

Breathing Section: ACES

Updated References

Acute Respiratory Distress Syndrome

History:

- originally described according to cause of lung injury (for example ‘respirator lung’, Da Nang lung, shock lung etc.)
- Ashbaugh (Lancet 1967) first published description of ‘acute respiratory distress in adults’ which highlighted pathophysiology of lung injury common to many otherwise unrelated diseases (aspiration, trauma, near-drowning etc.) although some of the patients may have had volume overload contribute to lung injury
- originally called ‘adult respiratory distress syndrome’ but now referred to as ‘acute respiratory distress syndrome’ because of recognition that ARDS occurs in children, and the clinical picture is acute

Reference:

Acute Respiratory Distress Syndrome: A Historical Perspective Am J Respir Crit Care Med 2005;172:798-806.

Definitions:

1. **ALI ‘Acute Lung Injury’**
 - American European Consensus Conference 1992 – acute lung injury identified and defined as ‘syndrome of inflammation and increased permeability that is associated with a constellation of clinical, radiologic, and physiologic abnormalities that cannot be explained by, but may coexist with, left atrial or pulmonary capillary hypertension’
2. **ARDS ‘Acute Respiratory Distress Syndrome’**
 - ARDS (‘acute’ not adult) defined as subset of ALI with more severe oxygenation defect (all patients with ARDS meet criteria of ALI)

Definitions: (Conference 1992)

A three-criteria system including chest radiograph, oxygenation score, and exclusion of cardiogenic causes.

1. Acute onset, bilateral infiltrates on chest radiography,
 2. Pulmonary-artery wedge pressure of < 19 mm Hg or the absence of clinical evidence of left atrial hypertension, and
 3. Acute lung injury considered present if Pa_{O_2}/FI_{O_2} is ≤ 300 and the ARDS subset was defined with a more severe oxygenation deficit, $Pa_{O_2}/FI_{O_2} \leq 200$.
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Problems with the definition:

- underlying cause (ie. precipitating etiology) not included, and may affect outcome
- strategy of ventilatory support not defined when hypoxemia quantified (for example level of PEEP)
- an alternative approach to the definition of ARDS includes a PEEP requirement for the oxygenation assessment and a static compliance of < 50 ml/cmH₂O, and presence of preexisting condition ('Delphi definition' – may be more specific than traditional definition)

References:

Clinical Review. Acute Respiratory Distress Syndrome. BMJ 2007;335:389-394.

Differentiating cardiogenic (hydrostatic) and noncardiogenic edema (ALI or ARDS):

- cardiogenic pulmonary edema is due to increased fluid filtration (due to high hydrostatic pressures) into interstitial space, and ultimately alveoli of lung; in ALI/ARDS the fluid increase is due to increased permeability of alveoli and fluid has increased protein content (think exudative vs transudative as analogy)
- with the clinical setting of ARDS there will be an underlying cause:
 - pulmonary: pneumonia, aspiration, inhalation, near-drowning etc. or
 - extrapulmonary: sepsis, trauma, transfusion-related acute lung injury (TRALI), overdose etc.
 - note that ARDS will usually develop within 24 hours of underlying cause (ie. A is for 'acute')
- some factors that may suggest cardiogenic edema: S3 gallop, other signs of heart failure (peripheral edema, hepatic congestion etc.), elevated JVP – however these are nonspecific
- radiographic features of cardiogenic/noncardiogenic edema are similar, but cardiogenic edema more often associated with cardiomegaly, pleural effusions, septal lines ('Kerley B'), central distribution of edema ('batwing'), whereas noncardiogenic edema the edema may be more patchy or peripheral, and air bronchograms are more likely to be present

Reference:

Acute Pulmonary Edema. NEJM 2005;353:2788-96.

Differential Diagnosis:

- note that diagnosis is inclusive so that ALI/ARDS can coexist with other diagnoses (ie. pneumonia)
- some other diagnoses that appear similar may in fact be subacute or chronic (ie. lymphangitic carcinomatosis)
- it is important to identify underlying cause of ARDS, since underlying cause may affect therapy (for example ARDS due to pneumonia)
- acute noninfectious diffuse parenchymal lung diseases include:

Acute Interstitial Pneumonia (AIP)

Pathology: Organizing diffuse alveolar damage

Etiology: Idiopathic (Hamman-Rich syndrome), Collagen vascular disease (CVD), cytotoxic drugs, infections

Bronchoalveolar lavage (BAL): Neutrophilia (> 10%)

Acute Eosinophilic Pneumonia (AEP)

Pathology: Eosinophilic infiltration and diffuse alveolar damage

Etiology: Idiopathic, drugs

BAL: Eosinophilia (> 25%)

Acute BOOP (Bronchiolitis Obliterans Organizing Pneumonia)

Pathology: Organizing pneumonia

Etiology: Idiopathic, CVD, drugs, radiation, infections

BAL: Neutrophilia, and sometimes lymphocytosis (< 25%), eosinophilia (< 25%)

Diffuse Alveolar Hemorrhage (DAH)

Pathology: Pulmonary capillaritis, bland hemorrhage, diffuse alveolar damage

Etiology: Vasculitides, CVD, ABMA disease, coagulopathies, diffuse infections – note hemoptysis absent in > 30%

BAL: RBCs, hemosiderin-laden macrophages

Acute Hypersensitivity Pneumonitis:

Pathology: Granulomatous and cellular pneumonitis with diffuse alveolar damage

Etiology: Environmental and workplace antigens

BAL: Lymphocytosis (> 25%) and sometimes neutrophilia (< 10%)

Reference:

‘Imitators’ of ARDS: Implications for Diagnosis and Treatment Chest 2004;125:1530-1535.

Outcomes:

1. Mortality

- overall survival improving over time
- large ARDS trials have 28-day mortality in range of 25 – 30%
- mortality higher in older patients (60% for age >85 years)
- note that degree of hypoxemia is a poor predictor of outcome, and most patients do not die of oxygenation/ventilation problems but rather sepsis and multiple organ failure
- ARDS may also evolve into progressive pulmonary fibrosis and pulmonary hypertension (with a poor prognosis)

2. Outcomes in survivors

- significant long term morbidity (major morbidity includes: neuromuscular dysfunction (critical illness polyneuropathy, myopathy), neurocognitive dysfunction and neuropsychological dysfunction (depression, PTSD)); also compressive neuropathy such as ulnar/peroneal neuropathy (6%), heterotopic calcification (55)
- persistent neuromuscular weakness
 - ~20% loss of base-line weight at time of discharge from ICU
 - weakness and fatigue prominent
 - most PFTs normal by 6 months however CO diffusion test low at 12 months
 - decrease in exercise tolerance (6 minute walk)
 - ~ 6% of patients had decrease in O2 saturation with exercise as 12 months
 - weakness worse if history of steroid Rx

Neurocognitive problems^{2,3}

- neurocognitive problems in 73% of patients at hospital discharge, and 46 – 47% at 1 and 2 years (plateau effect of improvement)
- depression common – (moderate to severe) in 16 – 23% at 1 and 2 years
- anxiety: 23% at 2 years
- mental health improved over first year, but not after that (actually declined somewhat)
- decreased quality of life
- post-traumatic stress symptoms in family members ~ 30%, worse if believed information incomplete or shared in end-of-life decision making⁵
- also significant caregiver burden related to degree of neurocognitive/neuropsychological morbidity, depression symptoms, lifestyle disruption and employment reduction were common among informal caregivers of critical illness survivors (regardless of patient pre-ICU functional status)
- chronically critically ill patients (tracheostomy, failure to wean) have frequent severe, prolonged and permanent brain dysfunction; ~ half of patients who were not comatose had delirium⁶

References:

1. Epidemiology and Outcomes of Acute Lung Injury. Chest 2007;131:554-562.
2. The Critical Care Experience. A Patients' View. Am J Respir Crit Care Med 2004;170:357-359.
3. One-Year Outcomes in Survivors of ARDS. NEJM 2003;348:683-693.
4. Two Year Cognitive, Emotional and Quality-of-Life Outcomes in ARDS. Am J Respir Crit Care Med 2005;171:340-347.
5. Incidence and Outcomes of ALI. NEJM 2005;353:1685-1693.
6. Risk of Post-traumatic Stress Symptoms in Family Members of ICU Patients. Am J Respir Crit Care Med 2005;171:987-994.
7. Quality of Life after ARDS: a meta-analysis. Int Care Med 2006;174:538-544.
8. Brain Dysfunction. Another Burden for the Chronically Critically Ill. Arch Int Med 2006;166:1993.

9. Long-term Neurocognitive Function after Critical Illness. Chest 2006;130:869-878.
10. Informal Caregiver Burden among Survivors of Prolonged Mechanical Ventilation. Am J Resp Crit Care Med 2007;175:167-173.

Pathophysiology:

1. Exudative phase:

- neutrophil accumulation with activation and production of proinflammatory cytokines (however ARDS described in patients with absolute neutropenia)
- decreased surfactant production and inactivation of surfactant
- alveolar and capillary injury
- platelet activation and aggregation
- coagulation system involved with increased coagulability (protein C and S levels fall, increased expression of tissue factor and antifibrinolytic proteins)

2. Fibroproliferative phase

- chronic inflammation
- fibrosis

Reference:

Cellular Stress Failure in Ventilator Injured Lungs. Am J Respir Crit Care Med 2005;171:1328-42. (Basic science review of cellular stress, and VILI)

Transfusion Related Acute Lung Injury (TRALI)

- spectrum from mild decrease in oxygenation (ALI) to ARDS; case reports in literature that suggest transfusion may be associated with worsening of preexisting ARDS
- clinically may be difficult to distinguish TRALI from cardiogenic pulmonary edema
- definition:
 - clinical diagnosis
 - syndrome of hypoxia and pulmonary edema without evidence of congestive heart failure within 6 hours of transfusion
 - usually resolves within 24 – 72 hours
- close temporal relation to transfusion (often within 30 – 60 minutes, almost always w/i 2 hours)
- incidence ~ 1/ 1000 to 1/5000 blood products transfused; (underdiagnosed and under-reported therefore incidence may be higher)
- fatal in 5 – 10%
- etiology:
 - most often associated with plasma containing products – FFP and platelets
 - ? passive transfusion of plasma-containing blood product with HLA class antibody from donor or antigranulocyte antibodies
 - ? biologically active lipids that accumulate in blood products over time
- management: oxygenation, ventilation if required
 - no role for steroids
 - notify blood bank (this will allow identification of implicated donors to prevent TRALI in other recipients if antibodies detected)

Management and Therapy of ARDS

Nutrition:

- feeding with eicosapentaenoic acid (fish oil), gamma linoleic acid (borage oil) and antioxidants may improve outcome in patients with ARDS; recommended by Critical Care Nutrition group

Role of Fatty Acids in ARDS:

- fatty acids: aka 'fish oils'
- nomenclature refers to where the double bond is in the molecule, omega3 and 6 FA are polyunsaturated (PUFA) because they have 2 or more double bonds
- FA important in cell membranes as well as metabolic precursors of eicosanoids

omega 3:

metabolized to 3-series of prostanoids and 5-series of leukotrienes

- anti-inflammatory effects (for example TXA₂ vasoconstrictive, platelet aggregation and TXA₃ little effect on vasoconstriction, no effect on platelets)
- competitive inhibitors of 2- and 4- series eicosanoids
- dietary sources include canola oil, flax, fish

omega 6:

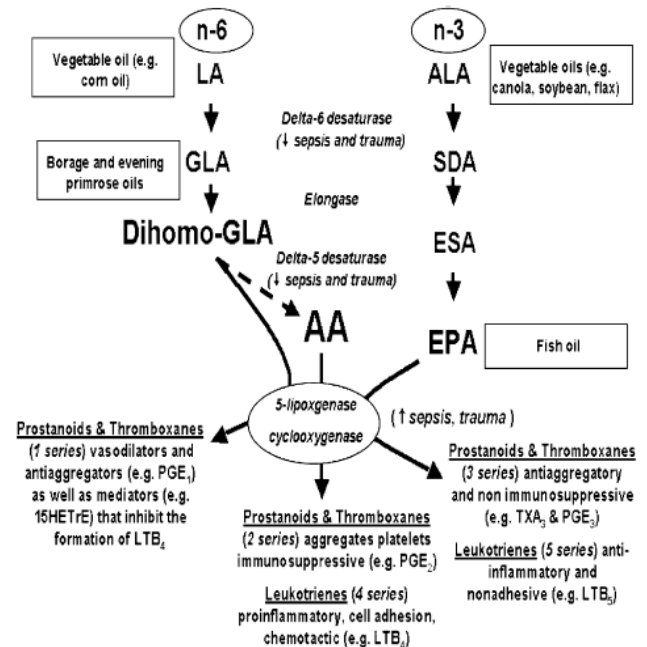
- precursor of 2- and 4- series of prostanoids (PGE₂, TXA₂ (thromboxane A₂), leukotriene B₄...) which are proinflammatory, vasoconstrictive, increase platelet aggregation, immunosuppressive (impair RES function, leukocyte migration)
- in addition use of GLA increases PG1 (vasodilator) and EPA moves metabolic pathway away from the production of arachidonic acid

eicosapentaenoic acid (EPA): (omega-3)

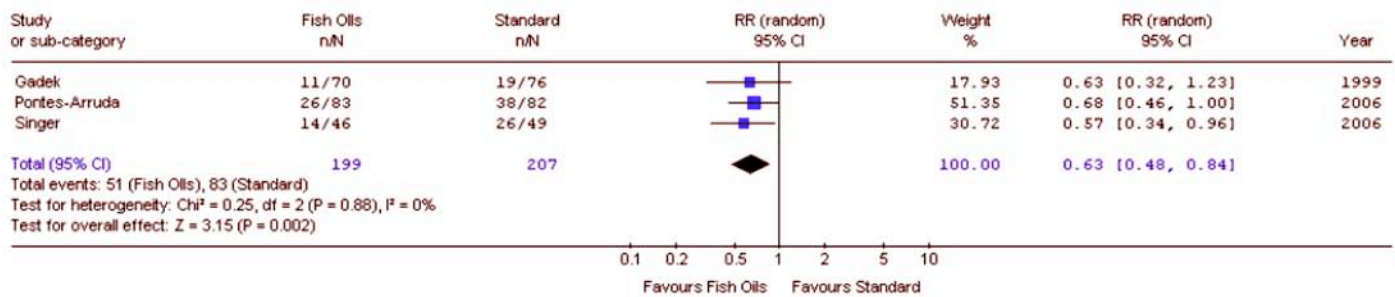
- can displace arachidonic acid in cell membranes, metabolites of -3 and -5 series anti-inflammatory

gamma linoleic acid (GLA): from borage oil

- metabolite of linoleic acid
- suppresses to PGE₁ (vasodilator and antiplatelet effect) and inhibition of formation of LTB₄



- ARDS is an inflammatory process
- feed with altered lipid profile possible benefit



Canadian Clinical Practice Guidelines:

'based on 1 level 1 study and 2 level 2 studies we recommend use of an enteral formula with fish oils, borage oils and antioxidants in patients with respiratory distress syndrome'

References:

1. Effect of enteral feeding with eicosapentaenoic acid and gamma-linolenic acid on outcome of mechanically ventilated critically ill patients. Crit Care Med 2006;34:supp
2. Effect of enteral feeding with EPA-GLA and antioxidants in patients with ARDS Crit Care Med 1999;27:1409-1420
3. A nutritional strategy to improve oxygenation and decrease morbidity in patients who have acute respiratory distress syndrome. Respir Care Clin 2006;12:547-566.
4. Current clinical applications of omega-6 and omega-3 FA. Nut Clin Practice 2006;21:323-338.

Oxepa®

- 1.5 kcal/ml
 - 10.15 g omega-3/l and EPA 4.6 (vs Jevity = 2.4/0)
 - 4.29 GLA/l (vs Jevity = 0)
 - omega 6:3 = 1.8:1 (vs Jevity = 5.5:1)
 - 20% fish oil
 - 20% borage oil
- + canola, soy

Ventilator Management:

Ventilator-induced lung injury (VILI) - pathophysiology

1. barotrauma: parenchymal stress or alveolar rupture
2. volutrauma: alveolar overdistension with damage to alveolar epithelium and capillary endothelium; observation that lung fraction open to gas exchange in ARDS is relatively small ('baby lung model'), so that usual tidal volume is actually a large tidal volume for the ventilated portion of the lung
3. atelectrauma: injury due to repetitive opening and closing of lung units with associated shear stress
4. biotrauma: inflammatory reaction of lung to injury including alveolar overdistension, with release of systemic inflammatory mediators/cytokines

Lung protective ventilation:

- designed to decrease lung injury due to mechanical ventilation
- experimentally alveolar distending pressures of 30 – 35 cm H₂O maximally distend normal alveoli
- ARDSNet trial – randomized patients with ARDS to control group (TV ~ 12 ml/kg PBW, plateau pressure < 50 cmH₂O) vs. lung protective strategy (TV ~ 6 ml/kg, Ppl < 30)
- decrease mortality from 39.8% to 31%

Ventilator Management Protocol ARDSNet

1. ventilator mode: assist/control volume cycled
2. tidal volume 6 ml/kg PBW
3. goals:
 - 1) Ppl < 30 cm H₂O
 - 2) TV as low as 4 ml/kg to limit Ppl as needed
 - 3) oxygen saturation 88-95%
 - 4) PEEP titrated as per algorithm
 - 5) pH 7.30 – 7.45
 - 6) for pH < 7.3
 - i. increase ventilator rate (max 35/min)
 - ii. if pH < 7.3 consider bicarbonate infusion
 - iii. pH < 7.15 use bicarbonate infusion
 - iv. if ongoing acidosis with pH < 7.15 and bicarbonate infusion then increase TV

Algorithm for Management of PEEP Used in ARDSNet Study

FiO₂	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	16	18	20-24

References:

1. Review: Ventilatory Management of ALI and ARDS. JAMA 2005;294;2889-2896. (Good review article)

2. Low Tidal Volume Ventilation does not increase Sedation use in Patients with ALI. Crit Care Med. 2005;33:766-771. (Use of ARDSNet protocol did not result in increased sedation requirements compared to control population – contrary to popular opinion).
3. Clinical implementation of the ARDSNet protocol is associated with reduced hospital mortality compared with historical controls. Crit Care Med 2005;33:925-929.
4. Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. Am J Respir Crit Care Med 2005;172:1241-45. (Authors try to answer the question of whether there is a safe upper limit to inspiratory plateau pressure in patients with ALI/ARDS. They were unable to determine a safe upper limit, and suggest that use of TV 6 ml/kg PBW should be used, even if higher tidal volumes do not cause Pplat to be higher than 30.)
5. Low-Tidal-Volume Ventilation in the ARDS. NEJM 2007;357:1113-1120. (Review)
6. Ventilator-associated Lung Injury. Lancet 2003;361:332-340.
7. Acute lung injury and ARDS: A clinical review. Lancet 2007;369:1553-1565.
8. Refining Ventilatory Treatment for ALI and ARDS. JAMA 2008;299:691-693.

Role of steroids in late ARDS:

- using steroids to try to prevent ARDS doesn't work, and may worsen outcome
- steroid Rx in early ARDS not useful
- small studies have suggested benefit of steroid in 'late' ARDS (> 1 week, unresolving ARDS) in lung function
- most recent study: placebo controlled trial of steroids (Solumedrol 2 mg/kg bolus then 0.5 mg/kg q 6 h with tapering dose over 21 days)
- overall no benefit on survival although steroids increased number of ventilator free-days and shock-free days during first 28 days
- if steroids were started 2 or more weeks after onset of ARDS there was an increased mortality rate at 60 and 180 days
- overall conclusion – no support for routine use of steroids in persistent ARDS

References:

1. Efficacy and Safety of Corticosteroids for Persistent ARDS. NEJM 2006;354:1671-1684.
2. Lung Inflammation in ARDS – Friend or Foe? NEJM 2006;354:1739
3. Nonventilatory Treatments for Acute Lung Injury and ARDS. Chest 2007;131:913-920.
4. Corticosteroids in the prevention and treatment of ARDS in adults: meta-analysis. BMJ 2008;336:1006-1009.

Pulmonary Artery Catheter:

- multicentre randomized trial (n = 1000) showed no change in outcome with use of PAC in patients with ARDS
- therapy was guided by use of PAC or CMP monitoring, protocol driven, and extensive education done with respect to use of PAC
- more arrhythmias with PAC
- conclusion: no evidence to support use of PAC in patients with ARDS

Reference:

Pulmonary Artery Catheter versus Central Venous Catheter to Guide Treatment of Acute Lung Injury. NEJM 2006;354;2213.

Fluid Management:

- randomized trial of conservative vs liberal fluid strategy using protocols over 7 days in 1000 patients
- over the 7 days the conservative strategy group had a cumulative fluid balance of -136 ml, and the liberal-strategy group had a balance of +6992 ml
- restrictive fluid management in patients with ARDS seems to result in better oxygenation, decreased ventilator days and no increase in nonpulmonary organ failure, overall no difference in 60-day mortality

References:

1. Comparison of Two Fluid-Management Strategies in Acute Lung Injury. NEJM 2006;354.
2. Fluid-Management Strategies in Acute Lung Injury – Liberal, Conservative or Both? NEJM 2006;354 (accompanying editorial by E. Rivers – is it best to resuscitate aggressively with fluids in the first few hours with severe sepsis, and then to be more conservative with fluid?)
 - addition of albumin to furosemide therapy improved oxygenation and associated with more negative fluid balance
3. A Randomized Controlled Trial of Furosemide with or without Albumin in Hypoproteinemic Patients with ALI. Crit Care Med 2005;33:1681-1687.

Positive End Expiratory Pressure:

ALVEOLI trial ¹

- randomized controlled trial of two protocols for PEEP, using a lower PEEP (from the original ARDSNet protocol) and a protocol designed to provide higher levels of PEEP in response to oxygenation (n=549)
- protocol changed early in trial to provide an increased difference in PEEP between the two groups
- recruitment maneuvers used in first 80 patients in higher PEEP group however improvement in oxygenation found to be small and transient, associated with occasional hypotension so recruitment maneuvers not used for the rest of the trial
- results: clinical outcomes similar in the two groups (trial stopped early for futility)

LOV and EXPRESS trials ^{2,3}

- LOV trial used ARDSnet ventilation strategy in control group and compared with a protocol to recruit and open lung using recruitment maneuvers and higher PEEP levels
- EXPRESS study used bedside assessment of lung mechanics to identify minimal distension strategy (lower PEEP group) vs. recruitment strategy (higher PEEP group)
- no effect on mortality for higher/lower level PEEP in these studies, also note higher levels of PEEP within a limited plateau pressure were not associated with harm

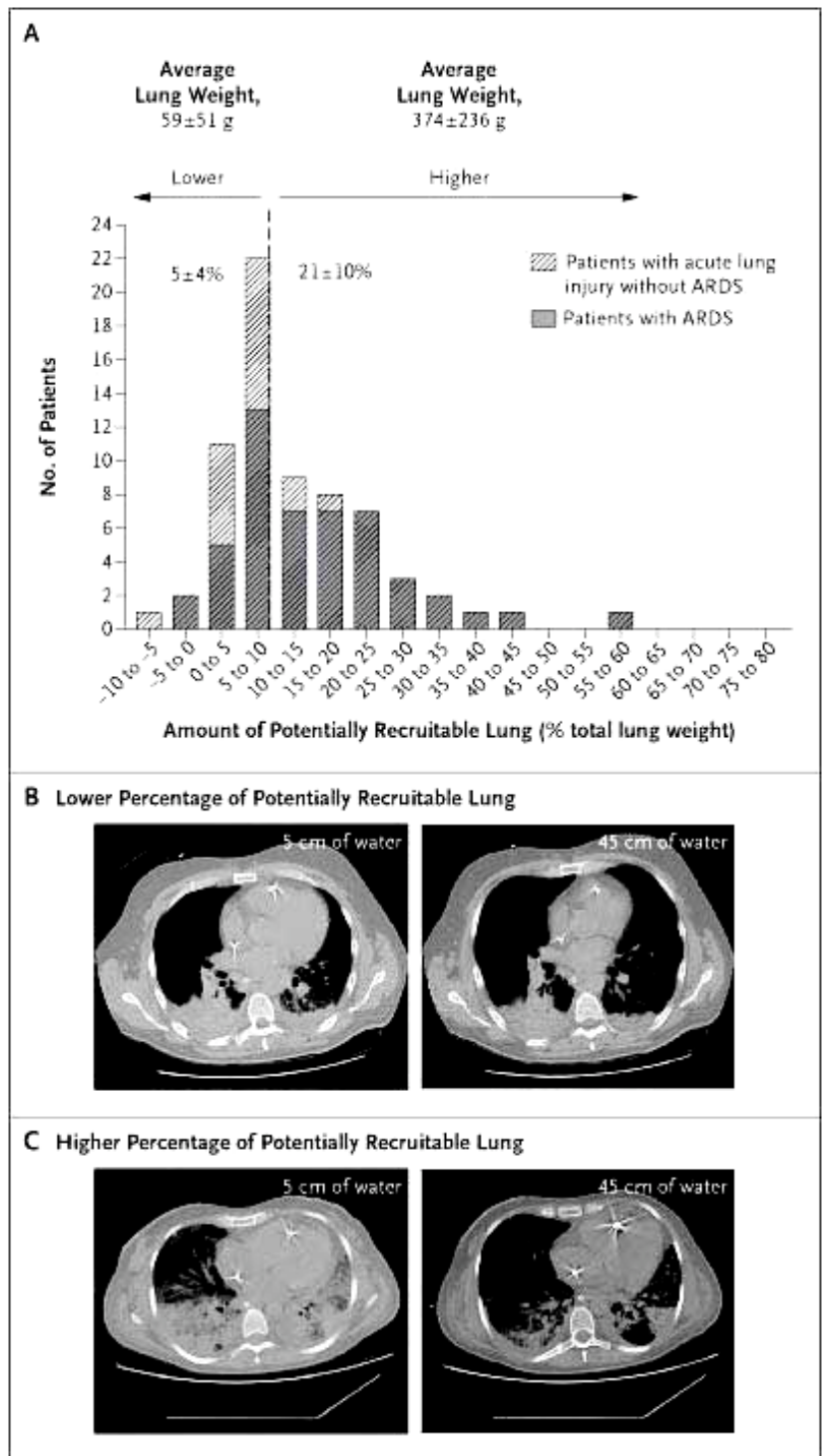
References:

1. Higher versus Lower Positive End-Expiratory Pressure in Patients with Acute Respiratory Distress Syndrome. NEJM 2004;351:327-36. ('ALVEOLI trial')
2. Lung Open Ventilation (LOV) Study. Ventilatory strategy using low tidal volumes recruitment maneuvers, and high PEEP for ALI and ARDS. A RCT. JAMA 2008;299:637-645.
3. Expiratory Pressure (Express) Study. PEEP in ALI and ARDS, a RCT. JAMA 2008;299:646-655.
4. Mechanical Ventilation in ARDS: A State of the Art Review. Chest 2007;131:921-929,

Lung Recruitment in ARDS – Determined by CT Scan

- 68 patients with ALI or ARDS had CT scans at airway pressures of 5, 15, and 45 cm of water
- after a recruitment maneuver PEEP of 5 or 15 randomly applied
- percentage of potentially recruitable lung varied widely, from virtually none to over 50% of lung weight
- higher percentage of recruitable lung associated with worse gas exchange, lower lung compliance and higher mortality rate
- use of higher PEEP in patients with lower percentage of recruitable lung had little benefit

Panel A shows the frequency distribution of the 68 patients in the overall study group according to the percentage of potentially recruitable lung, expressed as the percentage of total lung weight. Acute lung injury without ARDS was defined by a $\text{PaO}_2:\text{FIO}_2$ of less than 300 but not less than 200, and ARDS was defined by a $\text{PaO}_2:\text{FIO}_2$ of less than 200. The percentage of potentially recruitable lung was defined as the proportion of lung tissue in which aeration is restored at airway pressures between 5 and 45 cm of water. Panel B shows representative CT slices of the lung obtained 2 cm above the diaphragm dome at airway pressures of 5 cm of water (left) and 45 cm of water (right) from a patient with a lower percentage of potentially recruitable lung (at or below the median value of 9 percent of total lung weight). Lung injury developed in the patient after an episode of severe acute pancreatitis ($\text{PaO}_2:\text{FIO}_2$, 296 at an airway pressure of 5 cm of water; PaCO_2 , 34 mm Hg; and respiratory-system compliance, 44 ml per centimeter of water). The percentage of potentially recruitable lung was 4 percent, and the proportion of consolidated lung tissue was 33 percent of the total lung weight. Panel C shows representative CT slices of the lung obtained 2 cm above the diaphragm dome at airway pressures of 5 cm of water (left) and 45 cm of water (right) from a patient in the group with a higher percentage of potentially recruitable lung. Lung injury developed in the patient after an episode of severe pneumonia ($\text{PaO}_2:\text{FIO}_2$, 106 at a PEEP of 5 cm of water; PaCO_2 , 58 mm Hg; and respiratory-system compliance, 25 ml per cm of water). The percentage of potentially recruitable lung was 37 percent, and the proportion of consolidated lung tissue was 27 percent of the total lung weight.



References:

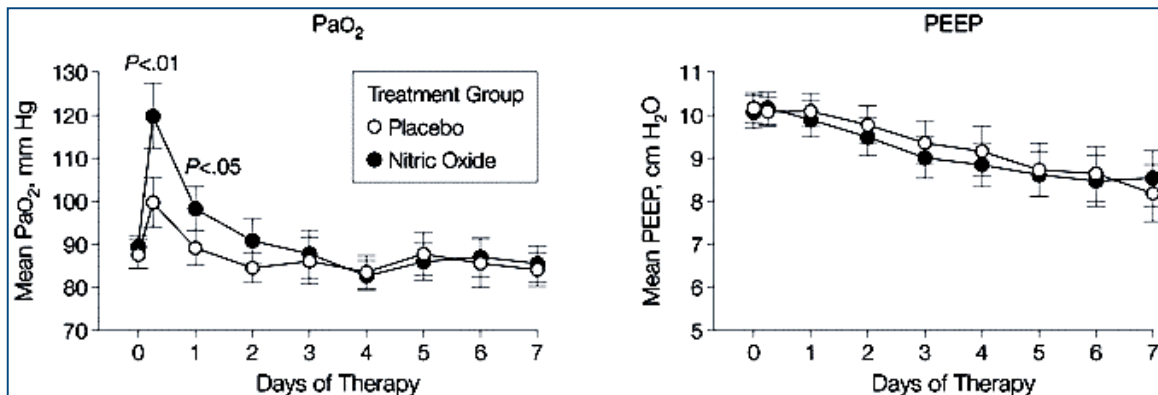
1. Lung Recruitment in Patients with ARDS. NEJM 2006;354;1775-86.
2. PEEP or No PEEP – Lung Recruitment may be the Solution. NEJM 2006;354;1839-41.
3. Tidal Recruitment and Overinflation in ARDS. Am J Resp Crit Care Med 2007;175:160 , 104.

Nitric Oxide

- overall no sustained benefit in ARDS
- note: in Ontario nitric oxide supplied as medical gas with delivery system, cost is as high as ~\$100/hour

Oxygenation:

- improvement of ventilation/perfusion distribution by selective vasodilation of pulmonary vessels of ventilated lung units
- improvement of oxygenation seen in patients with ARDS (original report NEJM 1993 – pulmonary artery pressure decreased from ~37 → 30 and PO₂/FIO₂ increased from 152 → 199)
- overall response rates in ARDS with improvement in oxygenation ~60%
- effect seen with ~5 ppm (lower dose effective after 24 – 48 hours)
- effect on oxygenation is **not** sustained, and studies show that oxygenation in control and iNO groups is the same after ~72 hours, and no effect on outcomes so role of NO in ARDS appears limited



Meta-analysis of nitric oxide: conclusion: 'nitric oxide is associated with limited improvement in oxygenation in patients with ALI or ARDS but confers no mortality benefit and may cause harm. We do not recommend its routine use in these severely ill patients.'²

References:

1. Inhaled Nitric Oxide Therapy in Adults (Review Article): NEJM 2005;353:2683-2695.
2. Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis. BMJ 2007.

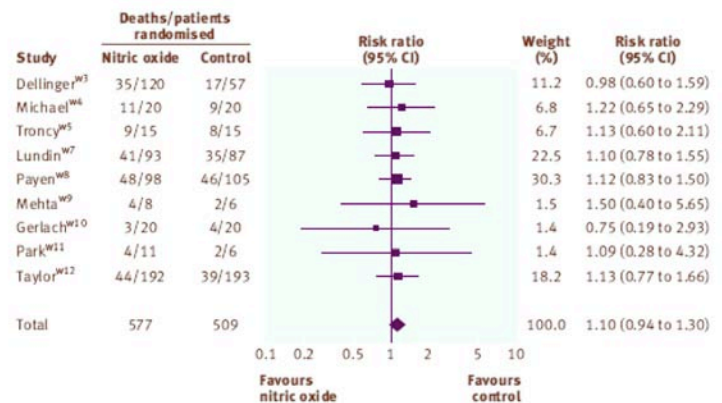


Fig 2 | Effect of nitric oxide on mortality. Weight is the relative contribution of each study to the overall estimate of treatment effect on a log scale assuming a random effects model. Two trials with ≥50% of control patients crossing over to nitric oxide also reported mortality data.^{W4} Inclusion of these trials did not alter summary mortality estimate (risk ratio 1.09, 0.94 to 1.27)

Prone Position:

- prone positioning improves oxygenation in the majority of patients with ARDS, however randomized trials have not shown an overall benefit in outcome
- mechanisms for improved oxygenation include: recruitment of dependent atelectatic lung, improved respiratory mechanics, better ventilation of dorsal lung, and less weight of the heart on the lungs, better secretion drainage
- previous trials however used prone positioning for a relatively short part of each day (7 to 9 hours/24)
- more recent study randomized patients (n=136) to prone positioning for an average of 17 hours/day for ~ 10 days
- trend (not statistically significant) to lower morbidity and mortality in prone patients

Reference:

A Multicenter Trial of Prolonged Prone Ventilation in Severe ARDS. Am J Respir Crit Care Med 2006;173:1233-39.

High-Frequency Oscillatory Ventilation

- respiratory rate 3 – 10 Hz (180-600/min) with a humidified inspiratory bias flow, piston pump and a resistance valve that allows control of mean airway pressure
- no evidence of improved outcome yet

Reference:

High-Frequency Oscillatory Ventilation for Adult Patients with ARDS. Chest 2007;131:1907-1916.

Noninvasive Ventilation:

- noninvasive ventilation decreased need for intubation and mortality in patients with acute cardiogenic pulmonary edema, no difference apparent between use of CPAP vs PPV

Reference:

Noninvasive ventilation in acute cardiogenic pulmonary edema. Systematic review and Meta-analysis. JAMA 2005;294:3124-3130.

- CPAP may improve oxygenation, decrease intubation, pneumonia and ICU length of stay in patients with hypoxemia post major elective abdominal surgery

Reference:

Continuous positive airway pressure for treatment of postoperative hypoxemia: A randomized controlled trial. JAMA 2005;293:589-595.

- in patients with ALI NIPPV decreases inspiratory muscle work, CPAP alone improves oxygenation but has little effect on unloading of respiratory muscles

Reference:

Physiologic effects of noninvasive ventilation during ALI. Am J Respir Crit Care Med 2005;172:1112-1118.

- NIPPV may be used in patients with decreased level of consciousness due to respiratory failure/hypercapnia due to COPD exacerbation

Reference:

NIPPV in patients with acute exacerbations of COPD and varying levels of consciousness. Chest 2005;128:1657-66.

NIPPV to treat hypercapnic coma secondary to respiratory failure. Chest 2005;127:952-960.

- NIPPV does not seem to be helpful (and may increase mortality) in trying to avoid reintubation when patients develop respiratory distress after extubation, although the time to reintubation may be lengthened (? postponing the inevitable); (Noninvasive positive-pressure ventilation for respiratory failure after extubation. N Engl J Med 2004;350:2452–2460)
- early use of NIPPV however may be useful when used in patients at risk of reintubation, applied immediately after extubation for a 24 hour period

Reference:

Early NIPPV averts extubation failure in patients at risk. Am J Respir Crit Care Med 2006;173:1640-170.