Suncoast Pulmonary Symposium

Management of Refractory Hypoxemia

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Presenter Disclosure Information

John Davies MA RRT FAARC:

Within the past 12 months, the presenter has had a financial interest/arrangement or affiliation with the organizations listed below:

Teleflex	Consultant
Philips Healthcare	Advisory Board

- What are “conventional” strategies to provide protection and oxygenation?
  - Low Vt strategy
  - Pplat
  - PEEP

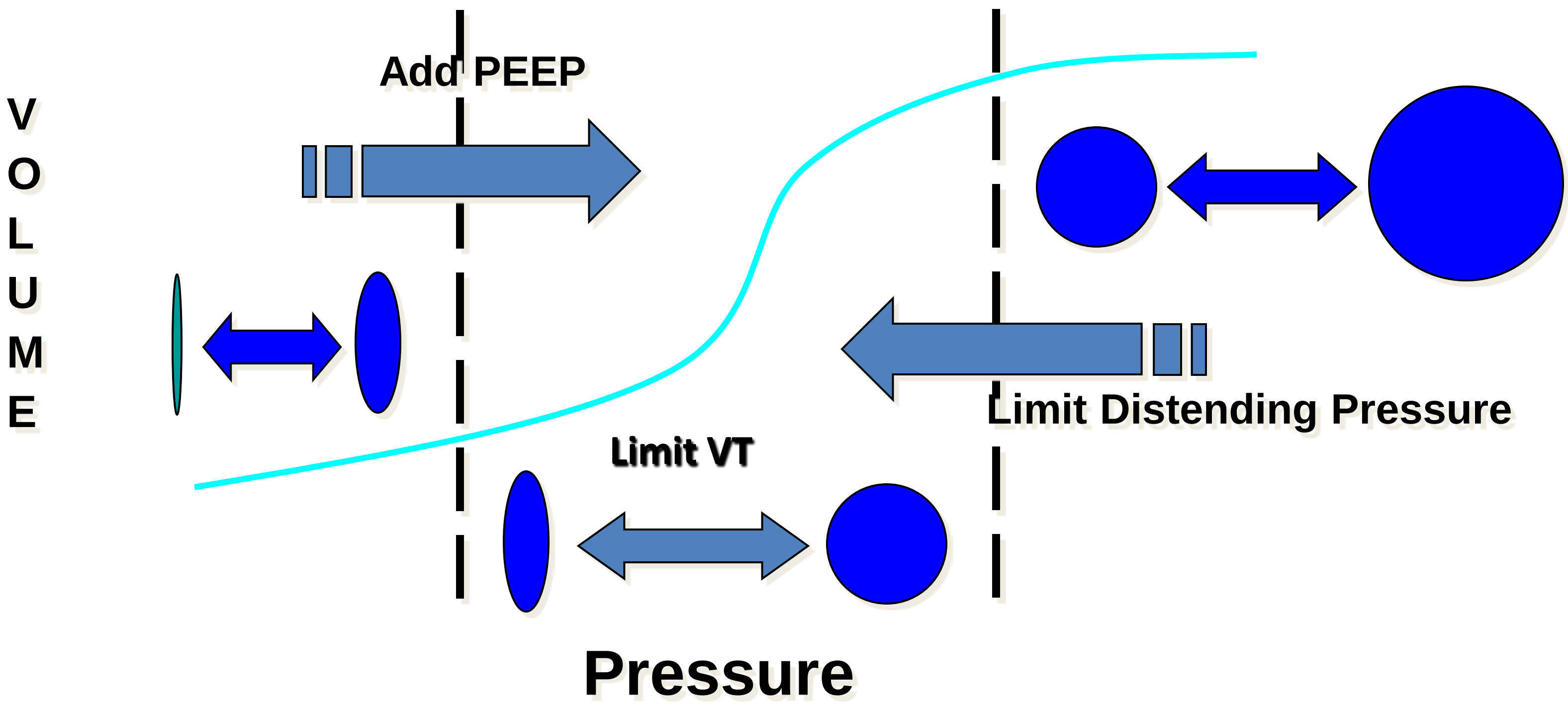
- Unconventional strategies
  - APRV
  - HFOV
  - Prone Ventilation
  - Inhaled Nitric Oxide
  - Extra Corporeal Life Support

Lung Destructive Ventilation

- Oxygen Toxicity
- Barotrauma
- Ventilator-induce lung injury (VILI)
  - Alveolar overdistention (volutrauma)
  - Repetitive cyclic alveoli recruitment and collapse (atelectrauma)
  - Release of inflammatory mediators (biotrama)

Preventing Overdistention and Collapse Injury

“Lung Protective” Ventilation



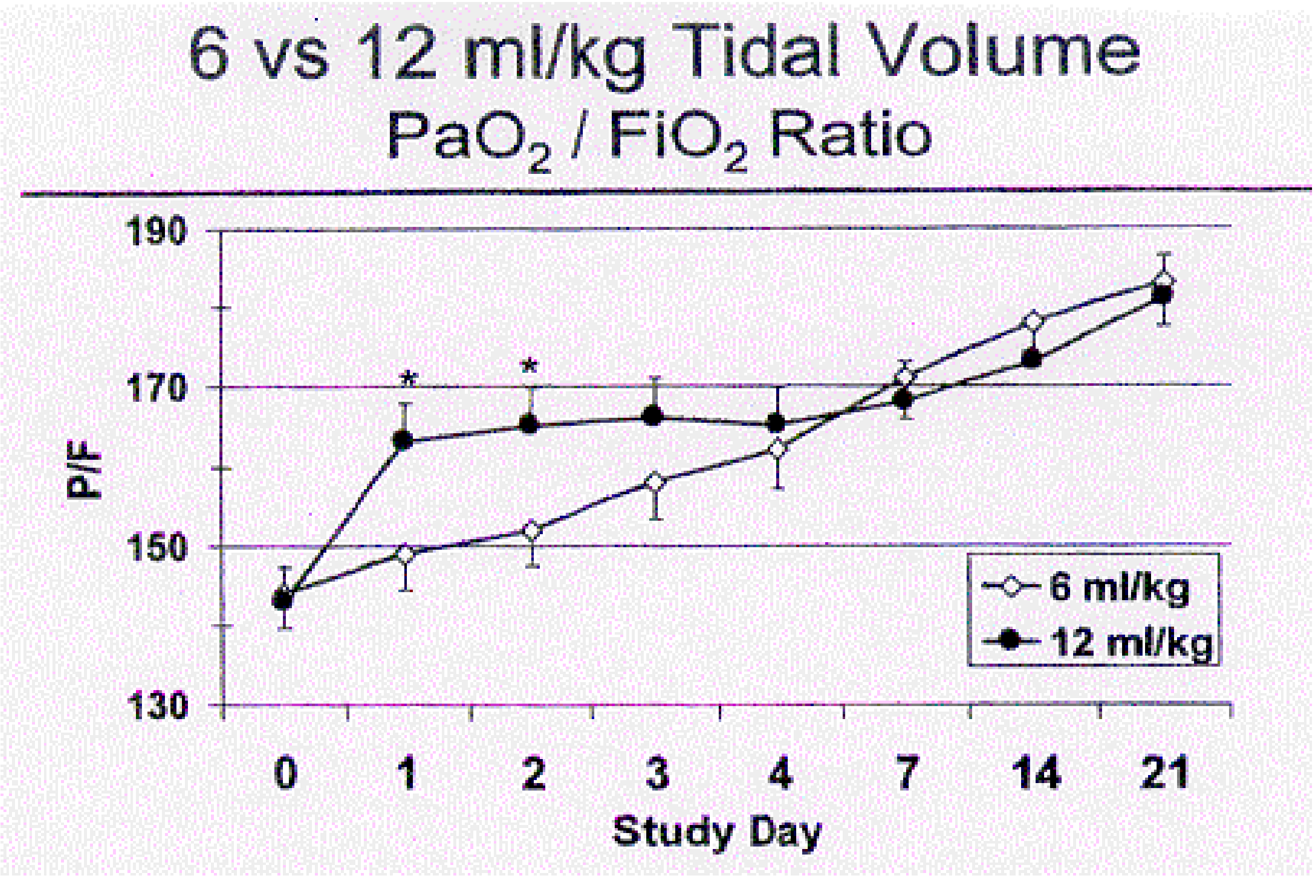
Vt Strategy

- Low volume ventilation:
  - Set tidal volume of 6 ml/kg *(ARDS Network. NEJM 2000;342:1301-8)*
  - Mortality was reduced by 22%

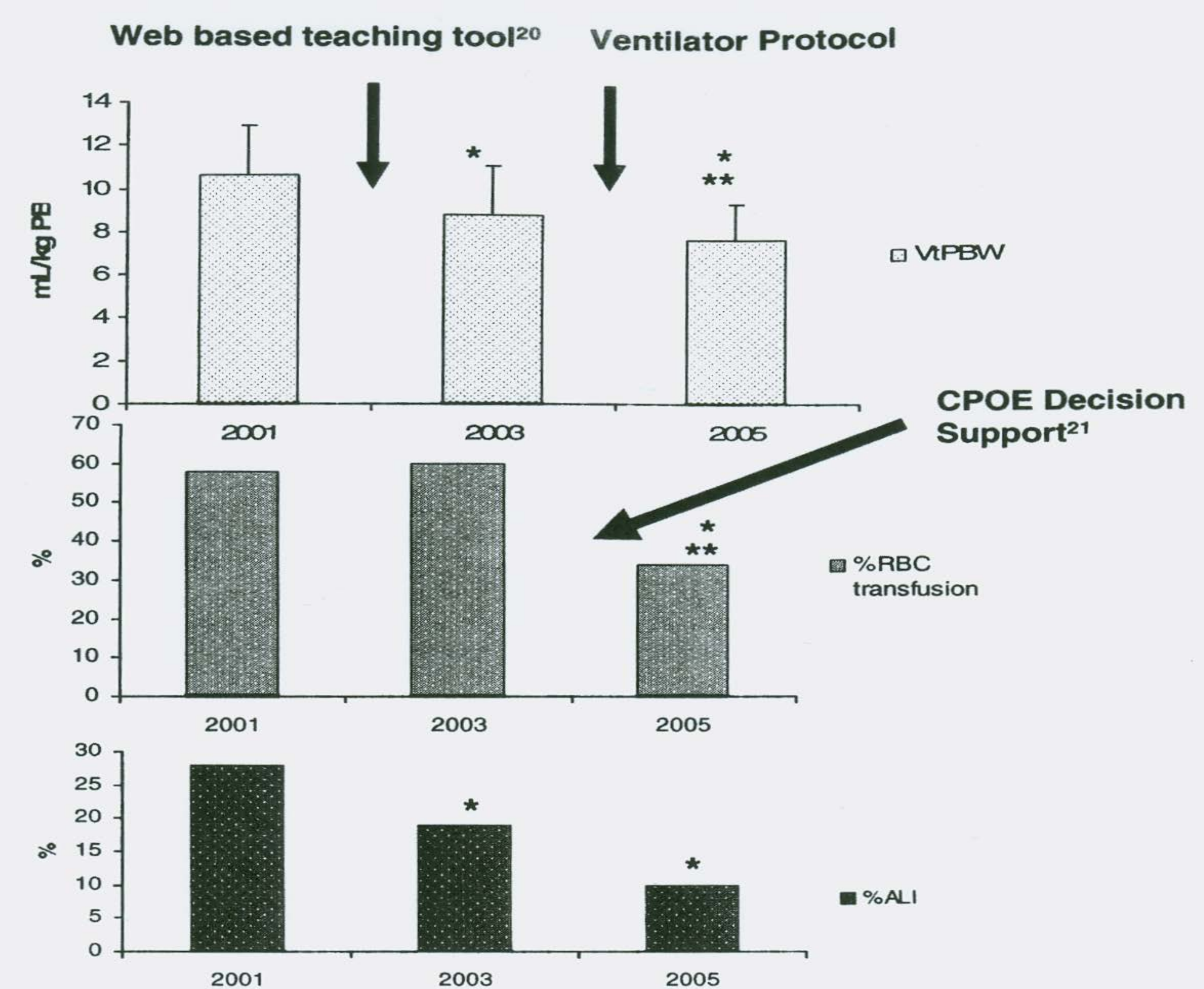
- Is PCV better than VCV ?
  - Clinical trials did not demonstrate the difference

Results

- Trial was stopped after fourth interim analysis.
- Mortality rates
  - 12 cc/Kg VT group- 39.8%
  - 6cc/Kg Vt group- 31.0%
- Vt & Plat were significantly lower
- What group had better PaO_2's?
- 12 & they died more often- so better PaO2 does not translate into better ou



Crs also better in the HIGH Vt group

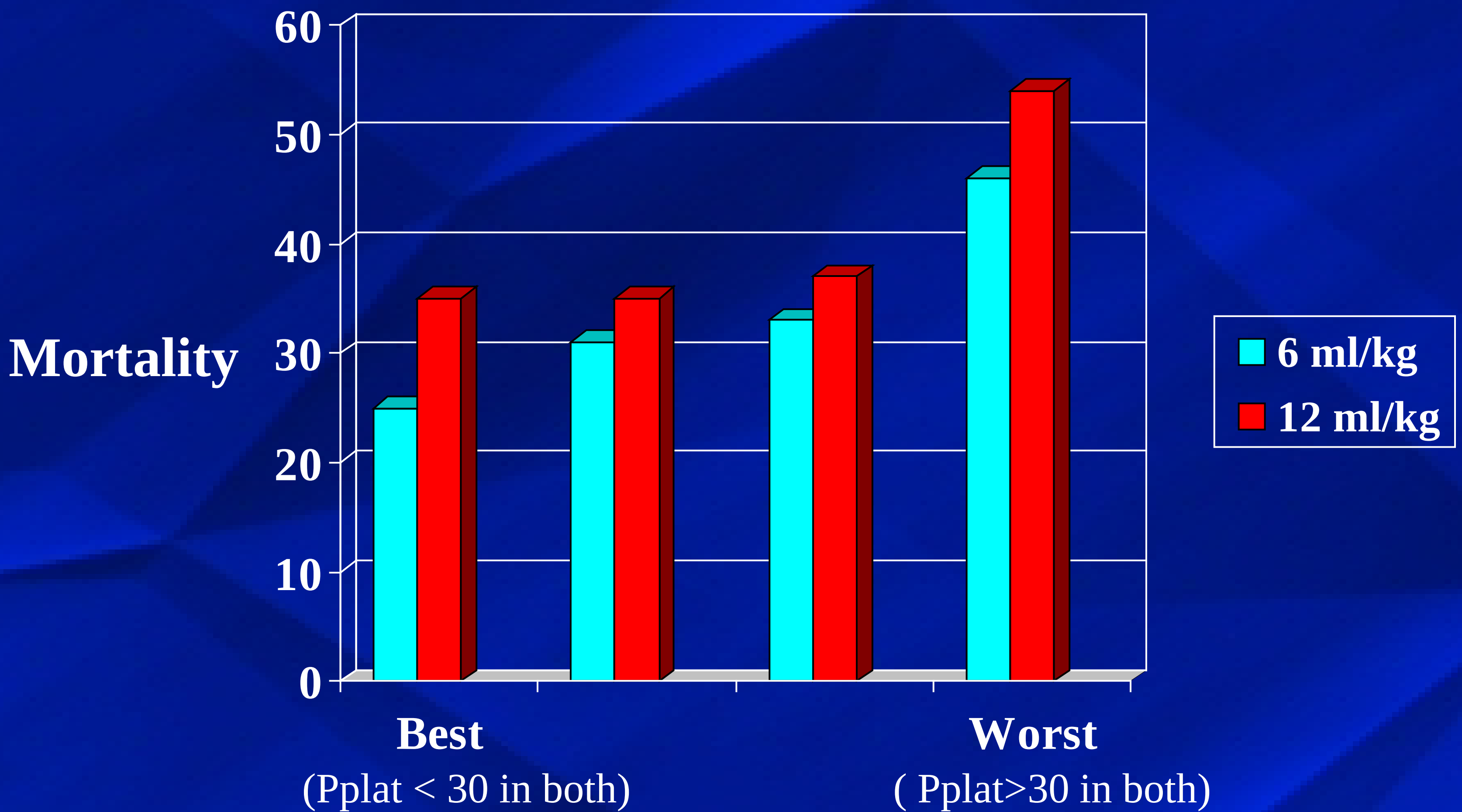


CCM 2007;35:1660

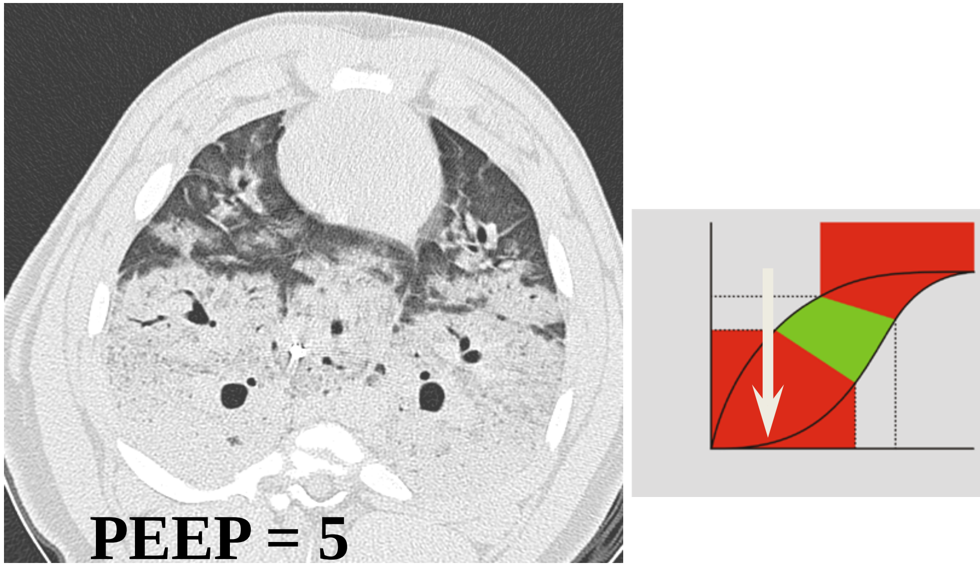
Plateau Pressure

- Plateau Pressure ≤ 30~35 cmH_2O
  - The normal lung is maximally distended at a transpulmonary pressure between 30~35 cm H_2O
  - A plateau pressure above the upper inflection point of pressure volume curve causes alveolar overdistention
  - Transpulmonary pressure
    - $Ptp = Paw - Pes$

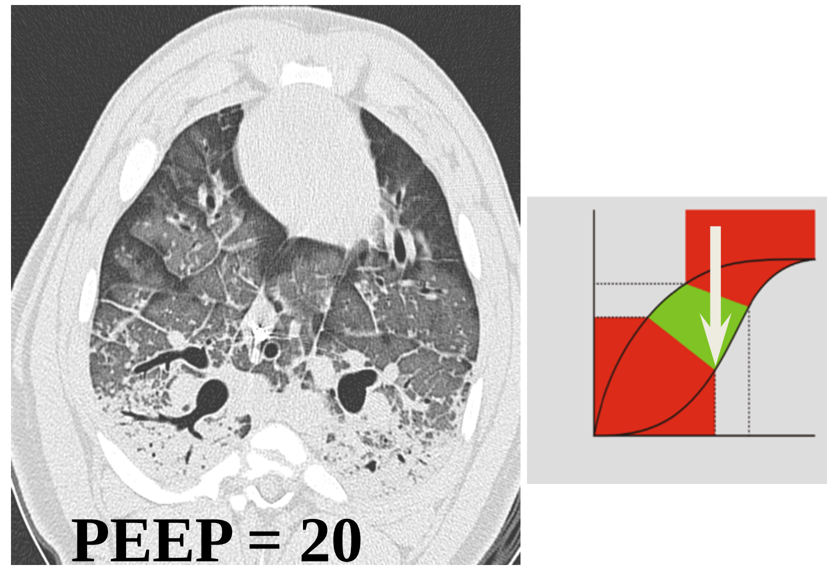
Stretch Injury – Max stretch or tidal stretch?



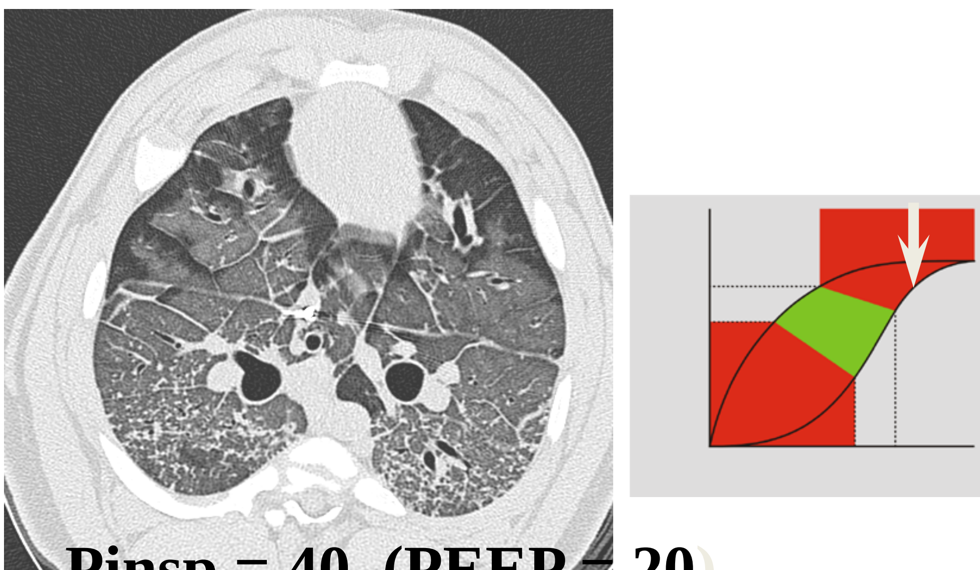
NEJM 2000;342:1301



PEEP = 5



PEEP = 20



Pinsp = 40 (PEEP = 20)

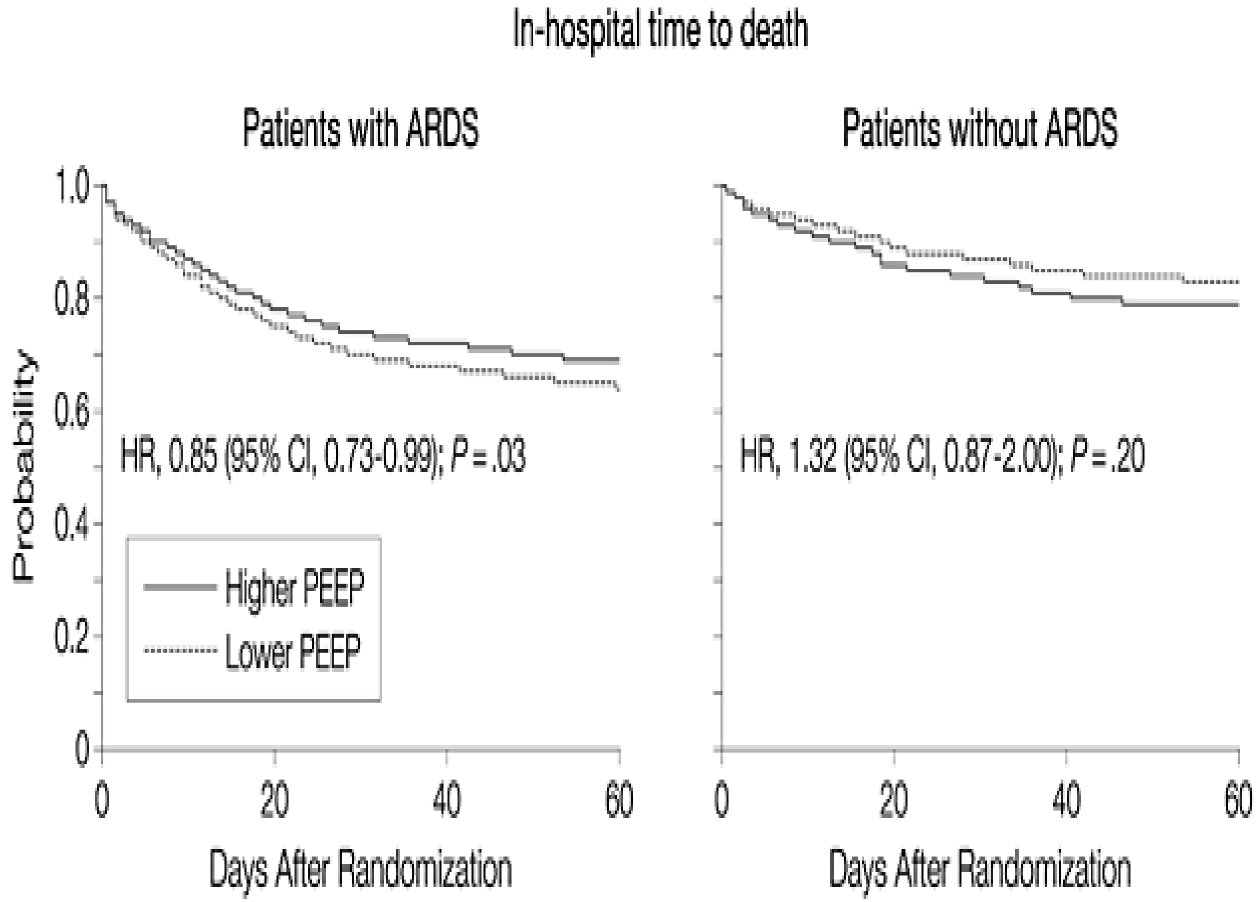
PEEP/FiO_2

- Visual
  - CT, EIT
- Mechanical
  - PV curves, “Best” compliance, Stress Index
- Gas exchange
  - PEEP/FiO2 Tables
    - Goal is “adequate”, not “maximal” PaO

ARDSNet vs 2 Other Trials in 2008:
Canadian* (n=983) European** (n=767)

PEEP		
ARDSNet	8.9	14.7
Canadian	10.1	15.6
European	7.1	14.6
Crs		
ARDSNet	.44	.55
Canadian	.46	.46
European	.44	.47
PaO2/FiO2		
ARDSNet	168	222
Canadian	149	187
European	150	218
Pplat		
ARDSNet	24.0	27.0
Canadian	24.9	30.2
European	21.1	27.5

No mortality benefit to aggressive vs conservative PEEP in any of these trials



JAMA 2010;303:865

No. at risk

Higher PEEP	949	760	693	666	183	158	148	144
Lower PEEP	939	723	649	619	219	196	186	183

- What are “conventional” strategies to provide protection and oxygenation?
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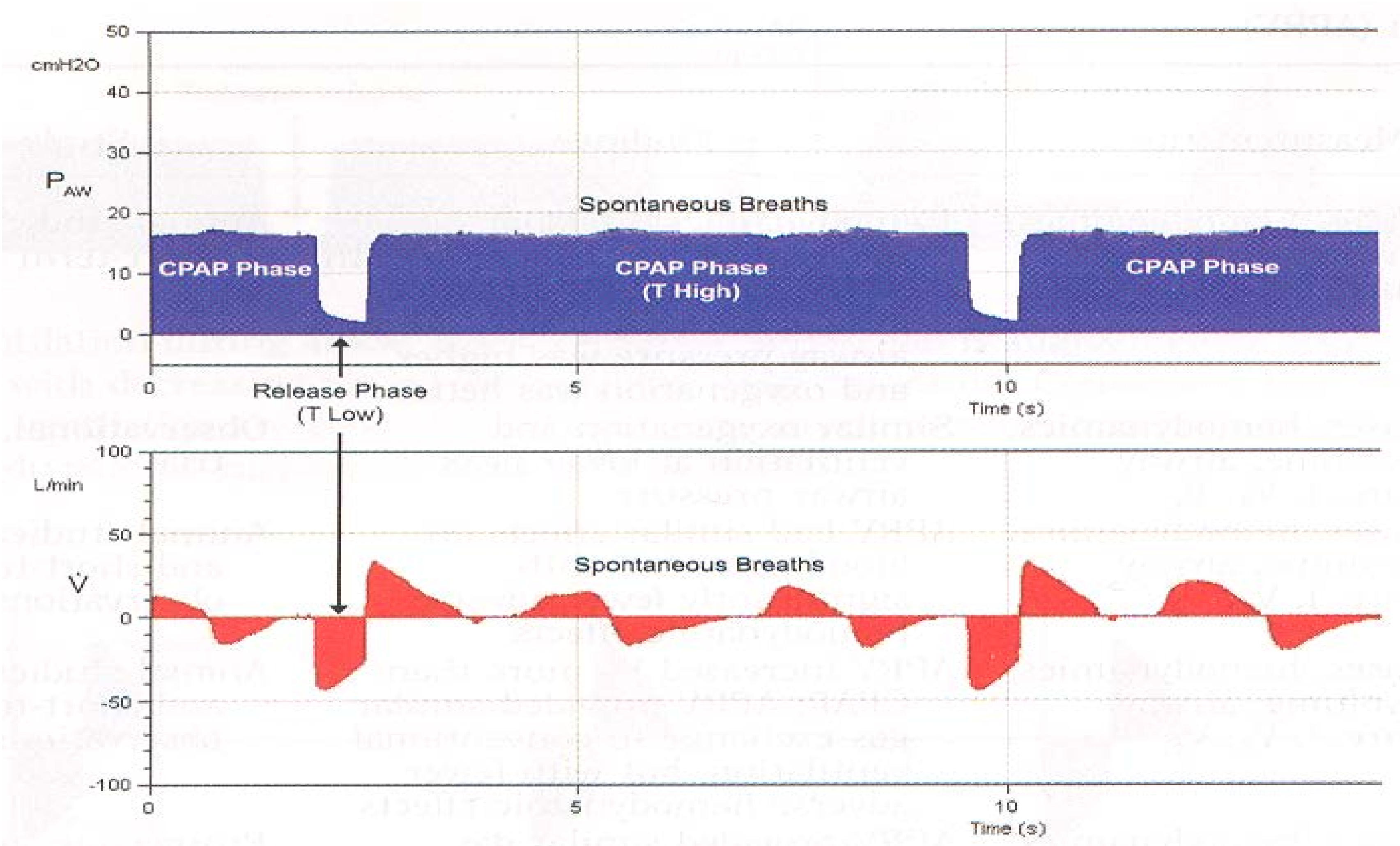
Airway Pressure Release Ventilation (APRV)

- Pressure-limited, time cycled ventilatory approach that allows spontaneous breathing during “inspiration”
  - High continuous airway pressure (P_{high})
  - Time at P_{high} (T_{high})
  - Periodic releases to a lower pressure level (P_{low})
  - Time at P_{low} (T_{low})

APRV



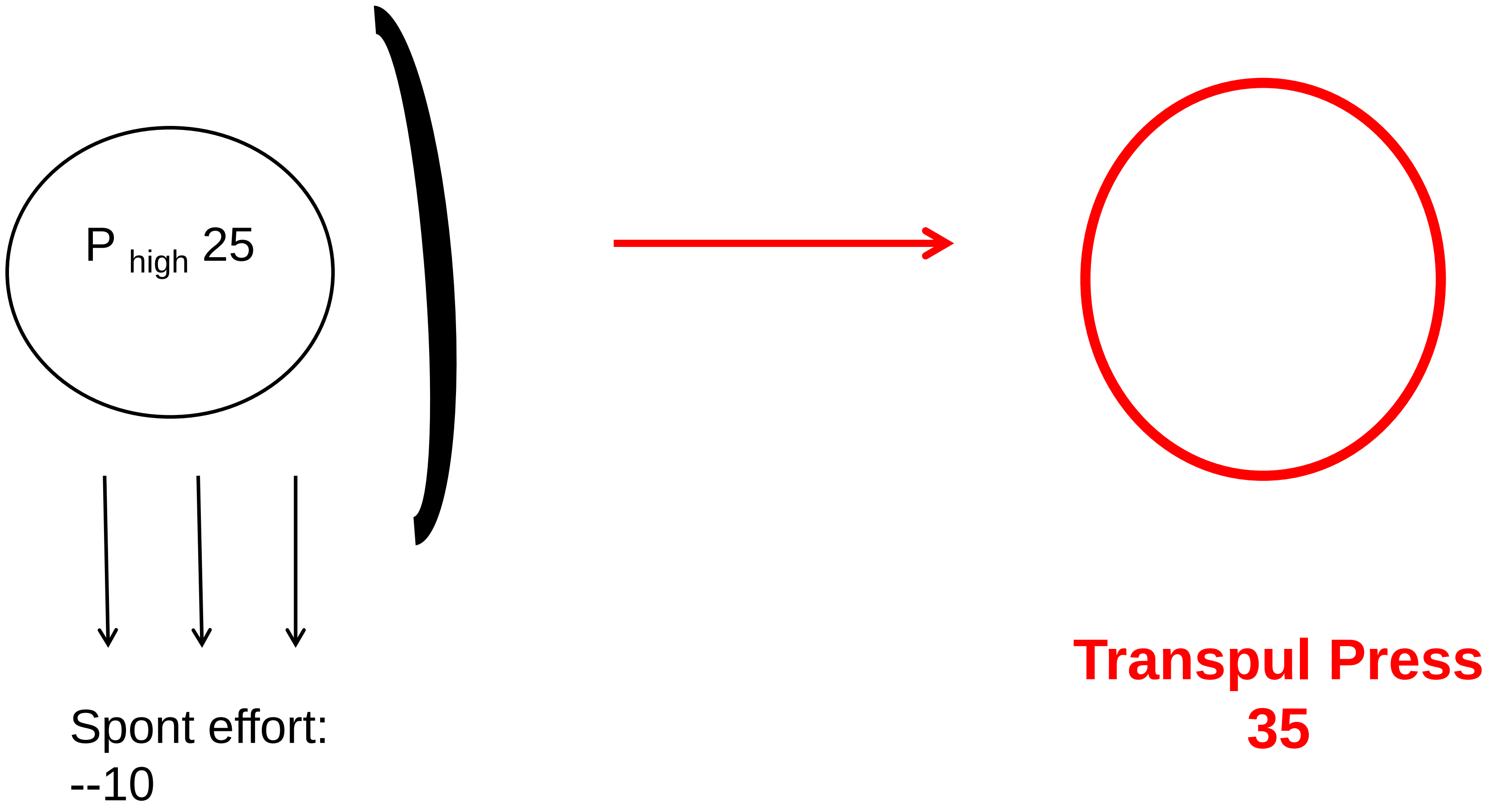
50
cmH2O
40
30
P_{AW}
20
10
0
Spontaneous Breaths
CPAP Phase
CPAP Phase
(T High)
CPAP Phase
0
5
10
Time (s)
Release Phase
(T Low)
100
L/min
50
V̇
0
-50
-100
Spontaneous Breaths
0
5
10
Time (s)

APRV

- Alveolar stretch
  - Improvements in oxygenation
  - Spontaneous breathing may have some benefits hemodynamically and aeration but potentially harmful increases in transpulmonary pressure
  - Rapid flow reversals?

- Comfort
  - Conflicting evidence
  - Recent study showed an increase in sedation use!
    - Maxwell, et al. J Trauma 2010; 69:501

Lung Stretch



APRV

- Easy mode to set up?
  - Terminology and no standard way of setup
  - T_{low} can be a challenge to set correctly
  - Oxygenation/ventilation trade offs

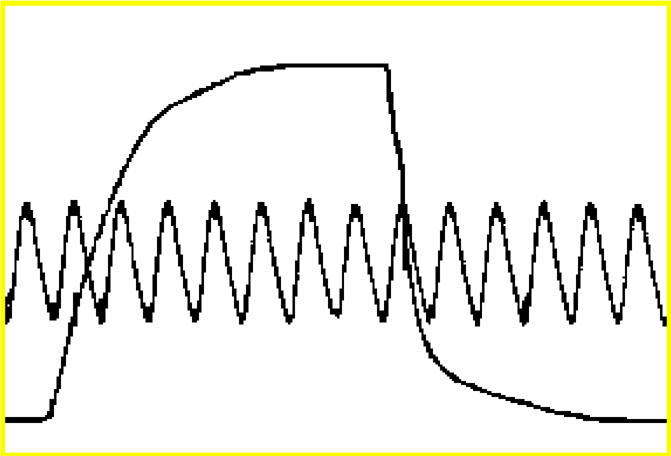
- Outcomes
  - None demonstrated as better to date in terms of mortality

High Frequency Oscillatory Ventilation (HFOV)

Advantages-

Enables ventilation above the “closing volume” with lower alveolar pressure swings.

Safe way of using “Super PEEP”.



Multicenter Oscillatory Ventilation for ARDS Trial (MOAT) - 2002 RCT

Derdak, AJRCCM 2002 13 university-affiliated medical centers

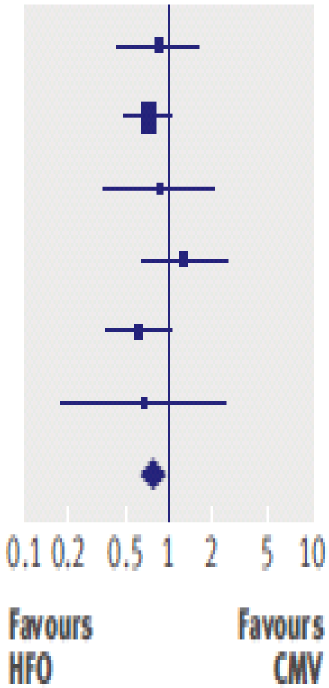
- Prospective randomized controlled trial of the SensorMedics 3100B HFOV for adults with ARDS
- Early Entry, Non-Crossover Trial
- PCV vs HFOV
- 30 day mortality:
  - 37% HFOV
  - 52% CV

MOAT - 2002 RCT

- Not powered to evaluate mortality (would need n=199)
- Higher VT (8 cc/kg measured wt, 10.6 cc/kg ideal wt) and peak Paw (38 cm H2O at 48h) in CV group than current ARDS Network trial standard of care for ARDS (6 cc/kg, 30 cm H2O)

Recent Studies

	High frequency oscillation	Conventional mechanical ventilation	Risk ratio (95% CI)	Weight (%)	Risk ratio (95% CI)
Arnold 1994	10/29	12/29		13.0	0.83 (0.43 to 1.62)
Derdak 2002	28/75	38/73		42.6	0.72 (0.50 to 1.03)
Shah 2004	6/15	6/13		7.9	0.87 (0.37 to 20.4)
Bollen 2005	16/37	8/24		12.5	1.30 (0.66 to 2.55)
Mentzelopoulus 2007	11/27	18/27		20.6	0.61 (0.36 to 1.04)
Samransamruajkit 2005	2/6	5/10		3.4	0.67 (0.18 to 2.42)
Total (95% CI)	73/189	87/176		100.0	0.77 (0.61 to 0.98)



Test for heterogeneity: τ^2=0.00, χ^2=3.36, df=5, P=0.64, I^2=0%

Test for overall effect: z=2.12, P=0.03

Fig 2 | Hospital or 30 day mortality in patients with acute lung injury/acute respiratory distress syndrome allocated to high frequency oscillation or conventional mechanical ventilation

BMJ 2010;340:c2327

Recent Studies

- OSCAR Trial – Young, et al. NEJM 2013
  - 398 patients in 29 centers in Great Britain
  - HFOV vs. local physician practice
  - 3 centers had experience with HFOV, 6 centers “limited” experience and 20 centers no previous experience with HFOV
  - No difference in mortality

Recent Studies

- OSCILLATE Trial – Ferguson, et al. NEJM 2013
  - 548 pts, 39 centers, 5 countries
  - HFOV vs. Low Vt, high PEEP strategy in ARDS
  - In hospital mortality in the HFOV group was 47% vs. 35% in the control group
  - Used higher mean airway pressures
  - 75 potential eligible subjects not enrolled

Prone Ventilation

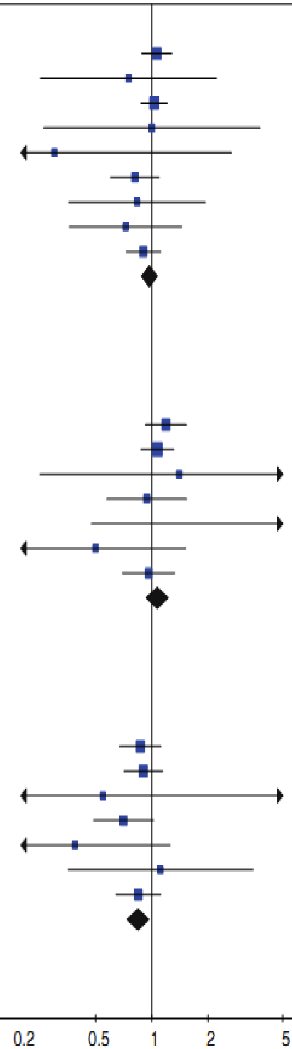
- Gained support in recent years for improvement in oxygenation
  - Improved VQ matching
  - Improved recruitment?
- Questions remain as to the appropriate timing and duration
- Pt response is variable
- Serious adverse events
  - Facial ulcers, extubation, dislo

Prone Ventilation

- In 2008 4 meta-analyses were published
  - No mortality benefit
- Taccone, et al. JAMA 2009; 302:1977
  - RCT 25 European centers
    - Oxygenation often improves (P/F increase approx 25mmHg)
    - Increased sedation/paralytic use, airway obstruction, hypotension, ett displacement, loss of venous access
    - Positive effect in severe ARDS?
    - No effect on mortality

Prone – a subset analysis

Study or sub-category	Prone n/N	Supine n/N	Risk Ratio 95% CI	Weight %	Risk Ratio 95% CI
All Patients					
Gattinoni 2001	92/148	87/149		27.67	1.06 [0.88, 1.28]
Beuret 2002	4/12	4/9		0.81	0.75 [0.25, 2.22]
Guerin 2004	179/413	159/377		36.18	1.03 [0.87, 1.21]
Curley 2005	4/51	4/51		0.53	1.00 [0.26, 3.78]
Voggenreiter 2005	1/21	3/19		0.20	0.30 [0.03, 2.66]
Mancebo 2006	38/76	37/60		10.47	0.81 [0.60, 1.10]
Chan 2007	5/11	6/11		1.33	0.83 [0.36, 1.94]
Fernandez 2008	8/21	10/19		1.97	0.72 [0.36, 1.45]
Taccone 2009	79/166	91/172		20.84	0.90 [0.73, 1.11]
Subtotal (95% CI)	410/919	401/867		100.00	0.97 [0.88, 1.07]
Test for Overall Effect: p=0.54					
Heterogeneity: $I^2 = 0\%$					
$PaO_2/FiO_2 \geq 100$ Subgroup					
Gattinoni 2001	57/95	52/103		28.45	1.19 [0.92, 1.53]
Guerin 2004	126/323	110/302		44.31	1.07 [0.88, 1.31]
Curley 2005	3/30	2/28		0.62	1.40 [0.25, 7.77]
Mancebo 2006	16/33	16/31		7.54	0.94 [0.58, 1.53]
Chan 2007	3/4	0/4		0.25	7.00 [0.47, 103.27]
Fernandez 2008	3/12	7/14		1.46	0.50 [0.16, 1.52]
Taccone 2009	40/93	43/96		17.37	0.96 [0.70, 1.33]
Subtotal (95% CI)	248/590	230/578		100.00	1.07 [0.93, 1.22]
Test for Overall Effect: p=0.35					
Heterogeneity: $I^2 = 0\%$					
$PaO_2/FiO_2 < 100$ Subgroup					
Gattinoni 2001	35/53	35/46		28.31	0.87 [0.67, 1.12]
Guerin 2004	53/90	49/75		31.56	0.90 [0.71, 1.14]
Curley 2005	1/21	2/23		0.33	0.55 [0.05, 5.61]
Mancebo 2006	22/43	21/29		13.25	0.71 [0.49, 1.02]
Chan 2007	2/6	6/7		1.31	0.39 [0.12, 1.25]
Fernandez 2008	5/9	2/4		1.38	1.11 [0.36, 3.48]
Taccone 2009	39/73	48/76		23.86	0.85 [0.64, 1.11]
Subtotal (95% CI)	157/295	163/260		100.00	0.84 [0.74, 0.96]
Test for Overall Effect: p=0.01					
Heterogeneity: $I^2 = 0\%$					



Sud, et al. Int Care Med 2010; 36:585

Prone Ventilation

- Between 2008 and 2011
  - 5 meta-analyses published
    - All showed non-significant potential oxygenation benefits
      1. Sud, et al. Int Care Med 2010; 36:585-599
      2. Abroug, et al. Crit Care 2011; 15:R6
      3. Alsaghir, et al. CCM 2008; 36:603-609
      4. Kopterides, et al. J Crit Care 2009; 24:89-100
      5. Tiruvoipati, et al. J Crit Care 2008; 23:101-110

Prone Ventilation

– 3 showed mortality benefit in severe ARDS

1. Sud, et al. Int Care Med 2010; 36:585-599
2. Abroug, et al. Crit Care 2011; 15:R6
3. Kopterides, et al. J Crit Care 2009; 24:89-100

PROSEVA Study

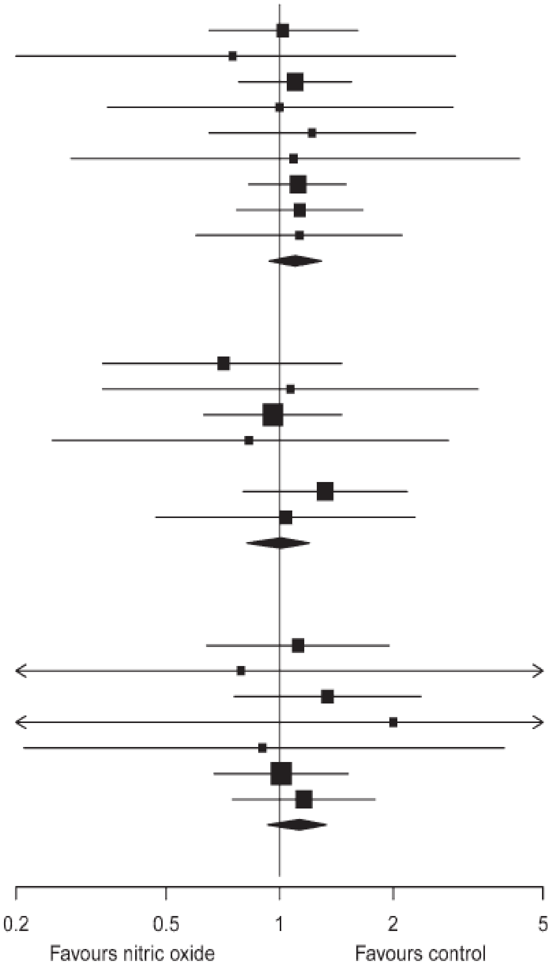
- Guerin, et al. NEJM 2013; 368:2159-2168
  - 27 centers in Europe
  - All centers > 5 yrs experience with prone ventilation
  - Prone 16 hrs vs. LOVT
  - Mortality: Prone 16%, LOVT 33%

Inhaled nitric oxide (iNO)

- FDA approved only for PPHN
- Has been used “off label” for adult cardiothoracic surgery patients and ARDS
- Transient improvements in oxygenation

iNO

Study	Nitric oxide Events	Nitric oxide Total	Control Events	Control Total	Weight	Risk Ratio [95% CI]
All Patients						
Dellinger et al, 1998	43	158	20	75	12.6%	1.02 [0.65, 1.61]
Gerlach et al, 2003	3	20	4	20	1.4%	0.75 [0.19, 2.93]
Lundin et al, 1999	41	93	35	87	21.9%	1.10 [0.78, 1.55]
Mehta et al, 2001	4	8	3	6	2.3%	1.00 [0.35, 2.88]
Michael et al, 1998	11	20	9	20	6.6%	1.22 [0.65, 2.29]
Park et al, 2003	4	11	2	6	1.4%	1.09 [0.28, 4.32]
Payen et al, 1999	48	98	46	105	29.5%	1.12 [0.83, 1.50]
Taylor et al, 2004	44	192	39	193	17.7%	1.13 [0.77, 1.66]
Troncy et al, 1998	9	15	8	15	6.6%	1.13 [0.60, 2.11]
Total (95% CI)	**207**	**615**	**166**	**527**	**100.0%**	**1.10 [0.94, 1.29]**
Overall effect: p=0.24; Heterogeneity: I^2=0%						
P/F <= 100 mmHg						
Dellinger et al, 1998	14	43	6	13	13.0%	0.71 [0.34, 1.46]
Gerlach et al, 2003	3	7	4	10	5.3%	1.07 [0.34, 3.36]
Lundin et al, 1999	22	46	22	44	38.7%	0.96 [0.63, 1.46]
Mehta et al, 2001	2	4	3	5	4.7%	0.83 [0.25, 2.80]
Park et al, 2003	1	1	0	0		Not estimable
Payen et al, 1999	19	35	14	34	27.2%	1.32 [0.80, 2.18]
Taylor et al, 2004	12	52	8	36	11.1%	1.04 [0.47, 2.28]
Subtotal (95% CI)	**73**	**188**	**57**	**142**	**100.0%**	**1.01 [0.78, 1.32]**
Overall effect: p=0.93; Heterogeneity: I^2=0%						
P/F > 100 mmHg						
Dellinger et al, 1998	29	115	14	62	17.6%	1.12 [0.64, 1.95]
Gerlach et al, 2003	0	13	0	10	0.4%	0.79 [0.02, 36.5]
Lundin et al, 1999	19	47	13	43	16.8%	1.34 [0.76, 2.37]
Mehta et al, 2001	2	4	0	1	0.8%	2.00 [0.16, 25.75]
Park et al, 2003	3	10	2	6	2.5%	0.90 [0.21, 3.94]
Payen et al, 1999	26	63	29	71	33.2%	1.01 [0.67, 1.52]
Taylor et al, 2004	32	139	31	156	28.6%	1.16 [0.75, 1.79]
Subtotal (95% CI)	**112**	**391**	**89**	**349**	**100.0%**	**1.12 [0.89, 1.42]**
Overall effect: p=0.33; Heterogeneity: I^2=0%						



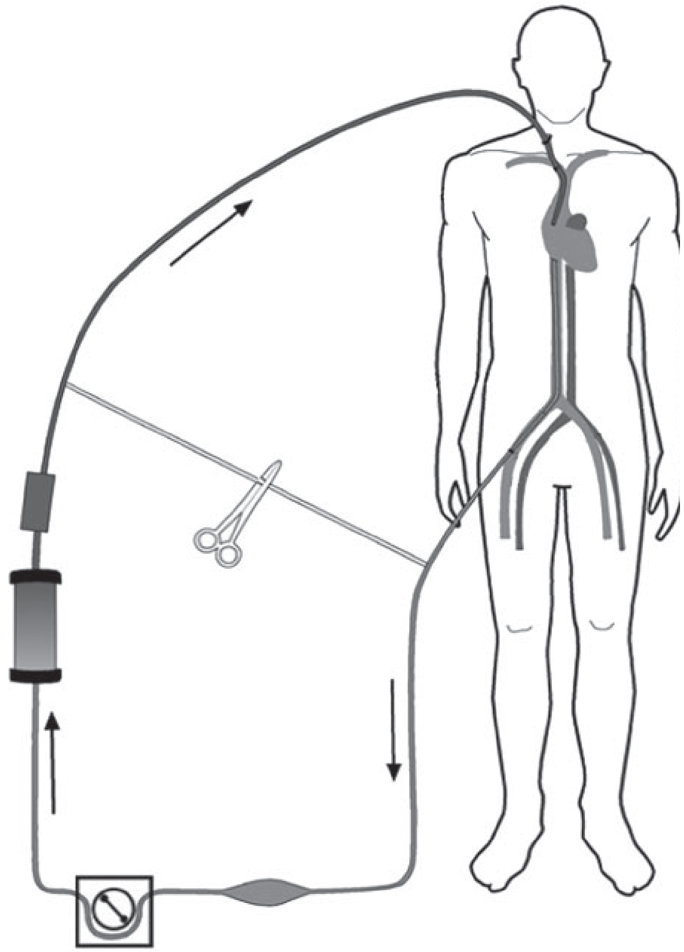
Adhikari, et al. CCM 2014; 42:404

iNO Issues

- Costly
- Requires specialized equipment
- Potential methemoglobinemia
- Rebound pul hypertesion if iNO stopped too abruptly
- Reactive nitrogen species (NO_2) may have pro-inflammatory effects
- No outcome studies showing a decrease in duration of MV mortality

Extracorporeal Membrane Oxygenation (ECMO)

- Dissociates mechanical ventilation and gas exchange
- Blood is removed from the patient, pumped through an artificial lung and then returned
- High cost, availability and resource allocation



Conventional Ventilation vs ECLS in Severe Acute Respiratory Distress Syndrome

- 180 patients with severe "potentially reversible" ARDS in UK
- Randomized to "usual care" or sent to one center for ECLS
  - Not all received ECLS – died en route, "too healthy"
  - Lack of standardization of the control group
- Survival:
  - 63 % ECLS vs 46% usual care
  - P = 0.03

Many Questions

- When should ECMO be initiated?
- Which patients are the best candidates?
- Strategies of lung rest and effects on the inflammatory cascade
- Best strategy for weaning – should the ET be removed completely?
- Transfusion thresholds
- Anticoagulation strategies
- Medication dosing
- Long-term effects of ECMO

Summary

- Lung protective ventilation provides the best strategy at this point to manage refractory hypoxemia
- There may be ways to augment conventional ventilation techniques to manage severe hypoxemia
  - Prone ventilation
  - ECMO
- When conventional ventilation fails there are some “unconventional” ventilation options
  - APRV
  - HFOV
  - With all 4 of the above strategies evidence of benefit remains scarce and further study is needed