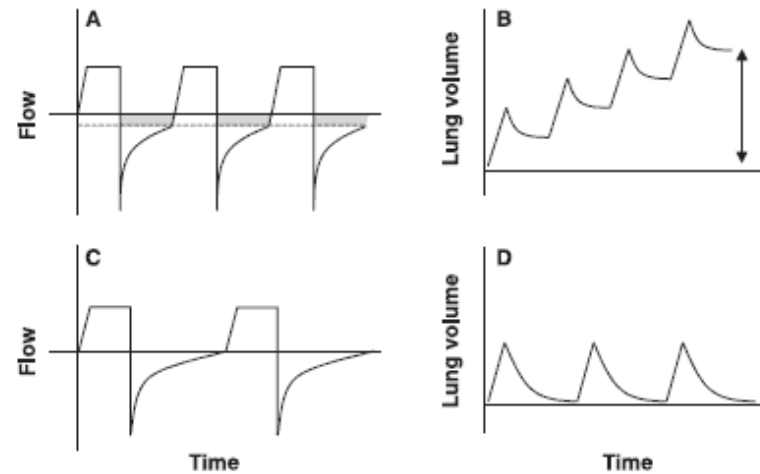


Figure 2 - Mechanics of dynamic pulmonary hyperinflation in the setting of severe airflow obstruction. A) A flow-time curve shows that inspiration begins before complete exhalation of the previous breath, leading to gas trapping (shaded area). B) Gas trapping over the course of several breaths leads to an increased end-expiratory lung volume. The trapped volume (V_{trap}) over functional residual capacity is indicated by the double-headed arrow. C) Increase in expiratory time and decrease in respiratory rate allow for complete exhalation prior to the initiation of the next breath. D) Increase in expiratory time and decrease in respiratory rate result in no air trapping and absence of dynamic hyperinflation

Low tidal volume ventilation in patients with acute respiratory distress syndrome or acute lung injury

Initial ventilator settings								
Calculate predicted body weight (PBW)								
Male =	50 + 2.3 [height (inches) - 60] OR 50 + 0.91 [height (cm) - 152.4]							
Female =	45.5 + 2.3 [height (inches) - 60] OR 45.5 + 0.91 [height (cm) - 152.4]							
Set mode to volume assist-control								
Set initial tidal volume to 8 ml/kg PBW								
Reduce tidal volume to 7 and then to 6 ml/kg over 1-3 hours								
Set initial ventilator rate \leq 35 breaths/min to match baseline minute ventilation								
Subsequent tidal volume adjustment								
Plateau pressure (Pplat) goal \leq 30 cmH ₂ O								
Check inspiratory plateau pressure with 0.5 second inspiratory pause at least every four hours and after each change in PEEP or tidal volume.								
If Pplat >30 cmH ₂ O, decrease tidal volume in 1 ml/kg PBW steps to 5 or if necessary to 4 mL/kg PBW.								
If Pplat <25 cmH ₂ O and tidal volume <6 ml/kg, increase tidal volume by 1 mL/kg PBW until Pplat >25 cmH ₂ O or tidal volume = 6 ml/kg.								
If breath stacking (autoPEEP) or severe dyspnea occurs, tidal volume may be increased to 7 or 8 mL/kg PBW if Pplat remains \leq 30 cmH ₂ O.								
Arterial oxygenation and PEEP								
Oxygenation goal PaO ₂ 55-80 mmHg or SpO ₂ 88-95 percent								
Use these FiO ₂ /PEEP combinations to achieve oxygenation goal:								
FiO₂	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
PEEP	5	5-8	8-10	10	10-14	14	14-18	18-24
PEEP should be applied starting with the minimum value for a given FiO ₂ .								

Adapted from: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000; 342:1301.

Application of LTVV

- A threshold P_{plat} below which safety is certain is not known
 - Goal of ≤ 30 is derived from ARMA trial
 - Plateau pressure should be kept as low as possible
- Oxygenation goal
 - PaO_2 between 55-80 mmHg
 - SpO_2 between 88-95%

Permissive Hypercapnia

- The understanding that protective lung ventilation strategies will occasionally limit alveolar ventilation
- Low tidal volume ventilation will sometimes lead to hypercapnia, which has been shown to be generally well tolerated in trials
- Safe for most patients
- Some patients exist in whom permissive hypercapnia may be harmful

Contraindications to Permissive Hypercapnia

- Cerebral disease
 - Mass lesions, trauma, cerebral edema
 - Seizure disorder
- Hypercapnia is associated with cerebral vasodilatation
 - Increases cerebral blood flow
 - May cause increased ICP and potentially reduce CPP
- May lower seizure threshold
- Associated with intraventricular hemorrhage in neonates

Hypercapnia may be Harmful...

- Patients with significant heart disease
 - Increased sympathetic tone
- Patients taking beta blockers
 - Negative inotropic effects
- Hypovolemia
 - Systemic vasodilation
 - Leads to hypotension

Open Lung Ventilation

- Combines low tidal volume ventilation with higher PEEP
 - Maximizes alveolar recruitment
- Low tidal volume ventilation mitigates alveolar overdistention
- Elevated PEEP seeks to minimize cyclic atelectasis

Open Lung Ventilation

- Has been shown to provide survival benefit in two trials
 - Trials have severe methodologic limitations
 - Unclear if survival benefits translate into real practice at this point
- May require permissive hypercapnia

**EFFECT OF A PROTECTIVE-VENTILATION STRATEGY ON MORTALITY IN THE
ACUTE RESPIRATORY DISTRESS SYNDROME**

**MARCELO BRITTO PASSOS AMATO, M.D., CARMEN SILVIA VALENTE BARBAS, M.D., DENISE MACHADO MEDEIROS, M.D.,
RICARDO BORGES MAGALDI, M.D., GUILHERME DE PAULA PINTO SCHETTINO, M.D., GERALDO LORENZI-FILHO, M.D.,
RONALDO ADIB KAIRALLA, M.D., DANIEL DEHEINZELIN, M.D., CARLOS MUNOZ, M.D., ROSELAINÉ OLIVEIRA, M.D.,
TERESA YAE TAKAGAKI, M.D., AND CARLOS ROBERTO RIBEIRO CARVALHO, M.D.**

Amato, et al.

- 53 patients randomized
 - Conventional ventilation
 - Lowest possible PEEP with V_t 12 mL/kg
 - Protective ventilation
 - PEEP above the lower inflection point on a static pressure-volume curve
 - V_t of <6 mL/kg
 - Driving pressure <20 cm above PEEP value
 - Preferential use of pressure-limited ventilatory modes

Amato, et al.

- Protective strategy improved survival at 28 days
- Higher rate of weaning from mechanical ventilation
- Lower rate of barotrauma among patients with ARDS
- Not associated with a higher rate of survival to hospital discharge

Application of Open Lung Ventilation

- No universally accepted protocol
- Applied PEEP is set at least 2 cm above the lower inflection point of the pressure-volume curve
 - 16 cm PEEP is generally used if the lower inflection point is uncertain

High PEEP Ventilation

- Type of open lung ventilation that does not require a pressure-volume curve
 - Less need for neuromuscular blockade
- Applied PEEP should open collapsed alveoli
 - Decreases alveolar overdistention
 - Each breath is more evenly spread over the lung
 - Cyclic atelectasis is reduced

High PEEP Ventilation

Higher vs Lower Positive End-Expiratory Pressure in Patients With Acute Lung Injury and Acute Respiratory Distress Syndrome Systematic Review and Meta-analysis

1. Briel, M., Meade, M., Mercat, A., Brower, R. G., Talmor, D., Walter, S. D., Slutsky, A. S., et al. (2010). Higher vs Lower Positive End-Expiratory Pressure in Patients With Acute Lung Injury and Acute Respiratory Distress Syndrome: Systematic Review and Meta-analysis. *JAMA: The Journal of the American Medical Association*, 303(9), 865–873. doi:10.1001/jama.2010.218

Briel, et al.

- Meta-analysis of 2299 patients in 3 trials
- All patients received LTVV
- Treatment with higher vs lower levels of PEEP was not associated with improved hospital survival among all comers
- Among the subgroup of patients with ARDS, higher levels of PEEP were associated with improved survival

Recruitment Maneuvers

- Brief application of high level of CPAP (35-40cmH₂O) for 40 seconds
- Clinical impact is uncertain
 - Meta-analysis found recruitment maneuvers do not affect mortality, LOS, barotrauma
 - Improve oxygenation
- Complications can include hypotension and transient desaturation

Prone Ventilation

- Mechanical ventilation taking place with the patient lying the prone position
- Improves oxygenation in many patients with ARDS
- Uncertain clinical benefits

Physiologic Effects

- Optimization of V/Q matching
- How prone positioning may improve ventilation:
 - Improves differences between dorsal and ventral pleural pressures
 - More homogenous lung recruitment
 - Unloads the weight of the heart which normally compresses lung beneath it in the supine position
 - Displaces diaphragm, decreasing posterior-caudal compression of the lung

Physiologic Effects

- How prone ventilation may improve perfusion:
 - V/Q matching is improved when prone as blood flow is relocated to ventilated portions of lung
 - More aerated lung is perfused as a percentage of total overall blood flow through the lung
 - Shunting is minimized
- No evidence to suggest real clinical benefit

Clinical Outcomes of Prone Ventilation

- Increases arterial PaO₂ in most patients with ARDS (uncontrolled trials)
- Predictors of sustained response
 - Improved oxygenation during a brief trial
 - Diffuse pulmonary edema and dependent atelectasis
 - Extrapulmonary causes of ARDS
 - Elevated intra-abdominal pressure

Mortality Benefit of Prone Ventilation

- Prone ventilation does not confer a mortality benefit (randomized trials/meta-analyses)
- Exception may be made for those patients with the greatest severity of illness
 - Two trials demonstrated mortality benefits among severely hypoxemic patients
 - P/F ratio < 100
 - Meta-analysis demonstrated 53% vs 63% mortality reduction among 555 patients

In the End...

- Prone ventilation is warranted in select patients (most critically ill)
- Prone ventilation should not be used as routine management in all patients with ARDS
- Duration of effective prone ventilation is unknown
- No good data to justify its use
- Best reserved as a rescue therapy

High-Frequency Ventilation

- Provides tidal volumes below that of anatomic dead space at frequencies of greater than 60 breaths/minute
- May decrease VILI and reduce barotrauma in patients with ARDS
- May improve V/Q matching and reduce risk of hemodynamic compromise

Potential Complications of HFV

- Desiccation of mucus
- Airway damage due to high gas velocities
- Air trapping
- High shear forces
 - Between areas of lung with different impedances

HFV in Practice

- Poor data to support routine use in patients with ALI/ARDS
- May improve oxygenation compared to conventional ventilation, but benefits are not sustained over time
- Should be reserved as salvage therapy for patients failing conventional ventilation
- Significant expertise and resources are necessary to safely and effectively perform HFV

Types of HFV

- High frequency jet ventilation (HFJV)
- High frequency oscillatory ventilation (HFOV)
- High frequency percussive ventilation (HFPV)
- High frequency positive pressure ventilation (HFPPV)

Novel Therapies

- Surfactant
 - No evidence to support routine use
 - More study is needed in formulation and delivery systems
- Inhaled vasodilators (NO, prostacyclin)
 - Have not been shown to reduce morbidity or mortality in patients with ARDS
- Liquid ventilation
 - May cause undue harm in ARDS patients
 - Cannot be recommended for use in ARDS at this time
- ECMO
 - Poor base of evidence to support use
 - Resource intensive
- Antiinflammatory agents

In Conclusion

- ARDS is reasonably common, but the incidence is declining
- Complications related to ARDS are generally related to concurrent critical illness, although barotrauma is common a significant iatrogenic complication
- Low tidal volume ventilation has been consistently shown to improve morbidity and mortality in ARDS
- The use of high levels of PEEP is probably beneficial
- Other ventilatory strategies are best used as salvage therapy for severely hypoxemic individuals
- A number of novel nonventilatory therapies are being studied in ARDS but are not yet proven to provide benefit