History of ARDS

- First noted in 1960s, a distinct type of hypoxemic respiratory failure characterized by acute abnormality in both longs.
- Called "Shock Lung" by military practitioners and "Adult Respiratory Distress Syndrome" by civilian practitioners.
- After the same process was noted over all age categories (including infants), the term was changed to Acute Respiratory Distress Syndrome.

Acute Lung Injury & Acute Respiratory Distress Syndrome

Tzong-Luen Wang
MD, PhD, JM, FESC, FACC, FCAPSC
Chief, Emergency Department, Shin-Kong WHS Memorial Hospital
Professor, Medical School, Fu-Jen Catholic University

Epidemiology of ARDS

- Estimated 190,000 cases each year and 74,000 deaths*
- Much lower incidence in younger patients (16 per 100,00 person years for ages 15-19) vs older patients (306 per 100,00 person years for ages 75-84)*
- Estimated that up to 20% of mechanically ventilated patients meet the criteria for diagnosis of ARDS**

* - Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. N Engl J Med 2005; 353:1685.

** - Zaccardelli DS, Pattishall EN. Clinical diagnostic criteria of the adult r espiratory distress syndrome in the intensive care unit. Crit Care Med 1996; 24:247.

Objectives

- Describe the clinical features and diagnosis of ALI / ARDS
- Review the epidemiology, pathophysiology and etiology of ALI / ARDS
- Review supportive care and oxygenation in ALI / ARDS
- Mechanical ventilation strategies for ALI / ARDS patients
- Novel therapies for the treatment of ALI / ARDS

What is ARDS?

- Asbaugh, Bigelow & Petty described ARDS as: *"A syndrome of acute respiratory failure in adults characterized by non-cardiogenic pulmonary edema manifested by severe hypoxemia caused by right to left shunting through collapsed or fluid-filled alveoli."* [1]
- The Berlin Definition: *"An acute, diffuse, inflammatory lung injury that leads to increased pulmonary vascular permeability, increased lung weight, and a loss of aerated tissue."* [2]

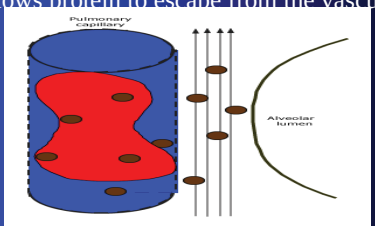
1- *Lancet*. 1967, Aug 12;2(7511): 319–323
2 - The ARDS Definition Task Force. Acute Respiratory Distress Syndrome: The Berlin Definition. *JAMA* 2012; May 21, 2012:Epub ahead of print.

ALI vs ARDS

- Acute Lung Injury (ALI) is a term used for patients with significant hypoxemia (PaO2 / FiO2 < 300)
- Acute Respiratory Distress Syndrome (ARDS) is a subset of ALI patients with severe hypoxemia (PaO2 / FiO2 < 300)

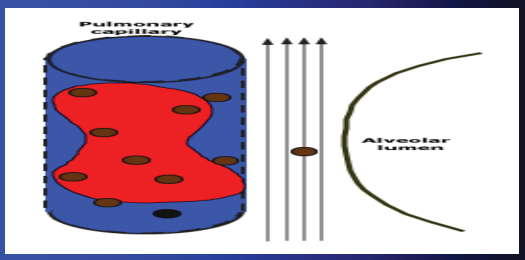
What is ARDS?

- Cytokines recruit neutrophils to the lungs, where they become activated and release toxic mediators (eg, reactive oxygen species and proteases) that damage the capillary endothelium and alveolar epithelium.
- Damage to the capillary endothelium and alveolar epithelium allows protein to escape from the vascular space.



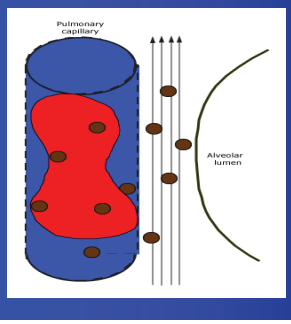
What is ARDS?

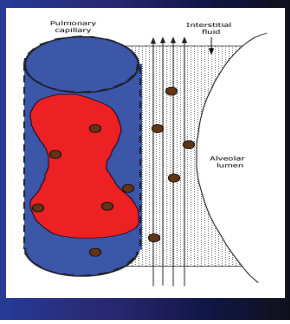
- In normal, healthy lungs there is a small amount of fluid that leaks into the interstitium. The lymphatic system removes this fluid and returns it into the circulation keeping the alveoli dry.



What is ARDS?

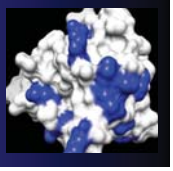
- The oncotic gradient that favors resorption of fluid is lost and fluid pours into the interstitium, overwhelming the lymphatic system.





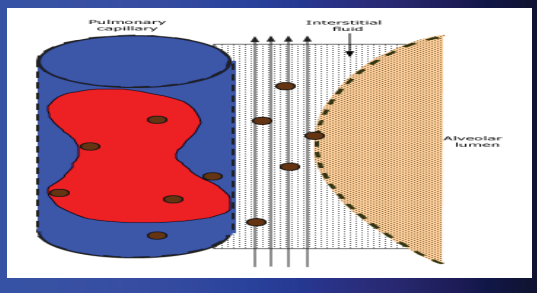
What is ARDS?

- ARDS is a consequence of an alveolar injury which produces diffuse alveolar damage. The injury causes the release of pro-inflammatory "cytokines".
- ***Cytokines*** are substances that are secreted by the immune system which carry signals locally between cells, and thus have an effect on other cells. They are a category of ***signaling molecules*** that are used extensively in cellular communication.



What is ARDS?

- Breakdown of the alveolar epithelial barrier allows the air spaces to fill with bloody, proteinaceous edema fluid and debris from degenerating cells. In addition, functional surfactant is lost, resulting in alveolar collapse.



What is ARDS?

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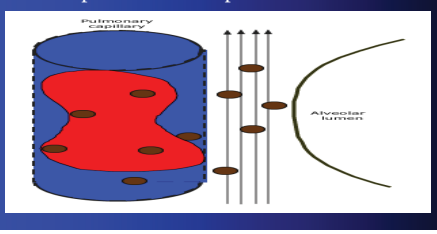


Exudative Stage (0-6 Days)

Characterized by:

- Accumulation of excessive fluid in the lungs due to exudation (leaking of fluids) and acute injury.
- Hypoxemia is usually most severe during this phase of acute injury, as is injury to the endothelium (lining membrane) and epithelium (surface layer of cells).
- Some individuals quickly recover from this first stage; many others progress after about a week into the second stage.

What is ARDS?

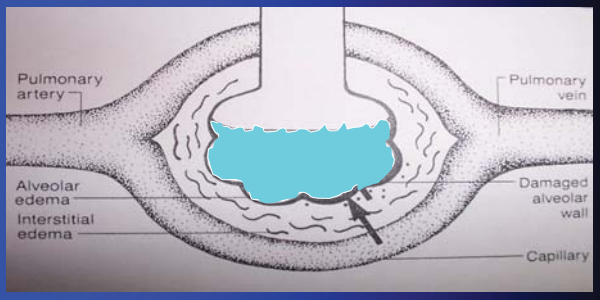
- Healthy lungs regulate the movement of fluid to maintain a small amount of interstitial fluid and dry alveoli.
- Lung injury interrupts this balance causing excess fluid in both the interstitium and alveoli.
- Results of the excess fluid include impaired gas exchange, decreased compliance, and increased pulmonary arterial pressure.

Proliferative Stage (7-10 Days)

Characterized by:

- Connective tissue and other structural elements in the lungs proliferate in response to the initial injury, including development of fibroblasts (cells giving rise to connective tissue).
- The terms "stiff lung" and "shock lung" frequently used to characterize this stage.
- Abnormally enlarged air spaces and fibrotic tissue (scarring) are increasingly apparent.

What is ARDS?



- Results of the excess fluid include impaired gas exchange, decreased compliance, and increased pulmonary arterial pressure.

Fibrotic Stage (>10-14 Days)

Characterized by:

- Inflammation resolves.
- Oxygenation improves and extubation becomes possible.
- Lung function may continue to improve for as long as 6 to 12 months after onset of respiratory failure, depending on the precipitating condition and severity of the initial injury.
- Varying levels of pulmonary fibrotic changes are possible.

What is ARDS?

- ARDS is a multisystem syndrome – not a “disease”
- Three distinct stages (or phases) of the syndrome including:
  1. Exudative stage
  2. Proliferative (or fibroproliferative) stage
  3. Fibrotic stage

Pneumonia

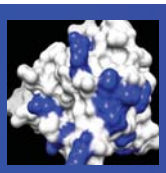
- Community acquired pneumonia is probably the most common cause of ARDS that develops outside of the hospital. [1]
- Nosocomial pneumonias can also progress to ARDS. Staphylococcus aureus, Pseudomonas aeruginosa, and other enteric gram negative bacteria are the most commonly implicated pathogens.

1 - Baumann WR, Jung RC, Koss M, et al. Incidence and mortality of adult respiratory distress syndrome: a prospective analysis from a large metropolitan hospital. Crit Care Med 1986; 14:1.

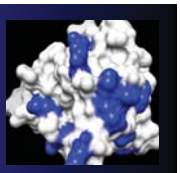
Causes of ARDS

- No "single" causative factor - can be triggered by traumatic or non-traumatic events.
- Over 60 possible causes have been identified but the four most frequent causes include:

1. Sepsis
2. Aspiration
3. Pneumonia
4. Severe Trauma



Cytokine Storm



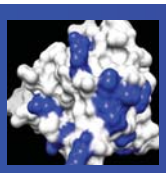
- When the immune system is fighting pathogens, cytokines signal immune cells such as T-cells and macrophages to travel to the site of infection.
- In addition, cytokines activate those cells, stimulating them to produce more cytokines.
- Normally, this feedback loop is kept in check by the body, however, in some instances, the reaction becomes uncontrolled, and too many immune cells are activated in a single place.

Sepsis

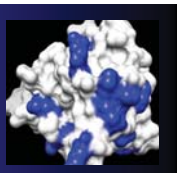
- Most common cause of ARDS. [1]
- Higher risk in septic patients with a history of alcoholism (70% incidence in pts with chronic alcohol use vs 31% in patients w/o chronic use)[2]

1 - Pepe PE, Potkin RT, Reus DH, et al. Clinical predictors of the adult respiratory distress syndrome. Am J Surg 1982; 144:124.

2 - Moss M, Bucher B, Moore FA, et al. The role of chronic alcohol abuse in the development of acute respiratory distress syndrome in adults. JAMA 1996; 275:50.



Cytokine Storm



- Precise reason for this is unknown but may be a result of an exaggerated response when the immune system encounters a *new* and *highly pathogenic organism (i.e. H1N1)*
- Cytokine storms in the lungs result in the accumulation of fluid and immune cells and can lead to ARDS (biotrauma)

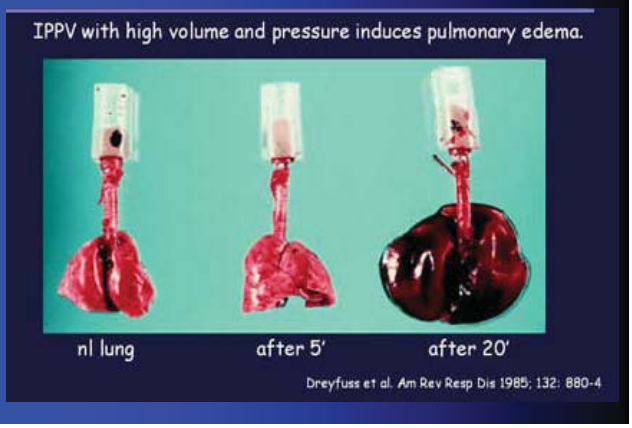
Aspiration

- Observational evidence 1/3 of patients with known aspiration of gastric contents develop ARDS due to injury caused by low pH (<2.5).[1]
- Animal studies have shown that aspiration of non-acidic gastric contents can also cause widespread damage to the lungs suggesting that gastric enzymes and small food particles also contribute to the lung injury. [2]

1 - Pepe PE, Potkin RT, Reus DH, et al. Clinical predictors of the adult respiratory distress syndrome. Am J Surg 1982; 144:124.

2 - Wynne JW. Aspiration pneumonitis. Correlation of experimental models with clinical disease. Clin Chest Med 1982; 3:25.

Results of Volutrauma



Severe Trauma

- ARDS is a complication of severe trauma and is most common following:

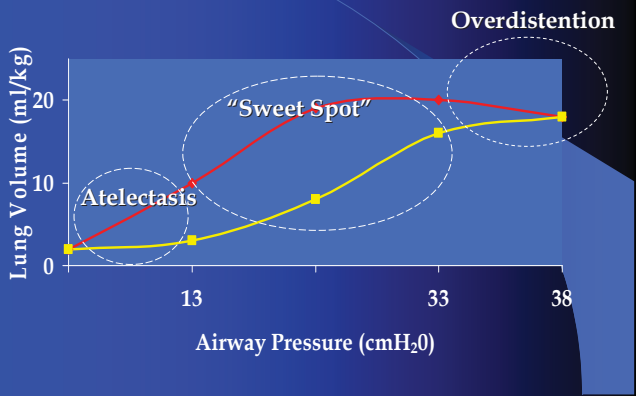
  A) Bilateral lung contusion following blunt trauma .[1]

  B) Fat embolism after long bone fractures – ARDS typically appears 12 to 48 hours after the trauma (occurs less frequently since immobilization protocol) [2]

1 - Baumann WR, Jung RC, Koss M, et al. Incidence and mortality of adult respiratory distress syndrome: a prospective analysis from a large metropolitan hospital. Crit Care Med 1986; 14:1.

2 - Schonfeld SA, Ploysongsang Y, DiLisio R, et al. Fat embolism prophylaxis with corticosteroids. A prospective study in high-risk patients. Ann Intern Med 1983; 99:438.

What's The Fuss?? – Lung Injury



Severe Trauma

- ARDS is a complication of severe trauma and is most common following:

  C) Sepsis that develops several days or more after severe trauma or burns.

  D) Massive traumatic tissue injury may directly precipitate or predispose a patient to ARDS.[1]

1 - Moore FA, Moore EE, Read RA. Postinjury multiple organ failure: role of extrathoracic injury and sepsis in adult respiratory distress syndrome. New Horiz 1993; 1:538.

Diagnosing ARDS

- Cardiogenic pulmonary edema and alternative causes of acute hypoxemic respiratory failure and bilateral infiltrates must first be excluded.

- New "Berlin Definition of ARDS" requires that all of the following criteria be present to diagnose ARDS:[1]

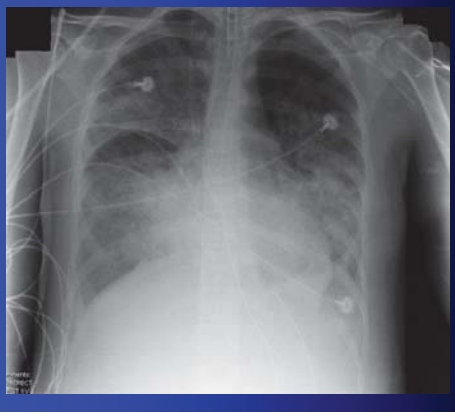
  1. Respiratory symptoms must have begun within one week of a known clinical insult, or the patient must have new or worsening symptoms during the past week.

Ventilator Associated Lung Injury

- Acute lung injury caused by mechanical ventilation.
- Can be caused by:

1. High inflation pressure → Barotrauma
2. Over distension → Volutrauma
3. Repetitive opening & closing of alveoli → Atelectrauma

"Ground Glass" appearance on CXR



Berlin Definition of ARDS

2. Bilateral opacities consistent with pulmonary edema must be present on a chest radiograph or CT scan. These opacities must not be fully explained by pleural effusions, lobar collapse, lung collapse, or pulmonary nodules.

3. The patient's respiratory failure must not be fully explained by cardiac failure or fluid overload. An objective assessment (eg, echocardiography) to exclude hydrostatic pulmonary edema is required if no risk factors for ARDS are present.

Clinical Presentation of ARDS

- Tachypnea
- Increasing dyspnea, hyperventilation
- Respiratory distress
- Labored respiration's, retractions
- Cyanosis
- Tachycardia, hypertension, restlessness, anxiety

Berlin Definition of ARDS

4. A moderate to severe impairment of oxygenation must be present, as defined by the ratio of arterial oxygen tension to fraction of inspired oxygen (PaO_2/FiO_2). The severity of the hypoxemia defines the severity of the ARDS:

   Mild ARDS – The PaO_2/FiO_2 is >200 mmHg, but ≤300 mmHg, on ventilator with PEEP ≥5 cm H_2O.

   Moderate ARDS – The PaO_2/FiO_2 is >100 mmHg, but ≤200 mmHg, on ventilator with PEEP ≥5 cm H_2O.

   Severe ARDS – The PaO_2/FiO_2 is ≤100 mmHg on on ventilator with PEEP ≥5 cm H_2O.

General Treatment & Support of ARDS

Key components of supportive care include:

1. Intelligent use of sedatives and neuromuscular blockade
2. Hemodynamic management
3. Nutritional support
4. Control of blood glucose
5. Evaluation and treatment of nosocomial pneumonia
6. Prophylaxis against deep vein thrombosis (DVT) and gastrointestinal (GI) bleeding.

Acute Respiratory Distress Syndrome

Characterized by:

- Acute onset
- Bilateral infiltrates on CXR sparing the costophrenic angles
- PaO2 / FiO2 < 300 (< 200 is severe)
- Increased edema and decreased surfactant production
- Ground glass appearance on CXR

Low Tidal Volume Ventilation (LTVV)

- A 2004 meta-analysis of six randomized trials (1297 patients) found that LTVV significantly improved 28 day mortality (27.4 vs 37 %) and hospital mortality (34.5 vs 43.2 %), when compared to conventional mechanical ventilation.[1]
- A 2012 meta-analysis of four randomized trials (1149 patients) also found that LTVV reduced hospital mortality (34.2 vs 41 %), when compared to conventional mechanical ventilation.[2]

1. Petrucci N, Iacovelli W. Ventilation with lower tidal volumes versus traditional tidal volumes in adults for acute lung injury and acute respiratory distress syndrome. Cochrane Database Syst Rev 2004; :CD003844.
2. Putensen C, Theuerkauf N, Zinserling J, et al. Meta-analysis: ventilation strategies and outcomes of the acute respiratory distress syndrome and acute lung injury. Ann Intern Med 2009; 151:566.

Mechanical Ventilation & ARDS

- ARDS frequently requires mechanical ventilation
- Majority of patients require MV due to Type 1 – Hypoxemic Respiratory Failure
- Preponderance of evidence suggests that a "Low Tidal Volume Ventilation" strategy improves mortality. [1-4]

1. 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.
2. Petrucci N, Iacovelli W. Ventilation with lower tidal volumes versus traditional tidal volumes in adults for acute lung injury and acute respiratory distress syndrome. Cochrane Database Syst Rev 2004; :CD003844.
3. Putensen C, Theuerkauf N, Zinserling J, et al. Meta-analysis: ventilation strategies and outcomes of the acute respiratory distress syndrome and acute lung injury. Ann Intern Med 2009; 151:566.
4. Needham DM, Colantuoni E, Mendez-Tellez PA, et al. Lung protective mechanical ventilation and two year survival in patients with acute lung injury: prospective cohort study. BMJ 2012; 344:e2124.

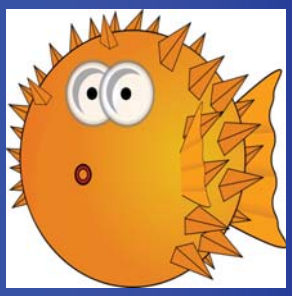
Low Tidal Volume Ventilation (LTVV)

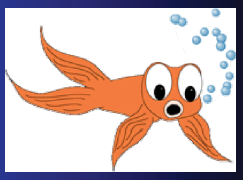
Problems / Questions

1. Hypercapnic respiratory acidosis in some patients.
   - Expected and generally well tolerated by patients.
2. Auto-PEEP
   - In theory, the higher respiratory rates used to maintain minute ventilation during LTVV may create auto-PEEP by decreasing the time available for complete expiration. A subgroup analysis from the ARDSnet trial detected negligible quantities of auto-PEEP in both the LTVV and conventional mechanical ventilation groups.[1]

1. Hough CL, Kallet RH, Ranieri VM, et al. Intrinsic positive end-expiratory pressure in Acute Respiratory Distress Syndrome (ARDS) Network subjects. Crit Care Med 2005; 33:527.

Tidal Volumes Over The Years…..





1990's 2010's

Low Tidal Volume Ventilation (LTVV)

Initial Settings[1]

1. Calculate Ideal Body Weight (IBW)
   - Males = 106 + [6 x (height in inches – 60 in)]
     Females = 105 + [5 x (height in inches – 60 in)]
2. Set initial tidal volume to 8 ml/kg IBW
3. Reduce tidal volume to 7 ml/kg IBW then 6 ml/kg IBW over the next 1-3 hours.
4. Set respiratory rate to $\leq$ 35 bpm to match baseline minute ventilation

1. 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.

Low Tidal Volume Ventilation (LTVV)

- Multicenter ARDSnet trial randomly assigned 861 mechanically ventilated patients with ARDS to receive LTVV (initial tidal volume of 6 mL/kg) or conventional mechanical ventilation (initial tidal volume of 12 mL/kg).
- The LTVV group had a lower mortality rate (31 versus 40 percent).
- The LTVV group had more ventilator-free days (12 versus 10 days). [1]

1. 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.

Volume Control Ventilation in ARDS

- As clinical path of disease worsens, lung compliance worsens and pressure required to deliver set tidal volume increases.
- Must use low tidal volume strategy (6-8ml/kg) with increased RR to maintain VE.
- Hypoxemia requiring additional PEEP further increasing inspiratory pressures.
- May be used in mild to moderate cases.

Low Tidal Volume Ventilation (LTVV)

Adjusting Settings

1. Adjustments to tidal volume are based on the Plateau pressure reading.
2. Goal is to maintain Plateau pressure $\leq$ 30cmH2O.
3. If Plateau pressure rises above 30 cmH2O, the tidal volume setting is decreased by 1 ml/kg IBW increments to a minimum of 4 ml/kg IBW.
4. Using LTVV when Plateau pressures are not high has also shown benefit.[1]

1. Hager DN, Krishnan JA, Hayden DL, et al. Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. Am J Respir Crit Care Med 2005; 172:1241

Pressure Control Ventilation in ARDS

- Utilized for unlimited flow, control of inspiratory time and limiting maximum pressure on inspiration.
- Control of inspiratory time can allow for prolonged inspiration with possible improvement in oxygenation – may require sedation / paralysis.
- Hypoxemia requiring additional PEEP typically reduces delivered TV unless additional insp pressure is added.
- Worsening of compliance will reduce TV and may require MV.

Open Lung Ventilation

- Ventilation strategy that combines low tidal volume ventilation (LTVV) and enough applied PEEP to maximize alveolar recruitment.
- Goal is to prevent overdistension and minimize cyclic atelectasis.
- Some studies report decrease in mortality and hospital stay but studies are flawed.
- No universally accepted protocol is yet available. Typically, LTVV is utilized with various methods (lower inflection point, using highest PEEP while maintaining Plateau pressure $\leq$ 30 cmH2O, etc.)

Airway Pressure Release Ventilation (APRV)

- APRV is a technique which allows spontaneous breathing on two CPAP levels.
- After establishing an optimum level of CPAP, ventilatory support is achieved by adjusting the level of pressure release to a lower value (usually above zero).
- The baseline pressure is periodically released to the lower pressure level for a very brief period (usually 1 second or less).

What Mode Is Best in ARDS???

- Volume Control (VC)
- Pressure Control (PC)
- Airway Pressure Release Ventilation (APRV)
- Oscillator / Jet Ventilation

- No mode or type of ventilation has been “proven” to work best in terms of

BiLevel vs APRV

In BiLevel normal ratio there IS time for spontaneous breathing from the lower PEEP level.

In APRV there IS NOT time for spontaneous breathing from the lower PEEP level.

Airway Pressure Release Ventilation (APRV)

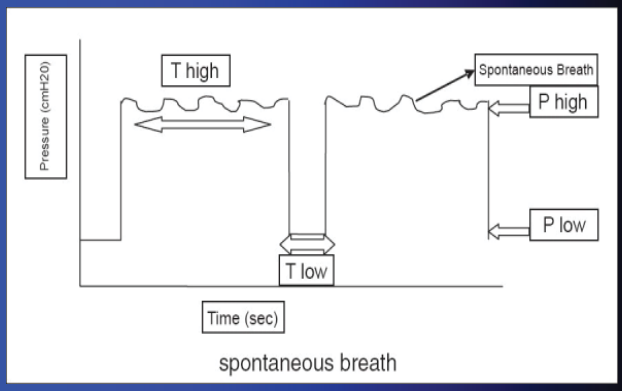
- CPAP is then reinstated and the previous volume is restored in the lungs.
- High CPAP level increases MAP.
- Timed intervals when pressure drops allows for ventilation.
- Patient can be apnic and mode will still work.
- Newer ventilators have added the ability to add pressure support to spontaneous breaths

APRV – Initial Settings

- P-Low = 0-8 cmH2O
- P-High = set to deliver 4-8 ml/kg IBW but keep < 35 cmH2O
- T-Low = 0.5-1.0 sec
- T-High = set to ensure effective MV
- Release Rate = 10 per minute

(Note: Two of the above – T-Low, T-High, and Release Rate – are set depending on type of vent. Third value is determined by those settings.

Airway Pressure Release Ventilation (APRV)



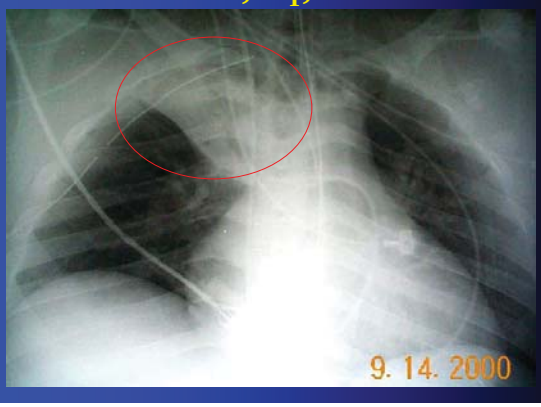
Settings Adjustment in APRV

- Nearly every setting change results in a positive….and negative effect on oxygenation and/or ventilation.

Airway Pressure Release Ventilation (APRV)

- APRV was originally intended for patients with stiff lungs.
- Recent research has proven the mode to be as effective as conventional ventilation in both ventilating and oxygenating patients with only mild pulmonary problems or with normal lung compliance.
- Clinical use is still mainly for patients with very low compliance and poor oxygenation.

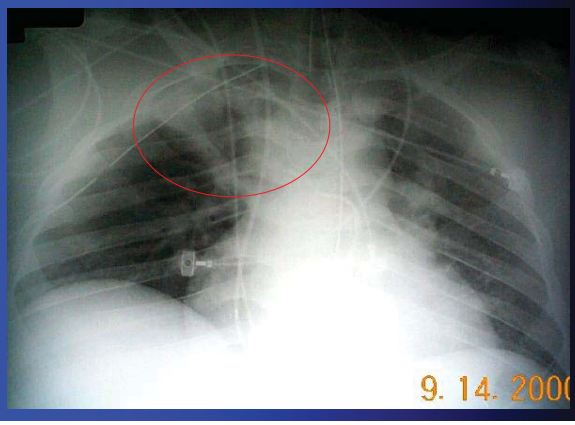
RUL COLLAPSE: Optimized PEEP, V_T, Flow



Managing Oxygenation in APRV

- Increase PEEP HI and/or decrease rate by small amounts. While either change may improve SpO2's, either change may reduce MV.
- Reduce TLow which may also reduce MV.
- Increase FiO2 as needed but the target level should be 0.60.

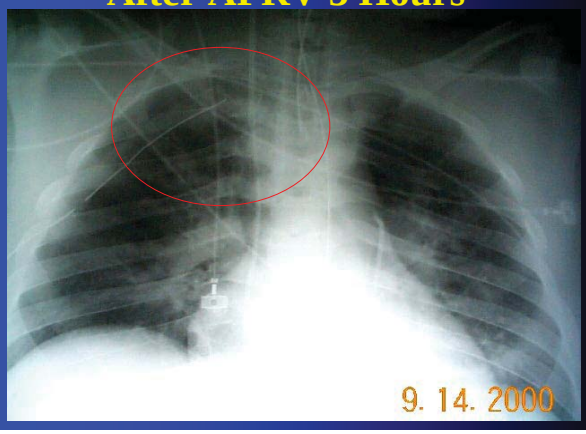
After APRV 1 Hour



Managing pH, PCO2, VE in APRV

- Decrease PEEP HI to allow the pt. to increase their spontaneous Tv.
- Increase frequency. This will increase the number of "Releases" per minute.

After APRV 3 Hours

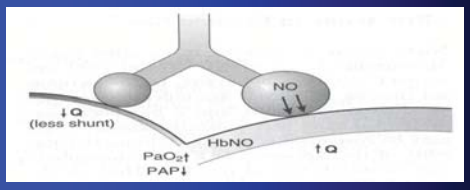


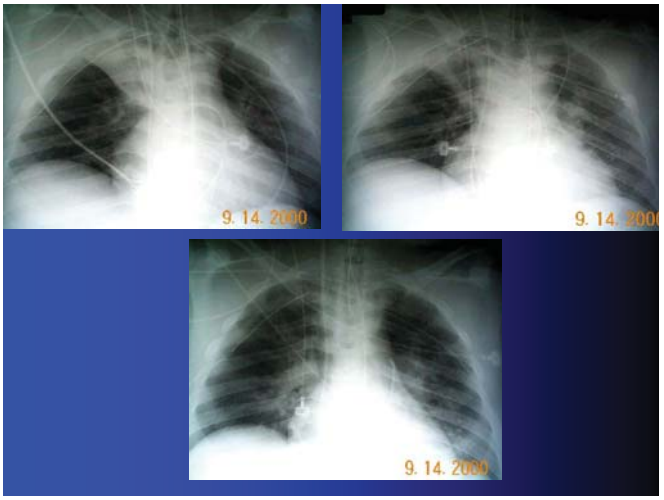
Weaning From APRV

- When oxygenation improves, initiate "Drop & Stretch" protocol.
- D&S protocol attempts to avoid de-recruitment by lowering P high by 2 to 3 cm H_2O at a time and lengthening T high by increments of 0.5 to 2.0 seconds.
- When P-High is < 16 cmH2O and T-High is 12-15 seconds, wwitch pt over to CPAP/PSV at standard settings.

Nitric Oxide

- Nitric oxide is a selective pulmonary vasodilator
- Redistributes pulmonary blood flow from unventilated lung units to ventilated lung units resulting in decrease V/Q mismatch
- Because it is selective it does not produce systemic side effects





Aerosolized Prostacyclin

- Aerosolized prostacyclin (Flolan) has been shown to be as effective as Inhaled Nitric Oxide (NO) as a selective pulmonary vasodilator.
- Flolan is FDA approved for the treatment of primary pulmonary hypertension by intravenous (IV) infusion.
- Prostacyclin, administered by inhaled aerosol, selectively dilates the pulmonary vascular bed.

Novel Therapies for ARDS

- Prone Positioning
- Nitric Oxide
- Inhaled Prostacycline
- Recruitment Maneuvers
- ECMO

Supportive Therapies to Improve Oxygenation

Recruitment Maneuvers

- A recruitment maneuver is a sustained increase in airway pressure with the goal to open collapsed lung tissue.

EXAMPLE

1. Sedation(?) & Pre-oxygenate with 100% FiO2
2. Change mode to CPAP and add 30 cm H_2O for 30 - 40 seconds.
3. Monitor Vt and oxygenation for 15 - 30 min. If unresponsive, repeat at CPAP of 35 to 40 cm H_2O.

Prone Positioning

- Most mechanically ventilated patients are cared for in the supine position.
- Studies have shown by flipping the patient over into the prone position may improve oxygenation.

Thank You!

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Effects of Lung Recruitment

Before Lung Recruitment

After Lung Recruitment

Other Novel Therapies

- Surfactant Therapy – inconsistent results
- Antioxidant Therapy – inconsistent results
- Glucocorticoid Therapy – inconsistent results (keep < 14 days)

In Summary….

- ARDS is a multisystem syndrome – not a "disease"
- Characterized by accumulation of excessive fluid in the lungs with resulting hypoxemia and ultimately some degree of fibrotic changes.
- The most frequent causes of ARDS include sepsis, aspiration, pneumonia and severe trauma
- Treatment is primarily supportive and can non-traditional types of ventilation and oxygenation strategies.