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Author: Thomas Sisson, MD, 2009

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Acute Respiratory Distress Syndrome

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Division of Pulmonary and Critical Care

Winter 2009

University of Michigan
Medical School

Case Presentation:

Mrs. K is a 56 yo woman With Sickle Cell Trait and Known Cholelithiasis (Gall Stones) Transferred to UMMC For Respiratory Failure.

-8/3/06: 9/10 Abdominal Pain, Nausea and Vomiting.

-RUQ U/S Demonstrated Gall Stones and Evidence of Acute Cholecystitis.

-8/4/06: Surgery.

-8/5/06: POD #1, Unremarkable Recovery.

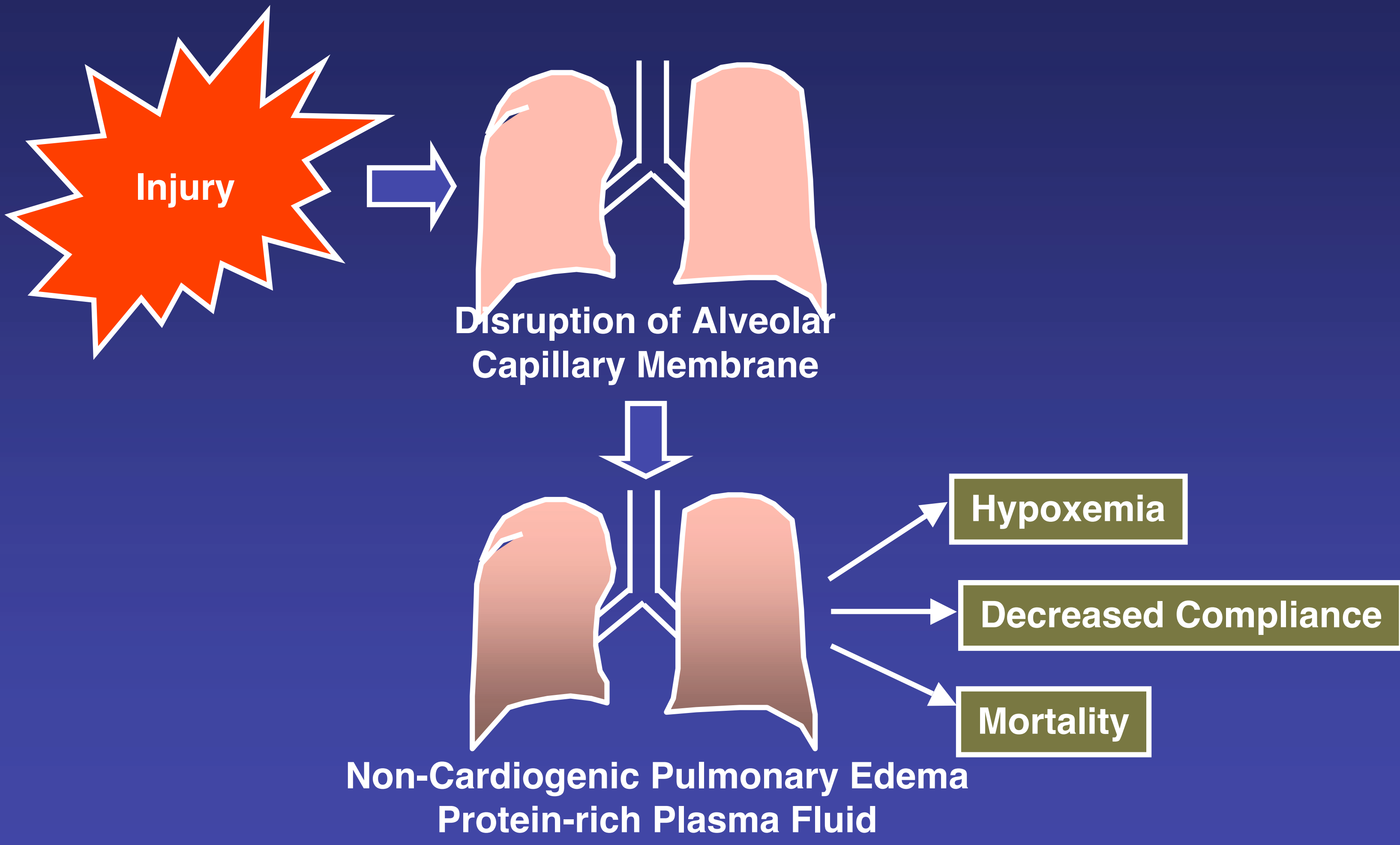
-8/6/06: POD #2, Altered Mental Status, Fevers (T-105.0F), Abdominal Pain. WBC - 31.7K, Amylase and Lipase Markedly Elevated. Abdominal CT Scan Reveals a Large Fluid Collection Around the Pancreas.

-8/7/07: POD #3, Hypotensive and Tachypnea. Mechanical Ventilation Initiated Secondary to Respiratory Distress. Transferred to UMMC.

Vent settings: Rate-12, Tidal Volume-500 ml, FiO2-60%
ABG: pH-7.38, pCO_2-28, pO_2-63, O2 sat-88%
Chest X-ray: Bilateral Patchy Parenchymal Opacities

Does Mrs. K Have ARDS?

What is Acute Respiratory Distress Syndrome (ARDS)?



Clinical Risk Factors:

Direct Lung Injury

Common Causes

Pneumonia (Bacteria, Viruses, Fungi)
Aspiration of Gastric Contents

Uncommon Causes

Pulmonary Contusion
Fat Embolism
Amniotic Fluid Embolism
Near-drowning
Inhalational Injury (Smoke, NH_3)
Reperfusion Injury after Transplant

Indirect Lung Injury

Common Causes

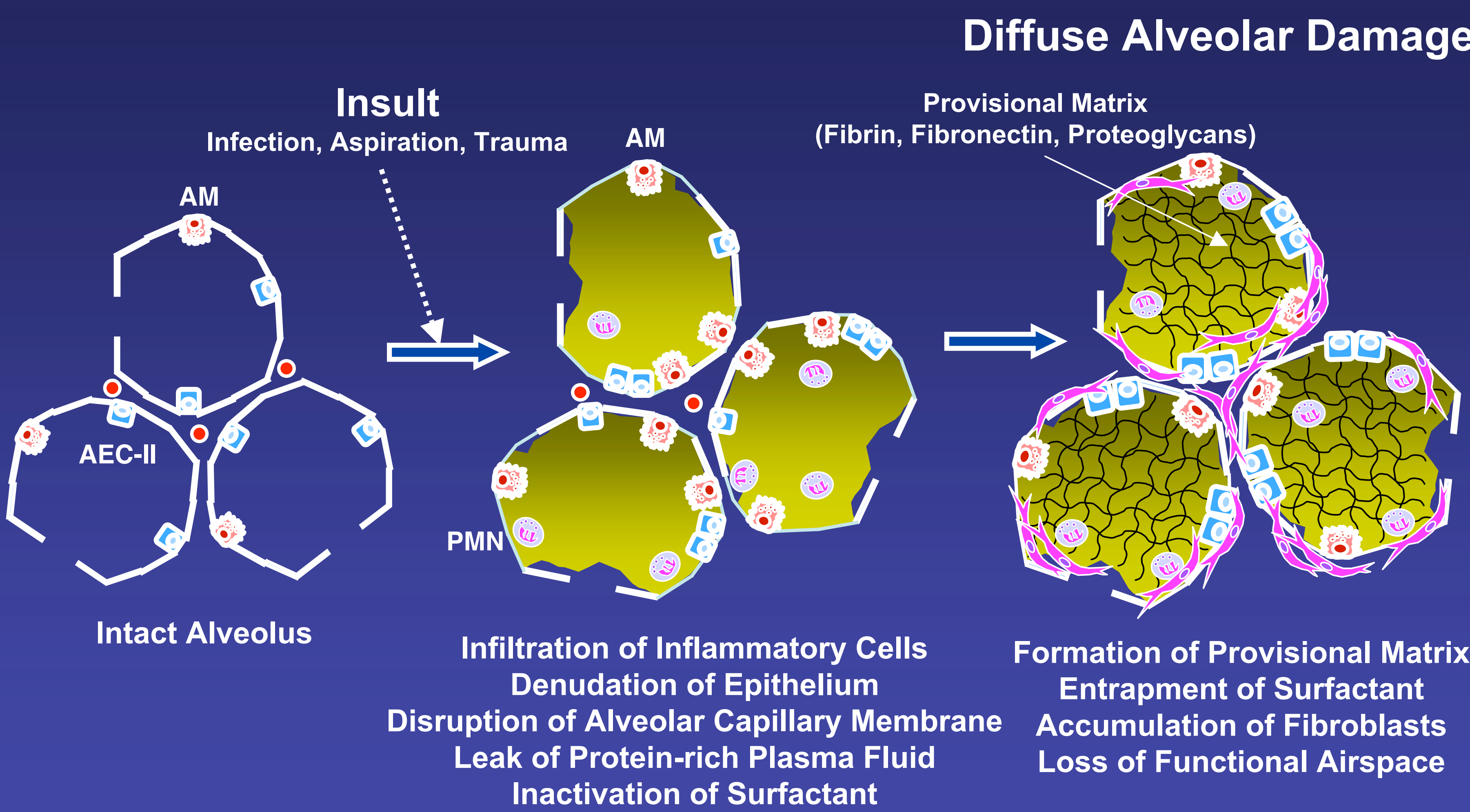
Sepsis
Severe Trauma with Shock
Acute Pancreatitis

Uncommon Causes

Multiple Transfusions
Drug Overdose
Diffuse Intravascular Coagulation

Smoking Does Not Directly Cause ARDS
but May Increase Risk of Developing the Disorder

Pathogenesis of ARDS



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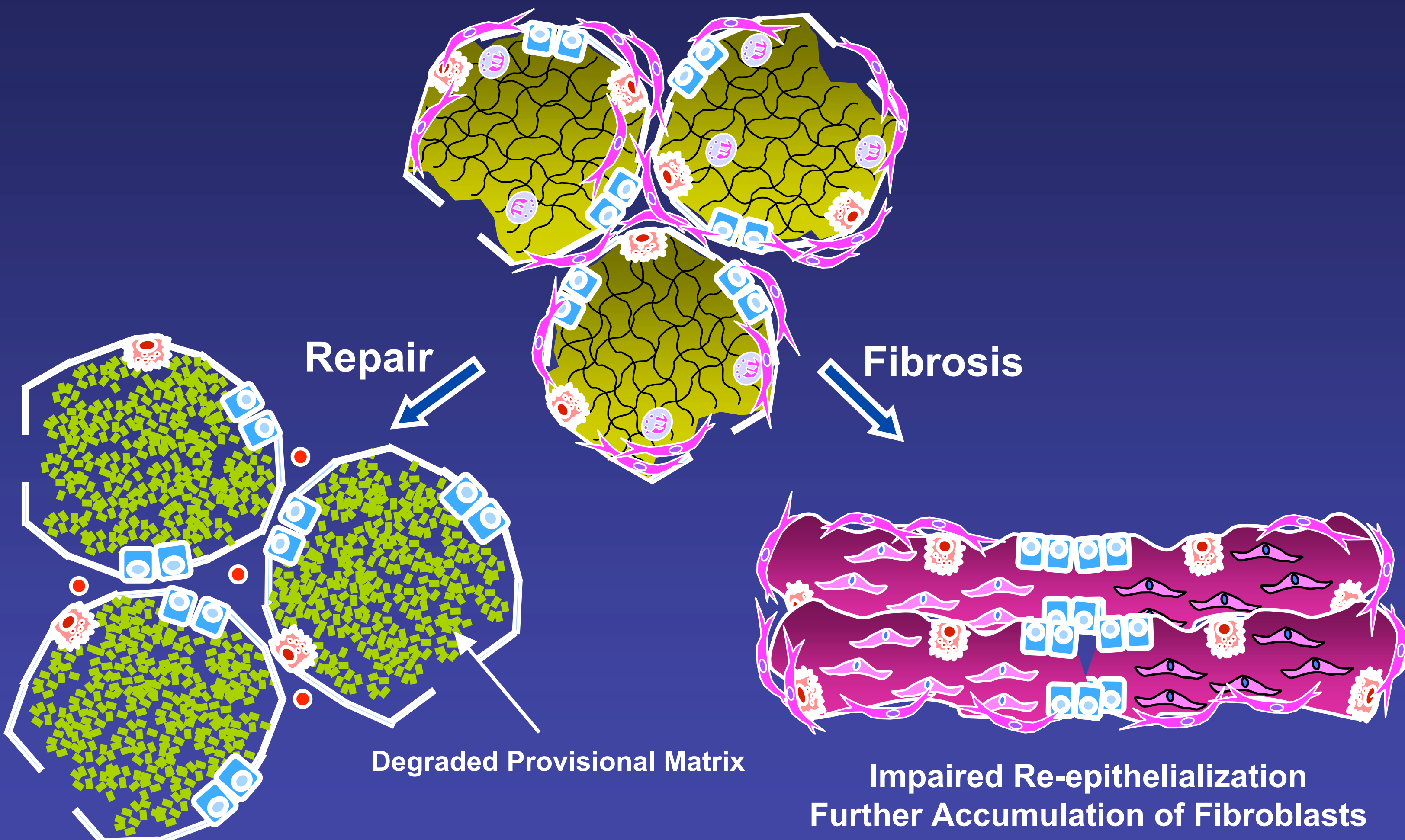
Pathogenesis of ARDS



Reconstitution of Epithelium
Removal of Provisional Matrix
Apoptosis of Fibroblasts
Limiting Myofibroblast Differentiating

Impaired Re-epithelialization
Further Accumulation of Fibroblasts
Myofibroblast Differentiation
Deposition and Accumulation of Collagen

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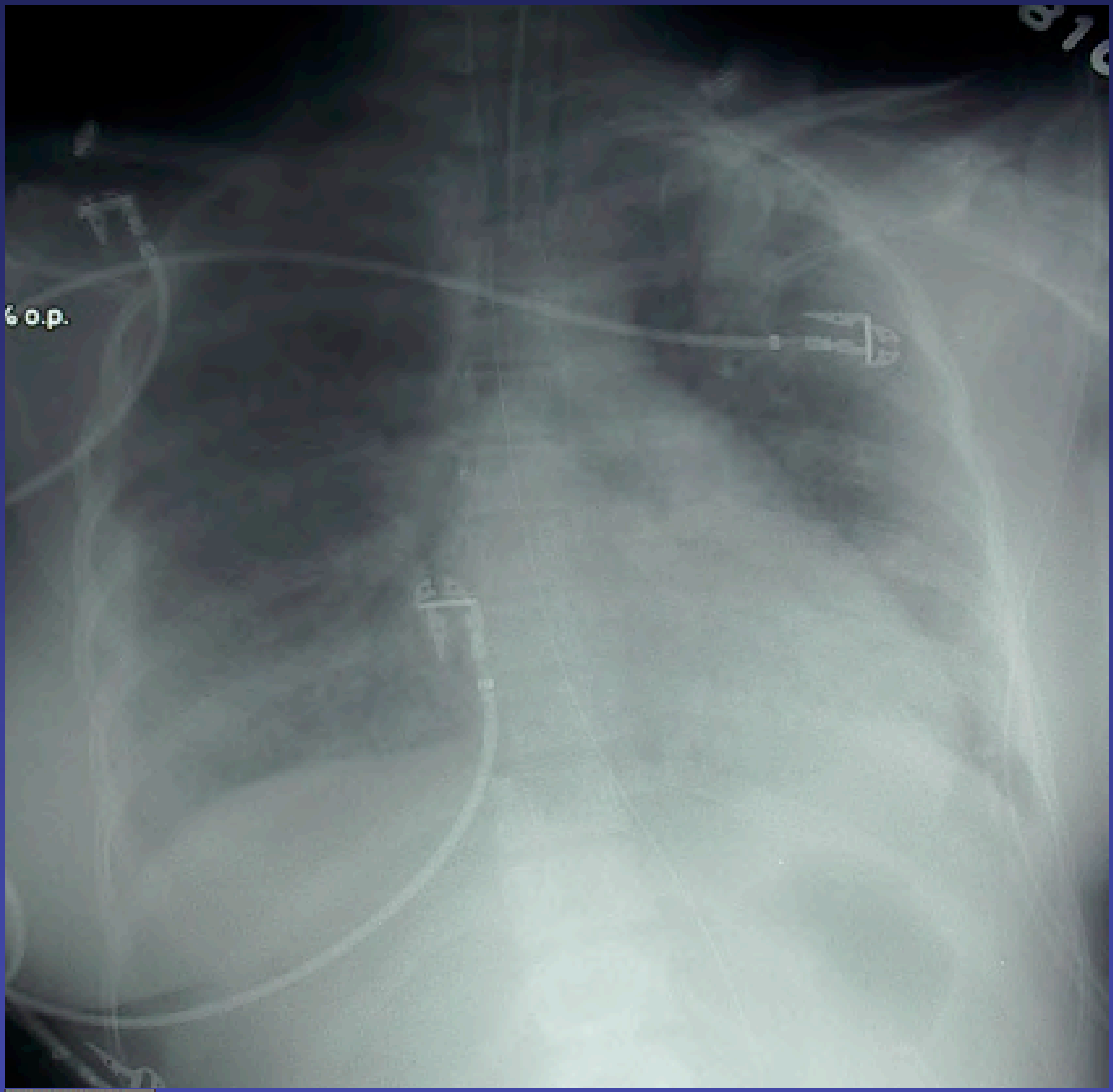
Chest X-ray: Alveolar Injury and Fluid Leak Results in Diffuse Bilateral Infiltrates



PD-INEL Source Undetermined

Chest CT Scan: Bilateral Infiltrates Are Heterogeneous

PD-INEL Source Undetermined

Evolution of Pathogenesis:

Exudative Phase (7 Days)	⇨	Proliferative Phase (14 Days)	⇨	Fibrotic Phase (21 Days)
Alveolar Wall Damage With Flooding		Type II Alveolar Cell Hyperplasia Myofibroblast Infiltration Resolution of Edema		Extensive Fibrosis With Loss of Normal Lung Architecture
↓↓ $Pa0_2$ ↓ Compliance Bilateral Infiltrates		↓↓ $Pa0_2$ ↓ Compliance Bilateral Infiltrates		↓↓ $Pa0_2$ ↓ Compliance Infiltrates ± Bullae

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How is ARDS Diagnosed?

Clinical Diagnostic Criteria:

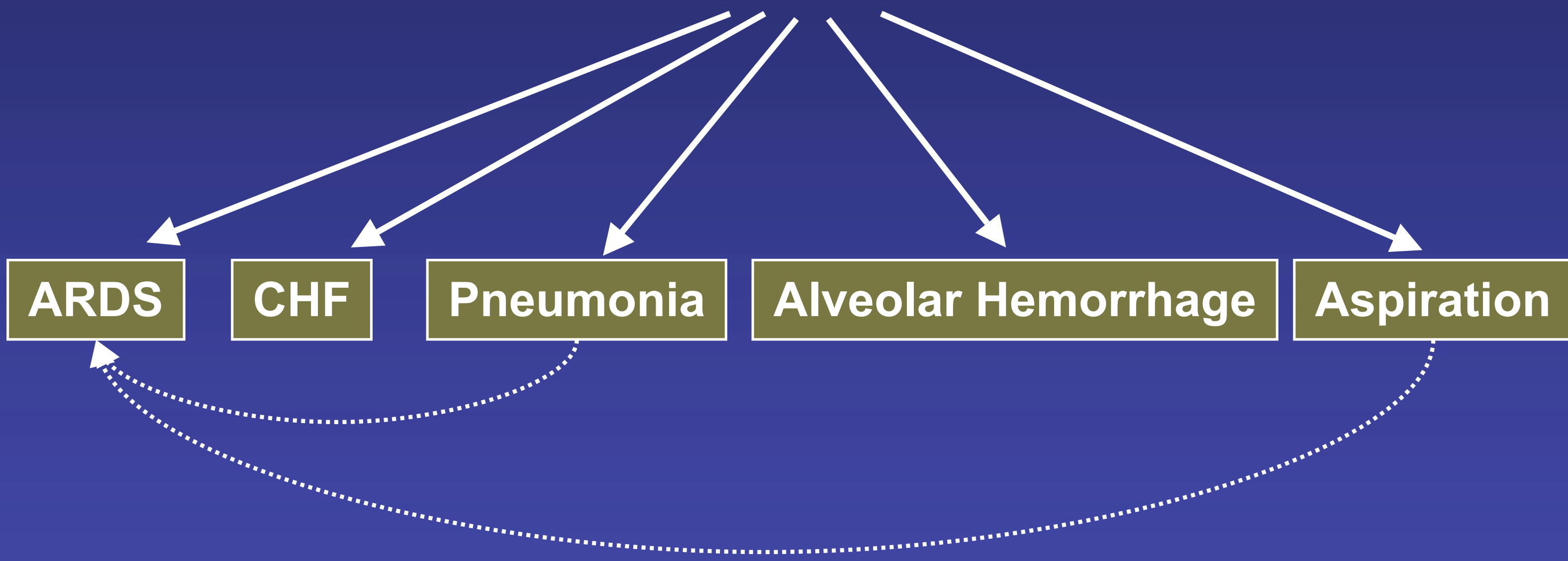
- Acute Onset: 6-72 Hours (in setting of a risk factor).
- Chest X-ray: Diffuse Bilateral Infiltrates.
- Hypoxemia.
  - PaO_2/FIO_2 <300: Acute Lung Injury
  - PaO_2/FIO_2 <200: Acute Respiratory Distress Syndrome

  Example: PaO2=60 on 50% FiO2   P/F ratio= 120

- Non-Cardiogenic Pulmonary Edema. PCWP <18

Differential Diagnosis of ARDS

Definition is Non-Specific:
Many Diseases Can Present Acutely With Bilateral Infiltrates and Hypoxemia



Differential Diagnosis for ARDS

Congestive Heart Failure | **ARDS**

Clinical
Respiratory Disress
↑rr, ↓PaO_2, ↓$PaCO_2$

Congestive Heart Failure		ARDS
Acute Cardiac Event	**History**	Risk Factor (Acute Cardiac Event Can Coexist)
Low Flow: Cool Extremities S3 or S4 Gallop/Cardiomegaly Jugular Venous Distention Crackles (wet)	**Clinical Exam**	High Flow: Warm Extremities No Gallop/No Cardiomegaly No Jugular Venous Distention Crackles (dry) Evidence of Risk Factor
ECG: New or Old Infarct Chest Xray: Perihilar Infiltrates/Effusions Cardiac Enzymes: Elevated PCWP>18mmHg	**Laboratory**	ECG: Normal (Tachycardia) Chest Xray: Diffuse Cardiac Enzymes: Normal PCWP<18mmHg

Case Presentation: Does our patient have ARDS?

Clinical Diagnostic Criteria:

Acute Onset: 6-72 Hours (risk factor)

Respiratory Failure Within 48 Hours of Pancreatitis

Chest X-ray: Diffuse Bilateral Infiltrates

Yes

Hypoxemia:

PaO_2/FIO_2 <300: Acute Lung Injury

PaO_2/FIO_2 <200: Acute Respiratory Distress Syndrome

PaO2=63 on 60% FiO2 = 63/0.6 = 105

Non-Cardiogenic Pulmonary Edema: PCWP <18

Yes

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Management of ARDS:

Management of ARDS:

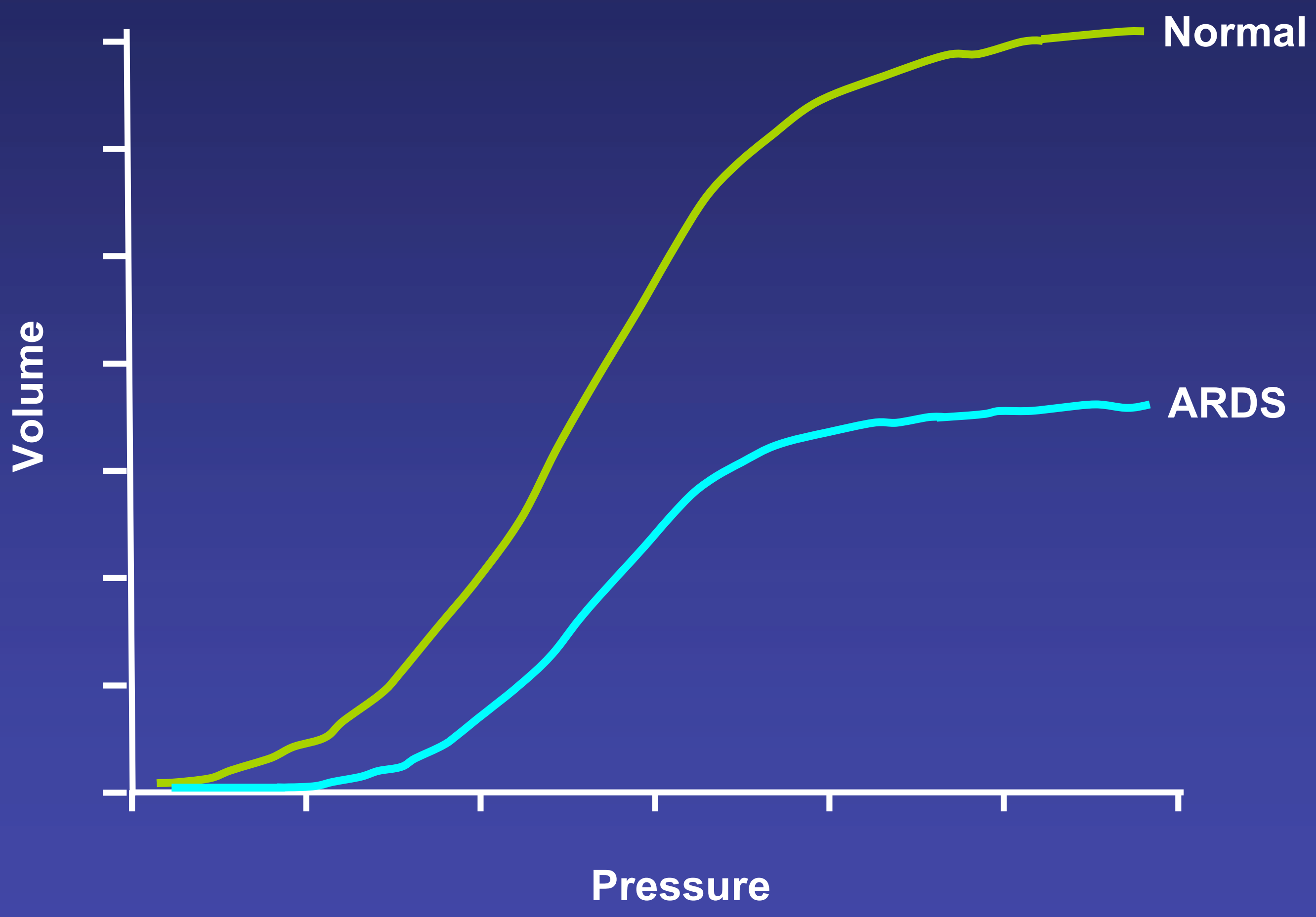
Problems

- **Reduced Compliance & Loss of Lung Volume**
- **Impaired Oxygenation:**
  V/Q Mismatch
  Shunting
- **High Mortality**

Mechanical Ventilation

TV and FiO2

Management of ARDS: Reduced Compliance



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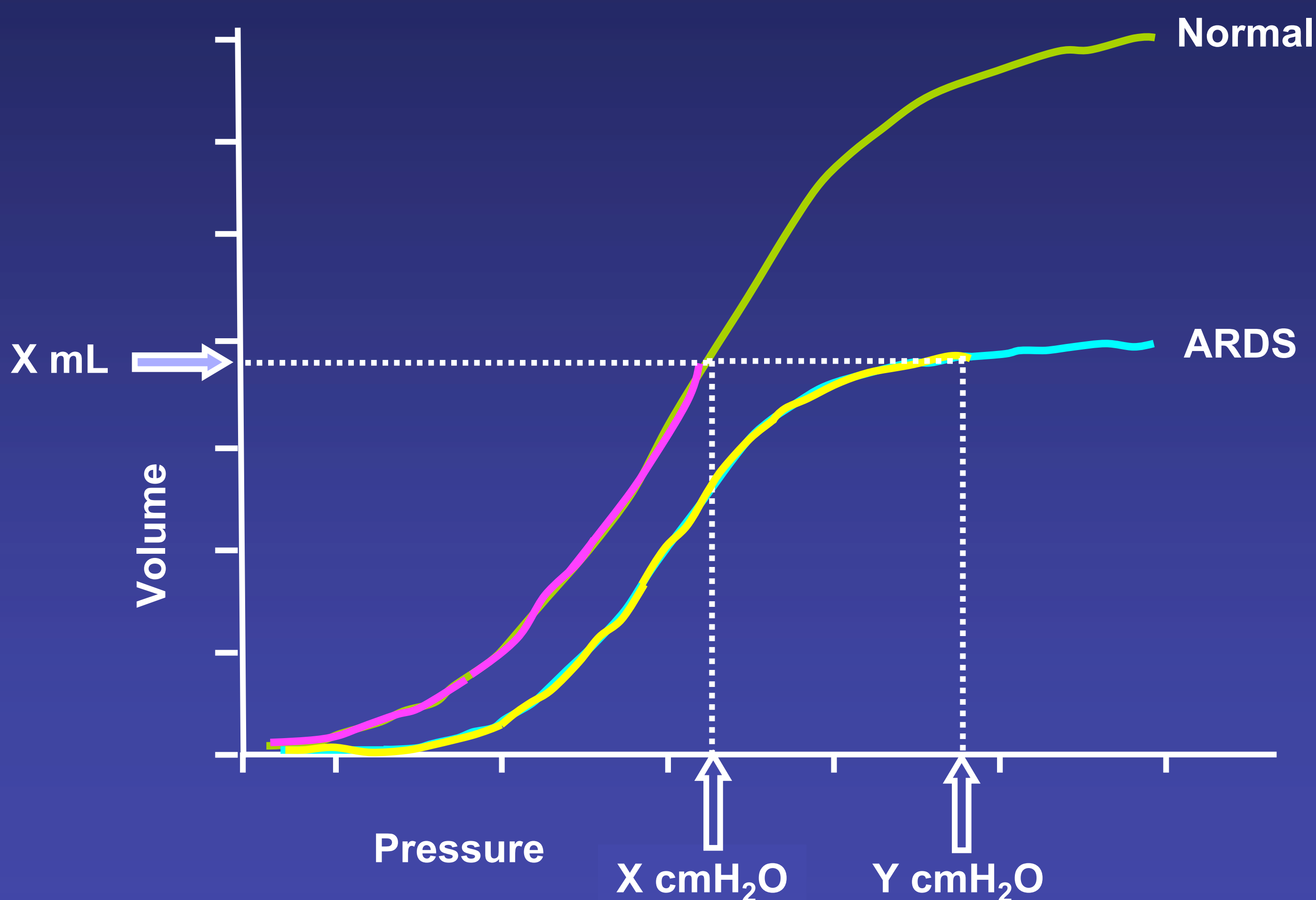
Management of ARDS: Reduced Compliance



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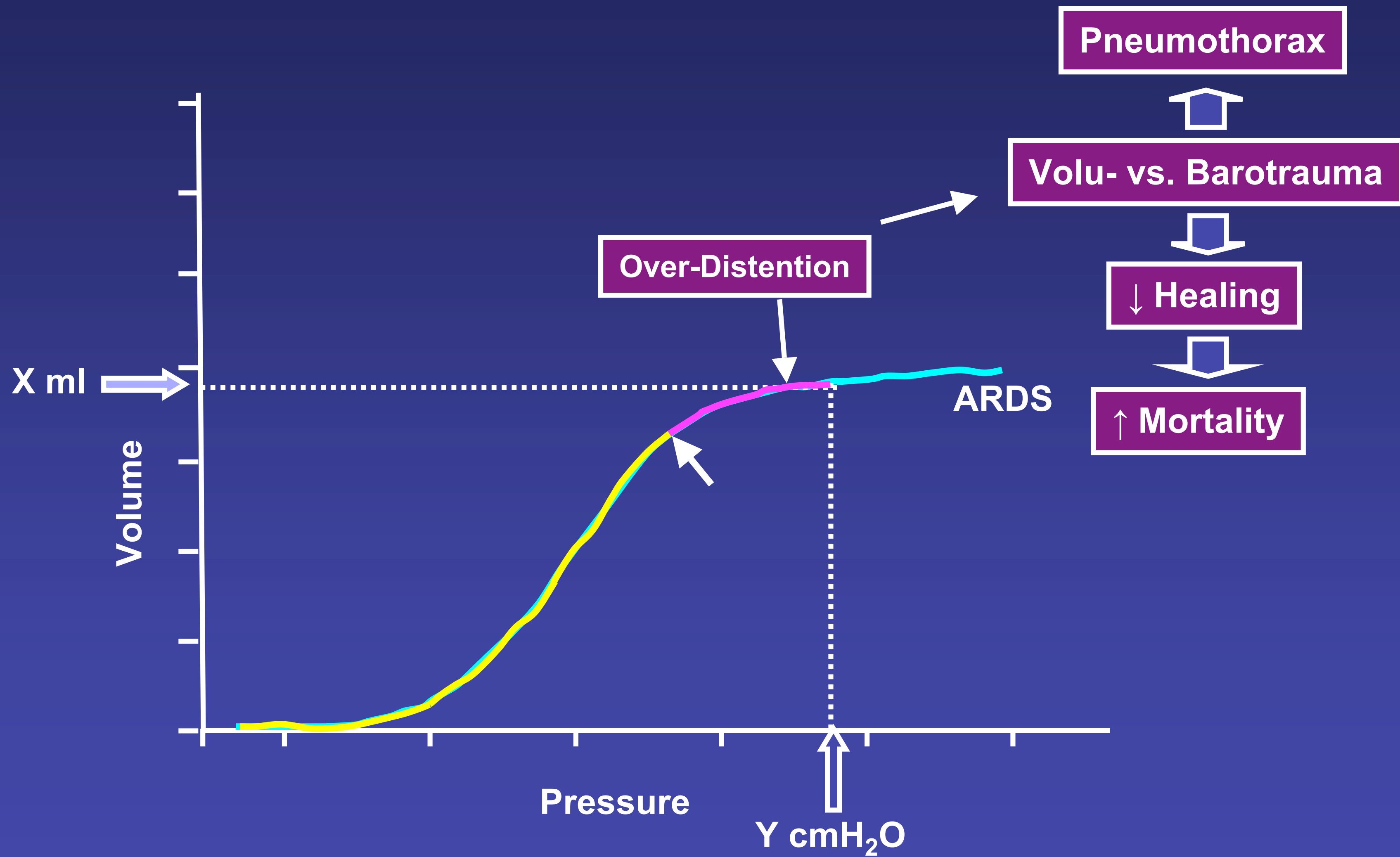
Management of ARDS: Reduced Compliance

Ventilator Associated Lung Injury (VALI)



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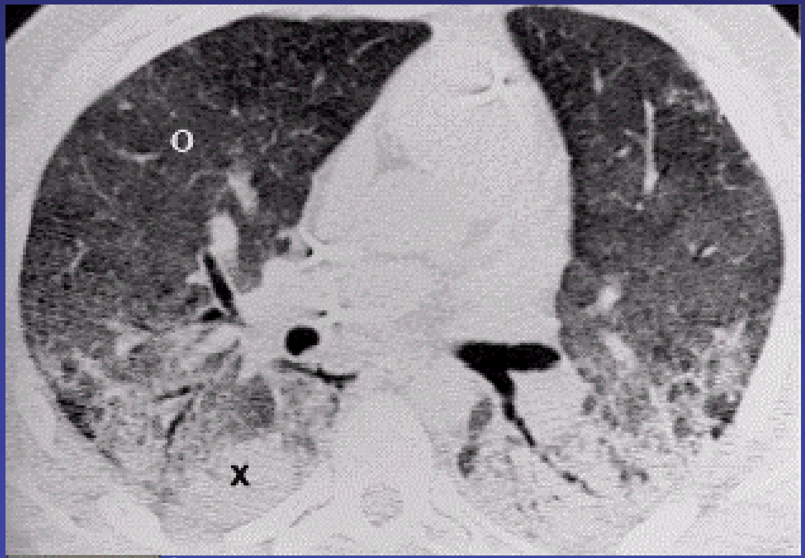
Management of ARDS: Reduced Compliance

Ventilator Associated Lung Injury (VALI)



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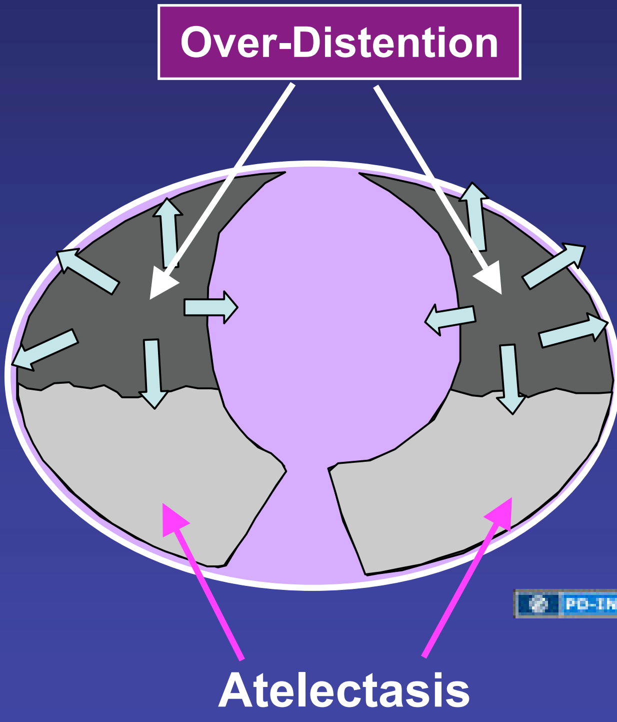

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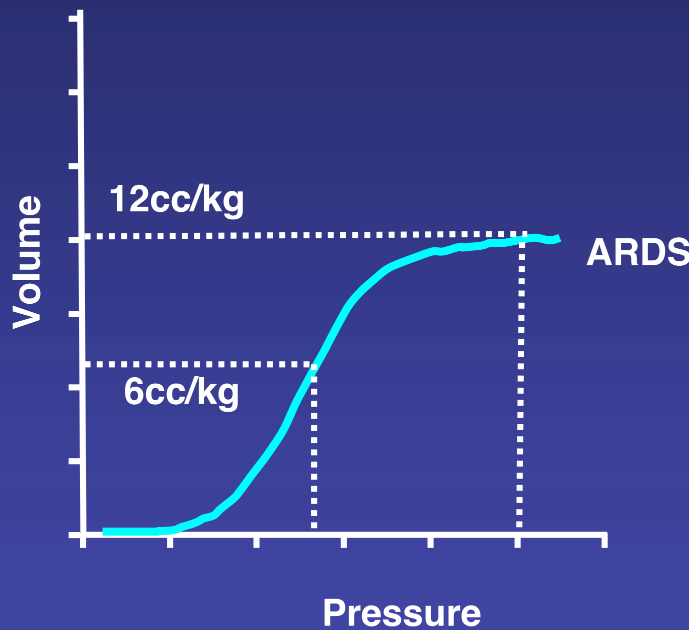
Management of ARDS: Reduced Compliance

ARDS Network

6cc/kg Tidal Volume | **12cc/kg Tidal Volume**

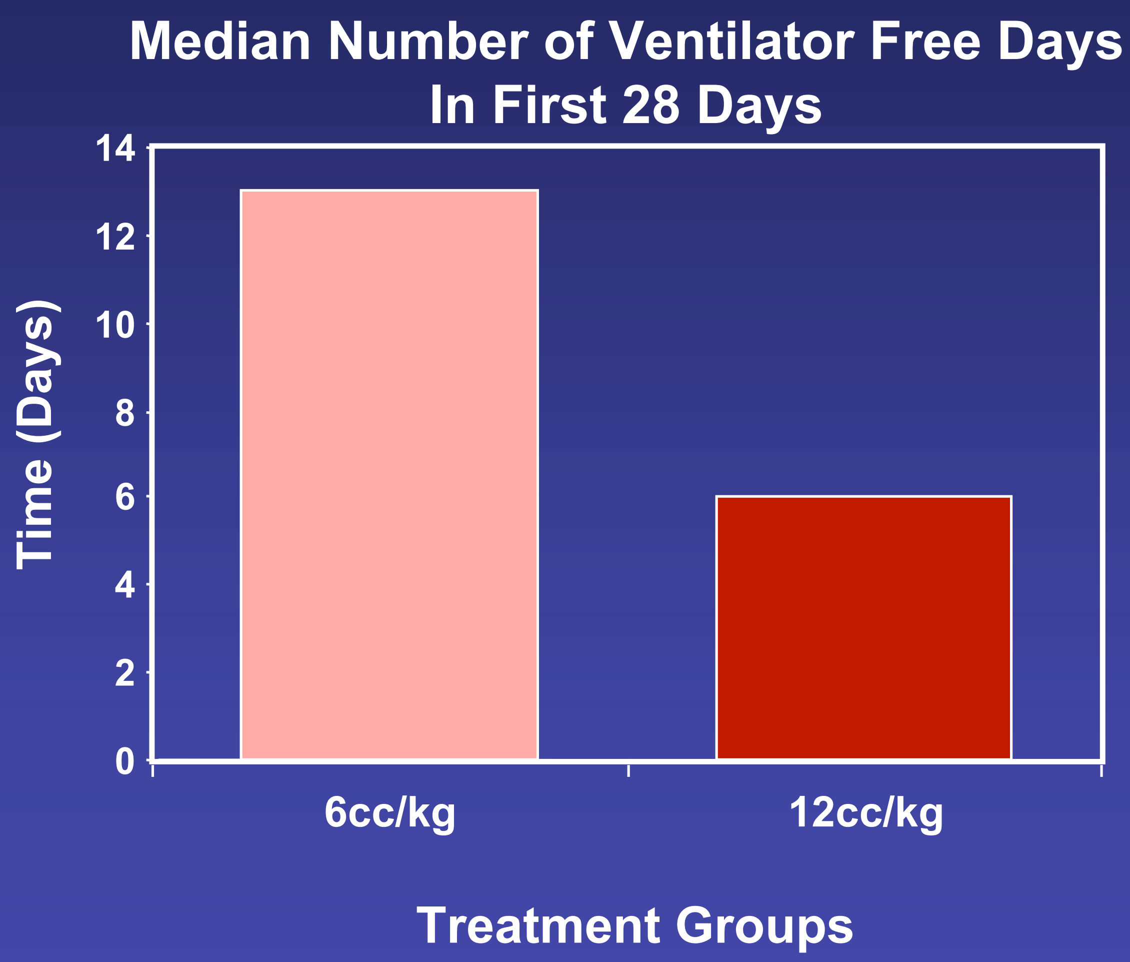
Mortality Prior to Discharge

Ventilator Free Days



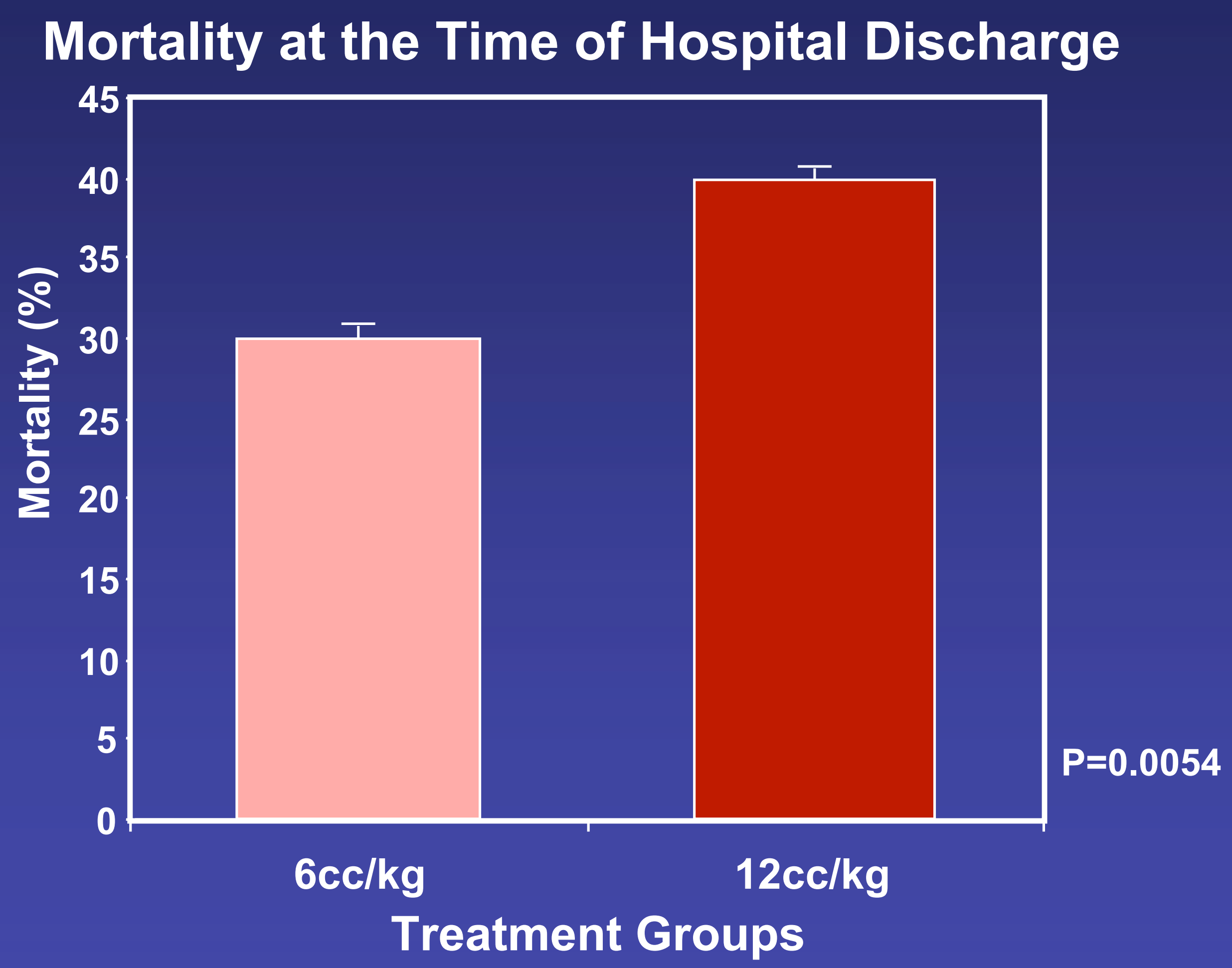
ARDSnet *NEJM* 2000

Management of ARDS: Reduced Compliance



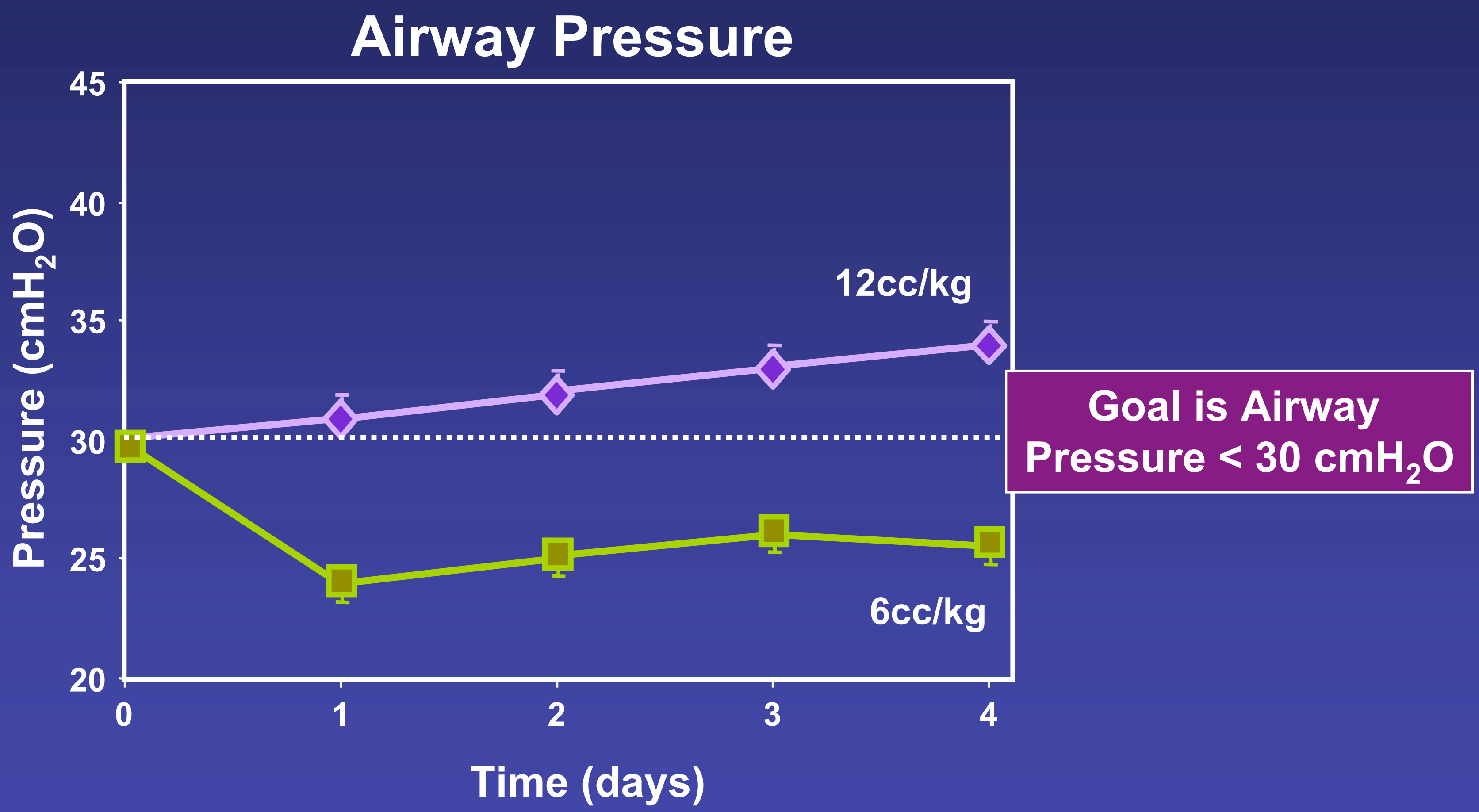
ARDSnet *NEJM* 2000

Management of ARDS: Reduced Compliance



ARDSnet *NEJM* 2000

Management of ARDS: Reduced Compliance



ARDSnet *NEJM* 2000

Case Presentation:

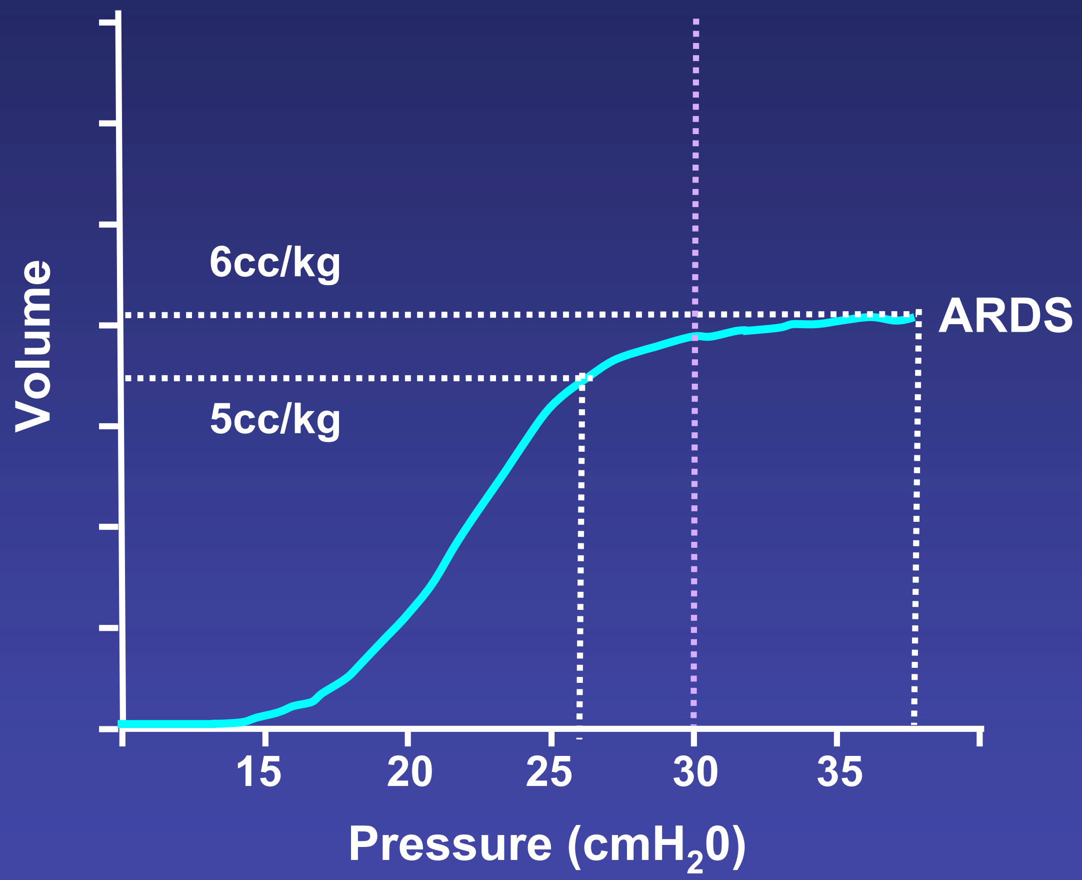
48 Hrs After Transfer to UMMC, Our Patient (Wgt 70kg) Remains on Mechanical Ventilation With the Following Ventilator Settings:

Rate-33, Tidal Volume-420 ml (6 ml/kg), FiO2-70%

Her Airway Pressure on This Tidal Volume is Measure at 38 cm$H_2$0.

What Should be Done Next?

Management of ARDS: Reduced Compliance



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Management of ARDS: Reduced Compliance

Problem: Low Tidal Volume Ventilation = Rapid Respiratory Rate

Patient Specific → Minute Ventilation

	Tidal Volume	X Respiratory Rate	= Minute Ventilation
Traditional 12cc/kg 70kg	840cc	17/min	14000 ml
Low Volume 6cc/kg 70kg	420cc	33/min	14000 ml
Low Volume 5cc/kg 70kg	350cc	40/min	14000 ml

40/min → Patient Discomfort; Breath Stacking

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Management of ARDS: Reduced Compliance

Rapid Respiratory Rate

↙ Patient Discomfort

↘ Breath Stacking

↘ Increased Intra-Thoracic Pressure (AutoPEEP)

↘ Hemodynamic Instability

ARDS Network

Respiratory Rate Limited to 35 Breaths/Minute

⇩

Sedation ± Paralysis

Management of ARDS: Reduced Compliance

Tidal Volume X Respiratory Rate **Minute Ventilation**

Low Volume
5cc/kg
70kg

350cc

35/min

12,250ml
Actual

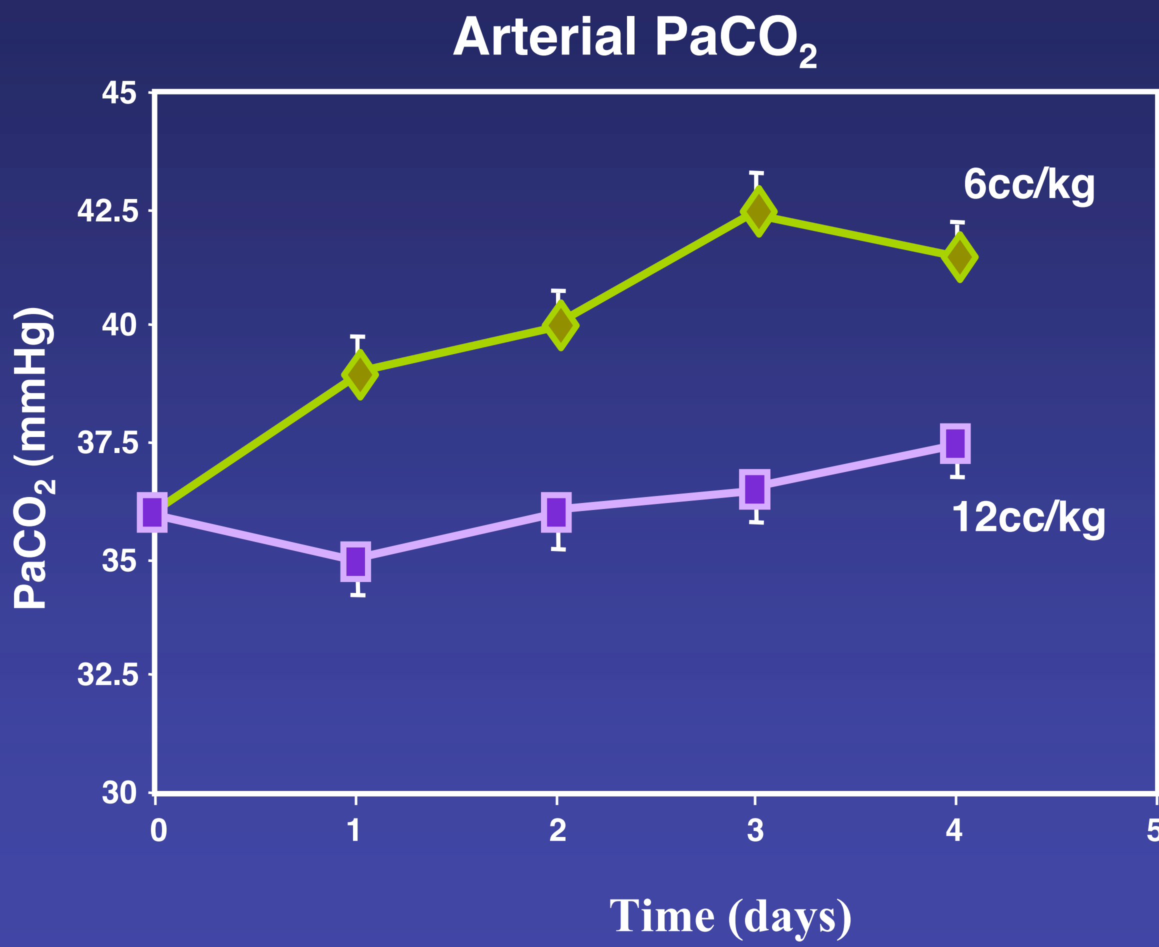
14000ml
Required

If Actual MV < Required MV ⟶ ↑$PaCO_2$ and ↓pH

Permissive Hypercapnea

Note: If pH Drops too Low, the Patient can Become Hypotensive

Management of ARDS: Reduced Compliance



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Management of ARDS:

Problems

Reduced Compliance

Impaired Oxygenation:
V/Q Mismatch
Shunting

High Mortality

Mechanical Ventilation

Management of ARDS: Impaired Oxygenation

PD-INEL Source Undetermined

Surfactant Inactivation

↓

Atelectasis

+

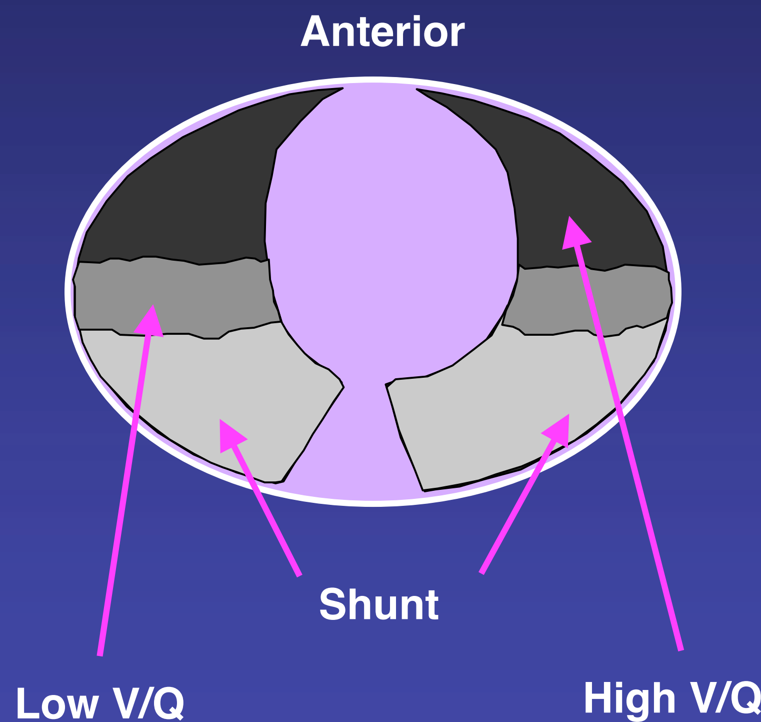
Alveolar Flooding

⇓

V/Q Mismatch
+
Shunting

Management of ARDS: Impaired Oxygenation

PD-INEL Source Undetermined



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Case Presentation:

Due to High Airway Pressures, Our Patient's Ventilator Settings Have Been Chnaged To:

Rate-35, Tidal Volume-350 ml (5 cc/kg).

Her FiO2 Requirements Have Now Increased to 80%.

Her Airway Pressure on the Current Tidal Volume is Measured at 26 cmH_20 (see above).

Her ABG is: pH-7.33, pCO_2-48, pO_2-51, O2 sat-88%

What Should be Done Next?

Management of ARDS: Impaired Oxygenation

Goal: Maintenance of Adequate Tissue Oxygenation

$$DO2 = CI \times (1.3 \times O_2sat \times HGB + .003 \times PaO_2)$$

Pa02 ≥ 55mmHg

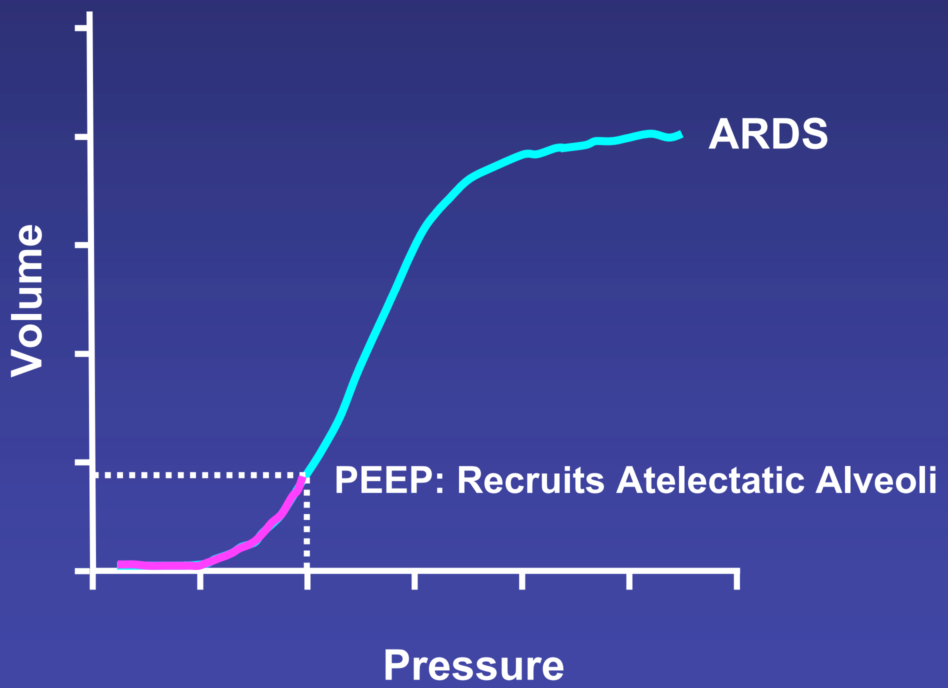
O_2 Sat ≥ 88

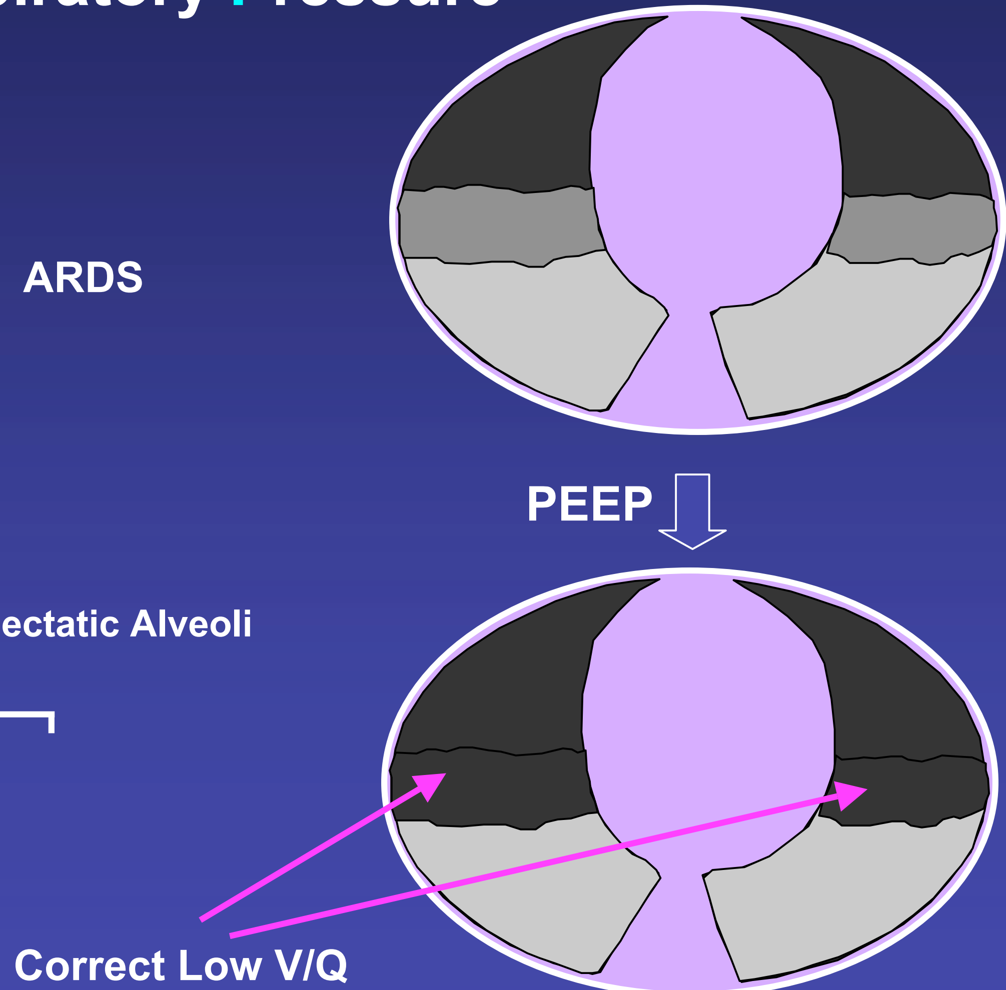
$FI0_2$ ≤ 50%

Note: High Levels of O2 Are Likely Toxic

Management of ARDS: Impaired Oxygenation

PEEP: Positive End-Expiratory Pressure





Management of ARDS: Impaired Oxygenation

PEEP Should be Adjusted to Maximize Oxygen Delivery and Not Simply O_2 Saturation

$$DO2 = CI \times [(1.3 \times O2\ Sat \times HGB) + (.003)PaO_2]$$

Problem: High Levels of PEEP Can Impair Venous Return and Decrease CI

⇩

Perform a Best PEEP Titration

Management of ARDS: Impaired Oxygenation

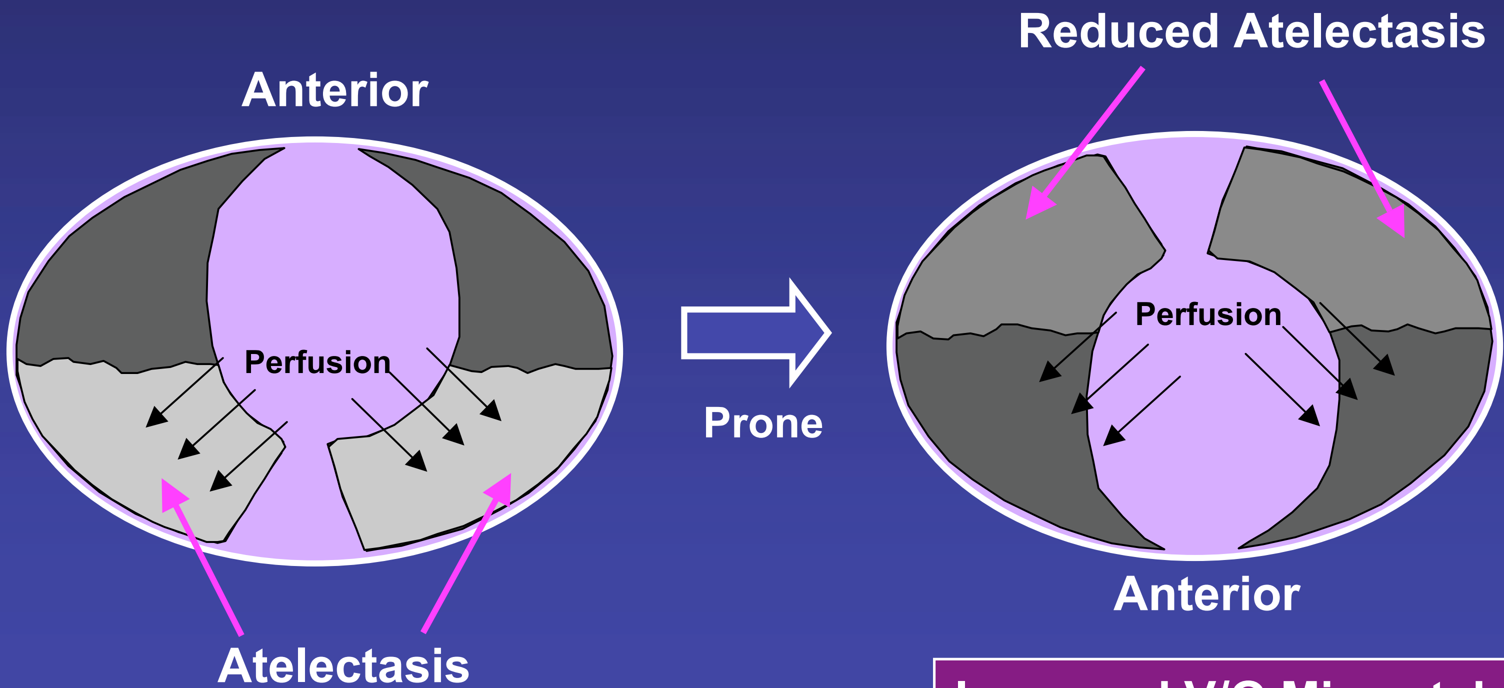
Best PEEP Titration: Maximize DO2=CI x (1.3 x O_2 Sat x HGB)

Example: FIO2=80% and O_2 Saturation = 86%

PEEP	O2 Saturation	Cardiac Index	O_2 Sat x CI
10	86%	3.5	3.01
12	88%	3.5	3.08
14	90%	3.5	3.12
16	91%	3.3	3.00
18	92%	3.3	3.04
20	94%	2.7	2.54

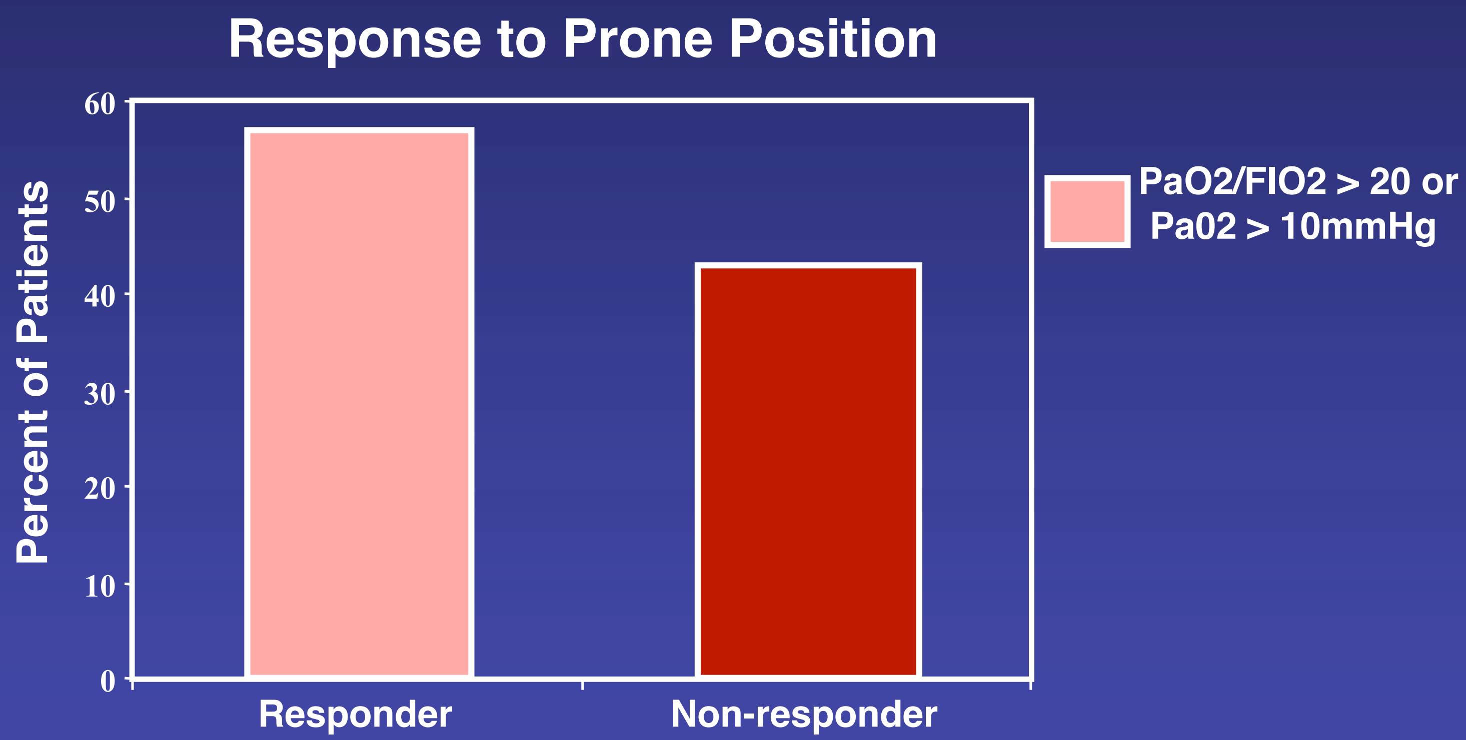
Management of ARDS: Impaired Oxygenation

Prone Positioning



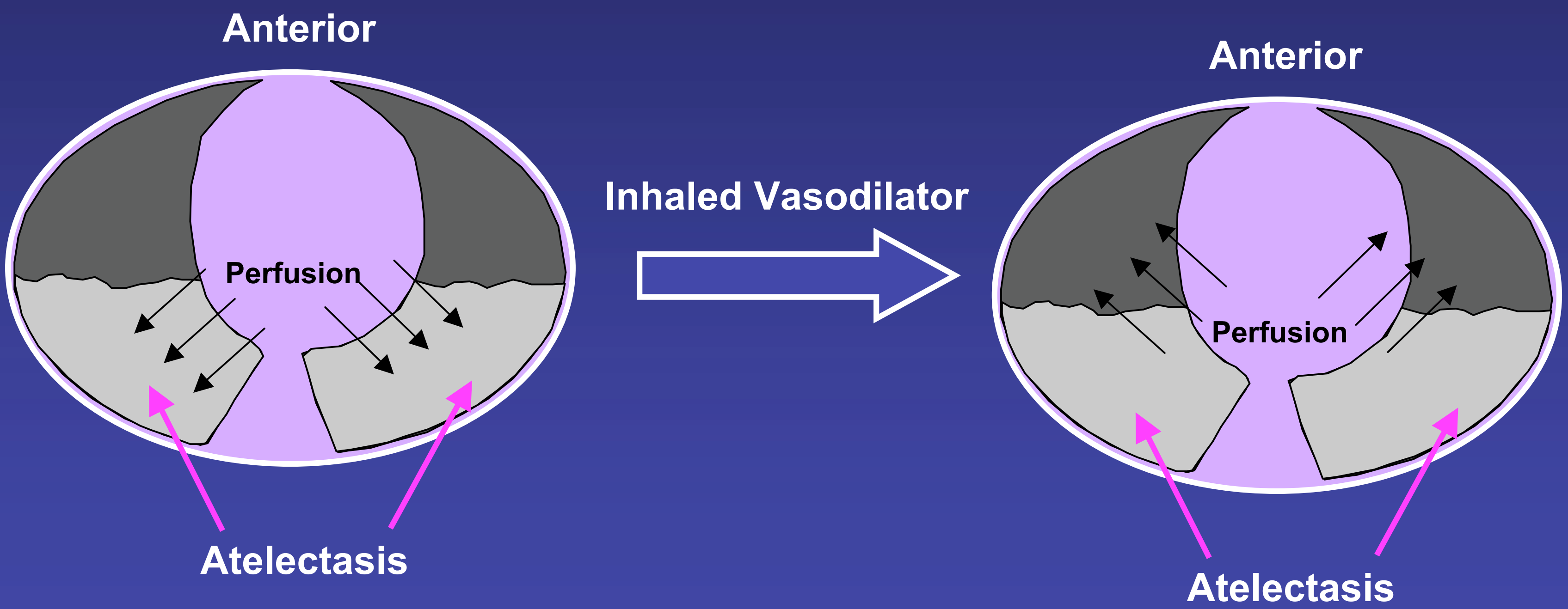
Improved V/Q Mismatch

Management of ARDS: Impaired Oxygenation



Jolliet et al. *Crit Care Med* 1998

Management of ARDS: Impaired Oxygenation



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Management of ARDS: Impaired Oxygenation

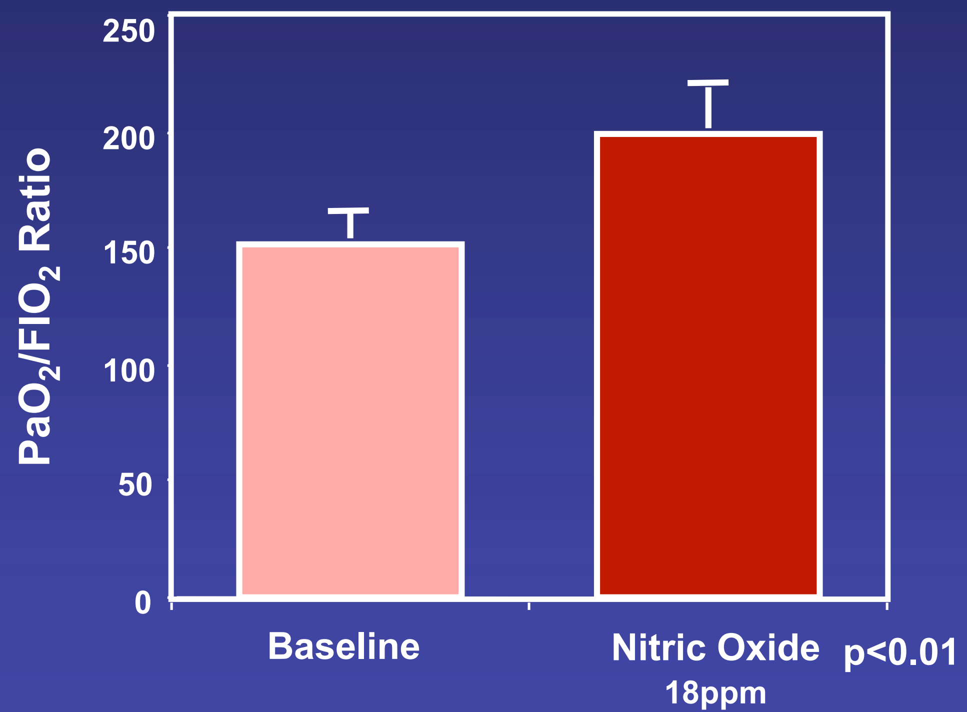
Inhaled Nitric Oxide

⇩

Reverses Hypoxemic Vasoconstriction

⇩

Improves V/Q Mismatch



Rossaint et al. *NEJM* 1993C

Management of ARDS: Impaired Oxygenation

Intratracheal Surfactant: Surfactant is Decreased/Inhibited in ARDS

ARDS
(within 48-72º)

Surfactant + Protein C
(n=224)

Placebo
(n=224)

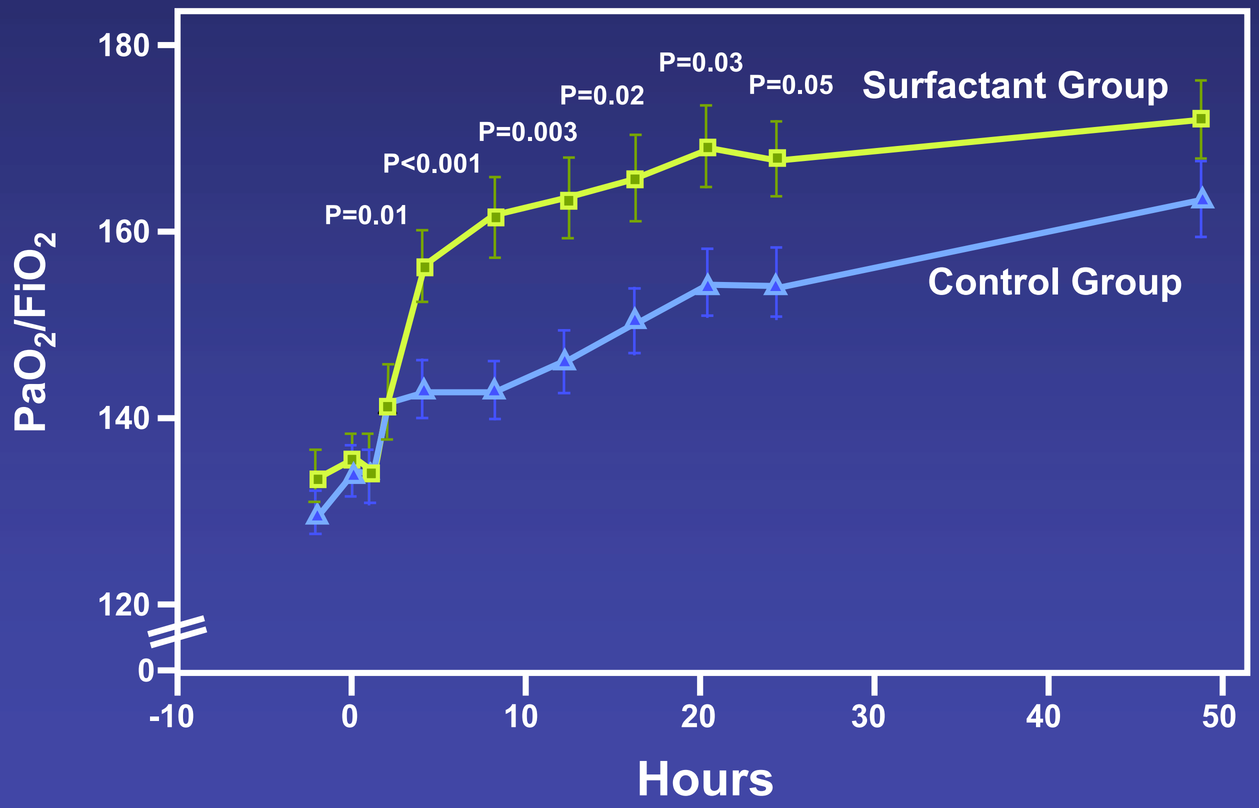
4 doses over 24 hours

PaO_2/FIO_2
Mortality

Spragg et al. *NEJM* 2004

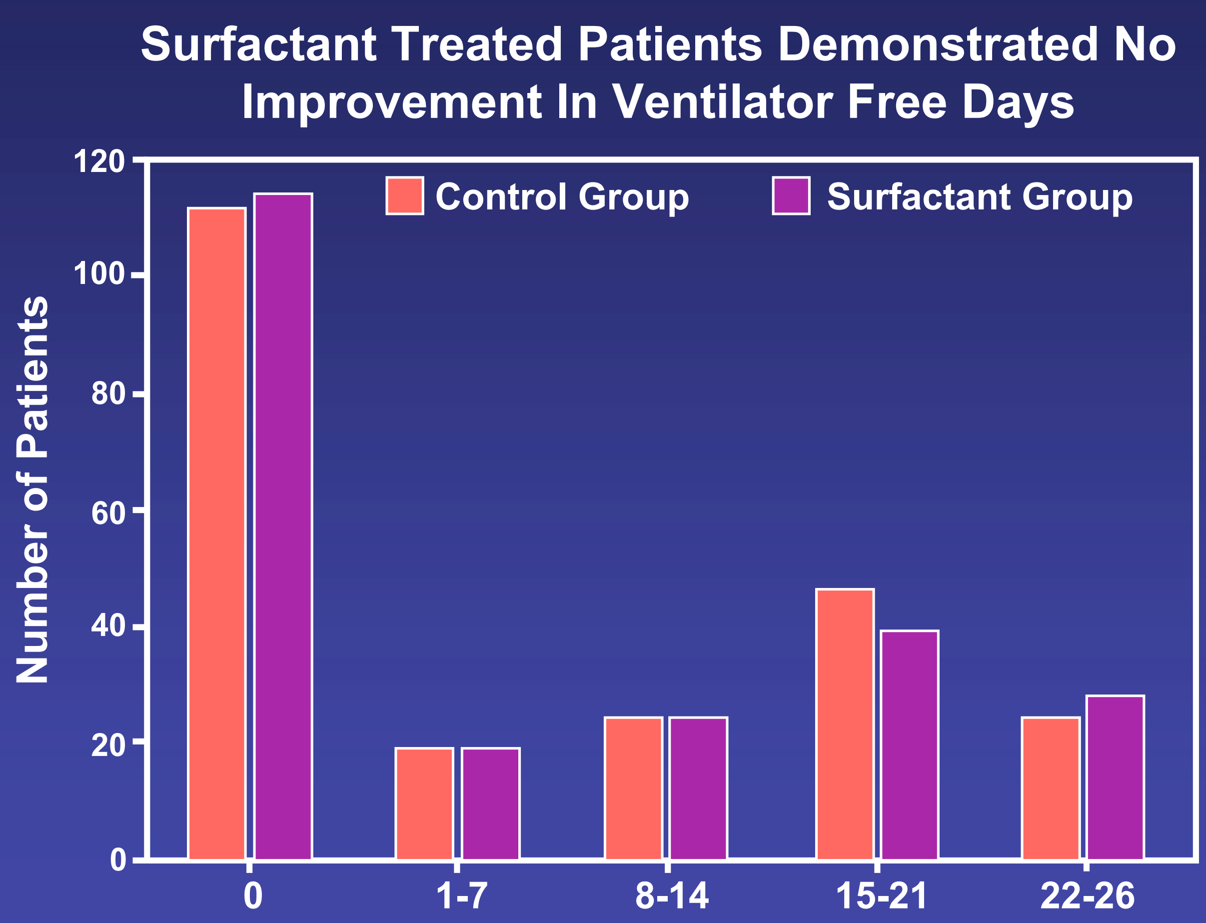
Management of ARDS: Impaired Oxygenation

Surfactant Treated Patients Demonstrated Improved P/F Ratio



Spragg et al. *NEJM* 2004

Management of ARDS: Impaired Oxygenation



Spragg et al. *NEJM* 2004

Case Presentation:

Because of High FiO2 Requirements (80%), Our Patient Underwent a Best PEEP Titration. Her Ventilator Settings Are Now:

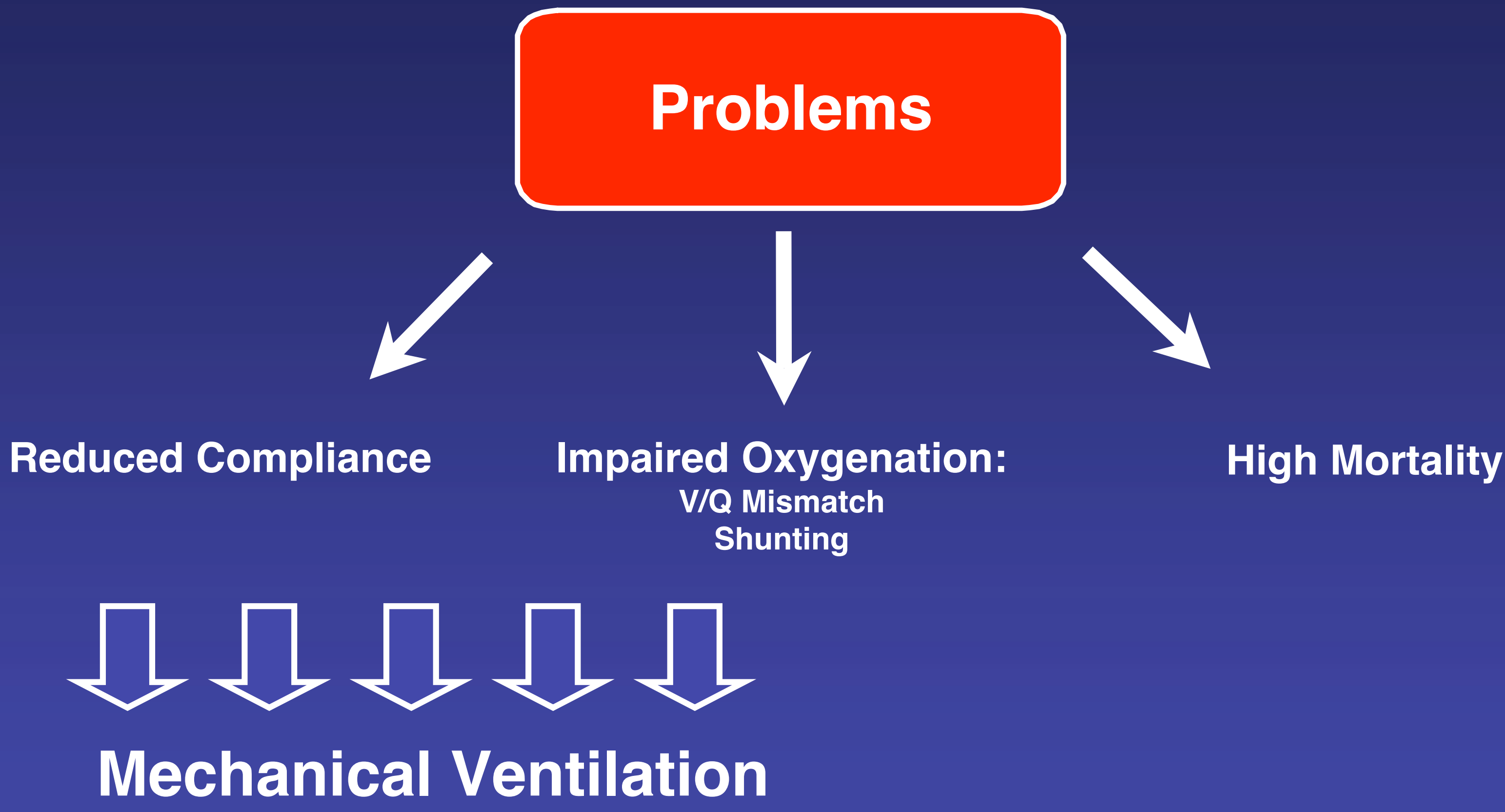
Rate-35, Tidal Volume-350 ml (5 cc/kg), PEEP-14 cmH2O.

Her FiO2 Requirements Are at 60%.

Her Airway Pressure on Her Current Tidal Volume Remains at 26 cmH_20.

Her ABG is: pH-7.33, pCO_2-48, pO_2-55, O2 sat-88%

Management of ARDS:



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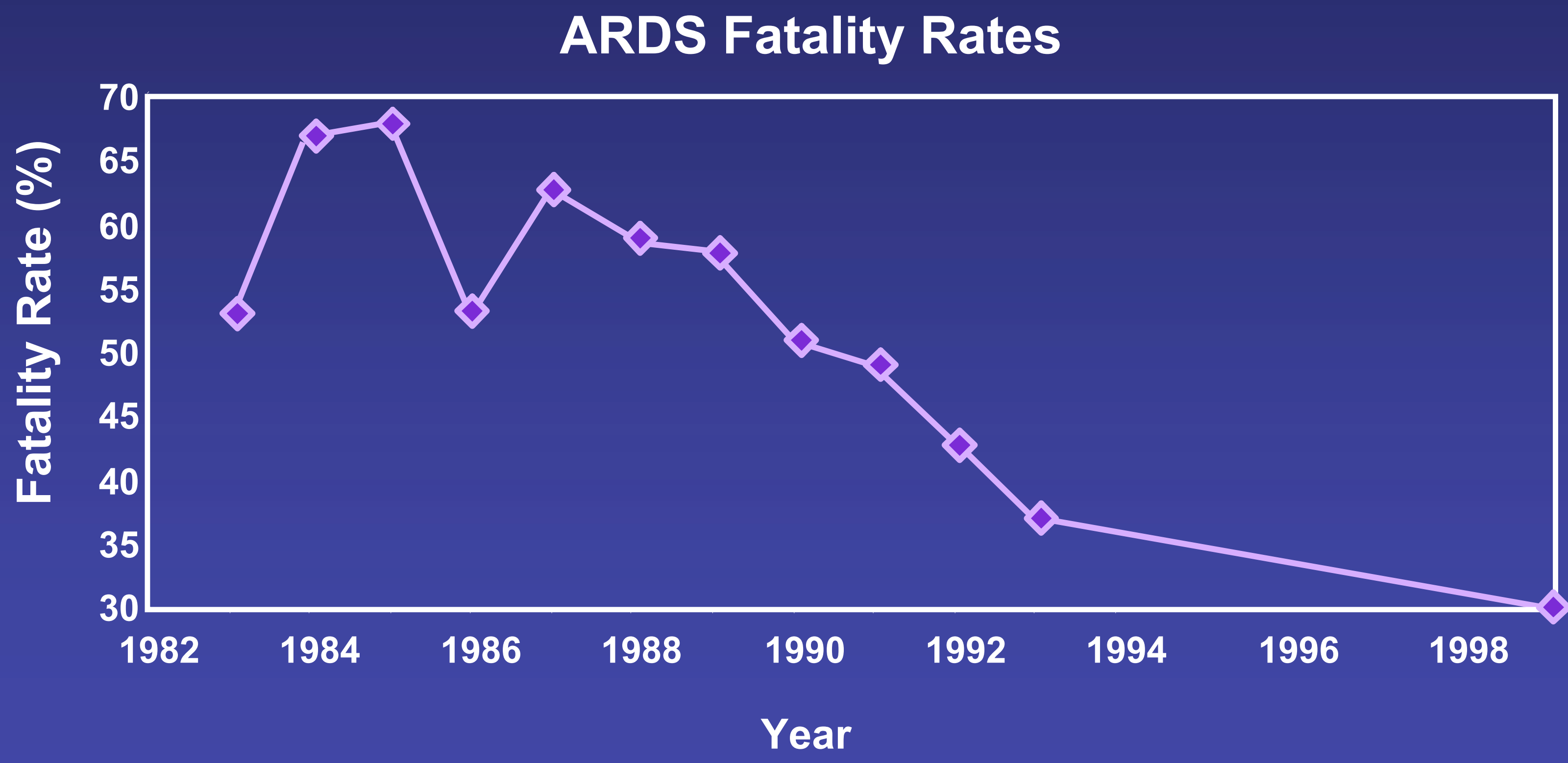
Trend in ARDS Mortality Rate



Hudson et al. *JAMA* 1995

Case Presentation:

Now that Our Patient has Stabilized on the Ventilator, Are There Any Treatments that Can Improve Her Likelihood of Survival?

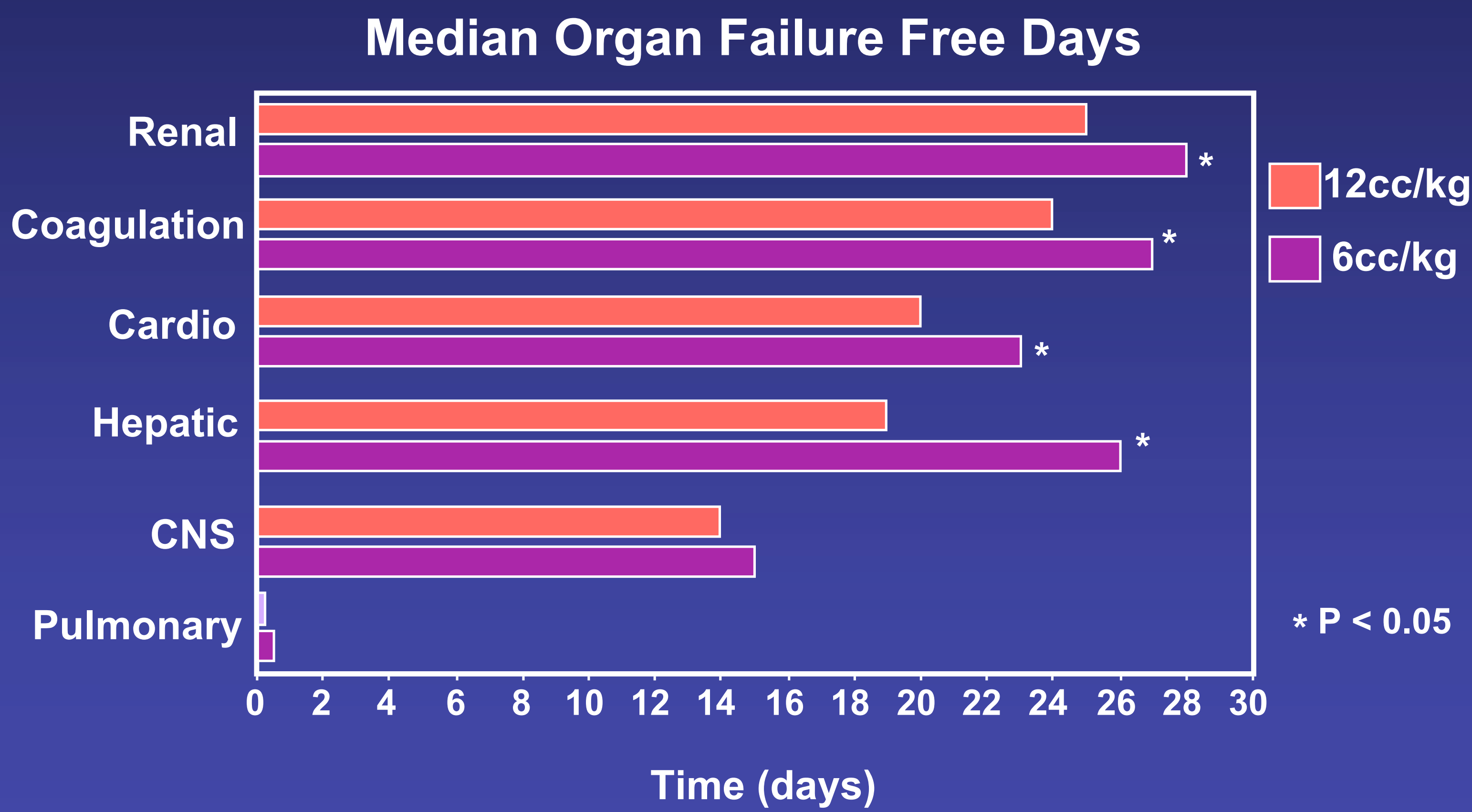
Risk Factors for ARDS Mortality

Variable	Odds Ratio	P Value
Non-Pulmonary Organ System Dysfunction	8.1	<0.0001
Chronic Liver Disease	5.2	<0.01
Sepsis	2.8	<0.05

Severity of ARDS as Measured by P/F ratio Has Minimal Impact on Survival

Matthay et al. *Am J Respir Crit Care Med* 1995

Multi-Organ Failure in ARDS Network Trial



ARDSnet *NEJM* 2000

Drug Treatment Trials to Reduce ARDS Mortality

Treatment	Year	Type of Study	No. of Patients	Findings	Study
Glucocorticoids (during the acute phase)	1987	Phase 3	87	No benefit	Bernard et al.[126]
Glucocorticoids (during the acute phase)	1988	Phase 3	59	No benefit	Luce et al.[127]
Alprostadil					
Intravenous	1989	Phase 3	100	No benefit	Bone et al.[128]
Liposomal	1999	Phase 3	350	Stopped for lack of efficacy	Abraham et al.[133]
Surfactant	1996	Phase 3	725	No benefit; new preparations and methods of delivery now being studied	Anzueto et al.[130]
Glucocorticoids during the fibrosing-alveolitis phase	1998	Phase 3	24	Decreased mortality, but study was small	Meduri et al.[131]
Inhaled nitric oxide	1998	Phase 2	177	No benefit	Dellinger et al.[129]
Inhaled nitric oxide	1999	Phase 3	203	No benefit	Payen et al.[130]
Ketoconazole	2000	Phase 2	234	No benefit	NIH Acute Respiratory Distress Syndrome Network[134]*
Procysteine	1998	Phase 3	214	Stopped for lack of efficacy	Bernard GR, unpublished data
Lisofylline	1999	Phase 2–3	235	Stopped for lack of efficacy	Unpublished data

PD-INEL NEJM, The Acute Respiratory Distress Syndrome

Drug Therapy to Reduce ARDS Mortality

Inflammation

Glucocorticoids ⊣

Exudative Phase (7 Days) → **Proliferative Phase** (14 Days) → **Fibrotic Phase** (21 Days)

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Drug Therapy to Reduce ARDS Mortality

Glucocorticoids: Inflammation Drives Fibroproliferative Phase of ARDS

ARDS
(≥7 days)

Glucocorticoids
(n=89)

Placebo
(n=91)

60 Days

PaO_2/FIO_2
Organ Dysfunction
Mortality

Steroid Dosing:
2 mg/kg x 1 dose
then 0.5 mg/kg every 6 hrs x 14 days
then 0.5mg/kg every 12 hrs x 7 days
then taper.

Treatment to Reduce ARDS Mortality

Variable	Placebo	Steroid	P Value
Ventilator Free Days at Day 28	6.8 ± 8.5	11.2 ± 9.4	<0.001
ICU Free Days at Day 28	6.2 ± 7.8	8.9 ± 8.2	0.02
60 Day Mortality (%)	28.6	29.2	1.0
60 day Mortality From Time of ARDS Onset (7-13 days)	36	27	.26
60 day Mortality From Time of ARDS Onset (After Day 13)	8	35	<0.001

PD-INEL Source Undetermined

Summary/ Key Points

ARDS is Diagnosed by Clinical Parameters:

- Acute Onset in Appropriate Setting
- Bilateral Infiltrates
- Reduced Oxygenation
- No Evidence of CHF

Definition Lacks Specificity. Differential Diagnosis Includes:

- Congestive Heart Failure
- Alveolar Hemorrhage
- Pneumonia
- Aspiration

Pathophysiology Includes:

- Systemic Inflammation
- Injury to the Alveolar Membrane
- Alveolar Flooding with Plasma Fluid
- Inactivation of Surfactant

⇨

Respiratory Distress
↑ Resp. Rate
Hypoxemia
↓ Compliance
Bilateral Infiltrates

Summary/ Key Points

Management Problems:

- Decreased Compliance
- Refractory Hypoxemia
- High Mortality

Strategies to Manage:

- Decreased Compliance
- Refractory Hypoxemia
- High Mortality

→

Low Tidal Volume Ventilation
Permissive Hypercapnea
Best PEEP Curve
Prone Positioning
Inhaled NO2

Risk Factors for Mortality:

- Multi-organ Failure
- Underlying Cause of ARDS
- Not Degree of Hypoxemia

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