ARDS – A Brief Overview
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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 ≤ 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 ≤ 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

• 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

• 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 protienaceous 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/ARDS
  – 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 causes


Etiologies

• Massive transfusion
  – >15 units of PRBC is a risk factor for the development of ALI/ARDS
  – 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


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

Randomized 861 patients with ALI/ARDS to traditional ventilation versus lower tidal volume ventilation
- Traditional ventilation: initial $V_t$ 12 mL/kg; plateau pressure $\leq 50$ cm H$_2$O
- Lower tidal volume ventilation: initial $V_t$, 6 mL/kg; plateau pressure $\leq 30$ cm H$_2$O

• 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 Vt which may undermine benefits of LTVV
- Can be ameliorated by delivering slightly higher Vt
  - Pplat should remain ≤ 30 cm H2O
Breath Stacking

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
  - $\text{PaO}_2$ between 55-80 mmHg
  - $\text{SpO}_2$ 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 vasodilatation
  - 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
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

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**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