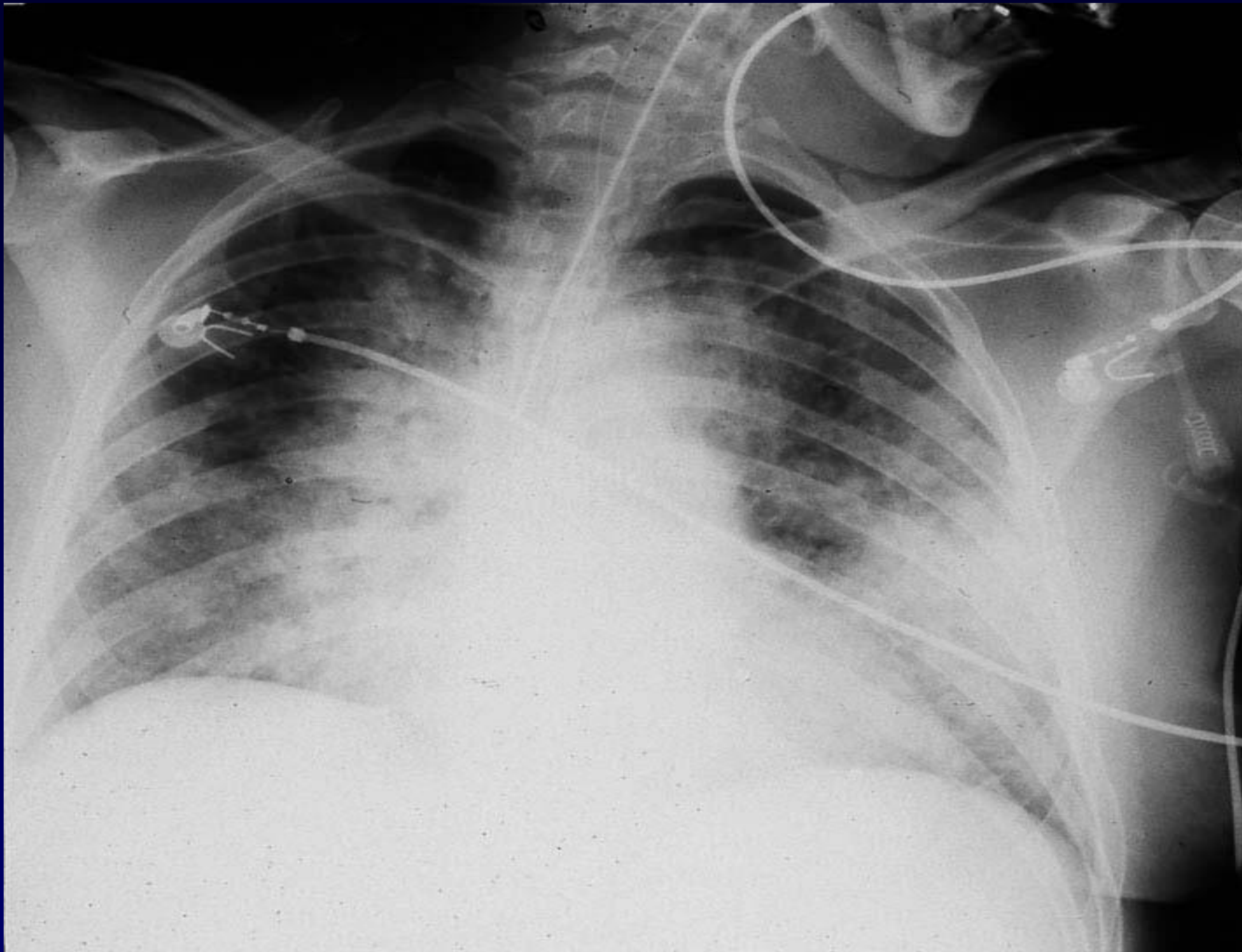
What is new in ARDS

Geoff Bellingan

Medical Director

University College Hospital



ARDS: Definitions

- History of predisposing condition
- Refractory hypoxaemia of acute onset
  - PaO_2/FiO_2 ratio:
    - <40 Acute Lung Injury - ALI
    - <27 Acute Respiratory Distress Syndrome - ARDS
- Bilateral pulmonary infiltrates (CXR)
- Absence of left ventricular dysfunction

American-European Consensus Conference on ARDS

Am . J. Resp. Crit. Care Med. 1994 **149:** 818

Lets just do those sums…

PaO_2 of 10 kPa	**PaO_2/FiO_2 ratio**	
– FiO_2 of 0.8 (80% oxygen)	12.5	ARDS
– FiO_2 of 0.6 (60% oxygen)	16.7	ARDS
– FiO_2 of 0.4 (40% oxygen)	25	ARDS
– FiO_2 of 0.3 (30% oxygen)	33.3	ALI
– FiO_2 of 0.26 (26% oxygen)	38.5	ALI
– FiO_2 of 0.21 (air)	47.6	normal

Despite worldwide acceptance this definition is hugely controversial

- Too broad a church
- What is acute?
- Why P/F <40 and <26.7?
- Role of CXR?
- What of inflammation?

- Epidemiological or clinical?

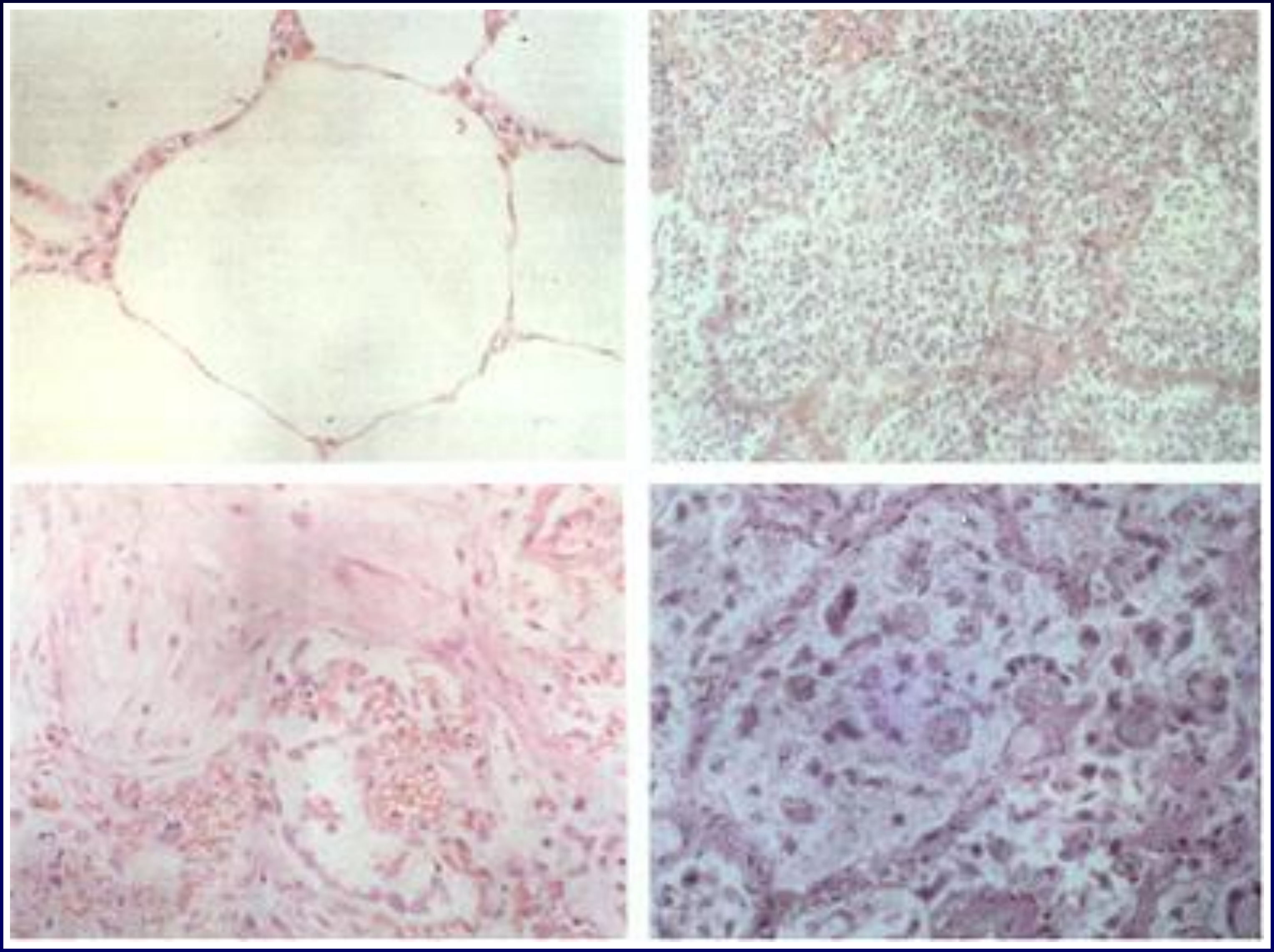
Ferguson, 2004; 2006

Bernard et al. The American-European consensus conference on ARDS. *Am J Respir Crit Care Med* 1994

ARDS: Understanding the pathogenesis

"Despite considerable effort, the committee could not reach a consensus on the order of events in the pathogenesis of acute lung injury and ARDS"

Bernard et al. The American-European consensus conference on ARDS. *Am J Respir Crit Care Med* 1994



ARDS: Pathophysiology

INJURY

↓

EXUDATION &
INFLAMMATION

↓

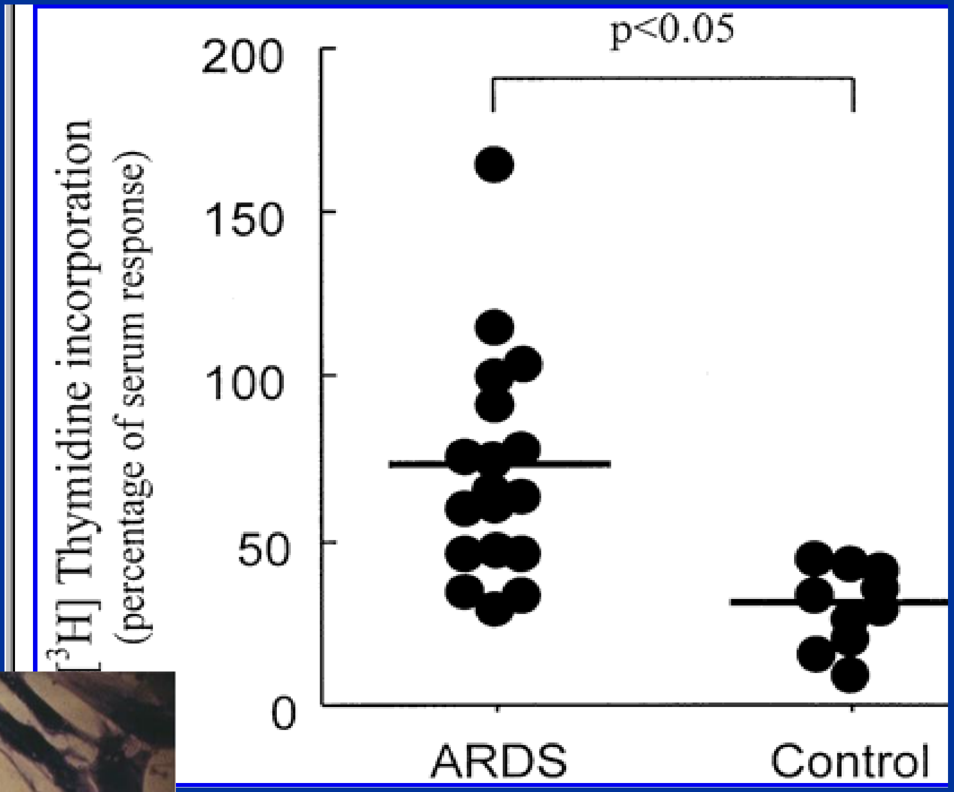
FIBROPROLIFERATION

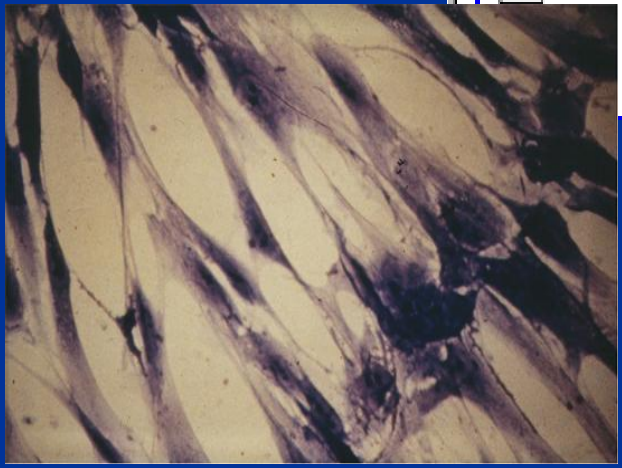
↙ ↘

SURVIVE DIE

A TOP investigator studies the problem

Fibroproliferative activity of BAL within 24 hours of ARDS





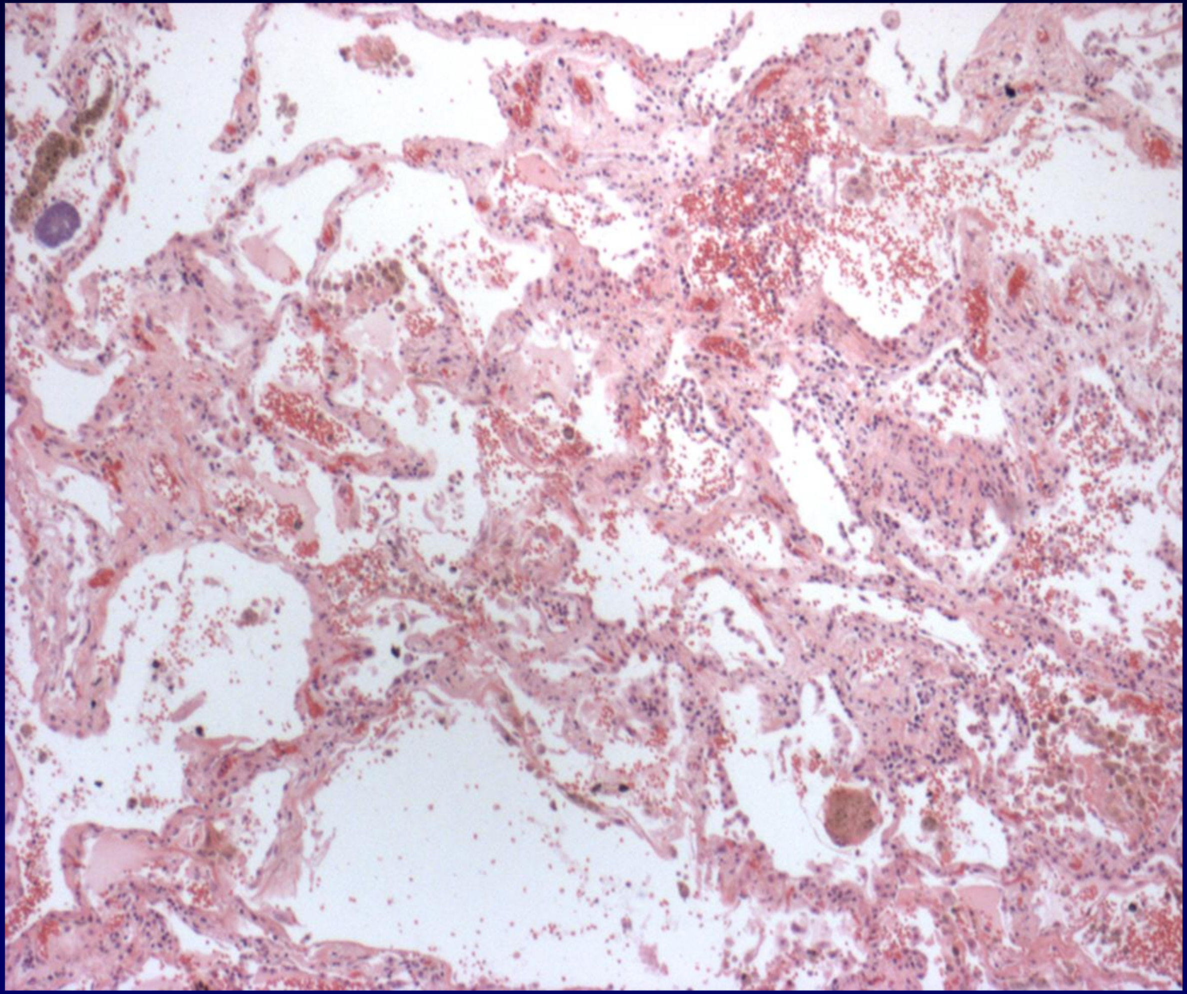
70% 32%

that of 10% serum

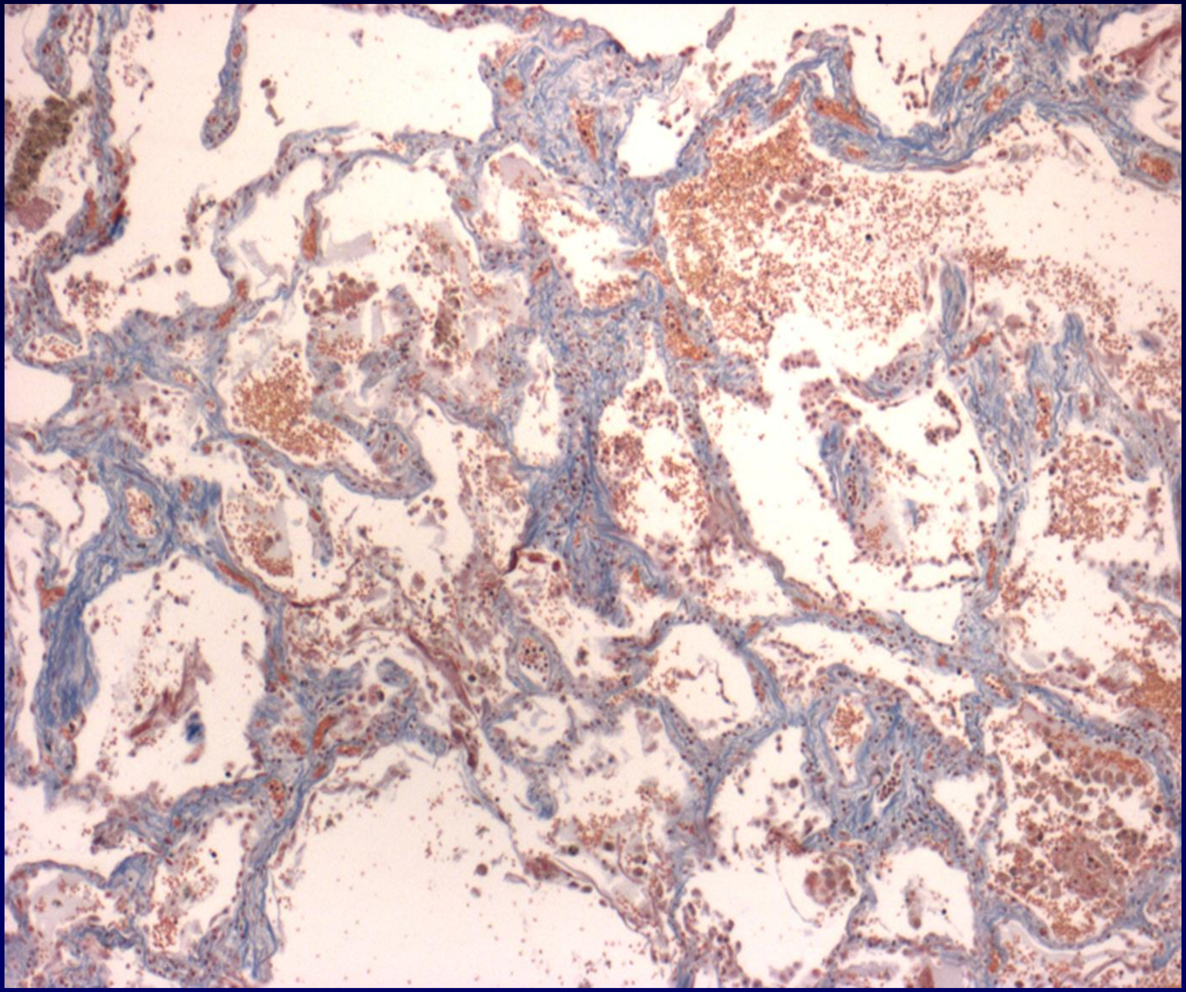
N-PCP A BETTER PREDICTOR OF OUTCOME….
WITHIN 24 h OF DIAGNOSIS

	Survivors (n= 28)	Nonsurvivors (n= 16)	p Value
BAL N-PCP-III, U/ml*	1.24 (0.60-3.42)	3.1 (1.8-11.4)	0.017
APACHE II score	17.5 ± 7.1	22.4 ± 8.3	0.0419
SAPS II score	32.7 ± 17.0	39.9 ± 17.0	0.128
PaO_2/FIO_2	13.6 ± 3.3	14.13 ± 3.4	0.183
Lung injury score	3.1 ± 0.6	3.55 ± 0.6	0.426

Haematoxylin/Eosin: Early



Martius Scarlet Blue: Early



ACE : D allele as a risk factor for ARDS

Genotype and allele frequency

	Genotype %				Allele		
	II	*ID*	*DD*	*p*	*I*	*D*	*p*
ARDS n=84	9	45	46		31	69	
CABG Control n=174	23	52	25	0.00002	49	51	0.0001
ICU Control n=88	38	36	25	0.00019	57	43	0.00022
Population Control n=340	24	51	25	0.00012	49	51	0.0001

Small differences in genotype make big differences to phenotype

Pathogenesis

ARDS Incidence

- 1972 National Heart and Lung Task Force = 75 per 100,000 inhabitants/year in USA
- 20 years later, first population studies = 1.5 - 4.5 per 100,000 /year in Europe.
- Using 1992 definitions, reported incidences =

ARDS	13-23 per 100,000 /year
ALI	18 per 100,000 /year

- Latest epidemiological figures

ARDS	59 per 100,000 /year
ALI	79 per 100,000 /year.

- ARDS: widespread, (>30,000/year in UK)
  massive socio-economic impact
  comparable to breast cancer, asthma, MI.

ARDS: Treatment

ARDS: Treatment

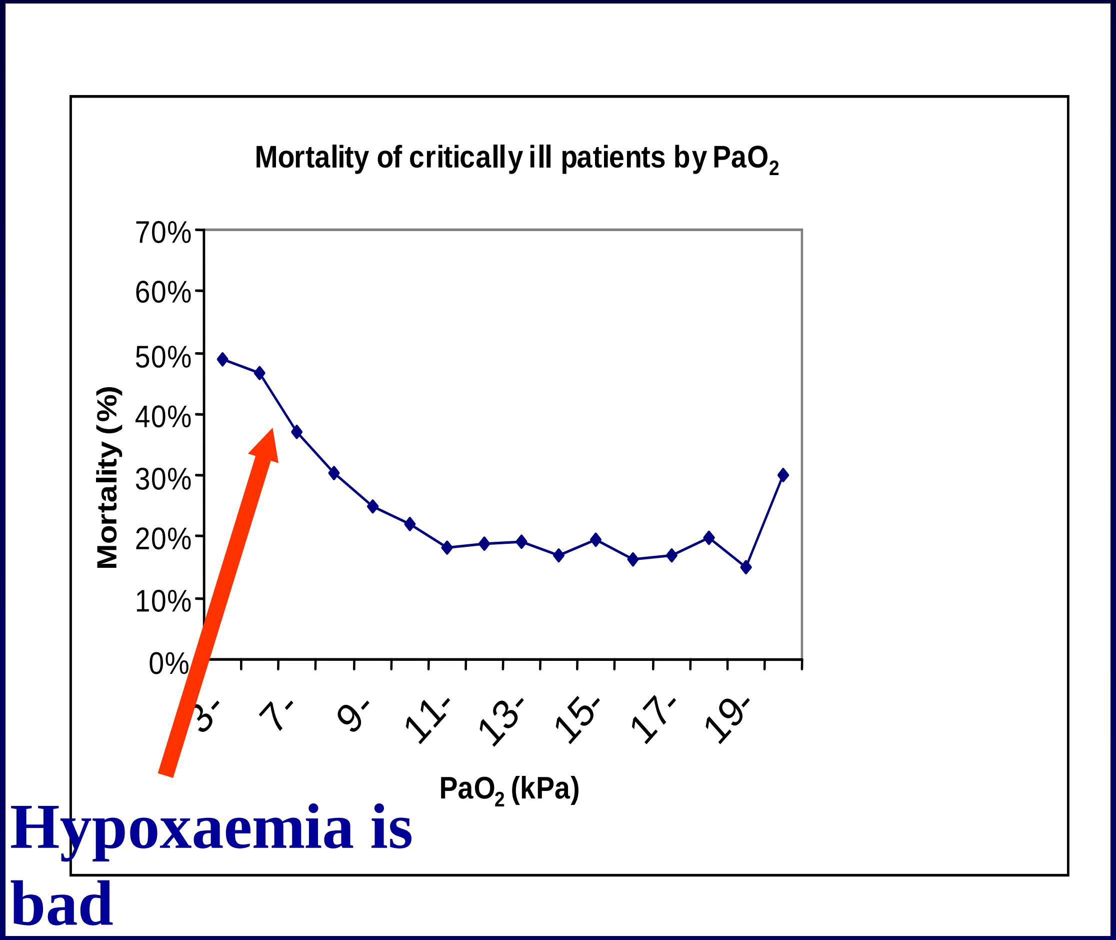
- Oxygen therapy
- Treat cause
- Organ support
  - respiratory NIPPV/IPPV
  - cardiac myocardial depression/sepsis
- Other treatments
  - Ventilatory strategies, Paralysis, Nitric Oxide, Heliox, Steroids, Surfactant, Antioxidants, immunomodulation…...
- Avoid mistakes

Controversies in Management

- What oxygen level?
- Which ventilation mode?
- What PEEP?
- When to CT?
- Rescue therapies: inverse ratio, prone, NO, >30 cmH_20, oscillation, ECMO etc.
- What CO_2?
- Fluid management?
- What Hb?
- Drugs: steriods, $beta_2$ agonists, surfactant, neuromuscular blockers, sildenafil…
- What mode to wean?
- When to tracheostamise?
- Future – oxygen / CO_2 removal and negative pressure ventilation?

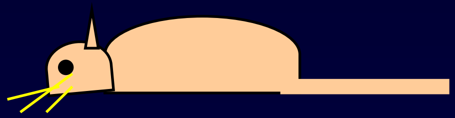
Hypoxaemia Kills

Mortality rises as PaO_2 falls below 10 kPa



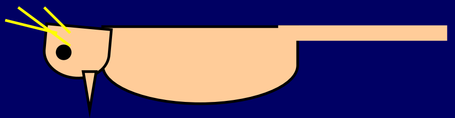
Bellingan, Wunch, Young, Rowan ATS 2005

Hyperoxia Kills



- 100% oxygen results in:
  - Progressive damage to the pulmonary endothelium and epithelium.
  - Free radical release,
  - Capillary leak
  - Impaired surfactant function
  - Maldistribution of microcirculatory perfusion

Death



Welty-Wolf 1997
Tsai 2003
Huang 1995

Hyperoxia is dangerous across species

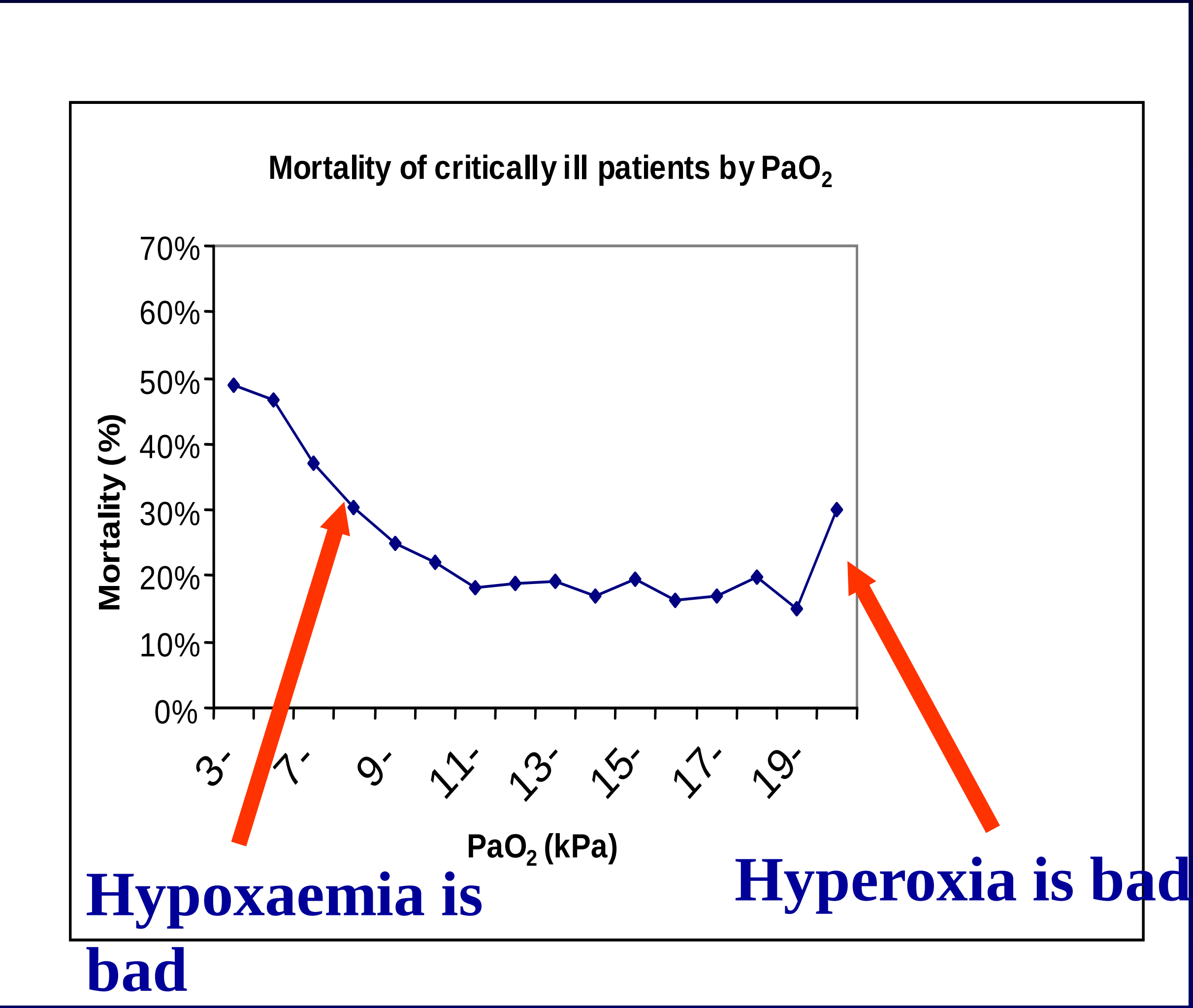
NATURE

Insects breathe discontinuously to avoid oxygen toxicity.

Hetz SK, Bradley TJ.

NATURE 2005 Feb 3;433:516-9.

Targeted Oxygenation



Is there one side of the balance better than the other????

The New England Journal of Medicine

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*

- 20 medical centres 1996 - 1999, stopped after 3 years n=861 (proposed 1600).
- Compared TV 12ml/kg (plateau <50cmH_2O) versus TV 6ml/kg (plateau < 30cm H_2O).
- Relative reduction in mortality of 22% (absolute 9%: 31 vs 39.8%)

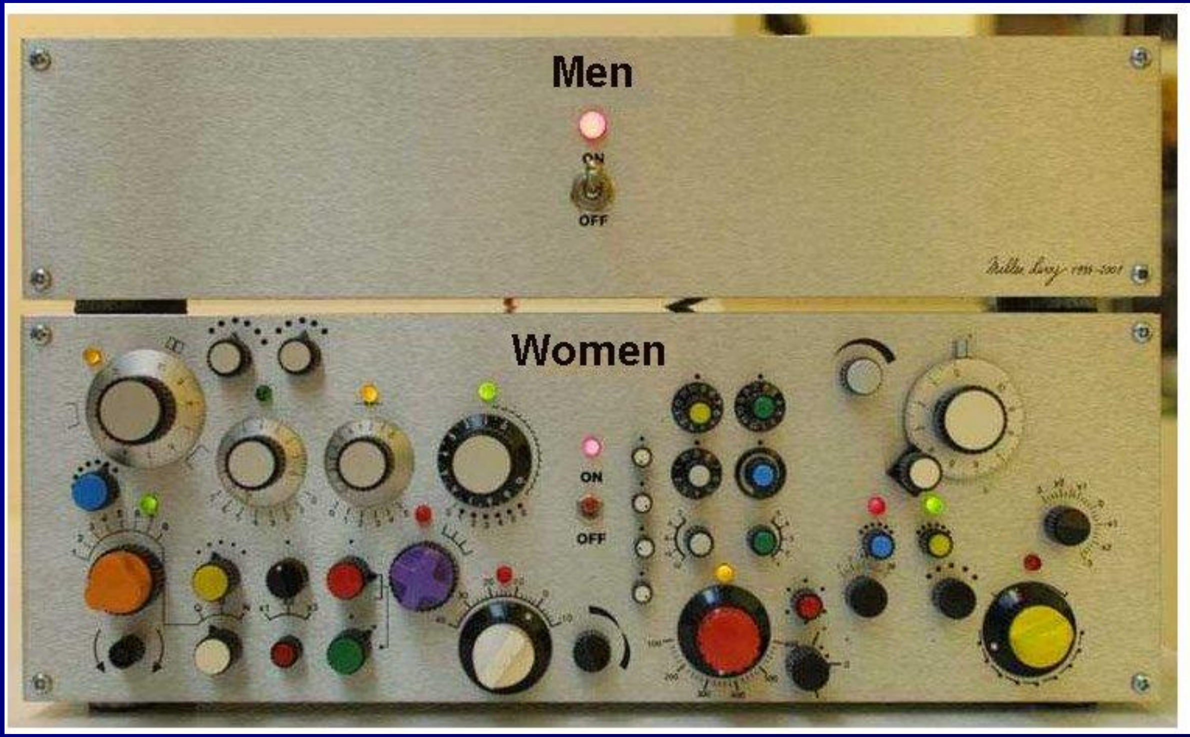
Problems (1)

- Unethical(?) exposure of controls to excess TV
- Not clear whether reduction in TV or reduction in plateau pressure or hypercapnic acidosis that conveys benefits
- Very wide scatter of TV and plateau pressure before trial entry
- Patients excluded from trial had significantly lower mortality than controls

  (Ferguson, 2005; Deans, 2005)

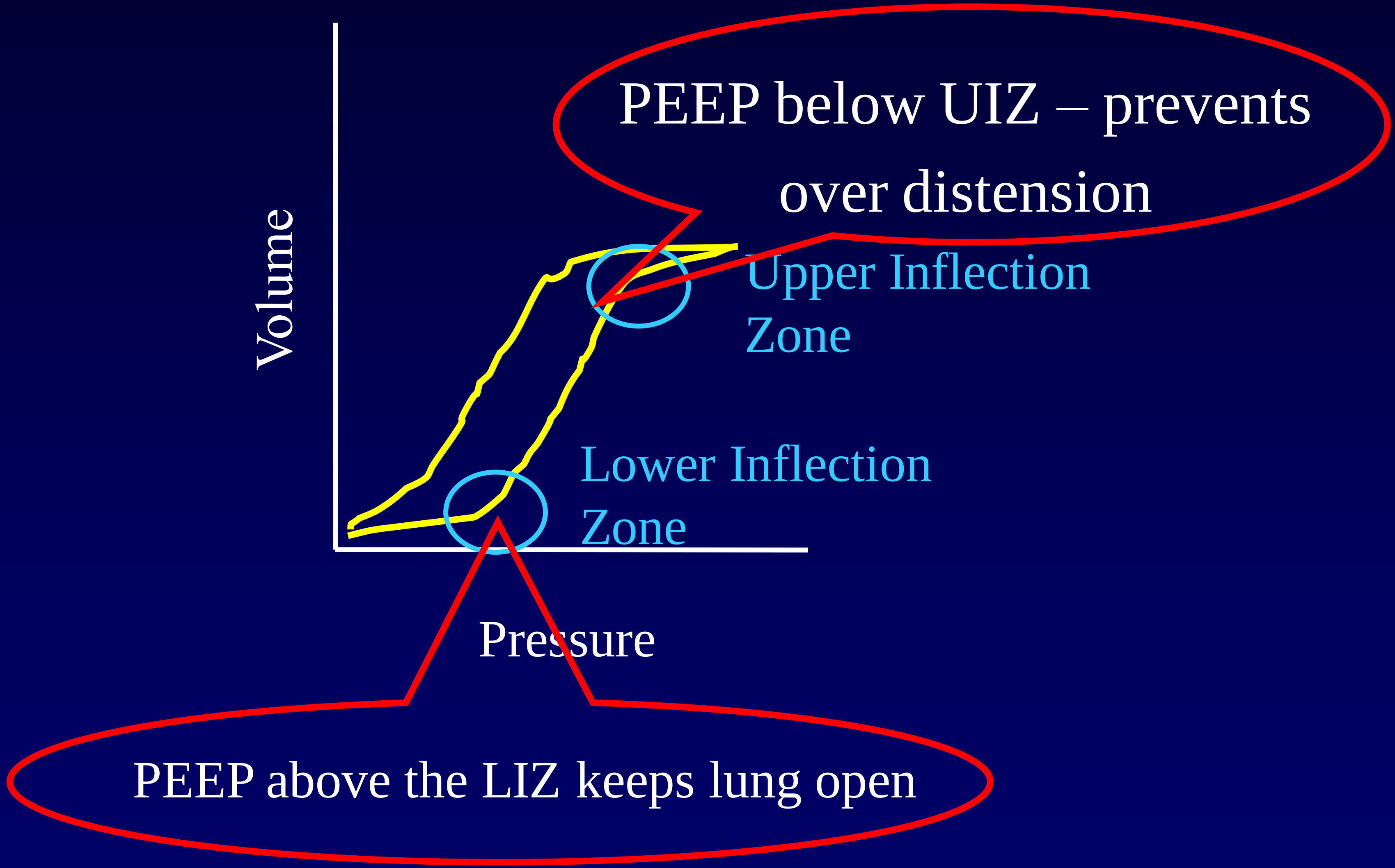

DELTA
Delta
Air Lines

ARDS: Ventilatory protocol



The Baby Lung concept

PEEP and PV curves



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*

High vs low PEEP: ALVEOLI trial

- 549 patients
- 6ml/kg TV, plateau pressure < 30 cm water
- Randomised to low or high PEEP.
- No difference in outcome.

Correct Level of PEEP: LOVE

Lung Open Ventilation Trial (Canada)

Primary endpoint: Hospital mortality

n=983, 30 centres
Inclusion: PF ratio <250

6 ml/kg VT

Plateau pressure <40 cm H_20 (LOVE)

Plateau pressure <30 cm H_20

Correct Level of PEEP: LOVE

Lung Open Ventilation Trial (Canada)

LOVE group developed less refractory hypoxaemia and had less ‘rescue’ therapies

No change in primary endpoint

Concluded that strategy was safe

Correct Level of PEEP: Express

Prospective RCT, 37 French ICUs

Primary endpoint: Death at 28 days

Inclusion: PF ratio <300

6 ml/kg VT

'Minimal distension' – PEEP 5-9 cm H_20

'Maximal recruitment' – PEEP increased to achieve plateau pressure 28-30 cm H_20

Correct Level of PEEP: Express

Improved oxygenation in the high PEEP group

Increased ventilator-free days and organ supported days in high PEEP group

No change in primary or secondary endpoints


BILLS
302

Correct Level of PEEP: Express

Subgroup analysis

In most hypoxic patients at start of trial there was improved mortality in the high PEEP group

??High PEEP in targeted groups??

High Frequency Oscillation (HFO)

- Oscar Trial – HTA funded UK mechanical ventilation tiral
- normal 6 mls/kg <30 cm H20 vs High Frequency Oscillation
- recruitment currently at well over 600 pts…target 802

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Comparison of Two Fluid-Management Strategies in Acute Lung Injury

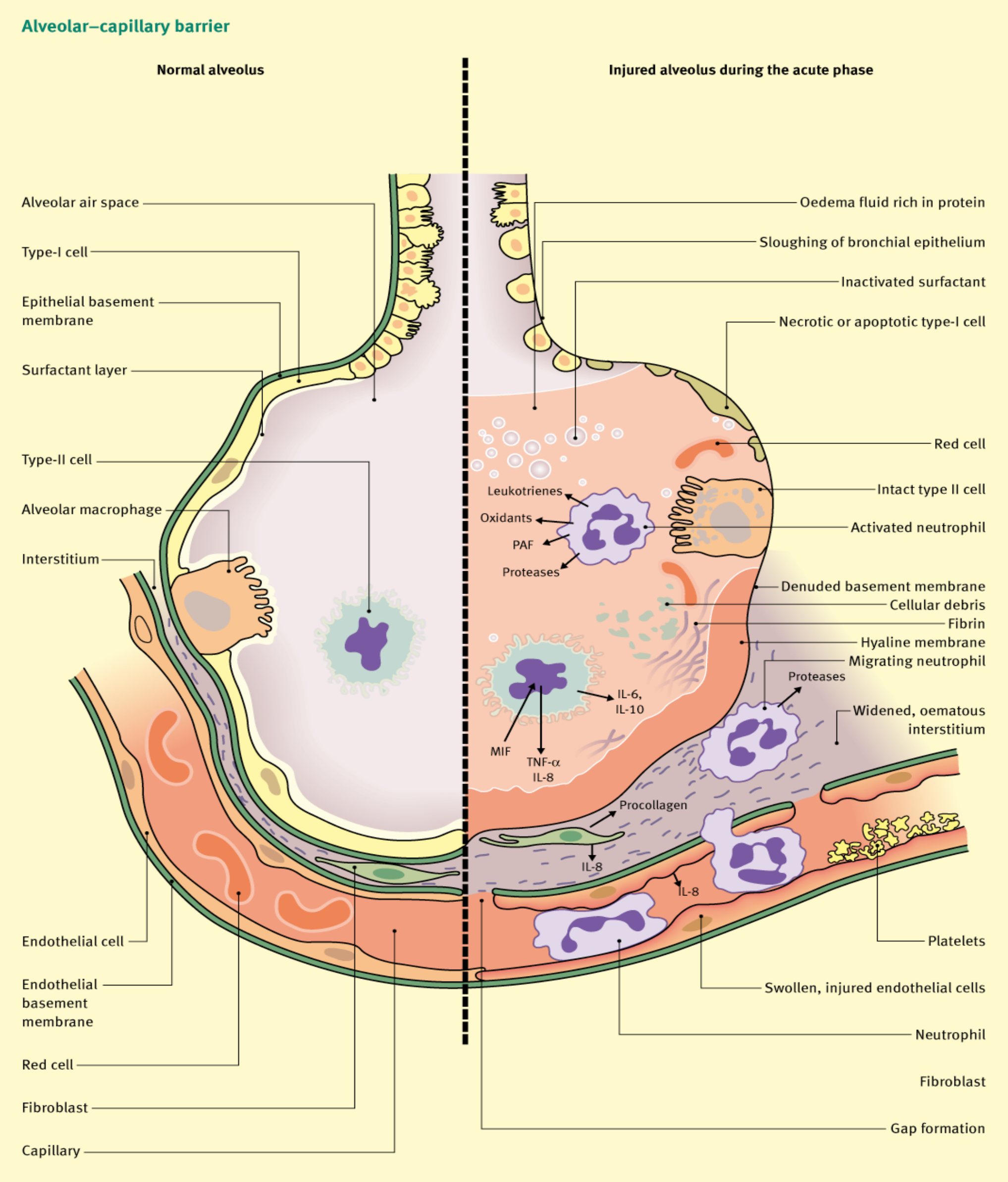
The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network*


GRILLADES
SANDWICHS
Ouvert Jour
LET'S HAVE ONE MORE
AND THEN WE'LL GO !!

Comparison of two fluid-management strategies

- Cumulative fluid balance during the first 7 days was:
  - 136+/-491 ml in the conservative group
  - 6992+/-502 ml in the liberal group ($P<0.001$).
- During first 28 days conservative strategy improved:
  - Oxygenation index [mean airway pressure x FiO_2/PaO_2 x 100]
  - Lung injury score
  - Ventilator-free days (14.6+/-0.5 vs. 12.1+/-0.5, $P<0.001$)
  - Days off ICU (13.4+/-0.4 vs. 11.2+/-0.4, $P<0.001$)
- Conservative group did not have any difference in:
  - Prevalence of shock
  - Use of dialysis

Pharmacological treatments????



PAF: Platelet-activating factor; TNF: Tumour necrosis factor; IL: Interleukin; MIF: Macrophage inhibitor factor

Source: Ware M. Medical progress: the acute respiratory distress syndrome. New Engl J Med 2000; 342: 1334–49. ©2000 Massachusetts Medical Society.

ARDS: successful treatments

- cisatracurium paralysis improves survival in early ARDS - ACURASYS trial . Papazian et al *NEJM*
- 340 patients - ARDS within 48 hours
- 90-day mortality 31.6% vs 40.7%, *P*=0.04.
- Confined to those with P/F ratio of <16.
- More ventilator-free time, less other organ failure
- Muscle weakness similar.

- May work by facilitating lung-protective ventilation.

ARDS: Steroids??

- No benefit in early ARDS
- Now no evidence it improves survival in late ARDS
  - It does speed extubation (more reintubations)
  - ? Increase CIPN
- No improvement or deterioration by 7 days
  - exclude infection
  - methylprednisolone 0.5 mg/kg QDS
  - reduce at 14 days and tail off from day 21 to 32
  - stop early (day 14) if non-responder

ARDS: other drugs

- Beta2 Agonists –BALTI 2 suspended
- Sildenafil – pulmonary hypertension and right heart failure
- *H*ydroxymethylglutaryl-CoA reductase inhibition with simvastatin in *A*cute lung injury to *R*educe *P*ulmonary dysfunction – The HARP-2 Trial
- Interferon Beta – Boosting endothelial CD73 and reducing lung leak – The Faron Trial

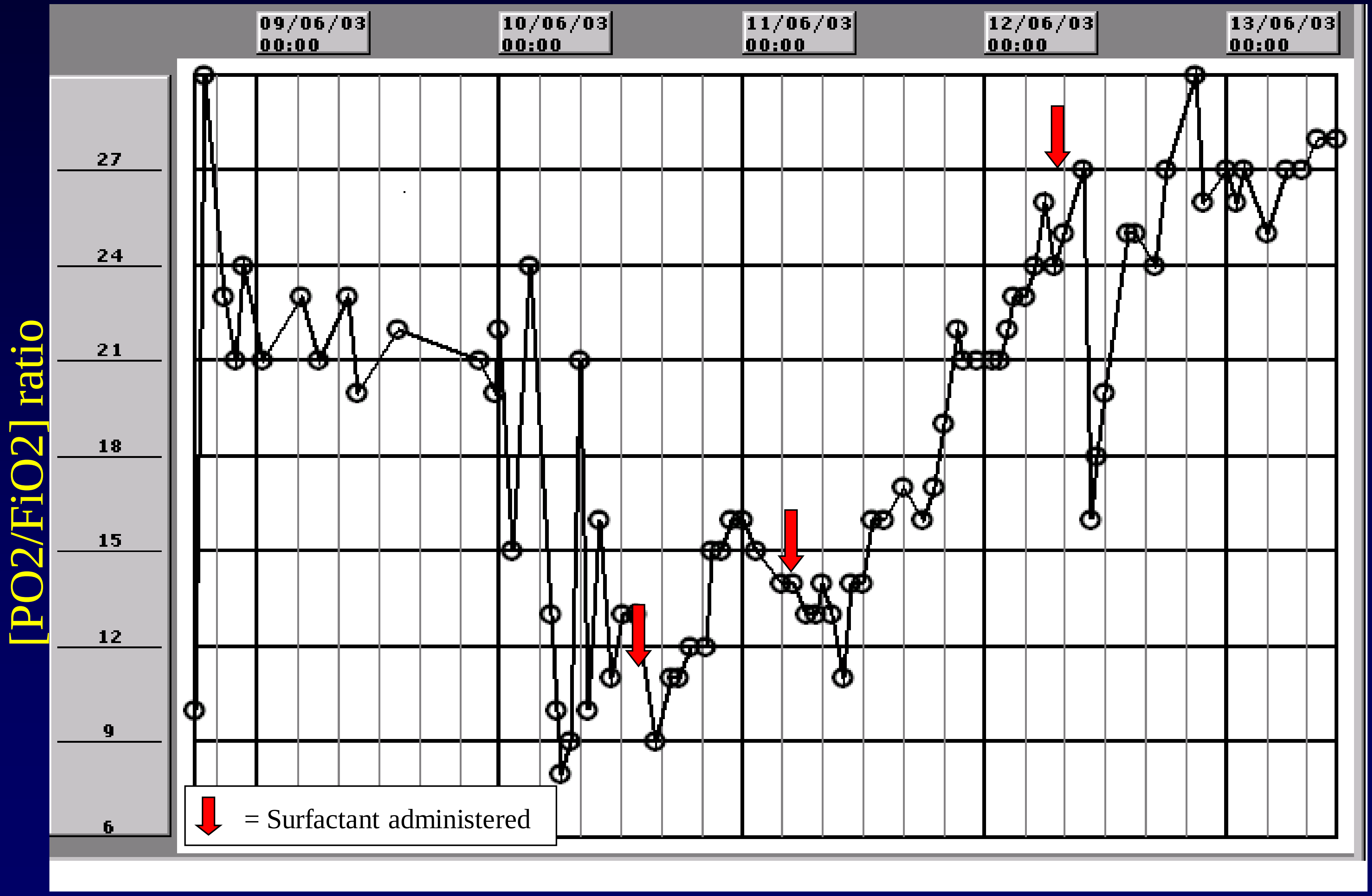
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Recombinant Surfactant Protein C–Based Surfactant on the Acute Respiratory Distress Syndrome

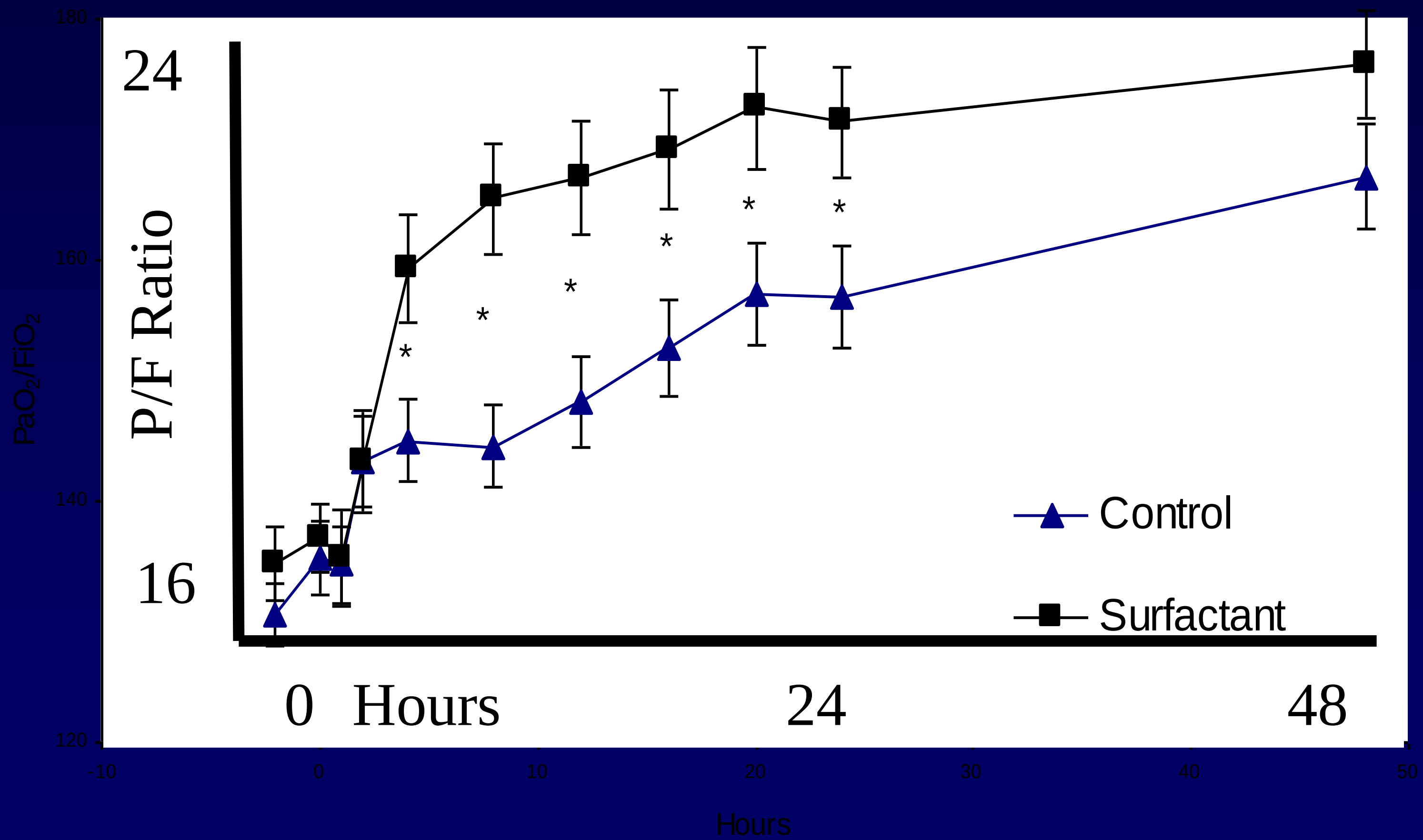
Roger G. Spragg, M.D., James F. Lewis, M.D., Hans-Dieter Walmrath, M.D., Jay Johannigman, M.D., Geoff Bellingan, M.D., Pierre-Francois Laterre, M.D., Michael C. Witte, M.D., Guy A. Richards, M.D., Gerd Rippin, Ph.D., Frank Rathgeb, M.D., Dietrich Häfner, M.D., Friedemann J.H. Taut, M.D., and Werner Seeger, M.D.

[PO_2/FiO_2] ratio / time

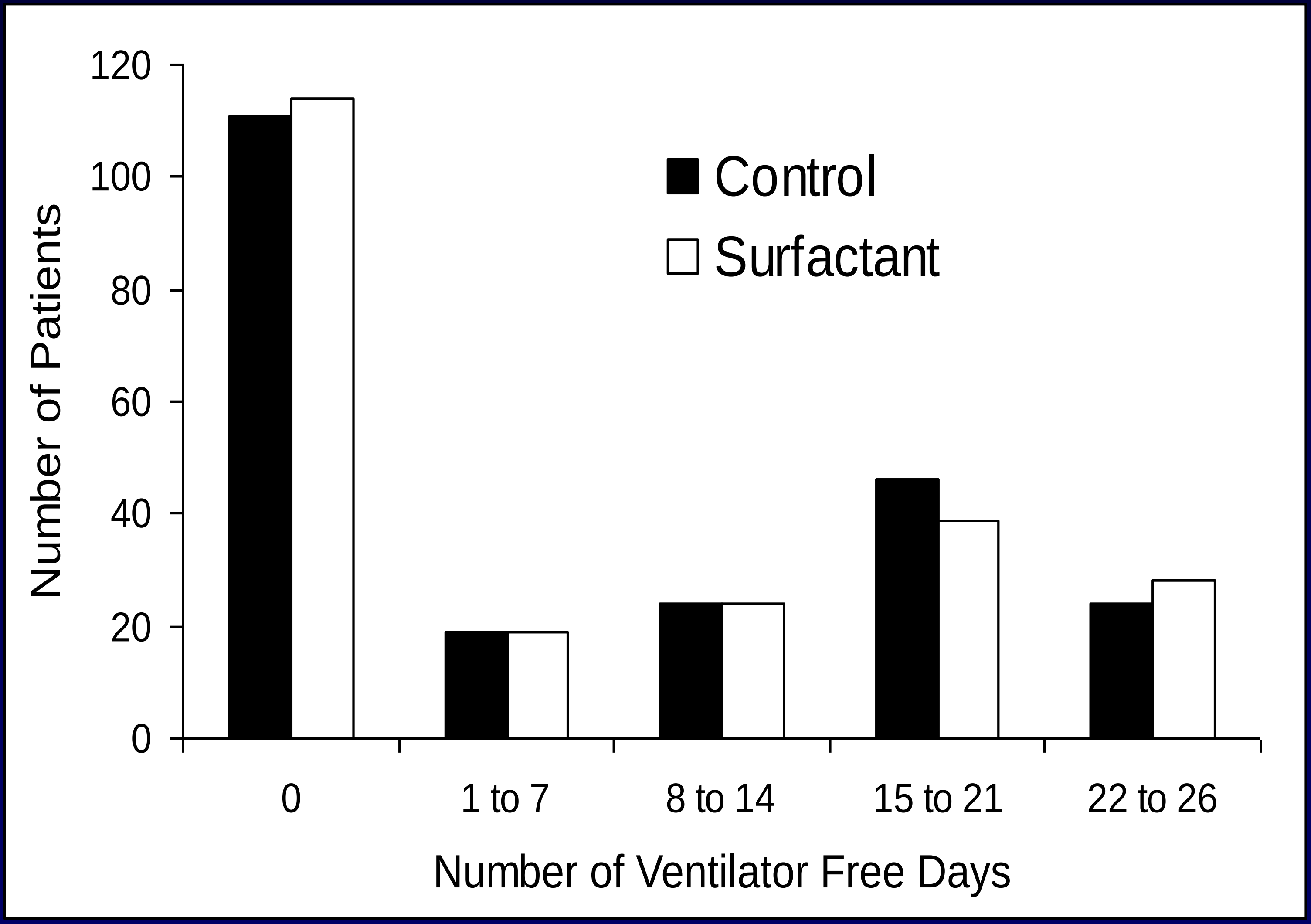


Venticute Surfactant Trial: Outcome *2)* Oxygenation

Treatment with surfactant increased significantly the area under the PaO_2/FiO_2 vs. time curve



Venticute Surfactant Trial: Outcome *1)*
Ventilator Free days



Negative Trials

- NO
- Continuous rotation
- Prostaglandin Inhibitors (Ketoconazole, Ibuprofen)
- Antioxidants (N-acetyl cysteine, procysteine, free radical scavengers)
- Almitrine

Not sure

- ECMO
- Oscillation
- Continuous supraglottic aspiration?