



**Brigham and Women's Hospital**

Founding Member, Mass General Brigham

# Respiratory Failure

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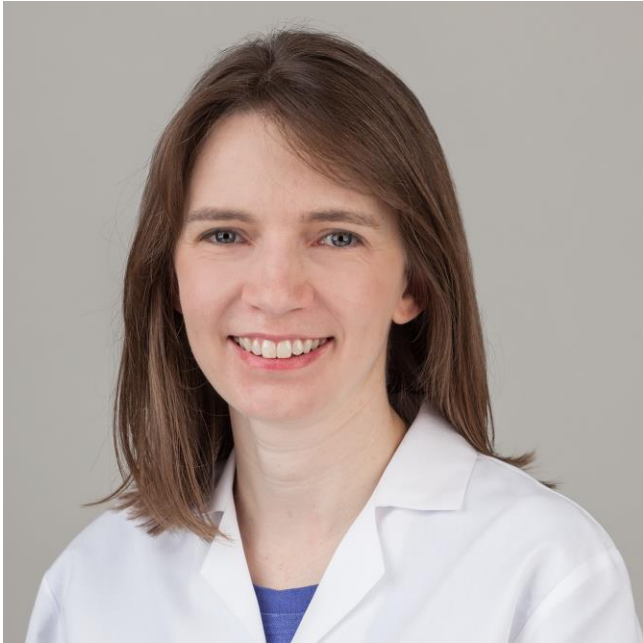
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# DISCLOSURES

Nothing to disclose



# Outline – Respiratory Failure

## 1. Hypoxemic Respiratory Failure

- a. Physiology
- b. ARDS
  - i. Special cases – Fat embolism, Transfusion related acute lung injury
  - ii. Management
    - 1. Low Tidal Volume Ventilation
    - 2. Prone positioning
    - 3. Neuromuscular Blockade
    - 4. ECMO

## 2. Hypercapnic Respiratory Failure

- a. Physiology
- b. COPD
- c. Neuromuscular Disease
- d. Obesity Hypoventilation Syndrome

What we will **NOT** cover in regards to respiratory failure that is potentially board relevant:

- 1. Pneumonia
- 2. Sepsis
- 3. Mechanical Ventilation



# Objectives

1

Describe the pathophysiology and clinical features of hypoxemic and hypercapnic respiratory failure.

2

Identify and review diagnostic criteria and evidence-based treatment strategies for ARDS.

3

Review physiology and presentation of hypercapnic respiratory failure as well as therapeutic strategies.

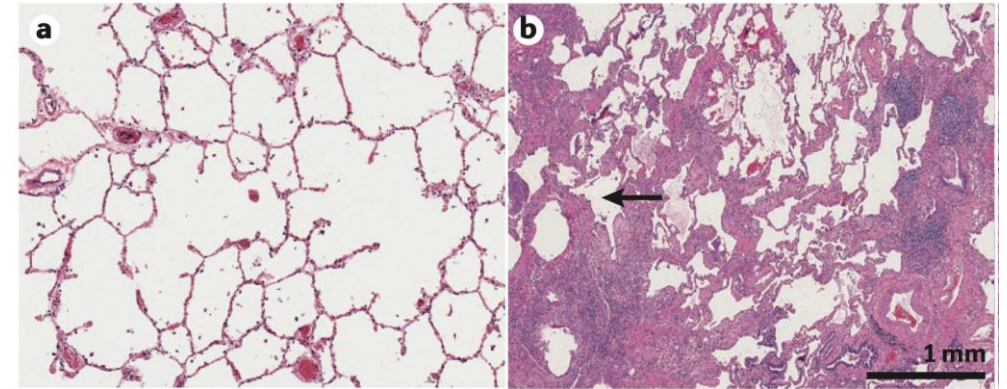


# Physiology of hypoxemia

“can’t breathe, won’t breathe”

1. Hypoventilation
2. Diffusion impairment
3. Shunt
4. VQ mismatch
5. Low inspired  $\text{FiO}_2$

ILD



Nature Reviews Disease Primers 2017; 3:17074

- Intracardiac (R→L)
- Intrapulmonary (arteriovenous malformation, hereditary hemorrhagic telangiectasia, hepatopulmonary syndrome)
- Physiologic - severe alveolar filling process (pneumonia, edema, ARDS, hemorrhage) with absence of ventilation but intact perfusion



# Physiology of hypoxemia

	<b>A-a gradient</b>	<b>Response to O<sub>2</sub></b>
1. Hypoventilation	None	+
2. Diffusion impairment	Increased	+
3. Shunt	Increased	None to minimal
4. VQ mismatch	Increased	+
5. Low inspired FiO <sub>2</sub>	None	+



# A-a gradient

$$\begin{aligned}\text{A-a gradient} &= P_A\text{O}_2 - P_a\text{O}_2 \\ &= (\text{alveolar gas equation}) - (P_a\text{O}_2 \text{ from ABG})\end{aligned}$$

$$\begin{aligned}\text{Normal A-a gradient (roughly)} &< 15 \\ &= \text{Age}/4 + 4\end{aligned}$$





# Alveolar gas equation for $P_AO_2$ - example

Normal

$$P_AO_2 = FiO_2 (P_{atm} - P_{H_2O}) - (P_aCO_2 / RER)$$

$$P_AO_2 = FiO_2 (760 - 47) - (P_aCO_2 / 0.8)$$

$$P_AO_2 = 0.21(760 - 47) - (40 / 0.8)$$

$$P_AO_2 = 150 - 50$$

$$P_AO_2 = 100$$

Altitude - Denver

$$P_AO_2 = FiO_2 (640 - 47) - (P_aCO_2 / 0.8)$$

$$P_AO_2 = 0.21(640 - 47) - (40 / 0.8)$$

$$P_AO_2 = 125 - 50$$

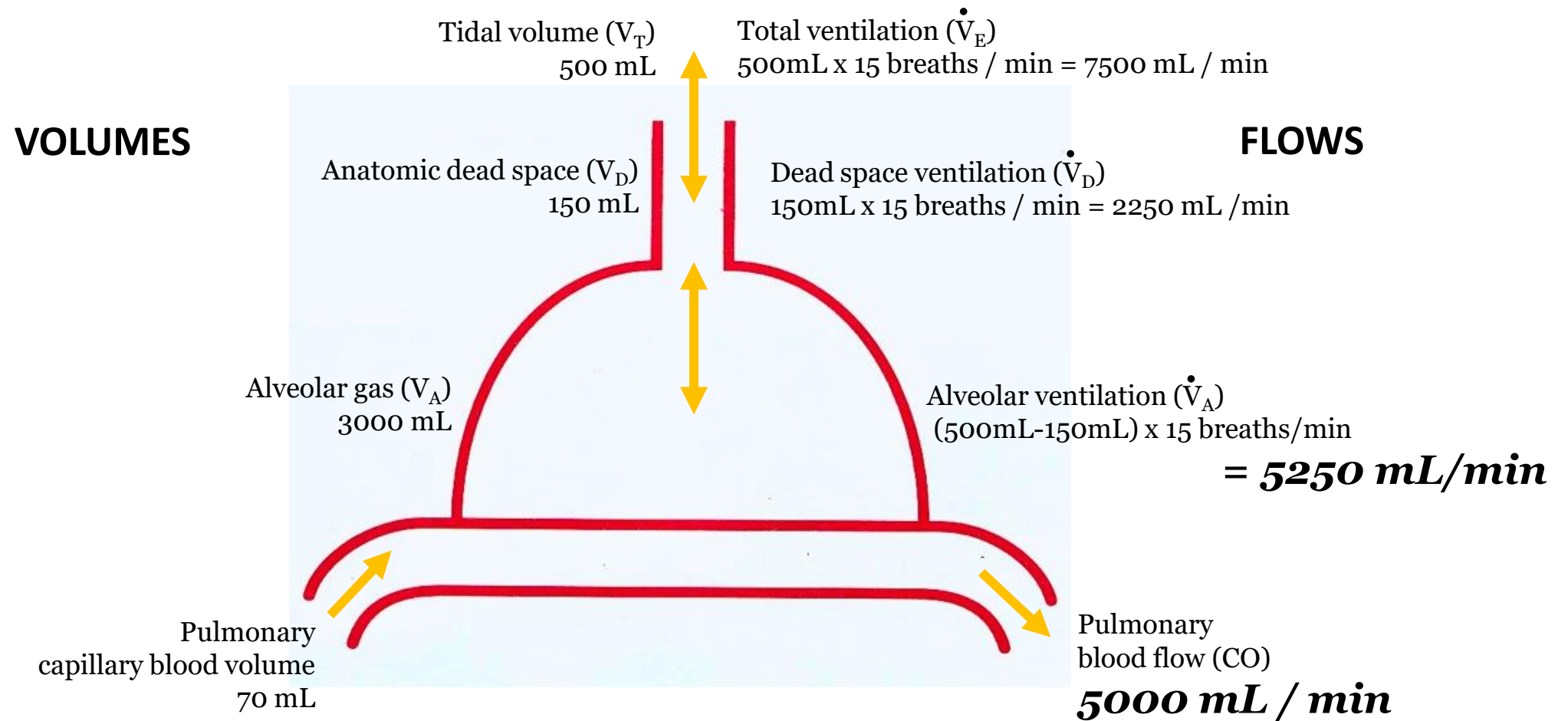
$$P_AO_2 = 75$$

***What that means for your practice.....***

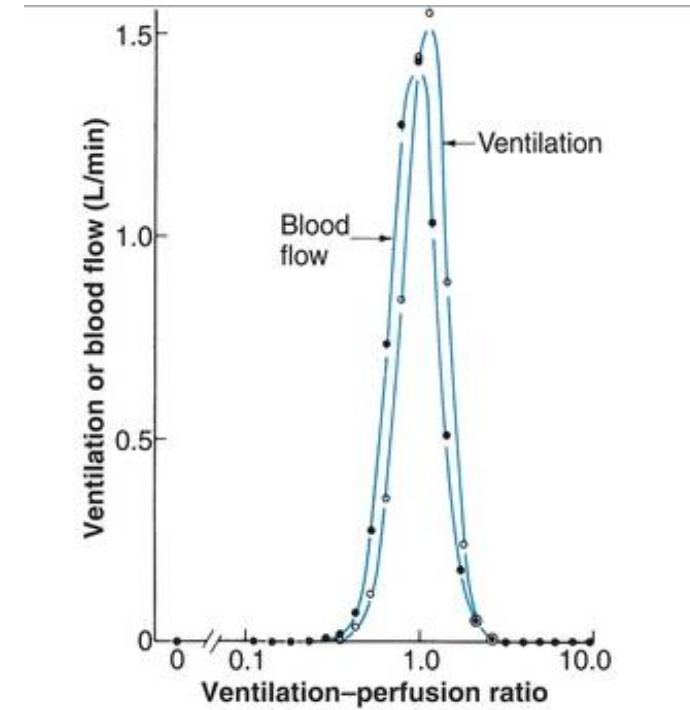
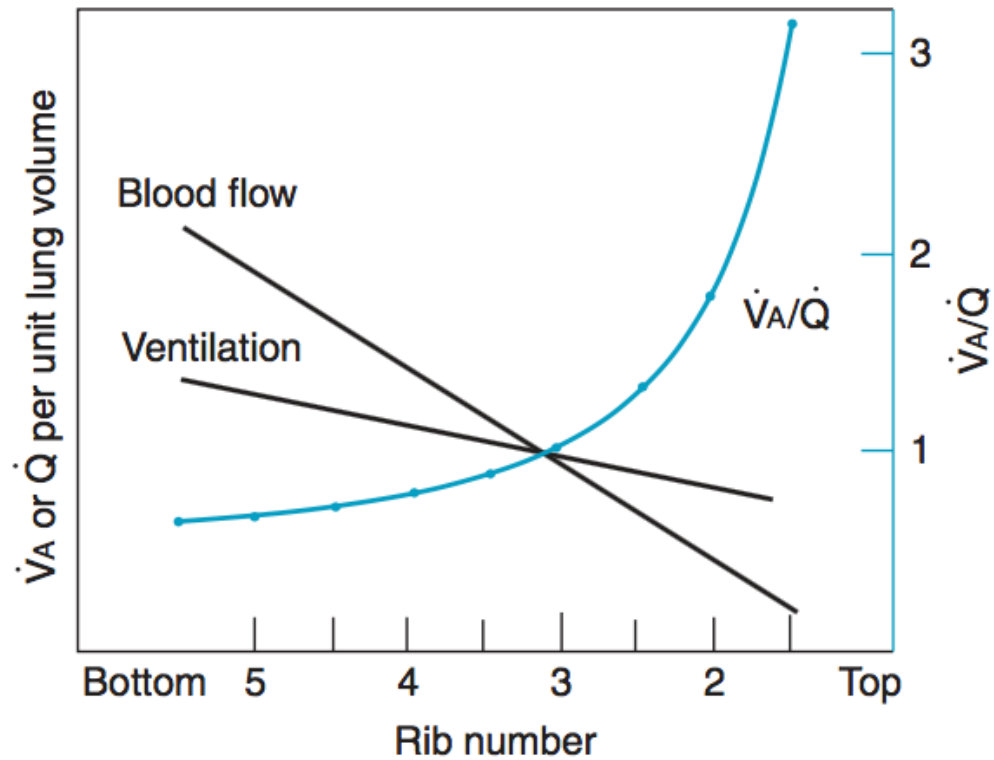
- at altitude (Denver), a  **$PaO_2$  of 60** on an ABG on room air still implies a normal A-a gradient ( **$75-60=15$** )
- at sea level, a  **$PaO_2$  of 60** on an ABG on room air implies an A-a gradient of  **$100-60=40$**  – look for reasons!



# Normal physiology - Ventilation/Perfusion (V/Q)



# Normal physiology – V/Q



V/Q is heterogenous across the lung



# V/Q mismatch

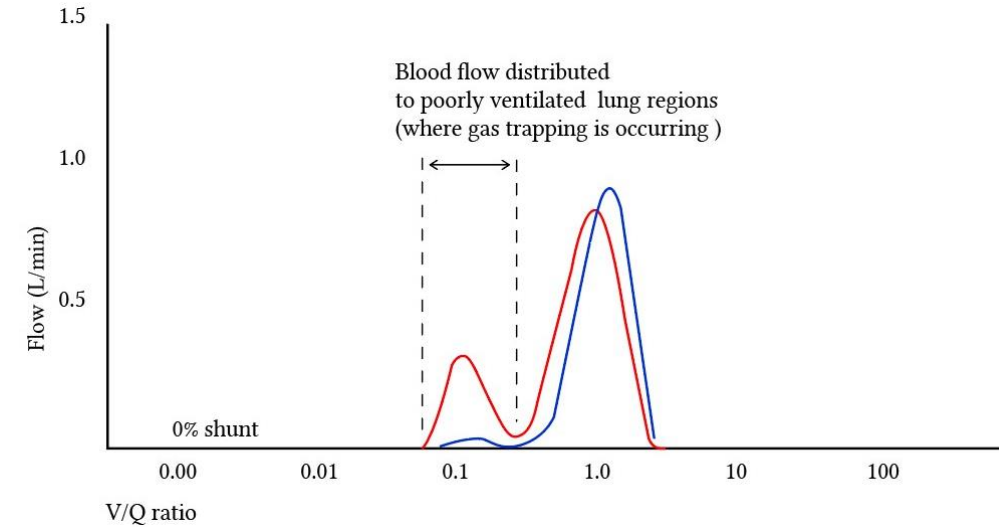
Most common cause of hypoxemia.

V/Q mismatch occurs because heterogeneity of either or both ventilation and perfusion worsen. The net effect is hypoxemia.

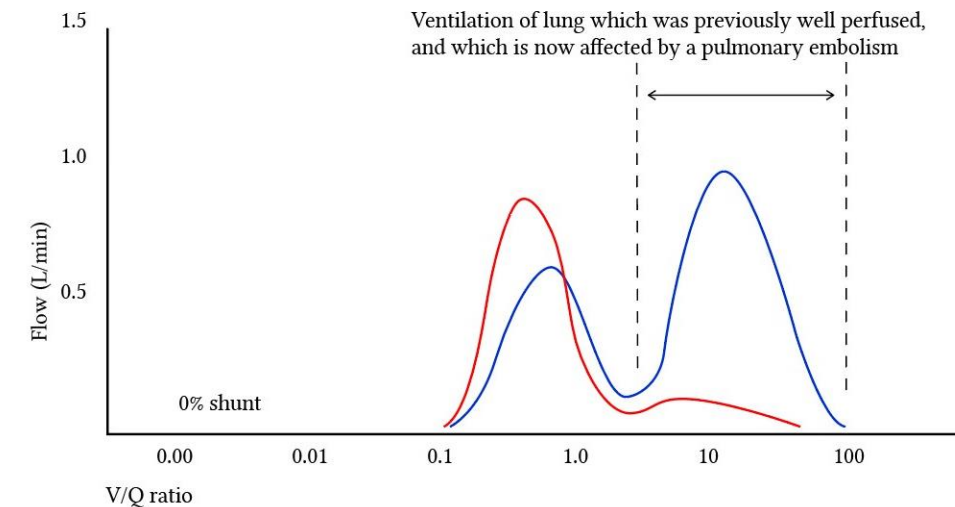
Examples: **Pulmonary embolism, Pneumonia, ARDS, COPD, Interstitial lung disease, and many more**



## Acute asthma exacerbation



## Pulmonary embolism




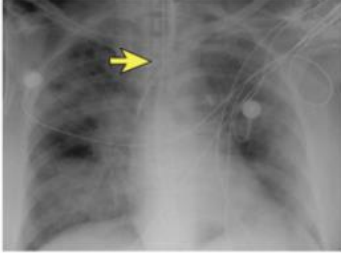



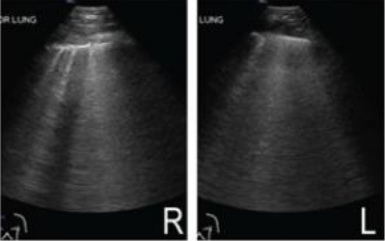
# ARDS Definition – Berlin Criteria 2012

**Table 3.** The Berlin Definition of Acute Respiratory Distress Syndrome

Acute Respiratory Distress Syndrome	
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging <sup>a</sup>	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation <sup>b</sup>	
Mild	$200 \text{ mm Hg} < \text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mm Hg}$ with PEEP or CPAP $\geq 5 \text{ cm H}_2\text{O}^c$
Moderate	$100 \text{ mm Hg} < \text{PaO}_2/\text{FiO}_2 \leq 200 \text{ mm Hg}$ with PEEP $\geq 5 \text{ cm H}_2\text{O}$
Severe	$\text{PaO}_2/\text{FiO}_2 \leq 100 \text{ mm Hg}$ with PEEP $\geq 5 \text{ cm H}_2\text{O}$



# ARDS – revised global definition

Patient Description	Imaging	Oxygenation	ARDS Categories
 <p>68-year-old M with abdominal sepsis, septic shock, and acute hypoxemic respiratory failure</p>		<p>Mechanically ventilated  <math>\text{FiO}_2</math> 0.5  <math>\text{PaO}_2</math> 75  <math>\text{P/F} = 150</math> mm Hg</p>	<p><b>Intubated ARDS</b>            Severity: Moderate  <i>Typical patient included in prior Berlin definition</i></p>
 <p>54-year-old F with history of breast cancer, COVID-19 pneumonia, and worsening shortness of breath for the past 6 days</p>		<p>High-flow nasal oxygen            HFNO 40L/min  <math>\text{FiO}_2</math> 0.80  <math>\text{SpO}_2</math> 91%  <math>\text{S/F} = 114</math></p>	<p><b>Nonintubated ARDS</b>  <i>New category in Global definition</i></p>
 <p>39-year-old F with abdominal sepsis and gram-negative bacteremia in a small under-resourced hospital without blood gases, radiography, or mechanical ventilation</p>		<p>Supplemental oxygen by face mask at 15L/min  <math>\text{FiO}_2</math> 0.6  <math>\text{SpO}_2</math> 85%  <math>\text{S/F} = 142</math></p>	<p><b>ARDS in resource-limited settings</b>  <i>New category in global definition, consistent with the Kigali modification</i></p>

# ARDS - Associated Conditions

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## **DIRECT LUNG INJURY**

### **Common causes**

Pneumonia

Aspiration of gastric contents

### **Less common causes**

Pulmonary contusion

Fat emboli

Near-drowning

Inhalational injury

Reperfusion pulmonary edema  
after lung transplantation or  
pulmonary embolectomy

## **INDIRECT LUNG INJURY**

### **Common causes**

Sepsis

Severe trauma with  
shock and multiple  
transfusions

### **Less common causes**

Cardiopulmonary bypass

Drug overdose

Acute pancreatitis

Transfusions of blood  
products

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# Specific etiologies - Fat embolism

## 1. Trigger

Long-bone or pelvic fracture (esp. femur), orthopedic surgery, severe trauma → fat droplets release into bloodstream

## 2. Pathophysiology

**Mechanical:** Fat globules lodge in pulmonary capillaries → ventilation–perfusion mismatch, capillary blockage

**Inflammatory:** Lipase-free fatty acid release injures endothelium → inflammation → increased permeability → edema & hemorrhage

## 3. Clinical Timeline

Onset: **12–72 hours post-injury**

Respiratory distress progressing to ARDS

## 4. Management

**Supportive only:** oxygen supplementation, early intubation and low-tidal-volume ventilation with PEEP, careful fluid/resuscitation

**Preventive:** early surgical stabilization of fractures reduces risk





# Specific etiologies – Transfusion Related Acute Lung Injury

New acute lung injury within **≤ 6 hours** of starting transfusion, without other clear causes of ALI/ARDS

Most onset occurs within **1–2 hours** post-transfusion

## 1. Pathophysiology

**Predisposing “first-hit”**: underlying illness / susceptible host (e.g. sepsis, surgery, inflammation)

**Transfusion “second-hit”**: donor-derived anti-HLA or anti-HNA antibodies (~80%) or other modifiers activate neutrophils → endothelial injury, capillary leak, pulmonary edema

## 2. Clinical Features

Sudden onset dyspnea, hypoxemia ( $\text{SpO}_2 < 90\%$  or  $\text{PaO}_2/\text{FiO}_2 \leq 300$  mmHg), tachypnea, often fever, hypotension or hypertension, sometimes cyanosis

Chest X-ray: bilateral fluffy infiltrates consistent with non-cardiogenic pulmonary edema

## 3. Diagnosis & Differential

Meets ALI/ARDS criteria temporally related to transfusion; no signs of circulatory overload

Key differential: **TACO** – look for signs of volume overload (elevated BNP, JVD), often managed with diuretics

## 4. Management & Prognosis

Stop transfusion, provide respiratory support, hemodynamic stabilization as needed. Most recover in **48–96 hours**; radiographic changes may last up to 7 days; mortality ~ 5–10%

## 5. Prevention Strategies

Avoid plasma from **multiparous female donors** (to reduce anti-HLA/HNA antibody risk),

Minimize unnecessary plasma transfusions, optimize volume status pre-transfusion, leukoreduce components when appropriate



# ARDS Management - Low Tidal Volume Ventilation

VOLUME 342

MAY 4, 2000

NUMBER 18



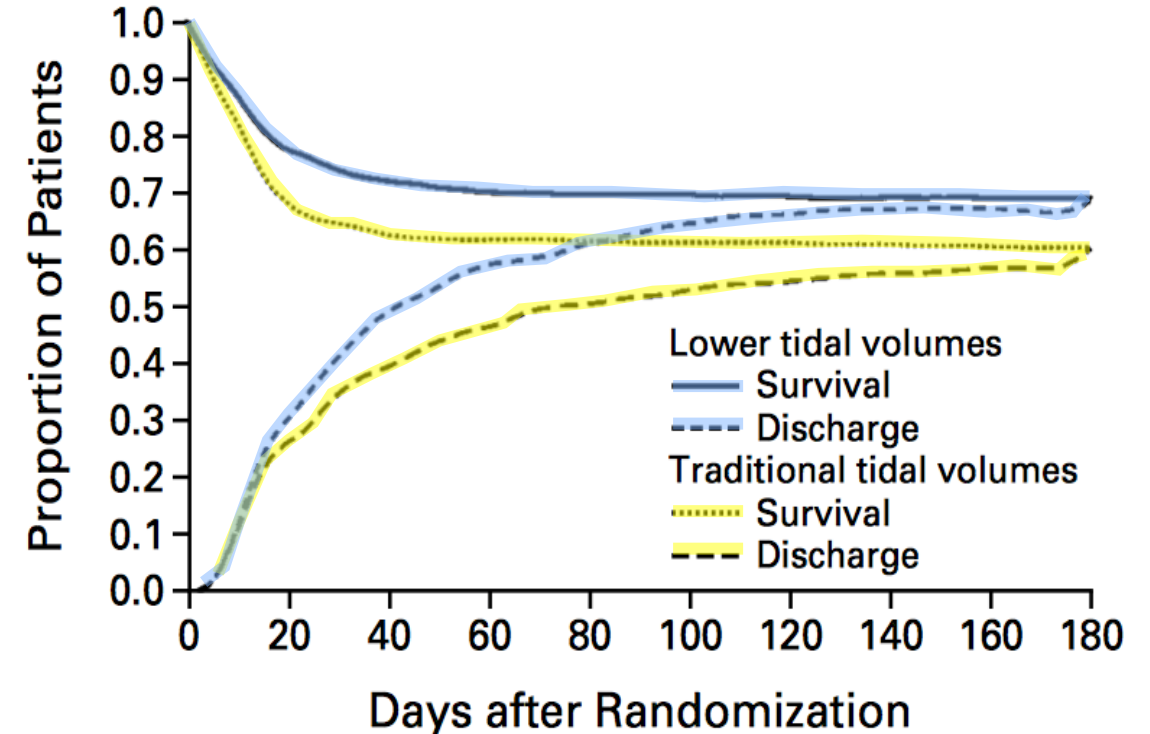
## VENTILATION WITH LOWER TIDAL VOLUMES AS COMPARED WITH TRADITIONAL TIDAL VOLUMES FOR ACUTE LUNG INJURY AND THE ACUTE RESPIRATORY DISTRESS SYNDROME

THE ACUTE RESPIRATORY DISTRESS SYNDROME NETWORK\*

12cc/kg & plateau <50cm H<sub>2</sub>O vs  
6cc/kg & plateau < 30cm H<sub>2</sub>O

Multicenter, randomized trial.

- **Primary outcome:** death before a patient was discharged home and was breathing without assistance



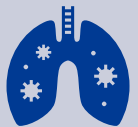
# ARDS Management - Low Tidal Volume Ventilation



## Conclusions

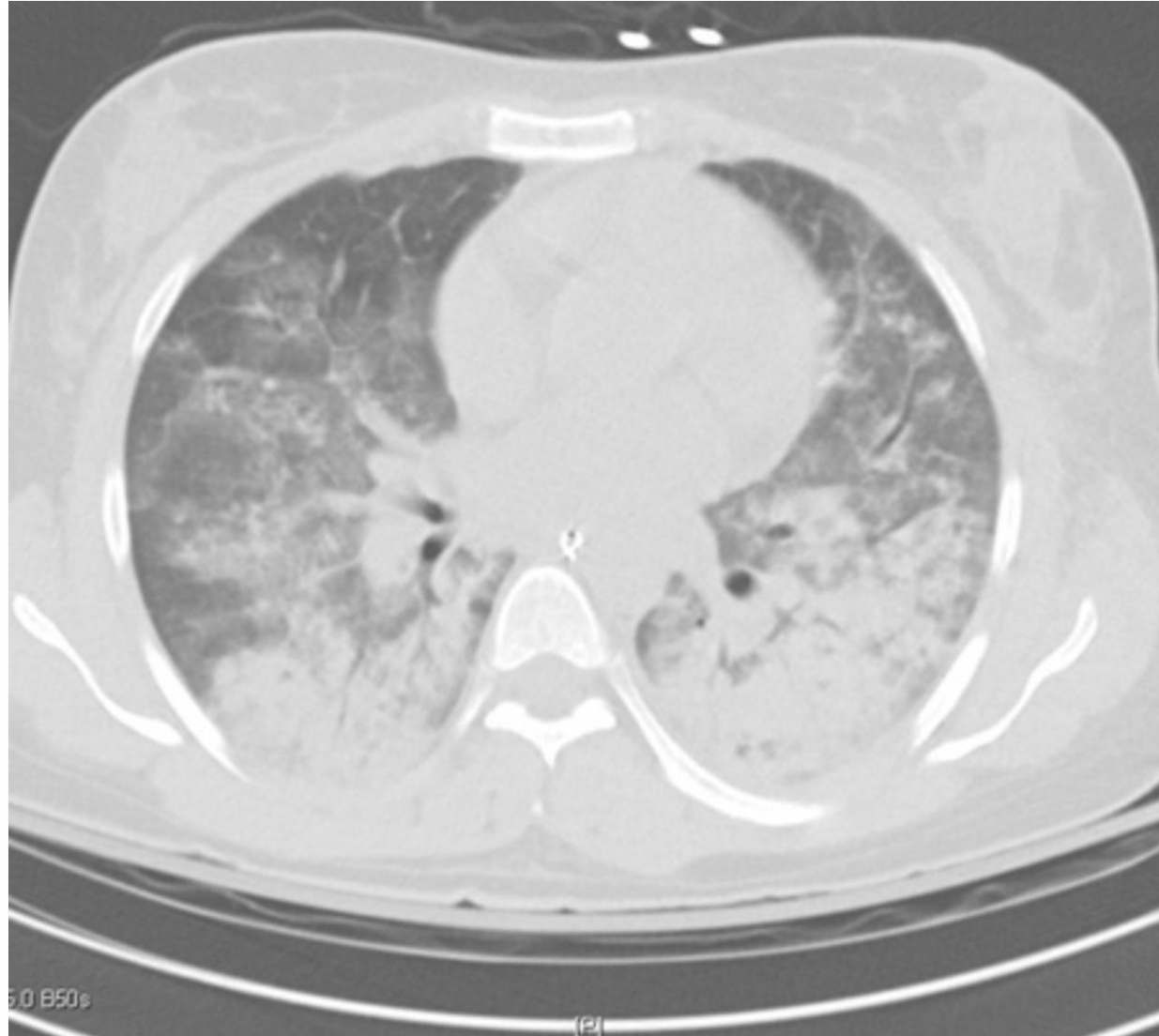


Trial stopped early due to the significant benefit of low tidal volumes at early analysis



6cc/kg IBW has become the standard of care and has been extrapolated to almost all intubated patients, regardless of underlying pathology

# ARDS Management - Proning



# ARDS Management - Proning

Prospective, multicenter, randomized, controlled trial

474 total patients randomized

Outcome	Supine Group (N = 229)	Prone Group (N = 237)	Hazard Ratio or Odds Ratio with the Prone Position (95% CI)	P Value
Mortality — no. (% [95% CI])				
At day 28				
Not adjusted	75 (32.8 [26.4–38.6])	38 (16.0 [11.3–20.7])	0.39 (0.25–0.63)	<0.001
Adjusted for SOFA score†			0.42 (0.26–0.66)	<0.001
At day 90				
Not adjusted	94 (41.0 [34.6–47.4])	56 (23.6 [18.2–29.0])	0.44 (0.29–0.67)	<0.001
Adjusted for SOFA score†			0.48 (0.32–0.72)	<0.001
Successful extubation at day 90 — no./total no. (% [95% CI])	145/223 (65.0 [58.7–71.3])	186/231 (80.5 [75.4–85.6])	0.45 (0.29–0.70)	<0.001
Time to successful extubation, assessed at day 90 — days				
Survivors	19±21	17±16		0.87
Nonsurvivors	16±11	18±14		
Length of ICU stay, assessed at day 90 — days				
Survivors	26±27	24±22		0.05
Nonsurvivors	18±15	21±20		
Ventilation-free days				
At day 28	10±10	14±9		<0.001
At day 90	43±38	57±34		<0.001



# ARDS Management - Proning

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## Conclusions:

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Decreases mortality, aids in overall liberation from the ventilator, decreases ICU LOS, increases ventilator-free days

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## Drawbacks:

Significant risk to the patient during proning procedure re: loss of airway, IV access, desaturations

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Labor intensive

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Cannot perform safely in hemodynamically unstable patients.

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Pressure ulcers

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Emesis / increased gastric residuals / challenge to maintain nutrition

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# ARDS Management – Neuromuscular Blockade

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## **Induction of paralysis may . . .**

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Increase chest wall compliance

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Eliminate patient-ventilator dyssynchrony

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Facilitate lung recruitment

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Reduce inflammatory mediator release

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Decrease lung hyperinflation

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Reduce oxygen consumption (controversial)

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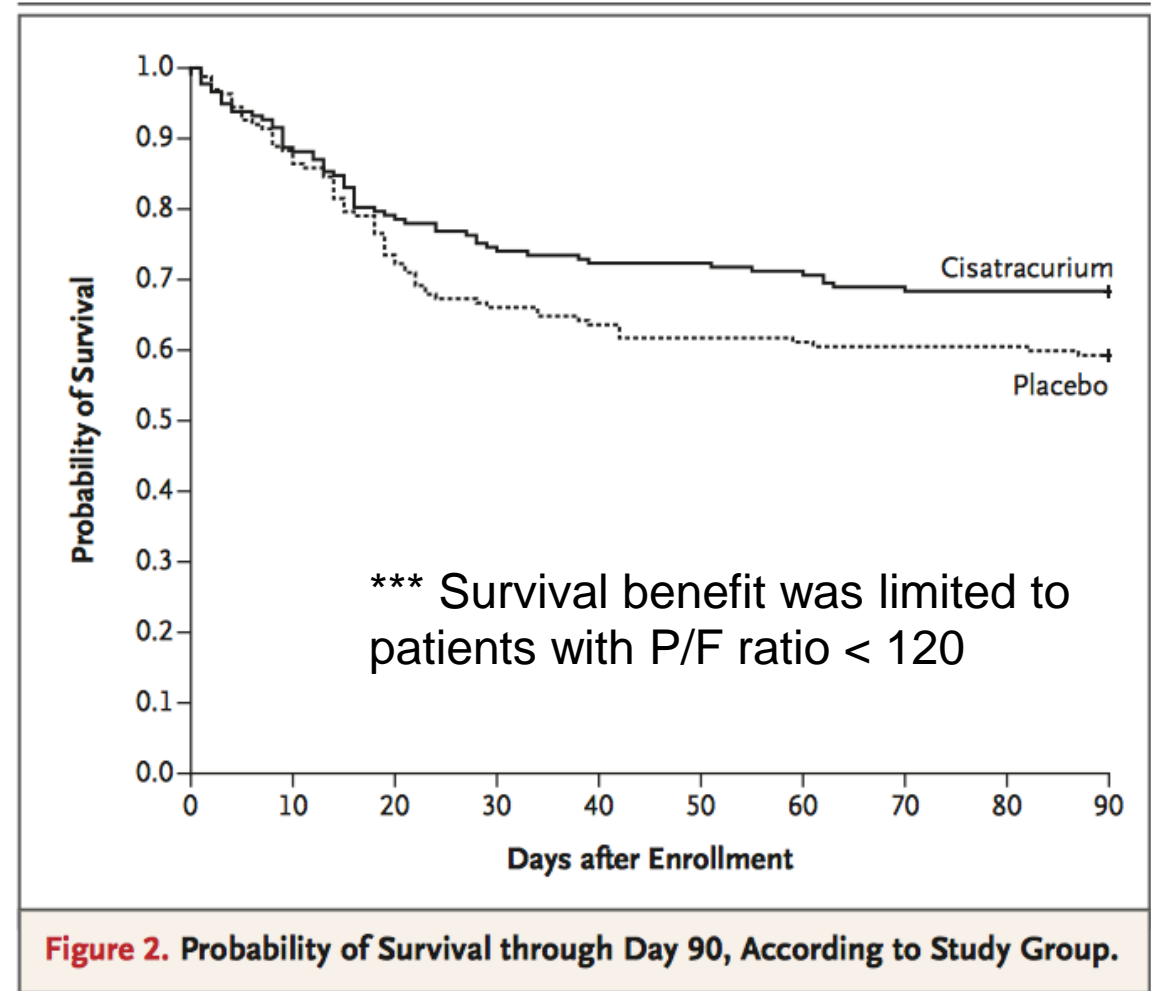


# ARDS Management – Neuromuscular Blockade

Multicenter, double-blind trial

340 patients presenting with severe ARDS ( $\text{PaO}_2/\text{FiO}_2 < 150$ ) within the previous 48 hours randomly assigned to cisatracurium or placebo for 48 hrs

**Primary outcome:** Proportion of patients who died either before hospital discharge or within 90 days after study enrollment





# ARDS Management – Neuromuscular Blockade



**Subsequent trial (ROSE) published 2019 failed to show benefit in hospital mortality, ventilator free days, or rates of barotrauma.**



**Conclusion:** Overall, no clear benefit but may be used in severe ARDS with ventilator dyssynchrony unresponsive to deep sedation

# ARDS Management - ECMO

## Indications for ECMO in ARDS

- Severe hypoxemia ( $\text{PaO}_2/\text{FiO}_2 < 80$  mmHg) despite optimal ventilator settings.
- Refractory hypercapnia with  $\text{pH} < 7.20$ .
- Failure of conventional therapies, including prone positioning and neuromuscular blockade

## Benefits

- Improves oxygenation and  $\text{CO}_2$  removal.
- Allows for lung-protective ventilation strategies.
- Potentially reduces ventilator-induced lung injury.

## Considerations

- Requires specialized centers with experienced multidisciplinary teams.
- Associated risks include bleeding, thrombosis, and infection.
- Patient selection is critical; early consultation with an ECMO center is advised.
- Ideal patient is young with single organ dysfunction. Best data comes from viral ARDS (flu, COVID).



# Use of HFNC in Severe Respiratory Failure

*The* **NEW ENGLAND**  
**JOURNAL of MEDICINE**

ESTABLISHED IN 1812

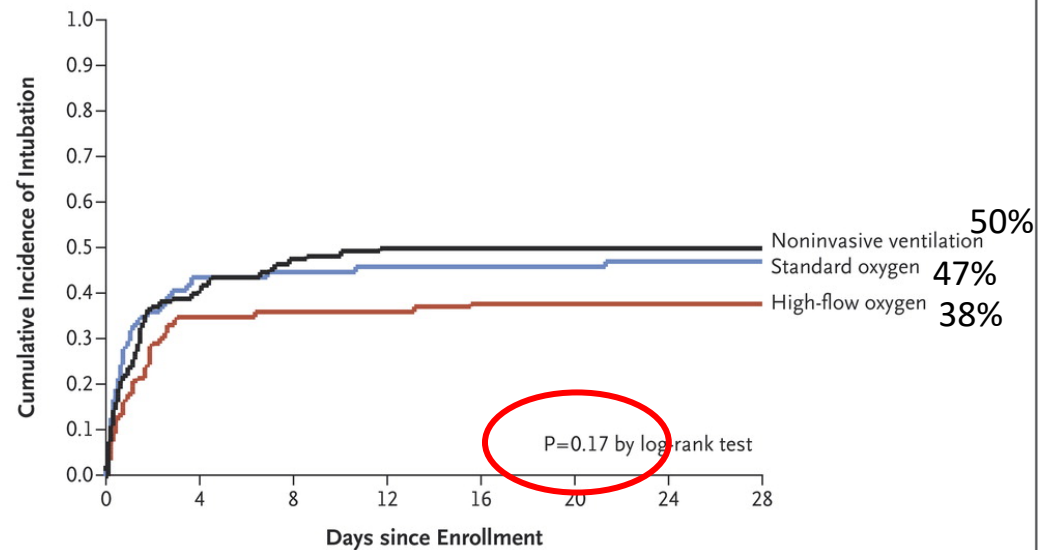
JUNE 4, 2015

VOL. 372 NO. 23

High-Flow Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure

## Incidence of Intubation

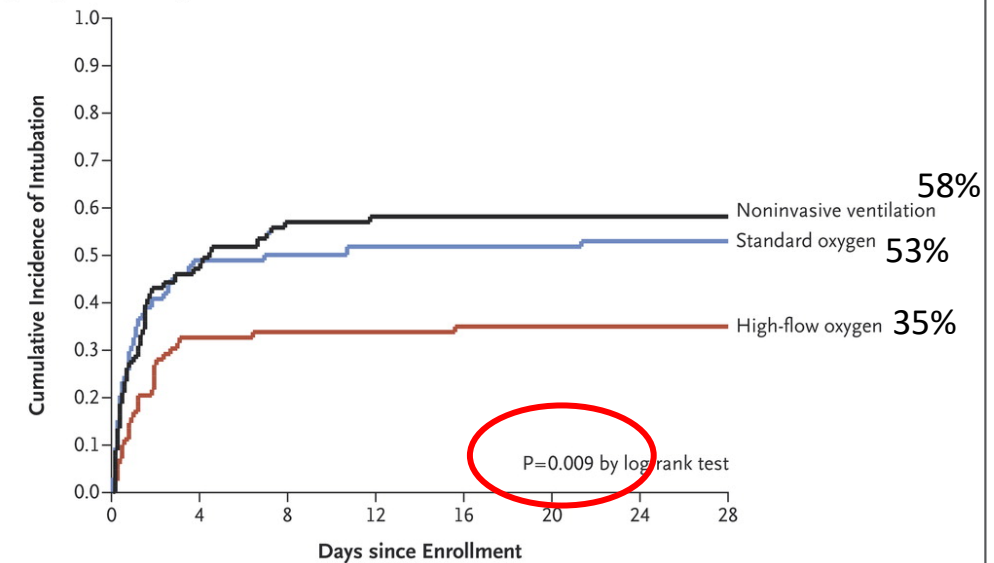
**A Overall Population**



No. at Risk

High-flow oxygen	106	68	67	67	65	65	65	65
Standard oxygen	94	52	50	49	49	49	48	48
Noninvasive ventilation	110	64	57	53	53	53	53	52

**B Patients with a  $\text{PaO}_2:\text{FiO}_2 \leq 200$  mm Hg**



No. at Risk

High-flow oxygen	83	55	54	54	53	53	53	53
Standard oxygen	74	37	35	34	34	34	33	33
Noninvasive ventilation	81	41	34	32	32	32	32	32



# Use of HFNC in Severe Respiratory Failure

HFNC is well-tolerated

HFNC may result in fewer intubations in patients with P:F <200 compared to standard O<sub>2</sub> or NPPV.

There may be a mortality benefit to HFNC compared to standard O<sub>2</sub> or NPPV.



# Hypercapnic Respiratory Failure - Definition

Elevated arterial  $\text{PaCO}_2$

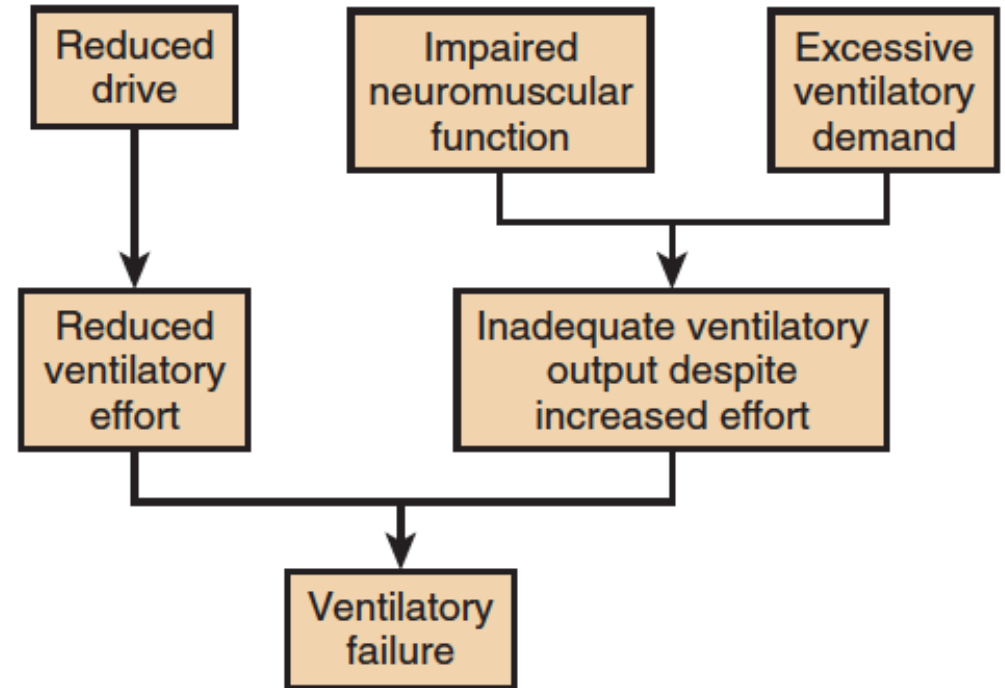
**Two principle causes:** hypoventilation or V/Q mismatch

Acute: (minutes to hours),

- no compensatory mechanisms,
- pH is low ( $<7.35$ ,  $\text{pCO}_2 > 50$ )
- expected pH change:  $\sim 0.08$  for every 10mmHg of  $\text{pCO}_2$  elevation

Chronic: (days to weeks)

- Compensated
- Close to normal pH (if kidneys are working)
- Expected pH change: 0.03 for every 10mmHg of  $\text{pCO}_2$  elevation



# Hypercapnic Respiratory Failure - Etiologies

## Acute

- Drug induced respiratory depression
- Severe airway obstruction (ie status asthmaticus, AECOPD)
- Increased dead space (acute PE)
- Errors in mechanical ventilation
- Fever, sepsis, hyperthermia
- Trauma (c-spine injury)
- Bicarb supplementation
- Hyperalimentation

## Chronic

- Primary alveolar hypoventilation (Ondine's curse)
- Progressive obstructive or restrictive lung disease
- Neuromuscular disease
- Myxedema
- OHS

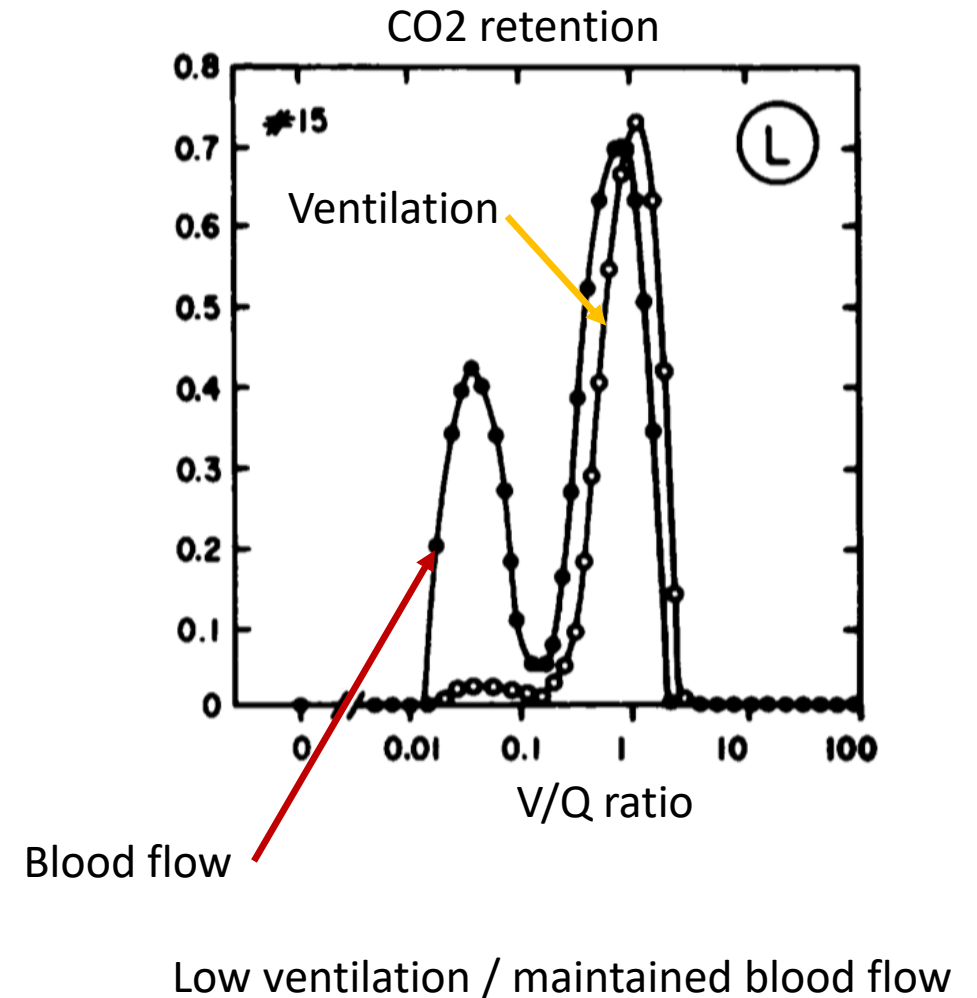


# Hypercapnic respiratory failure - AECOPD

- Often triggered by infection
- Decreased alveolar ventilation due to airway constriction and
- Air trapping
- Flattened diaphragms -> decreased inspiratory capacity
- Systemic inflammation-> impaired respiratory function, increased  $O_2$  extraction

## Treatment:

- Bronchodilators
- Corticosteroids
- Antibiotics
- NPPV vs invasive mechanical ventilation



# Management of patients with neuromuscular disease

Evaluate pulmonary mechanics

Acutely consider intubation (i.e. Guillain-Barre) if:

- FVC <15ml/kg IBW, ~<1000ml, or >50% decline
- MIP/NIF (<30cm H<sub>2</sub>O/-30cmH<sub>2</sub>O)

FVC <50% is criteria for Medicare reimbursement for home NPPV

Evaluate for hypercarbia – first symptom usually sleep fragmentation

- Awake Pa<sub>CO2</sub> > 45 correlates with sleep hypoventilation
- NPVV should be started when patients develop symptoms that are likely to respond. (Dyspnea at rest or orthopnea, poor sleep, daytime fatigue, hypersomnolence, or morning headaches)
- Goal of timely initiation is to avoid respiratory crises and the need for emergency intubation

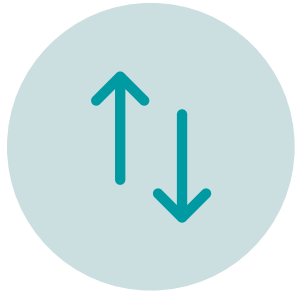
Evaluate for ability to protect airway/handle secretions

- Cough insufficiency
- Bulbar dysfunction





# NPPV in NMD has been shown to....



Reduce arterial  $P_{CO_2}$  and  
Increase arterial  $P_{O_2}$



Decrease symptoms of sleep-disordered breathing such as morning headache, nocturnal awakenings, vivid nightmares, and night sweats



Improve quality of life



Reduce morbidity and most likely reduce mortality.

# Obesity hypoventilation syndrome

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Obese (BMI>30)

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Awake hypoventilation (PaCO<sub>2</sub>>45mmHG)

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Comorbid OSA present in 90%

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Prevalence is >50% in hospitalized patients with BMI > 50

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Often mildly hypoxic (hypoventilation, V/Q mismatch and shunt due to premature airway closure)

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Serum bicarb is elevated

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Sometimes elevated hemoglobin

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Abnormal PFTs (reduced ERV and FRC)

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Impaired pulmonary mechanics (decreased chest wall compliance)

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# OHS therapy



Goal: reduction of daytime CO<sub>2</sub>  
prevention of hypoxia



Nocturnal CPAP vs BiPAP



Weight loss (including bariatric surgery, GLP-1 agonists)



Avoidance of other respiratory depressants

# Outline – Respiratory Failure

## **1. Hypoxemic Respiratory Failure**

- a. Physiology
- b. ARDS
  - i. Special cases – Fat embolism, Transfusion related acute lung injury
  - ii. Management
    - 1. Low Tidal Volume Ventilation
    - 2. Prone positioning
    - 3. Neuromuscular Blockade
    - 4. ECMO

## **2. Hypercapnic Respiratory Failure**

- a. Physiology
- b. COPD
- c. Neuromuscular Disease
- d. Obesity Hypoventilation Syndrome



# SUMMARY



Understanding the physiology underlying a patient's hypoxemia can help to target therapies.



Data on management of ARDS is decades old and we are in desperate need of targeted, patient-specific therapies for a very heterogeneous disorder.



Hypercapnic respiratory failure has multiple etiologies but is generally treated by supporting ventilation either noninvasively or with mechanical ventilation in addition to treating the underlying etiology when possible.

A 62-year-old man with obesity (BMI 38), obstructive sleep apnea, and a 30-year heavy smoking history is admitted to the ICU with septic shock secondary to pneumonia. He's initially intubated and placed on mechanical ventilation. Two days later, despite lung-protective ventilation (VT 6 mL/kg ideal body weight, FiO<sub>2</sub> 0.60, PEEP 10 cm H<sub>2</sub>O), his ABG shows:

pH 7.30

PaCO<sub>2</sub> 55 mm Hg

PaO<sub>2</sub> 70 mm Hg

HCO<sub>3</sub><sup>-</sup> 26 mEq/L

PaO<sub>2</sub>/FiO<sub>2</sub> ratio ≈ 117

He is deeply sedated, euvolemic, and hemodynamically stable. Plateau pressure is 29 cm H<sub>2</sub>O; driving pressure is 19 cm H<sub>2</sub>O.

**Next best step in management?**

- A. Increase PEEP to 14 cm H<sub>2</sub>O
- B. Switch to airway pressure release ventilation (APRV)
- C. Start prone positioning
- D. Increase tidal volume to 8 mL/kg
- E. Initiate neuromuscular blockade for 48 hours



A 60-year-old man with severe COPD ( $FEV_1 \sim 28\%$  predicted) is hospitalized for acute exacerbation. On admission, his ABG (on 2 L/min  $O_2$ ) shows:

pH 7.27

$PaCO_2$  70 mm Hg

$PaO_2$  60 mm Hg

$HCO_3^-$  31 mEq/L

He is started on bilevel NIV with IPAP 12 cm  $H_2O$ , EPAP 5 cm  $H_2O$ ,  $FiO_2$  0.35. Twelve hours later, he's more alert, respiratory rate is 24/min, and a repeat ABG shows:

pH 7.29

$PaCO_2$  65 mm Hg

$PaO_2$  65 mm Hg

He is tolerating the mask with minimal leaks.

**What is the most appropriate next step?**

- A. Maintain current settings and monitor ABG in another 12 h
- B. Increase IPAP to 16–18 cm  $H_2O$
- C. Increase EPAP to improve oxygenation
- D. Intubate and transition to invasive mechanical ventilation
- E. Wean NIV by alternating with high-flow nasal cannula



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