Rescue Therapies for ARDS

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ARDS

- First described in 1967 by Ashbaugh and colleagues
- 1994 Consensus Definition
  - Acute onset severe respiratory distress
  - Bilateral infiltrates on chest x-ray
  - PCWP <=18mmHg or lack of evidence of left atrial hypertension
  - Acute lung injury (PaO2/FiO2<=300)
  - ARDS if PaO2/FiO2<=200

Berlin Definition

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[a]	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[b]	
Mild	200 mm Hg $<$ Pa_{O_2}/F_{IO_2} $\leq$ 300 mm Hg with PEEP or CPAP $\geq$5 cm H_2O[c]
Moderate	100 mm Hg $<$ Pa_{O_2}/F_{IO_2} $\leq$ 200 mm Hg with PEEP $\geq$5 cm H_2O
Severe	Pa_{O_2}/F_{IO_2} $\leq$ 100 mm Hg with PEEP $\geq$5 cm H_2O

Abbreviations: CPAP, continuous positive airway pressure; F_{IO_2}, fraction of inspired oxygen; Pa_{O_2}, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

[a] Chest radiograph or computed tomography scan.

[b] If altitude is higher than 1000 m, the correction factor should be calculated as follows: [Pa_{O_2}/F_{IO_2} × (barometric pressure/760)].

[c] This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

ARDSNET

- 861 patients randomized into conventional VT:12cc/kg vs study VT: 6cc/kg
- Enrollment stopped because of mid-study analysis showing improved survival in lower VT group (Mortality 40% versus 31%)

ARDSNET, NEJM 342:1301-1308,2000

Lung-Protective Ventilation

ARDS Network, 2000: Multicenter randomized,861Pts

	Lung-protective ventilation	Conventional ventilation
Tidal Volume (ml/kg)	6	12
$P_{plateau}$	<30	<50
PEEP	Protocol	Protocol
Actual PEEP	8.1	9.1
Result (p<0.001)	31.0%	39.8%

Principle for FiO2 and PEEP Adjustment

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

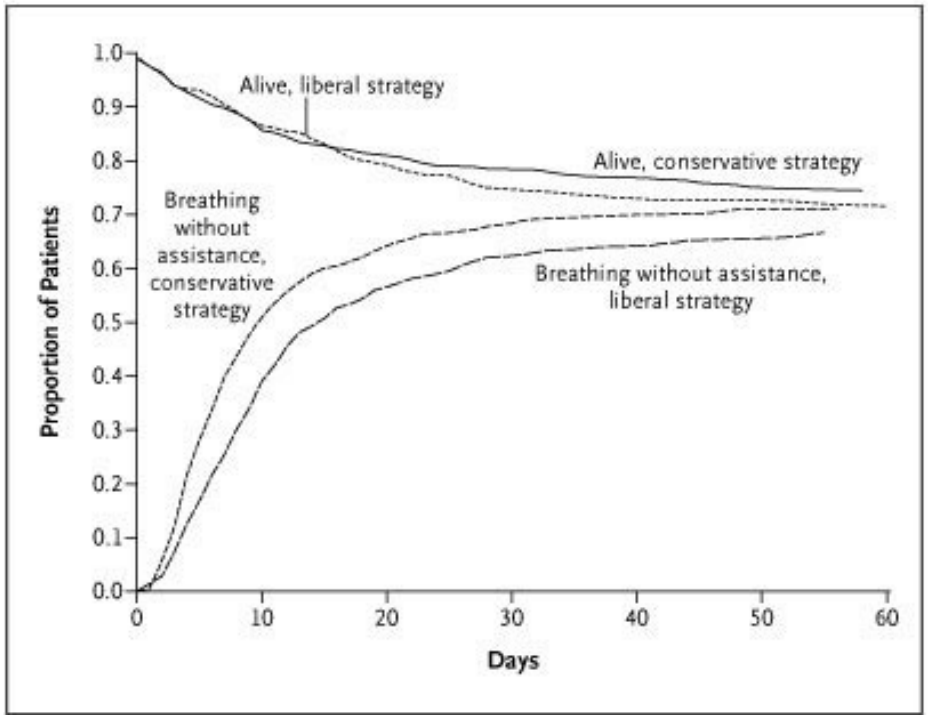
Comparison of Two Fluid-Management Strategies in Acute Lung Injury

- Large randomized prospective trial addressed the use of conservative (higher, more frequent lasix doses) verse liberal fluid management (more frequent fluid boluses)

ARDS Clinical Trial Network, 2006, Comparison of two fluid-management strategies in acute lung injury. NEJM. 254(24) 2564-2575

Table 3. Main Outcome Variables.*

Outcome	Conservative Strategy	Liberal Strategy	P Value
Death at 60 days (%)	25.5	28.4	0.30
Ventilator-free days from day 1 to day 28†	14.6±0.5	12.1±0.5	<0.001
ICU-free days†			
Days 1 to 7	0.9±0.1	0.6±0.1	<0.001
Days 1 to 28	13.4±0.4	11.2±0.4	<0.001
Organ-failure–free days†‡			
Days 1 to 7			
Cardiovascular failure	3.9±0.1	4.2±0.1	0.04
CNS failure	3.4±0.2	2.9±0.2	0.02
Renal failure	5.5±0.1	5.6±0.1	0.45
Hepatic failure	5.7±0.1	5.5±0.1	0.12
Coagulation abnormalities	5.6±0.1	5.4±0.1	0.23
Days 1 to 28			
Cardiovascular failure	19.0±0.5	19.1±0.4	0.85
CNS failure	18.8±0.5	17.2±0.5	0.03
Renal failure	21.5±0.5	21.2±0.5	0.59
Hepatic failure	22.0±0.4	21.2±0.5	0.18
Coagulation abnormalities	22.0±0.4	21.5±0.4	0.37
Dialysis to day 60			
Patients (%)	10	14	0.06
Days	11.0±1.7	10.9±1.4	0.96



- Outcomes: NO significant difference in 60-day mortality between the two groups, however the conservative fluid group had improved lung function, shorter durations of mechanical ventilation, and shorter ICU stays, SUPPORTING THE USE OF DIURETICS

Recap

- Lower tidal volumes (4-8 ml/kg IBW)
- Maintain plateau pressure <= 30 cm H2O
- Maintain modest PEEP levels (ARDSNET high vs low)
- Conservative fluid management (diuresis)
  - As long as patient is not showing signs of malperfusion (Oliguria, hypotension, shock)

Rescue Therapy

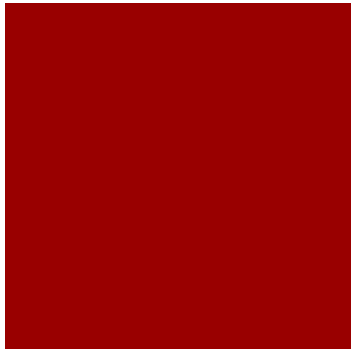
- Used in severe refractory hypoxia with high ventilator requirements
- Include both ventilatory and non-ventilatory strategies
- If a rescue therapy does not result in improved oxygenation or if complications develop, the rescue therapy should be abandoned

Refractory Hypoxemia

- PaO2/FIO2 ration of < 100 mm Hg
- Inability to maintain Plateau pressure less than 3O cm H20 despite low tidal volume ventilation (4 ml/kg IBW)
- Development of barotrauma
- An Oxygenation Index of > 40
  - OI = FIO2 x mPaw x 100/PaO2)

High Ventilator Requirements

- FiO2 >0.7 mmHg and a PEEP of 15 cm H20
- Pplat >30 cm H2O with a tidal volume of <6ml/kg IBW



Early identification of these patients for rescue therapy

Rescue Therapies

- PEEP (Positive End Expiratory Pressure)
- Lung Recruitment Maneuvers
- Transpulmonary Pressure Targeted Ventilation
- Neuromuscular Blockade (NMB)
- iNO (inhaled Nitric Oxide)
- Prone Positioning
- HFOV (High Frequency Oscillation Ventilation)
- ECMO (Extracorporeal Membrane Oxygenation)

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Higher Level of PEEP

- Has been shown in increase P/F ratio
- No mortality benefit seen
  - Though a trend towards a mortality benefit was see on the the meta-analysis
- Lower rates of refractory hypoxemia (Express and love studies)
- High PEEP is >10, Low PEEP <=10
  - PEEP of 8 to 15 cm H2O is very common in ARDS
  - PEEP of >24 is rarely required

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 22, 2004 VOL. 351 NO. 4

Higher versus Lower Positive End-Expiratory Pressures in Patients with the Acute Respiratory Distress Syndrome

The National Heart, Lung, and Blood Institute ARDS Clinical Trials Network*

Positive End-Expiratory Pressure Setting in Adults With Acute Lung Injury and Acute Respiratory Distress Syndrome

A Randomized Controlled Trial

Alain Mercat, MD; Jean-Christophe M. Richard, MD; Bruno Vielle, MD; et al

Article Information

JAMA. 2008;299(6):646-655. doi:10.1001/jama.299.6.646

Cochrane Library

Cochrane Database of Systematic Reviews

High versus low positive end-expiratory pressure (PEEP) levels for mechanically ventilated adult patients with acute lung injury and acute respiratory distress syndrome (Review)

Santa Cruz R, Rojas JI, Nervi R, Heredia R, Ciapponi A

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- **Lung Recruitment Maneuvers**
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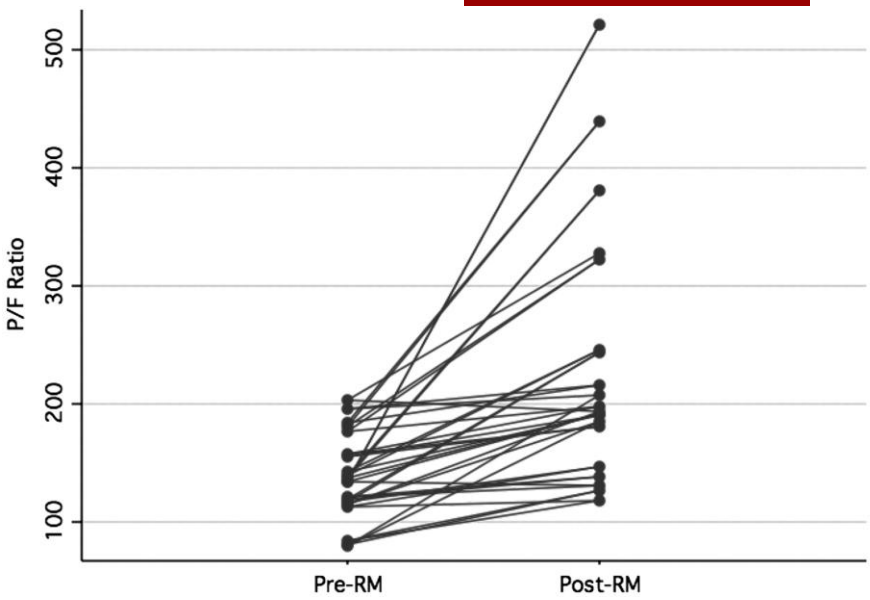
Lung Recruitment Maneuvers

- A recruitment maneuver is a transient increase in transpulmonary pressure to promote reopening of collapsed alveoli and thereby improving gas exchange
  - Intermittent PEEP increase: Intermittent increase in PEEP from baseline to set level for 2 consecutive breaths/min
  - Sustained high-pressure inflation: increasing PEEP to 30-50cm H2O for 20-40s
  - Pressure control + PEEP: pressure control ventilation of 10-15 cm H20 with PEEP 25-30 cm H2O to reach a peak inspiratory pressure of 40-45 cm H2O for 2 min
  - Intermittent sigh: three consecutive sighs/min with a tidal volume creating a Pplat of 45 cm H20
  - Extended sigh: Step wise increase in PEEP by 5 cm H2O with a simultaneous decrease in tidal volume over 9 minutes leading to implementing a CPAP level of 30 cm H2O for 30 sec

Lung Recruitment Maneuvers

- No RCTs demonstrate a mortality benefit from improvement in gas exchange.
- Though many studies have shown an increase in P/F Ratio (40 studies with 1,185 patients)



American Journal of Respiratory and Critical Care Medicine

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Article Tools

Recruitment Maneuvers for Acute Lung Injury

A Systematic Review

Eddy Fan [1,2], **M. Elizabeth Wilcox** [1], **Roy G. Brower** [2], **Thomas E. Stewart** [1], **Sangeeta Mehta** [1], **Stephen E. Lapinsky** [1], **Maureen O. Meade** [3], and **Niall D. Ferguson** [1]

Lung Recruitment Maneuvers

- Complication associated with lung recruitment maneuvers:
  - Hypotension 12%
  - Desaturation 8%
  - Arrhythmia 1%
- Only 1% of patients had RMs terminated due to an adverse event

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Lung Recruitment Maneuvers

- Routine use of these maneuvers is not recommended
- There role is in patients who develop life-threatening refractory hypoxemia
- Avoid these maneuvers in patients with:
  - Hemodynamic compromise
  - Those at risk for Barotrauma (ie. Emphysema)
- If the use of a recruitment maneuver results in improved oxygenation, then higher levels of PEEP should be used to help maintain the recruitment

Rescue Therapies

- PEEP (Positive End Expiratory Pressure)
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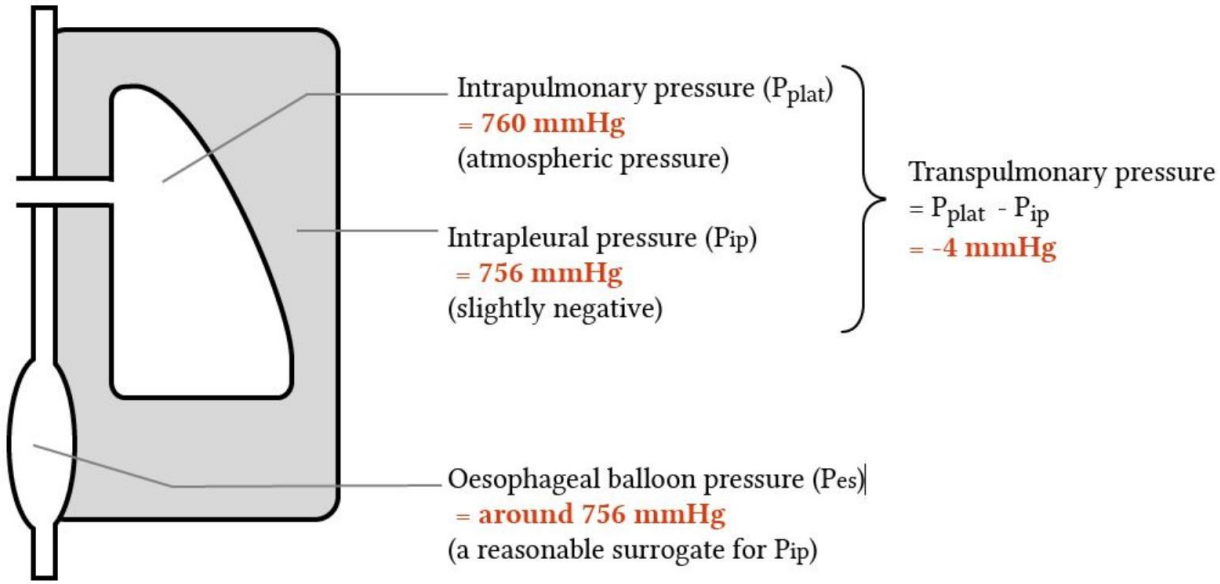
Transpulmonary Pressure Targeted Ventilation

- The theory:
  - Transpulmonary pressure = Pplat – Pesophageal
    - This is a surrogate for pleural pressure
  - The transpulmonary pressure excludes the effects of chest wall compliance on respiratory mechanics



Transpulmonary Pressure Targeted Ventilation

- So why are we interested in this form of invasive measuring in ARDS?
  - In the ARDSnet study FiO2 and PEEP were adjusted based off of arterial oxygenation, without reference to chest-wall or lung mechanics
  - The ALVEOLI trail (from ARDSnet) assessed Increased PEEP versus standard PEEP, again based off of oxygenation, with no mortality benefit seen.
  - In animal models increased PEEP has actually been shown to be protective against cellular damage

- So is there a better way to target increased PEEP for improved mortality?
  - Maybe

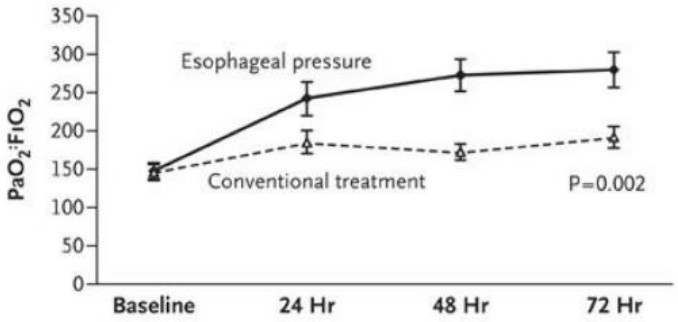
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 13, 2008 VOL. 359 NO. 20

Mechanical Ventilation Guided by Esophageal Pressure in Acute Lung Injury

Daniel Talmor, M.D., M.P.H., Todd Sarge, M.D., Atul Malhotra, M.D., Carl R. O'Donnell, Sc.D., M.P.H., Ray Ritz, R.R.T., Alan Lisbon, M.D., Victor Novack, M.D., Ph.D., and Stephen H. Loring, M.D.

Transpulmonary Pressure Targeted Ventilation



- Randomized trial of patients with ALI or ARDS into esophageal-pressure guided PEEP versus PEEP based of ARDSnet protocol
- Goal was to enroll 150 patients, stopped after 61 patients due to increased oxygenation (88 mmHg higher) in the esophageal-pressure guided group.
  - Effect was persistent over the entire follow-up time (24, 48, and 72 hours)
  - Respiratory compliance was also improved over these same time intervals

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- Improved lung compliance
- Improved oxygenation (PaO2, PaO2:FiO2)
- Accomplished with increased Pressures (PEEP, TV, Peak and Mean air way pressures)

Table 2. Measurements of Ventilatory Function at Baseline and 72 Hours.*

Measurement	Baseline			72 Hr†		
	Esophageal-Pressure–Guided (N=30)	Conventional Treatment (N=31)	P Value	Esophageal-Pressure–Guided (N=29)	Conventional Treatment (N=29)	P Value
PaO_2:FiO_2	147±56	145±57	0.89	280±126	191±71	0.002
Respiratory-system compliance (ml/cm of water)	36±12	36±10	0.94	45±14	35±9	0.005
Ratio of physiological dead space to tidal volume	0.67±0.11	0.67±0.09	0.95	0.61±0.09	0.64±0.10	0.27
PaO_2 (mm Hg)	91±25	107±44	0.09	124±44	101±33	0.03
FiO_2	0.66±0.17	0.77±0.18	0.02	0.49±0.17	0.57±0.18	0.07
PEEP (cm of water)	13±5	13±3	0.73	17±6	10±4	<0.001
Tidal volume (ml)	484±98	491±105	0.80	472±98	418±80	0.03
Tidal volume (ml per kg of predicted body weight)	7.3±1.3	7.9±1.4	0.12	7.1 ±1.3	6.8±1	0.31
Respiratory rate (breaths/min)	26±6	24±6	0.32	26±6	28±5	0.20
Inspiratory time (sec)	0.8±0.1	0.9±0.2	0.19	0.8±0.1	0.8±0.1	0.27
$PEEP_{total}$ (cm of water)	14±5	15±4	0.67	18±5	12±5	<0.001
Peak inspiratory pressure (cm of water)	35±8	35±7	0.85	32±8	28±7	0.007
Mean airway pressure (cm of water)	20±6	20±4	0.88	22±6	16±5	0.001
Plateau pressure (cm of water)	29±7	29±5	0.79	28±7	25±6	0.07
Transpulmonary end-inspiratory pressure (cm of water)	7.9±6.0	8.6±5.4	0.61	7.4±4.4	6.7±4.9	0.58
Transpulmonary end-expiratory pressure (cm of water)	−2.8±5.0	−1.9±4.7	0.49	0.1±2.6	−2.0±4.7	0.06
Esophageal end-inspiratory pressure (cm of water)	21.2±4.9	20.7±5.1	0.68	21.7±7.2	17.9±5.2	0.03
Esophageal end-expiratory pressure (cm of water)	17.2±4.4	16.9±5.0	0.79	18.4±5.9	14.3±4.9	0.008

* Plus–minus values are means ±SD. FiO_2 denotes the fraction of inspired oxygen, PaO_2 the partial pressure of arterial oxygen, PEEP positive end-expiratory pressure applied by the ventilator, and $PEEP_{total}$ airway pressure measured during end-expiratory occlusion.
† The values are given for the 29 surviving patients in each treatment group.

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Table 4. Clinical Outcomes.*

Outcome	Esophageal-Pressure–Guided (N=30)	Conventional Treatment (N=31)	P Value
28-Day mortality — no. (%)	5 (17)	12 (39)	0.055
180-Day mortality — no. (%)	8 (27)	14 (45)	0.13
Length of ICU stay — days			0.16
Median	15.5	13.0	
Interquartile range	10.8–28.5	7.0–22.0	
No. of ICU-free days at 28 days			0.96
Median	5.0	4.0	
Interquartile range	0.0–14.0	0.0–16.0	
No. of ventilator-free days at 28 days			0.50
Median	11.5	7.0	
Interquartile range	0.0–20.3	0.0–17.0	
No. of days of ventilation among survivors			0.71
Median	12.0	16.0	
Interquartile range	7.0–27.5	7.0-20.0	

* For patients who were deceased at day 28, a value of 0 days was assigned. ICU denotes intensive care unit.

- There is a trend towards improved 28-day mortality

Transpulmonary Pressure Targeted Ventilation

- They jury is still out.
  - This method of targeted PEEP, at least in this study, showed that we are actually putting PEEP below the closing pressure of the Alveoli.
  - Better targeting our PEEP to prevent alveolar collapse could help improve mortality

  - EPVent 2 Trail
    - While the EPVent trial was designed to look at PaO2 as its primary outcome, their subsequent trial will be looking at mortality
    - The results should be coming out sometime in late 2019-to-early 2020

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Neuromuscular Blockade

- The thought is that it works by three mechanisms
  - Improves compliance but reduced chest wall resistance
  - Eliminates the oxygen consumption from the work of breathing
  - Improved ventilation synchrony

Neuromuscular Blockade

- First studied in 2004.
  - No mortality benefit seen
  - …But it did improve oxygenation
  - Concerns: Increased risk of myopathy and polyneuropathy

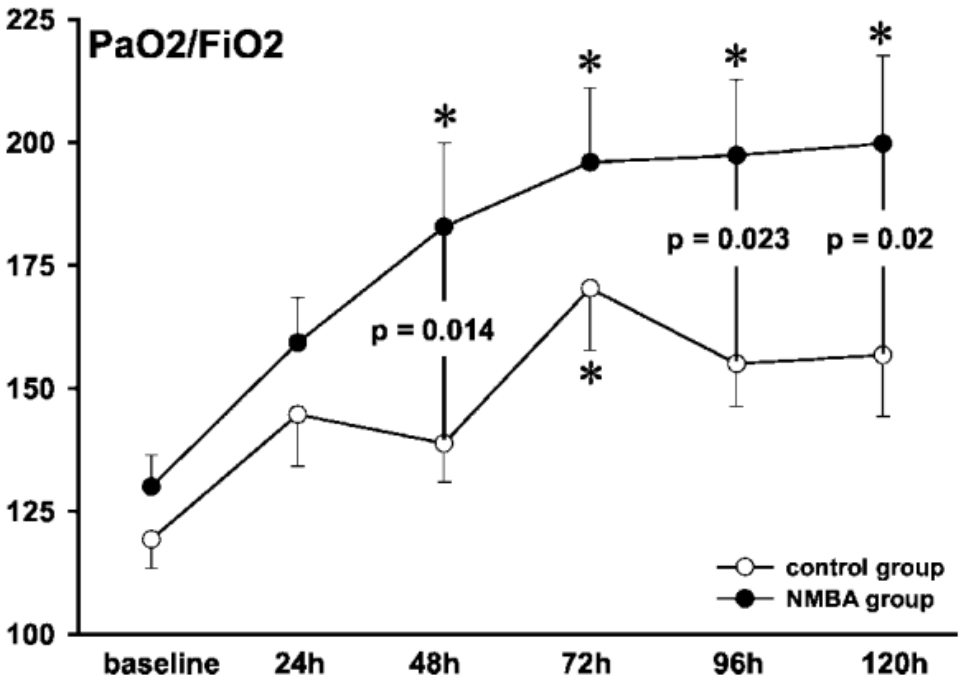
Crit Care Med 2004 Vol. 32, No. 1

Effect of neuromuscular blocking agents on gas exchange in patients presenting with acute respiratory distress syndrome*

Marc Gainnier, MD; Antoine Roch, MD; Jean-Marie Forel, MD; Xavier Thirion, MD, PhD; Jean-Michel Arnal, MD; Stéphane Donati, MD; Laurent Papazian, MD, PhD

Neuromuscular Blockade

- Design:
  - 56 patients were enrolled (28 patients/group)
  - p/f ratio was <150 and PEEP >5
  - Therapy started within 36 hours of eligibility with low TV ventilation
  - NMB was done with cisatracurium
- Improved p/f ratio at all time points



Crit Care Med 2004 Vol. 32, No. 1

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 16, 2010 VOL. 363 NO. 12

Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome

Laurent Papazian, M.D., Ph.D., Jean-Marie Forel, M.D., Arnaud Gacouin, M.D., Christine Penot-Ragon, Pharm.D., Gilles Perrin, M.D., Anderson Loundou, Ph.D., Samir Jaber, M.D., Ph.D., Jean-Michel Arnal, M.D., Didier Perez, M.D., Jean-Marie Seghboyan, M.D., Jean-Michel Constantin, M.D., Ph.D., Pierre Courant, M.D., Jean-Yves Lefrant, M.D., Ph.D., Claude Guérin, M.D., Ph.D., Gwenaël Prat, M.D., Sophie Morange, M.D., and Antoine Roch, M.D., Ph.D., for the ACURASYS Study Investigators*

- Large randomized controlled trial of 340 patients (p/f <150mmHg) were randomized into NMB vs placebo for 48 hours
  - Again, done with low TV ventilation

Neuromuscular Blockade

- Patients were randomized into
  - Treatment with cisatracurium vs placebo
  - No nerve monitoring was permitted to evaluate for adequate paralysis due to the placebo arm
  - All sedation was titrated to a Ramsey score of 6 (no response on glabellar tap)

N Engl J Med 2010;363:1107-16.

Neuromuscular Blockade

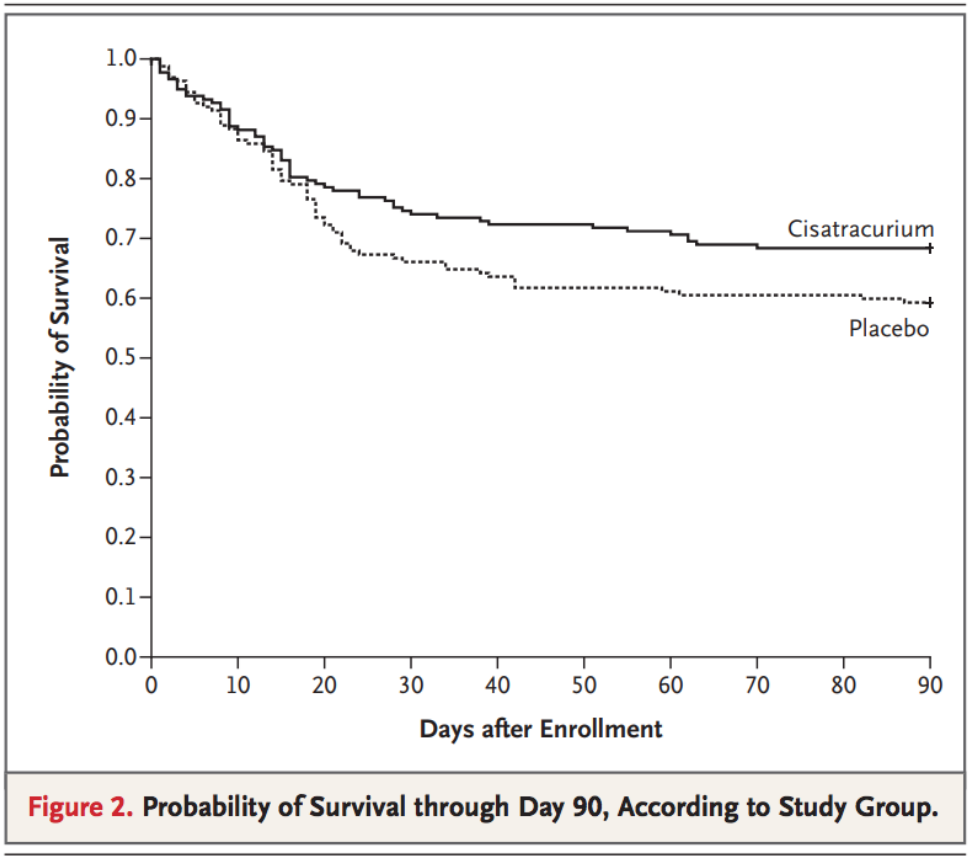


Figure 2. Probability of Survival through Day 90, According to Study Group.

N Engl J Med 2010;363:1107-16.

- Early NMB did show a trend toward improved mortality, though this did not reach statistical significance (p=0.08)

Neuromuscular Blockade

Table 3. Secondary Outcomes, According to Study Group.*

Outcome	Cisatracurium (N=177)	Placebo (N=162)	Relative Risk with Cisatracurium (95% CI)	P Value
Death — no. (% [95% CI])				
At 28 days	42 (23.7 [18.1–30.5])	54 (33.3 [26.5–40.9])	0.71 (0.51–1.00)	0.05
In the ICU	52 (29.4 [23.2–36.5])	63 (38.9 [31.7–46.6])	0.76 (0.56–1.02)	0.06
In the hospital	57 (32.2 [25.8–39.4])	67 (41.4 [34.1–49.1])	0.78 (0.59–1.03)	0.08
No. of ventilator-free days†				
From day 1 to day 28	10.6±9.7	8.5±9.4		0.04
From day 1 to day 90	53.1±35.8	44.6±37.5		0.03
No. of days without organ failure, from day 1 to day 28				
No cardiovascular failure	18.3±9.4	16.6±10.4		0.12
No coagulation abnormalities	22.6±8.9	20.5±9.9		0.05
No hepatic failure	21.3±9.6	19.1±10.6		0.05
No renal failure	20.5±10.1	18.1±11.6		0.05
None of the four	15.8±9.9	12.2±11.1		0.01
No. of days outside the ICU				
From day 1 to day 28	6.9±8.2	5.7±7.8		0.16
From day 1 to day 90	47.7±33.5	39.5±35.6		0.03
Hospital survivors admitted to other health care facilities from day 1 to day 90 — % (95% CI)	22.3 (15.8–30.5)	18.8 (12.2–27.8)		0.52
Barotrauma — no. (% [95% CI])‡	9 (5.1 [2.7–9.4])	19 (11.7 [7.6–17.6])	0.43 (0.20–0.93)	0.03
Pneumothorax — no. (% [95% CI])	7 (4.0 [2.0–8.0])	19 (11.7 [7.6–17.6])	0.34 (0.15–0.78)	0.01
MRC score — median (IQR)§				
At day 28	55 (46–60)	55 (39–60)	1.07 (0.80–1.45)	0.49
At ICU discharge	55 (43–60)	55 (44–60)	0.92 (0.71–1.19)	0.94
Patients without ICU-acquired paresis¶				
By day 28 — no./total no. (% [95% CI])	68/96 (70.8 [61.1–79.0])	52/77 (67.5 [56.5–77.0])		0.64
By ICU discharge — no./total no. (% [95% CI])	72/112 (64.3 [55.1–72.6])	61/89 (68.5 [58.3–77.3])		0.51

- What it did show though was
  - Fewer ventilator days
  - Fewer days in the ICU

N Engl J Med 2010;363:1107-16.

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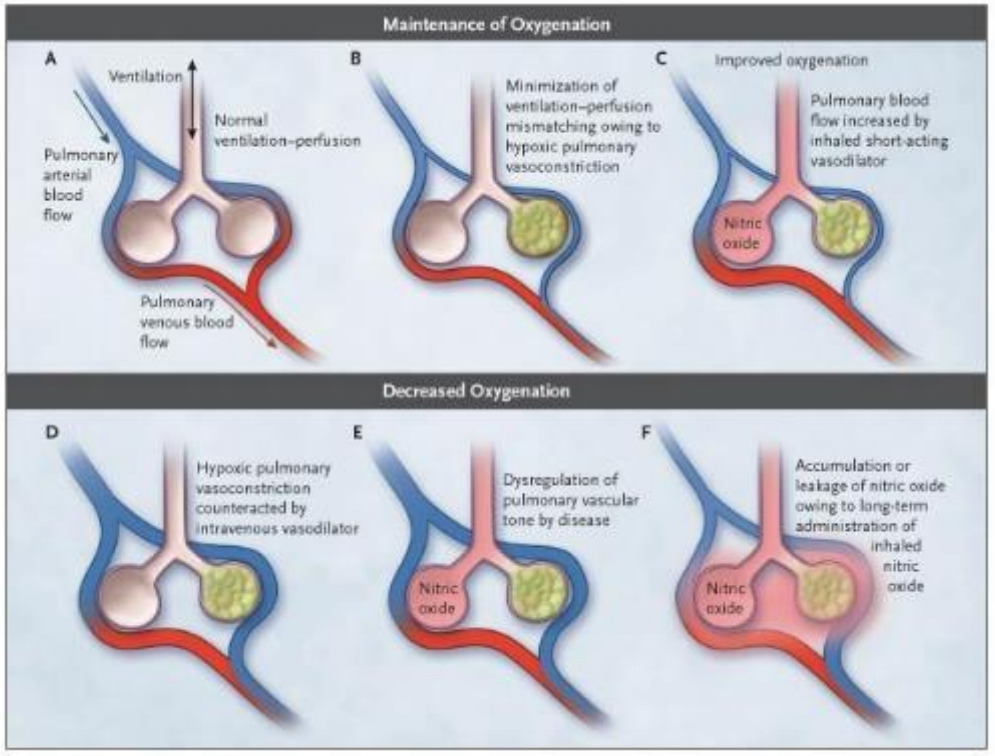
- Prone Positioning
- HFOV (High Frequency Oscillation Ventilation)
- ECMO (Extracorporeal Membrane Oxygenation)

Inhaled Nitric Oxide

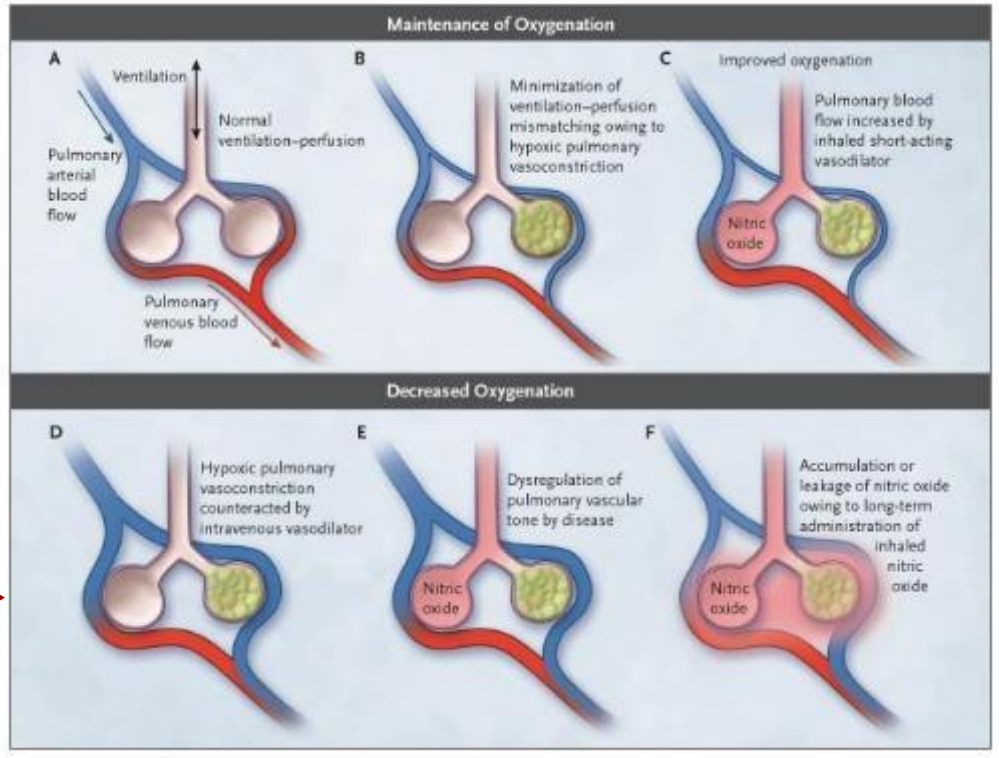
- The theory
  - iNO causes vasodilation of the pulmonary vasculature with the best ventilation to help improve V/Q matching



Inhaled Nitric Oxide

- The theory
  - iNO causes vasodilation of the pulmonary vasculature with the best ventilation to help improve V/Q matching

We will get to this in just a second →



Inhaled Nitric Oxide

Low-Dose Inhaled Nitric Oxide in Patients With Acute Lung Injury

A Randomized Controlled Trial

Robert W. Taylor, MD; Janice L. Zimmerman, MD; R. Phillip Dellinger, MD; et al

JAMA. 2004;291(13):1603-1609. doi:10.1001/jama.291.13.1603

- Randomized control trial (n=385) of moderate to severe ARDS (p/f <250)
  - Study group received 5ppm of iNO for up to 28 days

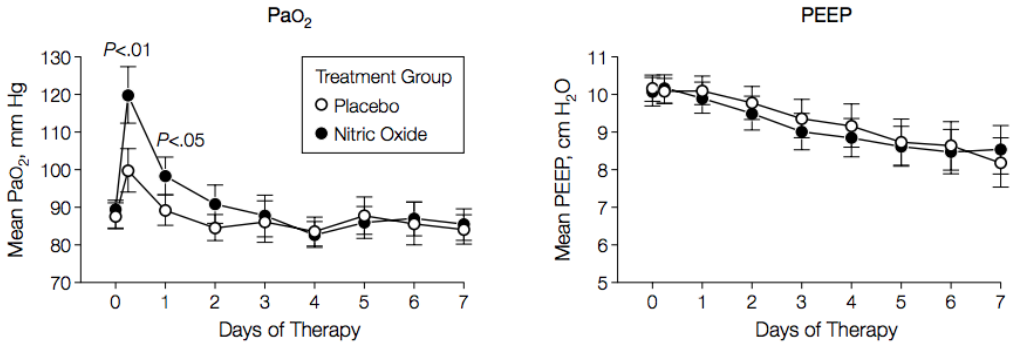
Inhaled Nitric Oxide

- No improvement in mortality of number of ventilator days
- Did see a short term improvement in oxygenation

Table 2. Efficacy Outcomes

Outcome	Placebo (n = 193)	Inhaled Nitric Oxide (n = 192)	*P* Value
Days alive without assisted breathing, mean (SD)	10.6 (9.8)	10.7 (9.7)	.97
Mortality, No. (%)	39 (20)	44 (23)	.54
Alive and without assisted breathing by day 28, No. (%)	127 (66)	127 (66)	.40
Days alive after successful 2-hour unassisted ventilation trial, mean (SD)	11.9 (9.9)	11.4 (9.8)	.54
Days alive after reaching oxygenation criteria, mean (SD)	17.0 (10.1)	16.7 (10.3)	.89

Figure 2. Mean PaO_2 and Positive End-Expiratory Pressure (PEEP) During the First 7 Days of Therapy



JAMA. 2004;291(13):1603-1609. doi:10.1001/jama.291.13.1603

Inhaled Nitric Oxi

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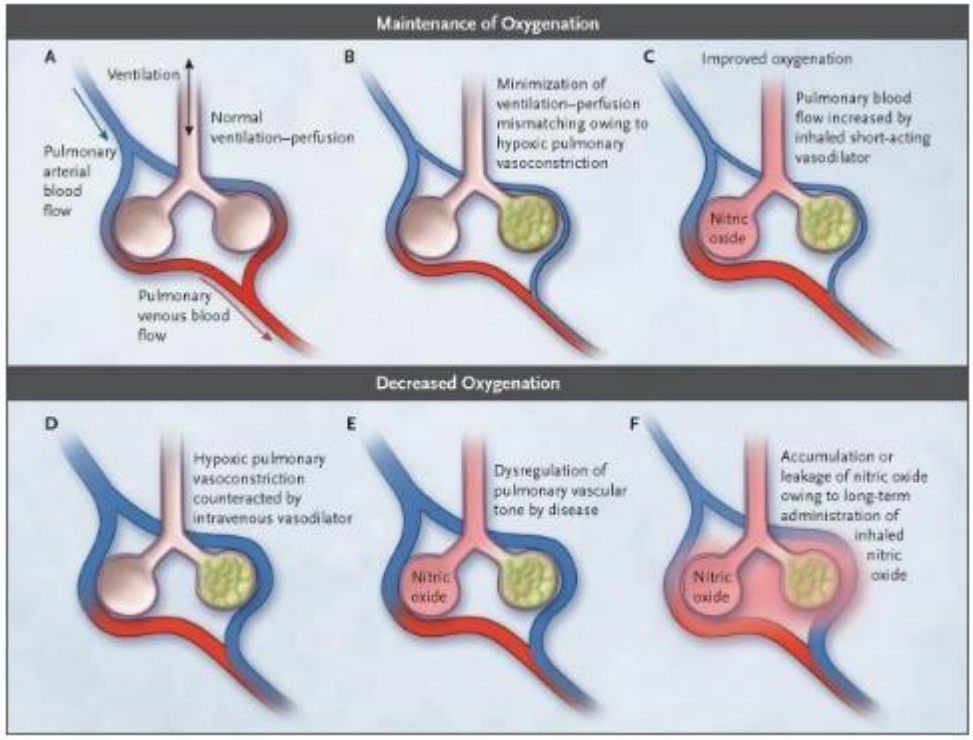
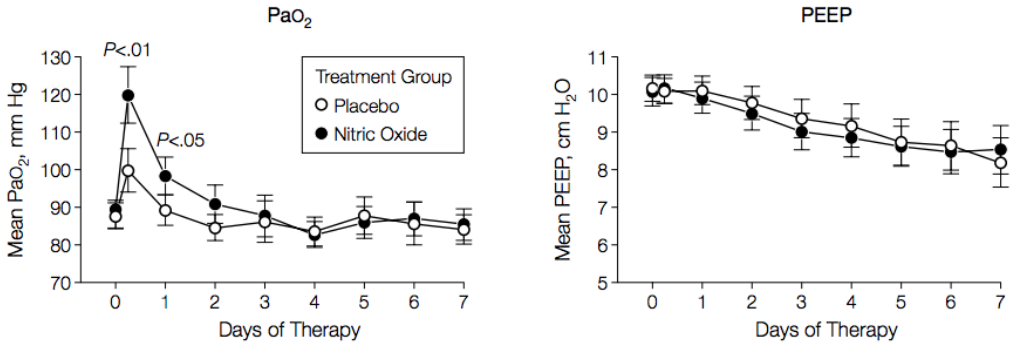


Figure 2. Mean PaO_2 and Positive End-Expiratory Pressure (PEEP) During the First 7 Days of Therapy



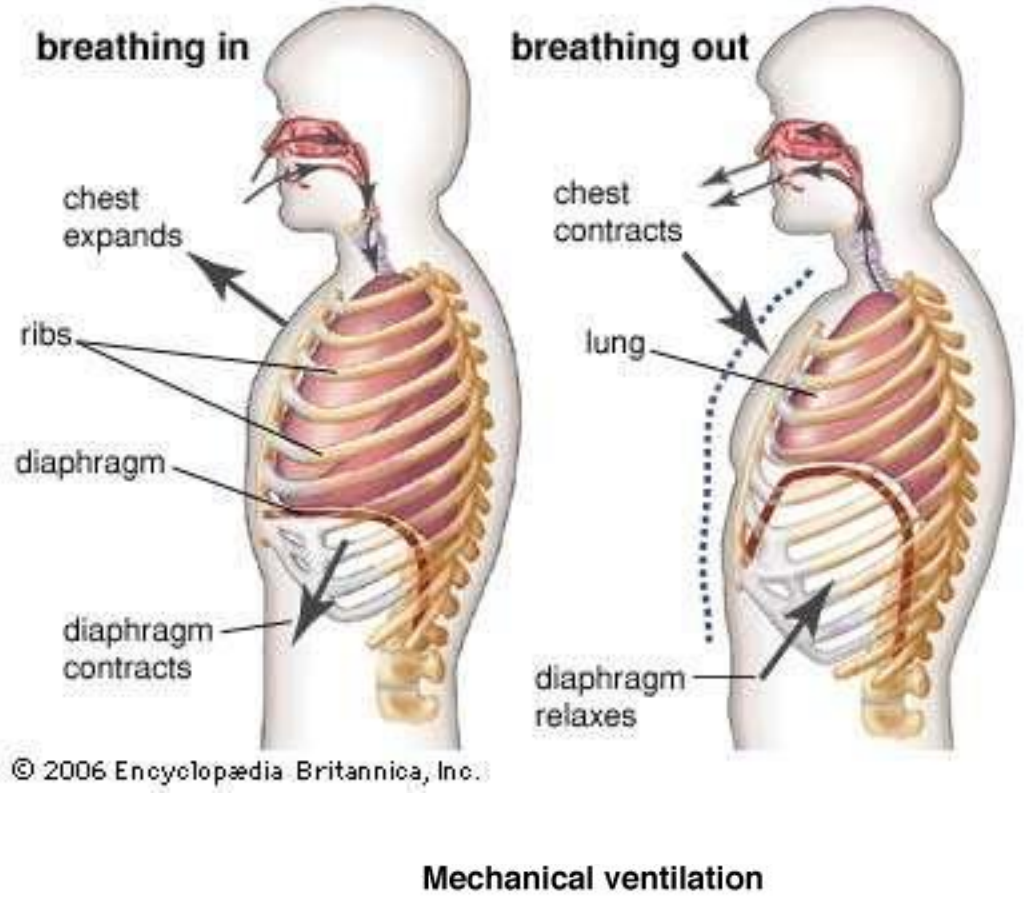
JAMA. 2004;291(13):1603-1609. doi:10.1001/jama.291.13.1603

Rescue Therapies

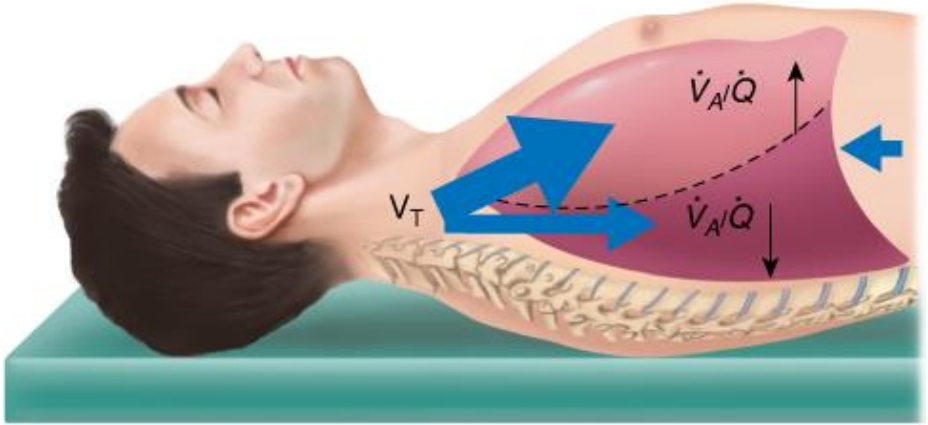
- PEEP (Positive End Expiratory Pressure)
- Lung Recruitment Maneuvers
- Transpulmonary Pressure Targeted Ventilation
- Neuromuscular Blockade (NMB)
- iNO (inhaled Nitric Oxide)
- **Prone Positioning**
- HFOV (High Frequency Oscillation Ventilation)
- ECMO (Extracorporeal Membrane Oxygenation)

Prone Positioning

- First used in the 1970's
- The benefit is improvement in the V/Q mismatch associated with laying supine and mechanical ventilation



Mechanical ventilation



Prone Positioning

- Multiple studies with different types of protocols (proning for 6 to 20 hours per day) have shown improved oxygenation, but no improvement in mortality
- The problem with all of these studies, was that they were using 10ml/kg TVs

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ESTABLISHED IN 1812 JUNE 6, 2013 VOL. 368 NO. 23

Prone Positioning in Severe Acute Respiratory Distress Syndrome

Claude Guérin, M.D., Ph.D., Jean Reignier, M.D., Ph.D., Jean-Christophe Richard, M.D., Ph.D., Pascal Beuret, M.D., Arnaud Gacouin, M.D., Thierry Boulain, M.D., Emmanuelle Mercier, M.D., Michel Badet, M.D., Alain Mercat, M.D., Ph.D., Olivier Baudin, M.D., Marc Clavel, M.D., Delphine Chatellier, M.D., Samir Jaber, M.D., Ph.D., Sylvène Rosselli, M.D., Jordi Mancebo, M.D., Ph.D., Michel Sirodot, M.D., Gilles Hilbert, M.D., Ph.D., Christian Bengler, M.D., Jack Richecoeur, M.D., Marc Gainnier, M.D., Ph.D., Frédérique Bayle, M.D., Gael Bourdin, M.D., Véronique Leray, M.D., Raphaele Girard, M.D., Loredana Baboi, Ph.D., and Louis Ayzac, M.D., for the PROSEVA Study Group*

- Large multicenter RCT (466 patients)
- Early initiation (within 36 hours of intubation)
- Prone therapy for 16hrs/day
- TVs 6 ml/kg, Plateau Press 30 cm H2O or less
- Every patient with NMB (prone group or not)

Table 3. Primary and Secondary Outcomes According to Study Group.*

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
Pneumothorax — no. (% [95% CI])	13 (5.7 [3.9–7.5])	15 (6.3 [4.9–7.7])	0.89 (0.39–2.02)	0.85
Noninvasive ventilation — no./total no. (% [95% CI])				
At day 28	10/212 (4.7 [1.9–7.5])	4/228 (1.8 [0.1–3.5])	0.36 (0.07–3.50)	0.11
At day 90	3/206 (1.5 [0.2–3.2])	4/225 (1.8 [0.1–3.5])	1.22 (0.23–6.97)	1.00
Tracheotomy — no./total no. (% [95% CI])				
At day 28	12/229 (5.2 [2.3–8.1])	9/237 (3.8 [1.4–6.0])	0.71 (0.27–1.86)	0.37
At day 90	18/223 (8.1 [4.5–11.7])	15/235 (6.4 [3.3–9.5])	0.78 (0.36–1.67)	0.59

* Plus–minus values are means ±SD. Hazard ratios are shown for mortality and successful extubation; odds ratios are shown for other outcomes. CI denotes confidence interval.

† There were no significant differences between the groups in organ dysfunction as assessed from the SOFA score (Table S4 in the Supplementary Appendix).

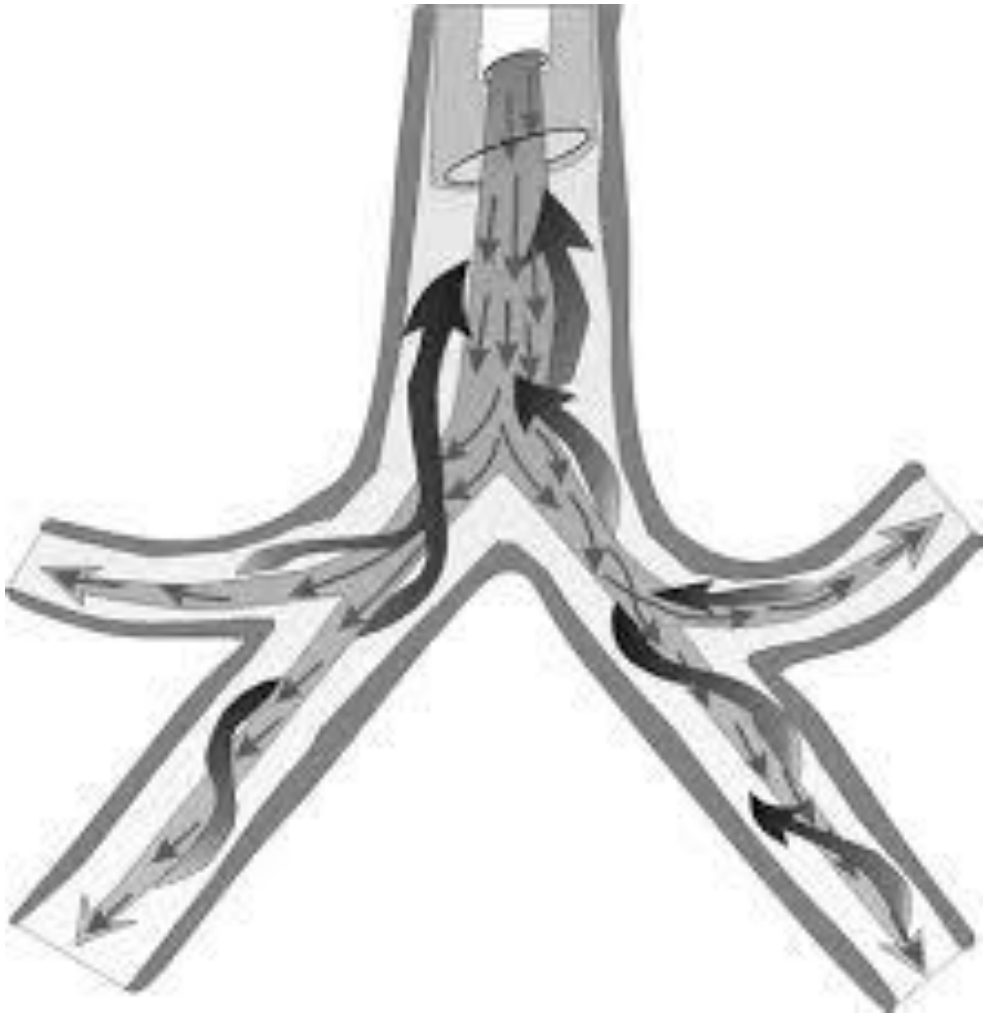
- Improved mortality
- Improved ICU LOS
- Improved Ventilator days

Rescue Therapies

- PEEP (Positive End Expiratory Pressure)
- Lung Recruitment Maneuvers
- Transpulmonary Pressure Targeted Ventilation
- Neuromuscular Blockade (NMB)
- iNO (inhaled Nitric Oxide)
- Prone Positioning
- **HFOV** (High Frequency Oscillation Ventilation)
- ECMO (Extracorporeal Membrane Oxygenation)

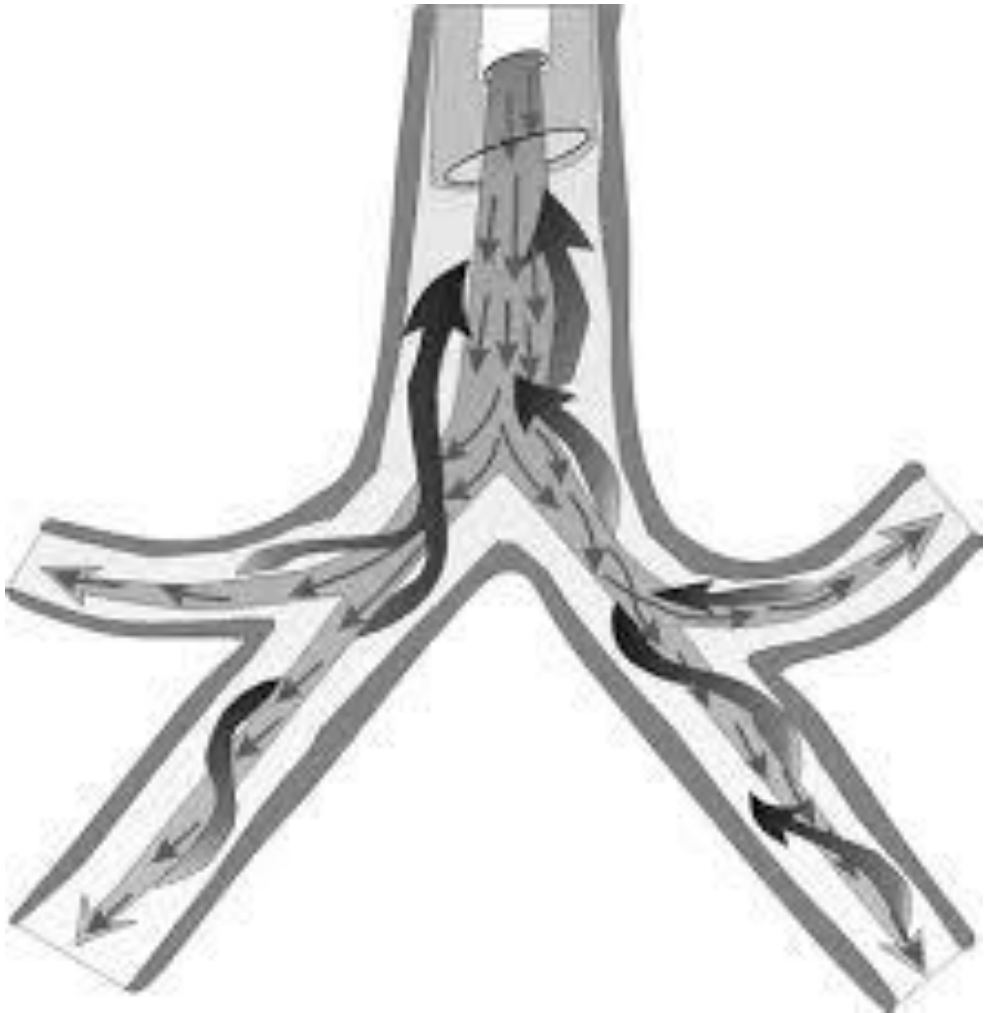
HFOV

- First use for hypoxic respiratory failure in the 1970's
- Respiratory rate set at 180-900 breaths/min
  - Creates a continuous laminar air flow



HFOV

- The theory
  - Small Tidal Volumes
    - Limit alveolar overdistention and decrease VILI
  - Higher, constant mean airway pressure
    - Increased alveolar recruitment



ORIGINAL ARTICLE

High-Frequency Oscillation for Acute Respiratory Distress Syndrome

Duncan Young, D.M., Sarah E. Lamb, D.Phil., Sanjoy Shah, M.D., Iain MacKenzie, M.D., William Tunnicliffe, M.Sc., Ranjit Lall, Ph.D., Kathy Rowan, D.Phil., and Brian H. Cuthbertson, M.D., for the OSCAR Study Group*

N Engl J Med 2013;368:806-13.

- OSCAR trail
  - Multicenter randomized trial of 795 patient in to HFOV versus conventional ventilation
  - No mortality improvement seen with HFOV

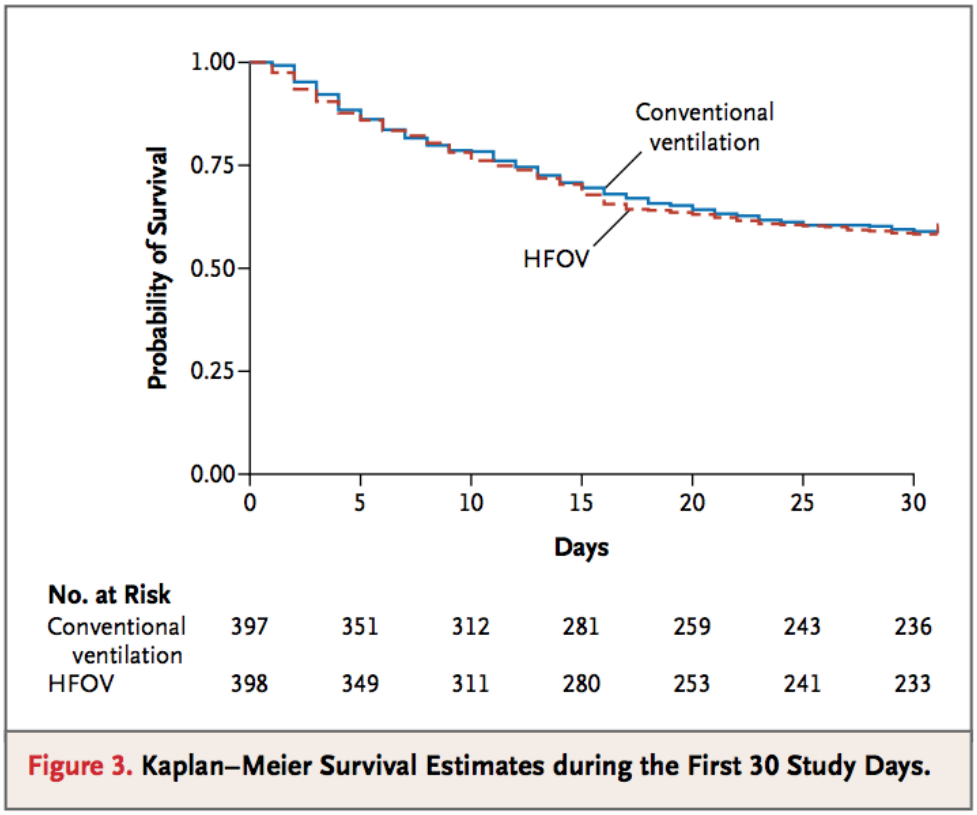


Figure 3. Kaplan–Meier Survival Estimates during the First 30 Study Days.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 28, 2013 VOL. 368 NO. 9

High-Frequency Oscillation in Early Acute Respiratory Distress Syndrome

Niall D. Ferguson, M.D., Deborah J. Cook, M.D., Gordon H. Guyatt, M.D., Sangeeta Mehta, M.D., Lori Hand, R.R.T., Peggy Austin, C.C.R.A., Qi Zhou, Ph.D., Andrea Matte, R.R.T., Stephen D. Walter, Ph.D., Francois Lamontagne, M.D., John T. Granton, M.D., Yaseen M. Arabi, M.D., Alejandro C. Arroliga, M.D., Thomas E. Stewart, M.D., Arthur S. Slutsky, M.D., and Maureen O. Meade, M.D., for the OSCILLATE Trial Investigators and the Canadian Critical Care Trials Group*

- OSCILLATE trial
  - Multicenter RCT of 1200 patients
    - Actually stopped after 548 patients had been randomized due to increased mortality in the HFOV group

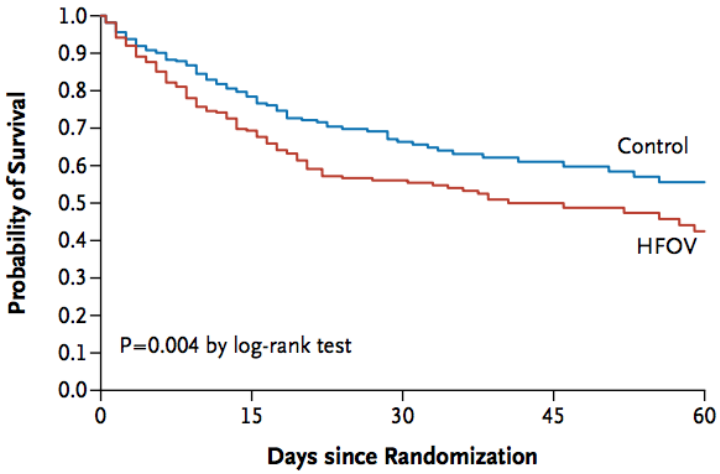


Figure 2. Probability of Survival from the Day of Randomization to Day 60 in the HFOV and Control Groups.

HFOV

- So why the difference in OSCAR and OSCILLATE?
  - The best theory is that they had different PEEP strategies, otherwise both protocols were identical
    - OSCAR used a PEEP of 10
    - OSCILLATE used a PEEP of 13
  - HFOV patient also required more sedatives, paralytics, and vasopressors than in the control groups

Rescue Therapies

- PEEP (Positive End Expiratory Pressure)
- Lung Recruitment Maneuvers
- Transpulmonary Pressure Targeted Ventilation
- Neuromuscular Blockade (NMB)
- iNO (inhaled Nitric Oxide)
- Prone Positioning
- HFOV (High Frequency Oscillation Ventilation)
- **ECMO** (Extracorporeal Membrane Oxygenation)

ECMO

Extracorporeal Membrane Oxygenation in Severe Acute Respiratory Failure
A Randomized Prospective Study

Warren M. Zapol, MD; Michael T. Snider, MD, PhD; J. Donald Hill, MD; et al

JAMA. 1979;242(20):2193-2196. doi:10.1001/jama.1979.03300200023016

- First reported in 1979
  - 90 patients randomized into VA ECMO versus conventional mechanical ventilation
  - Survival was 10% in both groups

ECMO

Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial

Giles J Peek, Miranda Mugford, Ravindranath Tiruvoipati, Andrew Wilson, Elizabeth Allen, Mariamma M Thalanany, Clare L Hibbert, Ann Truesdale, Felicity Clemens, Nicola Cooper, Richard K Firmin, Diana Elbourne, for the CESAR trial collaboration

***Lancet* 2009; 374: 1351–63**

- 180 patients randomized to conventional mechanical ventilation versus transfer for ECMO consideration
- 75% of patient transferred for ECMO received ECMO
- 93% of patients in ECMO arm received lung protective ventilation, compared to only 70% in the conventional arm
- 6 month survival in ECMO was 63% versus 67%
- Critiques
  - The study was not powered to detect a mortality difference
  - The treatment arms were not standardized

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 24, 2018 VOL. 378 NO. 21

ECMO

Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome

A. Combes, D. Hajage, G. Capellier, A. Demoule, S. Lavoué, C. Guervilly, D. Da Silva, L. Zafrani, P. Tirot, B. Veber, E. Maury, B. Levy, Y. Cohen, C. Richard, P. Kalfon, L. Bouadma, H. Mehdaoui, G. Beduneau, G. Lebreton, L. Brochard, N.D. Ferguson, E. Fan, A.S. Slutsky, D. Brodie, and A. Mercat, for the EOLIA Trial Group, REVA, and ECMONet*

- EOLIA Trial
  - 249 patients randomized into VV ECMO versus conventional mechanical ventilation
  - 98% of patients in the ECMO are received ECMO
  - 90% of patient in conventional group underwent prolonged prone positioning, and all received NMB
  - Despite aggressive rescue therapies in the the conventional group, 28% of patients crossed over to ECMO for severe refractory hypoxemia

ECMO

- EOLIA Trial
  - Mortality benefit did not reach statistical significance (p=0.07)
  - There was also a significantly higher incidence of bleeding requiring transfusion (46 vs 28%), as well as severe thrombocytopenia (27 vs 16%)
- So… is ECMO dead?

N Engl J Med 2018;378:1965-75.

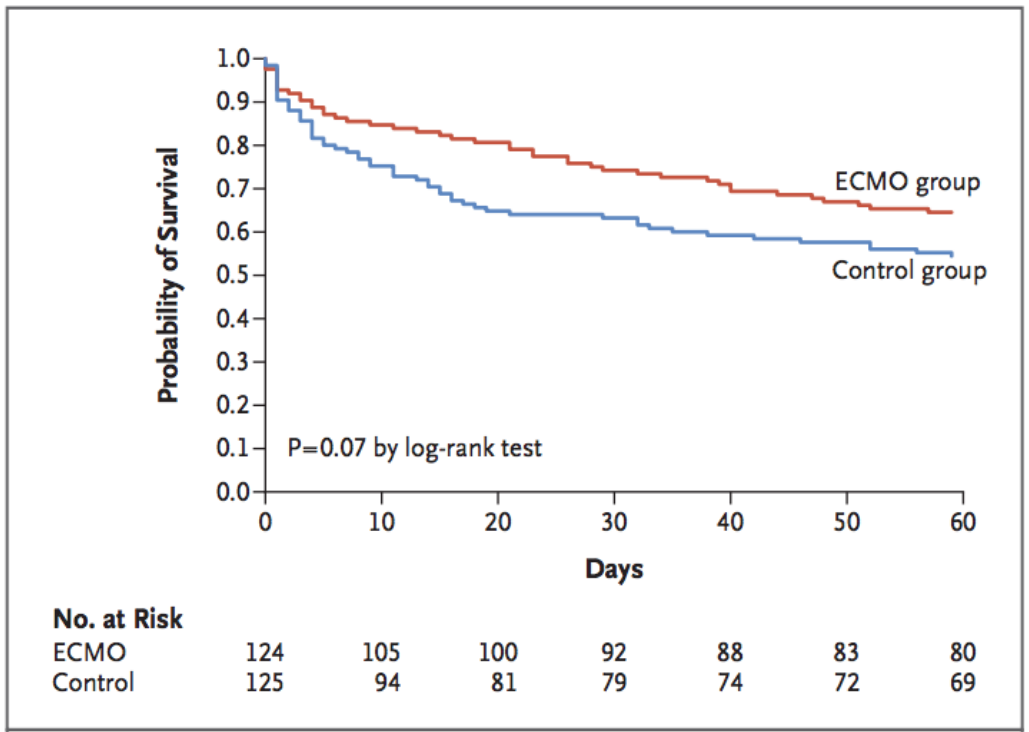


Figure 2. Kaplan–Meier Survival Estimates in the Intention-to-Treat Population during the First 60 Days of the Trial.

ECMO

- Despite the findings in the EOLIA trail, there is a little bit more to their data[3]
  - Emergency ECMO improves output by "buying time" in extremely hypoxemic patients
    - Of the 35 patients that failed conventional therapy, 15 survived, and it is unlikely that these patients would have survived without ECMO
  - ECMO improves outcome by reducing the invasiveness of mechanical ventilation
    - TV was reduced with 43% and RR by 23% with ECMO, this is an estimated 66% reduction in the mechanical power applied to the lungs. This was associated with a higher survival rate (81 vs 68 patients)

ECMO

- Despite the findings in the EOLIA trail, there is a little bit more to their data…continued[3]
  - Lastly if the cross-over patients without ECMO are considered to have a mortality rate between 0 and 33% then the p value of $p<0.001$ and $p=0.045$ is obtained, versus the $p=0.07$ given in the trial.

- I think VV ECMO has its role in severe ARDS… so who should we considered for it?

ECMO

- **Oxygenation Index**, survival without ECMO
- **RESP score**, survival if placed on ECMO

Oxygenation Index ☆

Predicts outcomes, especially in pediatric patients; helps determine need for ECMO.

When to Use

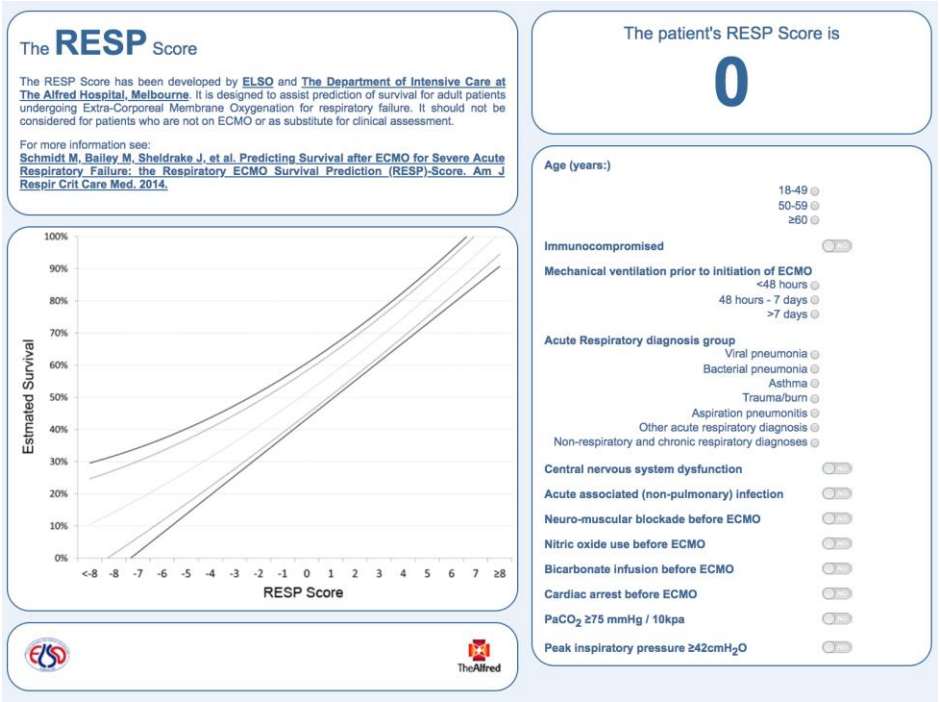
FiO_2		%
Mean airway pressure (P_{AW}) Note units (mm Hg vs cm H_2O)	Norm: 7.3 - 22.1	mm Hg ⇆
PaO_2	Norm: 75 - 100	mm Hg ⇆

Result:
Please fill out required fields.

» Next Steps | Evidence | Creator Insights

ADVICE

- OI <25: good outcome
- OI 25-40: >40% mortality
- OI >40: Consider ECMO



ECMO

- One final note
  - Improved survival with the outbreaks of H1N1 have been published from numerous countries
  - In most of these reports the common factors for the survival is patients
    - That are younger
    - Have fewer or no significant medical comorbidities

- ECMO is an expensive and invasive therapy, patient selection is key

Conclusions

- Improved mortality
  - Prone positioning – should be initiated within 36 hours of ARDS and be performed for at least 16 hours/day
- Trend towards improved mortality
  - High PEEP
  - Early NMB
  - ECMO (especially with appropriate patient selection)
- Improved oxygenation
  - iNO
  - Transpulmonary pressure targeted ventilation
  - Lung Recruitment maneuvers
- Increase mortality
  - HFOV – should probably be abandoned in adult patients

References

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2. Mercat A, et al. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2008, 299(6):646-55

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