ARDS
Are we any further ahead?

Dan Zuege MD MSC FRCPC
Medical Director PLC ICU
Pulmonary and Critical Care Medicine

Case Introduction

- Would we all recognize this patient on the ward?
- Would we put ARDS as one of his diagnoses?
- If he ends up in the ICU, what can you do for him? Will any of it make a difference?
- How well is he likely to do?

"Adult Respiratory Distress Syndrome"

"The acute onset of severe respiratory distress and cyanosis that was refractory to oxygen therapy and associated with diffuse CXR abnormality and decreased lung compliance"

Ashbaugh, Bigelow, Petty Lancet 1967

What is ARDS?

Adult Respiratory Distress Syndrome
Acute Respiratory Distress Syndrome
Acute Lung Injury

Why is a definition important?

Lung Injury Score

Table 1.1. Lung injury score

Component	Score
1. Chest roentgenogram	
Alveolar consolidation	0
Alveolar consolidation confined to 1 quadrant	1
Alveolar consolidation confined to 2 quadrants	2
Alveolar consolidation confined to 3 quadrants	3
Alveolar consolidation confined to 4 quadrants	4
2. PaO_2/FiO_2	
≥ 300	0
225–299	1
175–224	2
100–174	3
<100	4
3. PEEP (cm H_2O) (when ventilated)	
≤ 5	0
6–8	1
9–11	2
12–14	3
≥ 15	4
4. Respiratory compliance (mL/cm H_2O) (when available)	
≥ 80	0
60–79	1
40–59	2
20–39	3
≤ 19	4

The final lung injury score is the average score of the components that were used.

	Lung injury score
No lung injury	0
Mild-to-moderate lung injury	0.1–2.5
Severe lung injury (ARDS)	> 2.5

Source: Adapted from Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 1988; 138:720–723.

INJURY	CRITERIA
Acute lung injury	Acute onset $PaO_2/FiO_2 \leq 300$ mm Hg Bilateral pulmonary "infiltrates" on frontal chest radiograph Pulmonary artery wedge pressure ≤ 18 mm Hg (when measured) or no clinical evidence of left atrial hypertension
Adult respiratory distress syndrome	Acute onset $PaO_2/FiO_2 \leq 200$ mm Hg Bilateral pulmonary "infiltrates" on frontal chest radiograph Pulmonary artery wedge pressure ≤ 18 mm Hg (when measured) or no clinical evidence of left atrial hypertension

Chest X-Ray

"It was felt that the chest radiographic infiltrates should be bilateral and should be consistent with pulmonary edema, and, importantly, it was felt that these infiltrates could sometimes be very mild."

Bernard GR et al, AJRCCM 1994, 149:818

Inter-observer Variability in X-Ray Interpretation

21 experts reviewed 28 films

- 43% of films: complete agreement
- 32% films: significant disagreement
- % consistent with ALI/ARDS: 36 71%

Rubenfeld et al Chest 118:566, 2000

ARDS/ALI Definition – Best we can do for now..

INJURY	CRITERIA
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ARDS

A syndrome often progressive and characterized by distinct clinical, pathological and radiographic stages

Table 2. CLINICAL DISORDERS ASSOCIATED WITH ACUTE RESPIRATORY DISTRESS SYNDROME

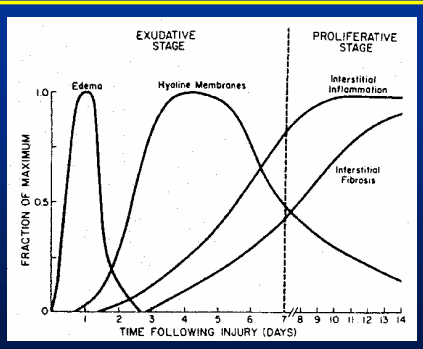
Direct Lung Injury	Indirect Lung Injury*
Aspiration of gastric contents	Severe sepsis
Severe thoracic trauma	Severe nonthoracic trauma
Pulmonary contusion	Multiple long bone fractures
Diffuse pulmonary infection	Hypovolemic shock
Bacterial	Hypertransfusion
Viral	Acute pancreatitis
Pneumocystis carinii	Drug overdose
Toxic gas (smoke) inhalation	Reperfusion injury
Near-drowning	Post-lung transplantation
	Post-cardiopulmonary bypass

*Caused by activation of an acute, systemic inflammatory response with hematogenous delivery of inflammatory mediators to the lungs.

Stages of ARDS

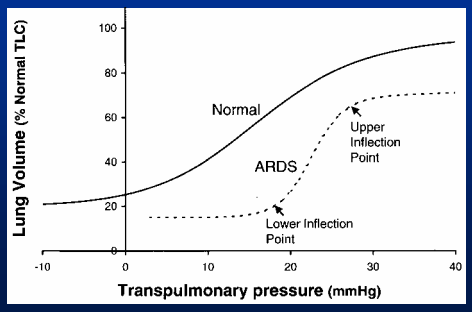
1. Exudative (acute) phase- 0 4 days
2. Proliferative phase- 4 8days
3. Fibrotic phase- >8 days
4. Recovery

Time Course of Evolution of ARDS

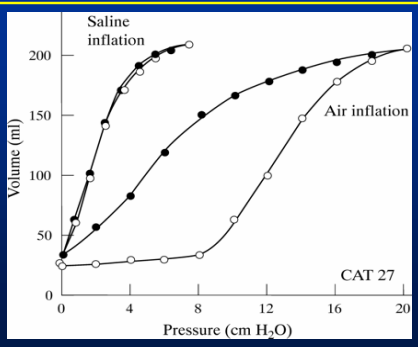


Katzenstein AA and FB Askin ,Surgical Pathology of Non-Neoplastic Lung Diseases.Philadelphia,Saunders,1982.

ARDS Physiology

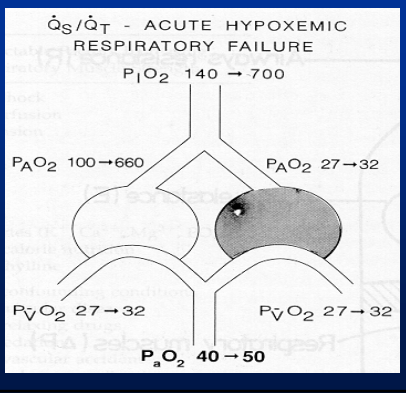


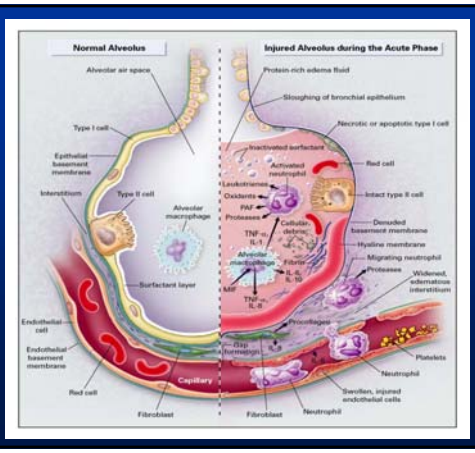
Pulmonary pressure volume curves : inflation and deflation / air vs saline.



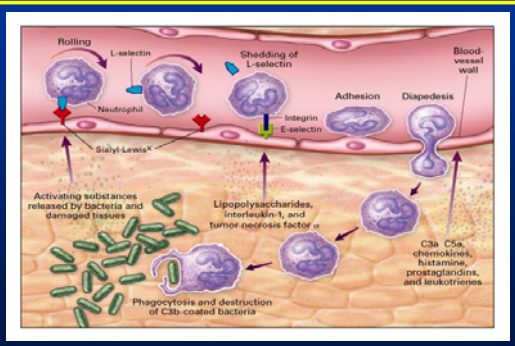
Jonson B. and C. Svantesson,Thorax 1999;54:82-87.

Shunt





ARDS and Inflammation



Genetics and Critical Care

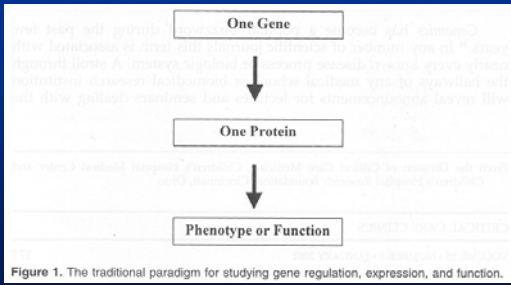
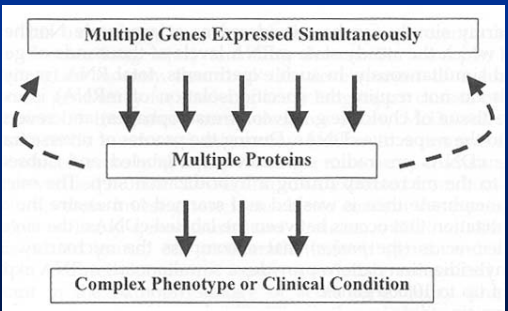


Figure 1. The traditional paradigm for studying gene regulation, expression, and function.

Genomics and Critical Care



Association of *TNF2*, a TNF-α Promoter Polymorphism, With Septic Shock Susceptibility and Mortality

A Multicenter Study

Table 6. Predictive Factors of Mortality Using a Multiple Logistic Regression Model

Deceased	Odds Ratio (95% Confidence Interval)	SE	z	P>|z|
Age*	1.46 (1.06-2.00)	0.24	2.32	.02
Derived probability of dying†	1.22 (1.01-1.46)	0.11	2.08	.04
TNF2	3.75 (1.37-10.24)	1.99	2.58	.01

*Odds ratio per 10 years of increase.
†Odds ratio per 10% increase of the Simplified Acute Physiologic Score (SAPS II)-derived probability of dying.

Mira JP et al JAMA 1999

Polymorphism in the Surfactant Protein-B Gene, Gender, and the Risk of Direct Pulmonary Injury and ARDS*

Michelle Ng Gong, MD; Zhou Wei, PhD; Li-Lian Xu, MD; David P. Miller, PhD; B. Taylor Thompson, MD; and David C. Christiani, MD, FCCP

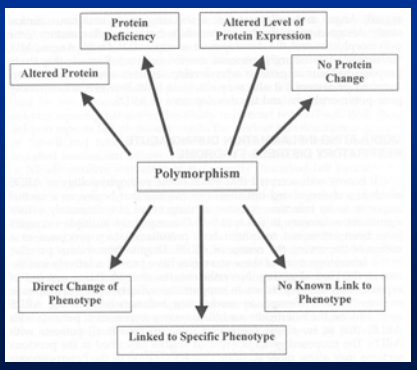
Table 4—*Logistic Regression Analysis for Variant SP-B Genotype and Development of ARDS and Direct Pulmonary Injury*

	Cohort		Men		Women	
Outcome	OR (95% CI)*	p Value	OR (95% CI)*	p Value	OR (95% CI)*	p Value
ARDS†	2.1 (0.9–4.7)	0.08	1.2 (0.4–3.8)	0.7	4.5 (1.1–18.8)	0.03
Direct pulmonary injury‡	1.6 (0.7–3.5)	0.3	0.8 (0.3–2.3)	0.7	4.6 (1.0–19.9)	0.04

*Adjusted for white race, age, history of alcohol abuse, diabetes, multiple (> 1) risk factors for ARDS, and APACHE III score. APACHE II score was recalculated without the age component prior to inclusion in the model.
†OR for developing ARDS compared to at-risk control subjects.
‡OR for being admitted to the ICU with direct pulmonary injury such as pneumonia or aspiration compared to patients admitted to the ICU with indirect pulmonary injury such as extrapulmonary infections, trauma or multiple transfusions.

Gong M et al CHEST 2004

Genomics and Critical Care



Back to the Case at hand…

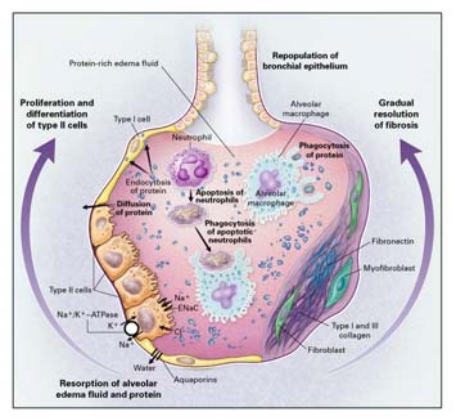
- Diagnoses: Severe CAP
  ARDS
  SIRS
- Initial management: Admitted
  Cultures
  Fluid (200 ml/hr NS)
  Oxygen
  Upright posture
  Good Antibiotics

ARDS - Treatment Principles

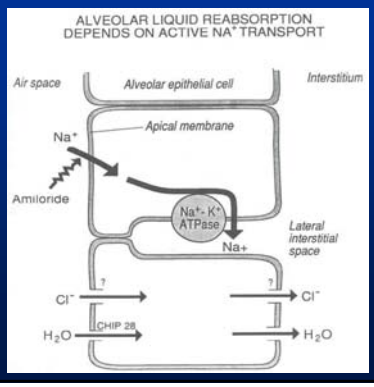
- Treat the primary problem!
- Physiologic Support
  - Of the lungs
  - Other organs
- Avoid Complications
  - Lung (barotrauma, VALI…)
  - Sepsis (pneumonia, other…)
  - Other (DVT, nutrition, 'stress' ulcers…)
- Disease Modifiers

How does the lung heal?

- Resorption of alveolar fluid
- Removal of alveolar protein
- Type II cell proliferation
- Resolution of inflammation



Lung Liquid Clearance and Na Transport



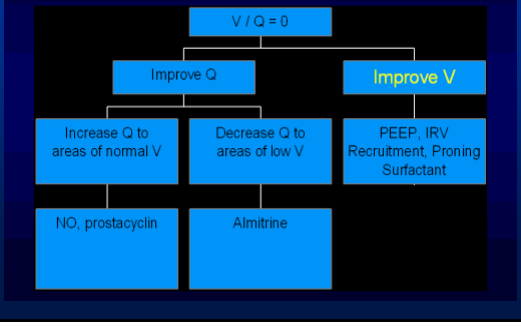
Treat the primary problem

- Infection – antibiotics, drainage
- Aspiration – prevent recurrence
- Drugs – identify culprit and avoid
- Fractures – operative fixation
- Pancreatitis – support, npo, +/- antibiotics

Physiologic support (lungs)

1. Adequate oxygenation
2. Adequate ventilation (C02 removal)
3. Anticipate and prevent complications

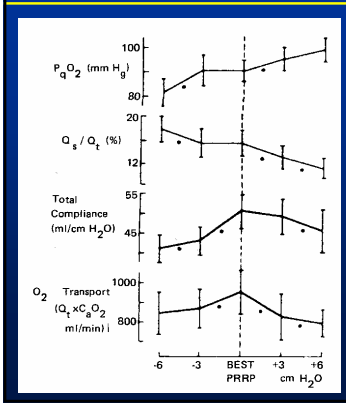
Goal #1: Improve Oxygenation, "Open The Lung"



Adequate oxygenation

1. Better Q relative to V
   - Pulmonary vasodilators (NO)
   - Increase cardiac output (fluid/other)
2. Better V relative to Q
   - PEEP
   - Inverse ratio ventilation
   - Recruitment maneuvers
   - Patient position
3. Fluid Management Overall – 'dry lungs are happy lungs'

Optimal PEEP

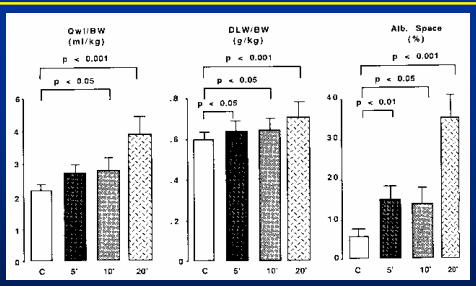


Changes in PaO_2, shunt (QS/QT), total compliance, and oxygen transport at values of PEEP higher and lower than an optimum level corresponding to best PEEP.

(From Suter et al., N.Engl.Med.1975:292:284–289.)

Zapol WM and F. Lemaire, ADULT RESPIRATORY DISTRESS SYNDROME, Marcel Dekker, Inc., 1991.

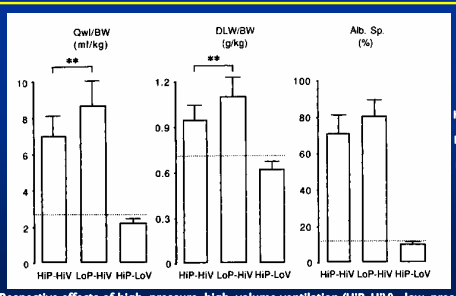
Lung Overinflation



Effect of 45 cmH_2O peak airway pressure ventilation of increasing duration on indices of pulmonary edema in rats. Extravascular lung water Qwl/BW, dry lung weight DLW/BW, and the distribution space in lungs of I–labeled albumin (Alb. Space) progressively increased as ventilation was continued. After 20 min of mechanical ventilation, there was a dramatic increase in all edema indices ($p < 0.01$ versus other groups). Moreover, at this stage, proteinaceous tracheal fluid was regularly found in the trachea. (Adapted from Dreyfuss et al.,Am.Rev.Respir.Dis.1985;132:880–884.)

Zapol WM and F. Lemaire, ADULT RESPIRATORY DISTRESS SYNDROME, Marcel Dekker, Inc., 1991.

Lung Overinflation



HIP–HIV : TV 40 ml/kg

LoP–HiV : TV 44 ml/kg

HIP–LoV : TV 19 ml/kg

Respective effects of high–pressure–high–volume ventilation (HIP–HiV), low–pressure–high–volume ventilation (LoP–HiV, iron lung), and high–pressure–low–volume ventilation (HIP–LoV, thoracoabdominal strapping during 45 cmH_2O IPPV). The dotted line represents the upper 95% confidence limit for control values. There was no edema in the animals that were not distended, but those with pulmonary distention presented high–permeability edema irrespective of airway pressure ($p < 0.0001$ versus controls). (Reproduced from Dreyfuss et al.,Am.Rev.Respir.Dis.1988;137:1159–1164.)

Zapol WM and F. Lemaire, ADULT RESPIRATORY DISTRESS SYNDROME, Marcel Dekker, Inc., 1991.

Tidal Ventilation at Low Airway Pressures: Lung Injury

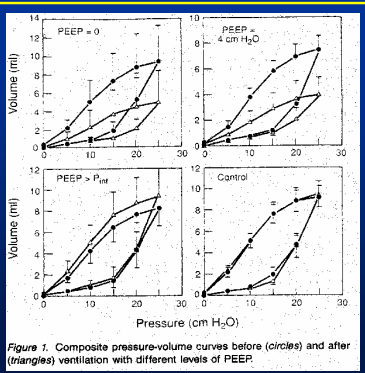
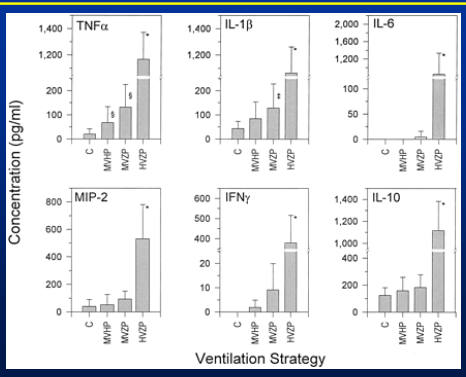


Figure 1. Composite pressure-volume curves before (*circles*) and after (*triangles*) ventilation with different levels of PEEP.

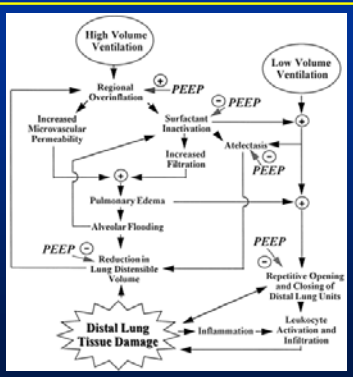
Muscedere JG et al., Am J Respir Crit Care Med., 1994; 149: 1327-34.

Ventilation strategy and lung lavage cytokine concentrations



Tremblay L. et al ,J. Clin.Invest. 1997; 99:944-952.

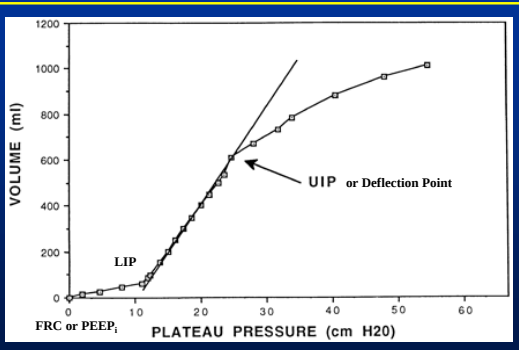
Injurious Ventilatory Strategies



PEEP generally opposes injury or edema formation (minus sign) except when it contributes to overinflation (plus sign)

Dreyfuss D. and G. Saumon, Am. J. Respir. Crit. Care Med., Volume 157, Number 1, January 1998, 294-323.

Inspiratory P / V curve in an ARDS patient



Roupie E. et al AJRCCM 1995; 152: 121-128

NIH NHLBI ARDS Network

Prospective, Randomized, Multi- Center Trial of 12 ml/kg Vs 6 ml/kg Tidal Volume Positive Pressure Ventilation for Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome

"Respiratory Management in ALI/ARDS"

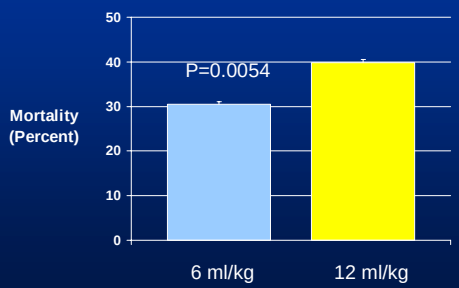
Primary Endpoints

Mortality prior to hospital discharge with unassisted breathing.

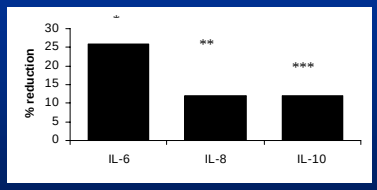
Ventilator Free Days (VFDs)

Days alive, off mechanical ventilation between enrollment and day 28

Mortality Prior to Hospital Discharge

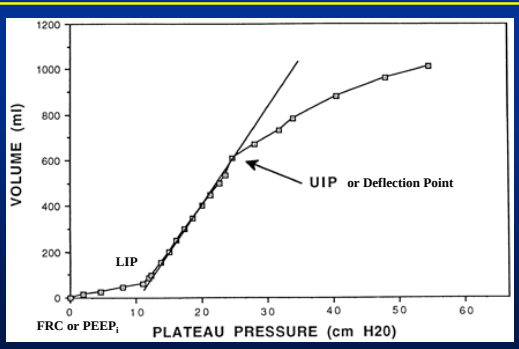


IL-6 and IL-8 are Significantly Decreased in Patients Ventilated with 6 ml/kg *vs* 12 ml/kg



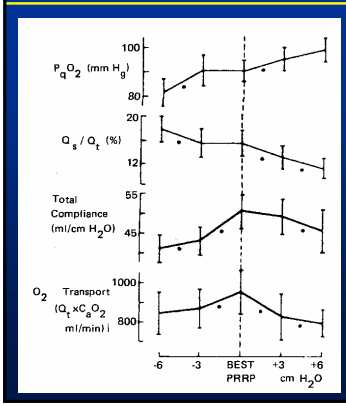
* p = 0.0006 , ** p = 0.04, *** p = 0.15

Inspiratory P / V curve in an ARDS patient



Roupie E. et al AJRCCM 1995; 152: 121-128

Optimal PEEP



Changes in PaO_2, shunt ($\dot{Q}S/\dot{Q}T$), total compliance, and oxygen transport at values of PEEP higher and lower than an optimum level corresponding to best PEEP.

(From Suter et al., N.Engl.Med. 1975:292:284–289.)

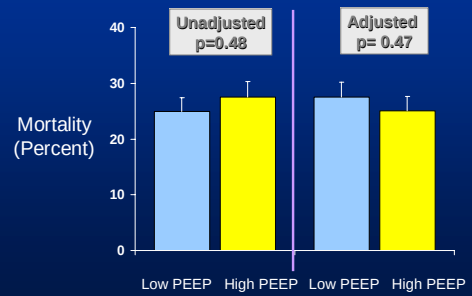
Zapol WM and F. Lemaire, ADULT RESPIRATORY DISTRESS SYNDROME, Marcel Dekker, Inc., 1991.

ALVEOLI Study

Prospective, Randomized, Multi-Center Trial of Higher PEEP/Lower F_iO_2 versus Lower PEEP/Higher F_iO_2 Ventilation in Acute Lung Injury and Acute Respiratory Distress Syndrome

NIH NHLBI ARDS Network

Mortality Before Hospital Discharge



'Conventional' Ventilation for ARDS – Current Approach

1. Avoid overdistension (VALI)- low tidal volume (~6 ml/Kg), relatively higher RR
2. Avoid underdistension (atelectasis, cyclical airway collapse, VALI)- relatively high PEEP (theoretically > lower inflection point of P V curve)
3. Try to ventilate on the deflation limb of P V curve- recruitment maneuvers
4. Enough oxygen
5. Tolerate hypercapnia

Patient Position

- Lateral?
- Prone?
- Head of bed up?

Randomized Trial of Prone Positioning

Patient selection:
patients with ALI/ARDS

Patients enrolled:
304: 152 each arm

Study protocol:
prone position for > 6 hours each day for 10 days

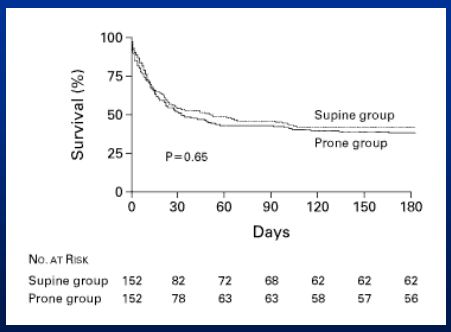
Gattinoni NEJM 2001;345:568-573

Oxygenation Improved Modestly Prone

Variable	Mean Change Supine	Prone	p value
PaO2	8.5 +/- 27	15+/- 26	0.04
FiO2	-7.6 +/-18	-12.7+/-19	0.02
P/F ratio	44.6+/-68	63+/-67	0.02

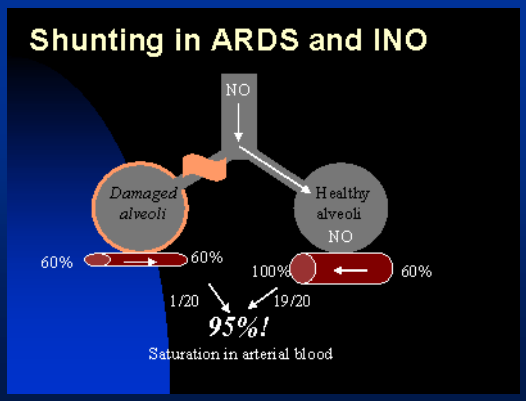
Gattinoni NEJM 2001;345:568-573

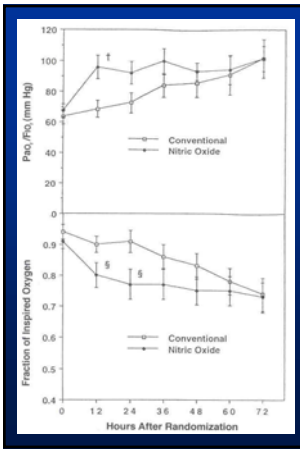
There Was No Improvement in Survival



Gattinoni NEJM 2001;345:568-573

Shunting in ARDS and INO

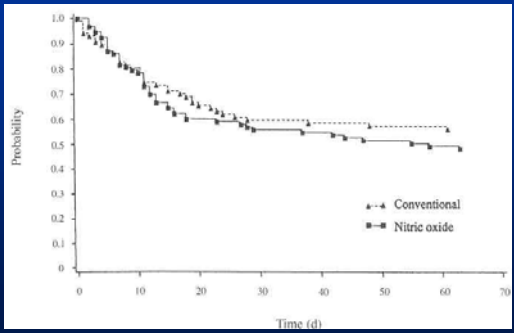




- RCT NO in ARDS
- Transient improvement in oxygenation only

Michael J et al AJRCCM 1994

NO in ARDS – NO effect on mortality



Lundin S et al Intensive Care Med 1996

HFOV in ALI/ARDS

Patients enrolled:

148 with ARDS (P/F <200 with PEEP>10)

Patients randomized to:

Conventional ventilation or HFOV

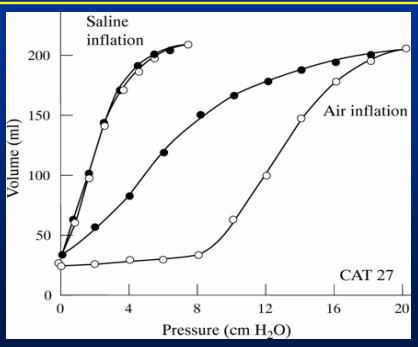
Derdak S et al AJRCCM 166:801, 2002

HFOV Trial Outcomes

Modality	N	30 day Mortality
HFOV	75	28 (37%)
Conventional	73	38 (52%)

Derdak S et al AJRCCM 166:801, 2002

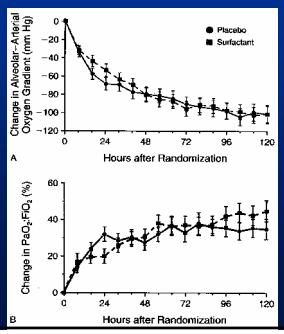
Pulmonary pressure-volume curves: inflation and deflation / air *vs* saline



Jonson B. and C. Svantesson,Thorax 1999;54:82-87.

AEROSOLIZED SURFACTANT IN ADULTS WITH SEPSIS-INDUCED ACUTE RESPIRATORY DISTRESS SYNDROME

Antonio Anzueto, M.D., Robert P. Baughman, M.D., Kalpalatha K. Guntupalli, M.D., John G. Weg, M.D., Herbert P. Wiedemann, M.D., Antoni Artigas Raventós, M.D., François Lemaire, M.D., Walker Long, M.D., David S. Zaccardelli, Pharm.D., and Edward N. Pattishall, M.D., for the Exosurf Acute Respiratory Distress Syndrome Sepsis Study Group*



- Exosurf Trial
- 725 ARDS patients randomized to surfactant or placebo
- No effects on physiology, length of stay or survival

Surfactant – Any Future?

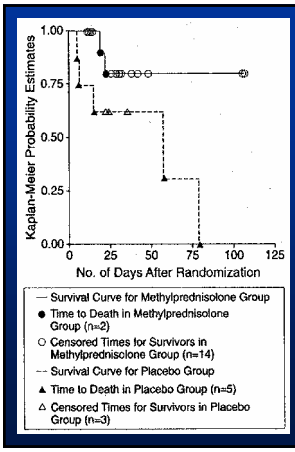
- Possible reasons for failure of Exosurf:
  - Poor delivery system (aerosolized *vs* instilled directly)
  - Low dose
  - Lack of surfactant proteins
  - Inhibition of surfactant via alveolar/plasma proteins
- New surfactant preparations under active study

Effect of Prolonged Methylprednisolone Therapy in Unresolving Acute Respiratory Distress Syndrome

A Randomized Controlled Trial

G. Umberto Meduri, MD; A. Stacey Headley, MD; Emmel Golden, MD; Stephanie J. Carson, RN; Reba A. Umberger, RN; Tiffany Kelso, PharmD; Elizabeth A. Tolley, PhD

- RCT of with ARDS of mean duration 9 days
- 24 patients over 2 years
- Built in cross overs
- "Sequential clinical trial"
- One tailed hypothesis



- New VAP
  - 9/16 - steroid
  - 1/8 - placebo
- Bottom line = poor study
- Ongoing NIH DB RCT (results likely 2005)

Alveolar Fluid Clearance Is Impaired in the Majority of Patients with Acute Lung Injury and the Acute Respiratory Distress Syndrome

LORRAINE B. WARE and MICHAEL A. MATTHAY

Cardiovascular Research Institute and Departments of Medicine and Anesthesia, University of California, San Francisco, San Francisco, California

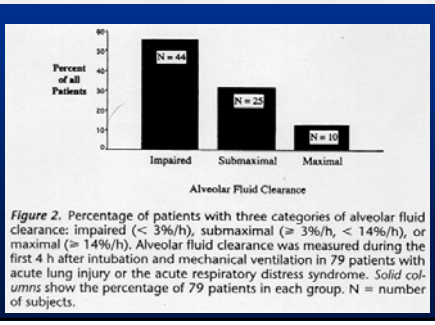
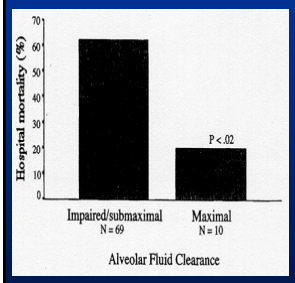
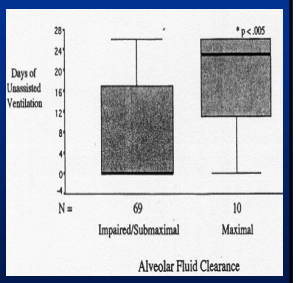


Figure 2. Percentage of patients with three categories of alveolar fluid clearance: impaired (< 3%/h), submaximal (≥ 3%/h, < 14%/h), or maximal (≥ 14%/h). Alveolar fluid clearance was measured during the first 4 h after intubation and mechanical ventilation in 79 patients with acute lung injury or the acute respiratory distress syndrome. *Solid columns* show the percentage of 79 patients in each group. N = number of subjects.

Outcomes *versus* Lung Liquid Clearance



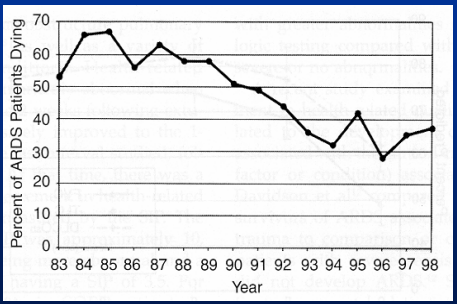


Modulators of Lung Liquid Clearance (experimentally)

- Hormones
  - Beta agonists
  - Dopamine
  - Gluco and mineralocorticoids
- Growth Factors – KGF, EGF
- Gene Transfer – Na-K-ATPase
- Excised human lung – beta agonists work

Lessons From Survivors

ARDS Mortality - Seattle



One-Year Outcomes in Survivors of the Acute Respiratory Distress Syndrome

- 109 survivors of ARDS (~93% of survivors)
- Patients evaluated in clinic 3, 6, and 12 months after ICU discharge
- Evaluation of symptoms, PFT's, 6MWD, QOL (SF-36), return to work

Herridge M et al NEJM 2003;348:683-693

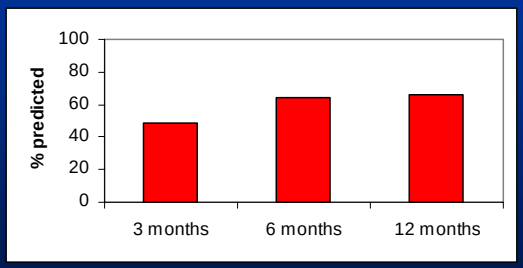
With the Exception of DLCO, Lung Function Returns to Normal

Table 2. Recovery of Pulmonary Function among Patients with the Acute Respiratory Distress Syndrome during the First 12 Months after Discharge from the ICU.

Variable	3 Mo (N=71)*	6 Mo (N=77)†	12 Mo (N=80)‡
	median (interquartile range)		
Forced vital capacity (% of predicted)	72 (57–86)	80 (68–94)	85 (71–98)
Forced expiratory volume in one second (% of predicted)	75 (58–92)	85 (69–98)	86 (74–100)
Total lung capacity (% of predicted)§	92 (77–97)	92 (83–101)	95 (81–103)
Residual volume (% of predicted)§	107 (87–121)	97 (82–117)	105 (90–116)
Carbon monoxide diffusion capacity (% of predicted)¶¶	63 (54–77)	70 (58–82)	72 (61–86)

Herridge M et al NEJM 2003

Six Minute Walk Test Improved Over Time but Limitations Persisted



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Short-Form General Health Score

	Score
Patients (3 months)	0
Patients (12 months)	25
Normal Subjects	84

49% of patients returned to work

Key limiting symptoms = fatigue, weakness (not respiratory)

Herridge M et al NEJM 2003

Quality of Life Scores are Poor

Table 2. Short Form 36 and St George's Respiratory Questionnaire Results for Acute Respiratory Distress Syndrome (ARDS) Survivors and Critically Ill or Injured Controls Matched for Severity of Illness*

	Population Controls†	All ARDS Cases (n = 77)	Matched ARDS Cases (n = 73)	Matched Controls (n = 73)
Short Form 36‡				
Physical functioning	84 ± 23	61 ± 25	62 ± 25	84 ± 17
Role-physical	81 ± 34	33 ± 33	34 ± 34	58 ± 32
Bodily pain	75 ± 24	53 ± 25	54 ± 25	68 ± 20
General health	72 ± 20	49 ± 21	50 ± 20	65 ± 19
Vitality	61 ± 21	49 ± 20	50 ± 19	64 ± 14
Social functioning	83 ± 23	60 ± 27	61 ± 27	78 ± 18
Role-emotional	81 ± 33	64 ± 41	66 ± 40	72 ± 36
Mental health	75 ± 18	64 ± 18	64 ± 18	75 ± 15
St George's Respiratory Questionnaire§				
Symptoms	12‖	45 ± 22	45 ± 22	26 ± 21
Activity	9‖	39 ± 23	39 ± 23	18 ± 17
Impacts	2‖	15 ± 16	15 ± 17	6 ± 9
Total¶	6‖	27 ± 17	27 ± 18	13 ± 11

*Values are expressed as mean ± SD. *P* values were calculated using the *t* test comparing matched ARDS cases vs controls. The *P* value for role-emotional is .30. All others are *P*<.001.
†Based on previously published articles by the Committee on Medical Aspects of Automotive Study[11] and Mueller et al.[12]
‡Higher score denotes better health-related quality of life.
§Lower score denotes better health-related quality of life.
‖The SD value was unavailable.
¶Values indicate total average overall.

Davidson TA et al JAMA 1999, 28:354

Conclusions

- Patients who survive ARDS have persistent functional disability as measured by an abnormal 6 minute walk test and a low score on the SF-36.
- Muscle weakness and fatigue were major contributors to this disability.
- ?Etiology – steroid myopathy
  critical illness neuromyopathy
  disuse myopathy
  weight loss…

Summary

- A definition of a syndrome is a key first step to understanding it
- We understand how lung injury develops much better than we understand how it resolves
- There is an increasing yet far from complete understanding of the influence of genetics on the incidence and outcome of ARDS
- Critical care is no longer just 'physiologic support' – the type of care influences outcome, including the potential for harm

Summary

- Mortality is improving – unclear why
- Outcome for survivors is good, but not as good as we previously thought (especially when we ask them!)
- We know more, but there is a long way to go
- Prediction- One day we will be able to modulate the recovery process from lung injury
- PS: The patient went home after 6 weeks of rehabilitation. He remains 'fatigued'.