Beyond LTV ventilation in ARDS ?

Arjun Srinivasan

Has Mortality from Acute Respiratory Distress Syndrome Decreased over Time?

A Systematic Review

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Rationale: It is commonly stated that mortality from acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) is decreasing.
Objectives: To systematically review the literature assessing ARDS mortality over time and to determine patient- and study-level factors independently associated with mortality.
Methods: We searched multiple databases (MEDLINE, EMBASE, CINAHL, Cochrane CENTRAL) for prospective observational studies or randomized controlled trials (RCTs) published during the period 1984 to 2006 that enrolled 50 or more patients with ALI/ARDS and reported mortality. We pooled mortality estimates using random-effects meta-analysis and examined mortality trends before and after 1994 (when a consensus definition of ALI/ARDS was published) and factors associated with mortality using meta-regression models.
Measurements and Main Results: Of 4,966 studies, 89 met inclusion criteria (53 observational, 36 RCTs). There was a total of 18,900 patients (mean age 51.6 years; 39% female). Overall pooled weighted mortality was 44.3% (95% confidence interval [CI], 41.8–46.9). Mortality decreased with time in observational studies conducted before 1994; no temporal associations with mortality were demonstrated in RCTs (any time) or observational studies (after 1994). Pooled mortality from 1994 to 2006 was 44.0% (95% CI, 40.1–47.5) for observational studies, and 36.2% (95% CI, 32.1–40.5) for RCTs. Meta-regression identified study type (observational versus RCT, odds ratio, 1.36; 95% CI, 1.08–1.73) and patient age (odds ratio per additional 10 yr, 1.27; 95% CI, 1.07–1.50) as the only factors associated with mortality.
Conclusions: A decrease in ARDS mortality was only seen in observational studies from 1984 to 1993. Mortality did not decrease between 1994 (when a consensus definition was published) and 2006, and is lower in RCTs than observational studies.

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

It is commonly stated and assumed that mortality from acute respiratory distress syndrome (ARDS) is decreasing.

What This Study Adds to the Field

We found that mortality from ARDS has not decreased substantially since the publication of a consensus definition in 1994. Based on our findings, a baseline mortality risk from ARDS of 40 to 45% for observational studies and 35 to 40% for randomized control trials should be expected. These results highlight the need for future effective therapeutic interventions for this highly lethal syndrome.

mortality from ALI/ARDS has decreased since the initial case descriptions (1–3, 5, 6), and overall mortality in recent large randomized controlled trials (RCTs) in patients with ALI/ARDS has been approximately 30% (7–10), significantly lower than previously reported (11–13). In fact, it has been suggested that a mortality of 25 to 30% should now be the reference standard for subsequent clinical trials and clinical practice in ALI/ARDS (14).

The claim that mortality in ARDS has decreased is contro-

Etiology and Outcomes of Pulmonary and Extrapulmonary Acute Lung Injury/ARDS in a Respiratory ICU in North India*

Ritesh Agarwal, DM; Ashutosh N. Aggarwal, DM, FCCP; Dheeraj Gupta, DM, FCCP; Digamber Behera, MD, FCCP; and Surinder K. Jindal, MD, FCCP

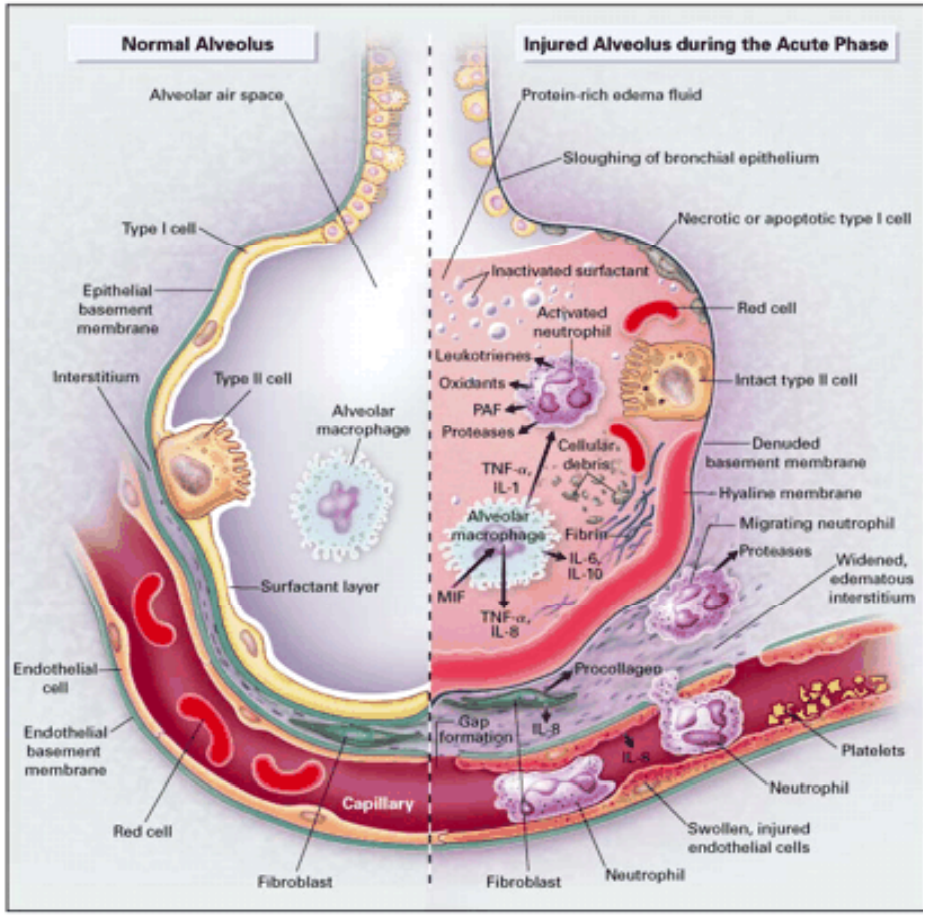
Objective: Outcomes in patients with ARDS/acute lung injury (ALI) may be dependent on the underlying cause. We describe the case mix, clinical behavior, and outcomes of patients with ALI/ARDS resulting from pulmonary causes (ALI/ARDSp) and extrapulmonary causes (ALI/ARDSexp).
Design: Retrospective study conducted between January 2001 and June 2005.
Setting: Respiratory ICU (RICU) of a tertiary care hospital in northern India.
Patients: All patients fulfilling the criteria for ALI/ARDS and requiring mechanical ventilation for > 24 h.
Measurements and results: Of the 180 patients (ARDS, 140 patients; ALI, 40 patients), 123 patients had ALI/ARDSp, whereas 57 patients had ALI/ARDSexp. The most common cause of ALI/ARDSp was infective pneumonia, whereas the most common cause of ALI/ARDSexp was sepsis. At ICU admission, although patients with ALI/ARDSexp were sicker than those with ALI/ARDSp, there was no difference between the two groups of patients in the development of new organ dysfunction/failure (Δ sequential organ failure assessment [SOFA] scores) or the time to develop the first organ dysfunction/failure (assessed by SOFA scores). The median length of RICU stay was similar in the two groups (5 days [interquartile range (IQR), 6 days] vs 5 days [IQR, 9.5 days], respectively, in patients with ALI/ARDSp and ALI/ARDSexp; $p = 0.4$). The hospital mortality rate was 47.8% and was not significantly different between the two groups (ALI/ARDSp group, 43.1%; ALI/ARDSexp group, 57.9%; $p = 0.06$). Multivariate analysis showed the following risk factors for death in the ICU: female gender (odds ratio [OR], 0.49; 95% confidence interval [CI], 0.25 to 0.94); SOFA scores (OR, 1.18; 95% CI, 1.07 to 1.3); and ΔSOFA scores (OR, 1.24; 95% CI, 1.09 to 1.41). There was no significant effect of the category of ARDS on outcome (OR, 1.6; 95% CI, 0.8 to 3.2).
Conclusions: Although patients with ALI/ARDSexp are sicker on ICU admission, the underlying cause of ARDS does not affect the length of ICU stay or hospital survival time.

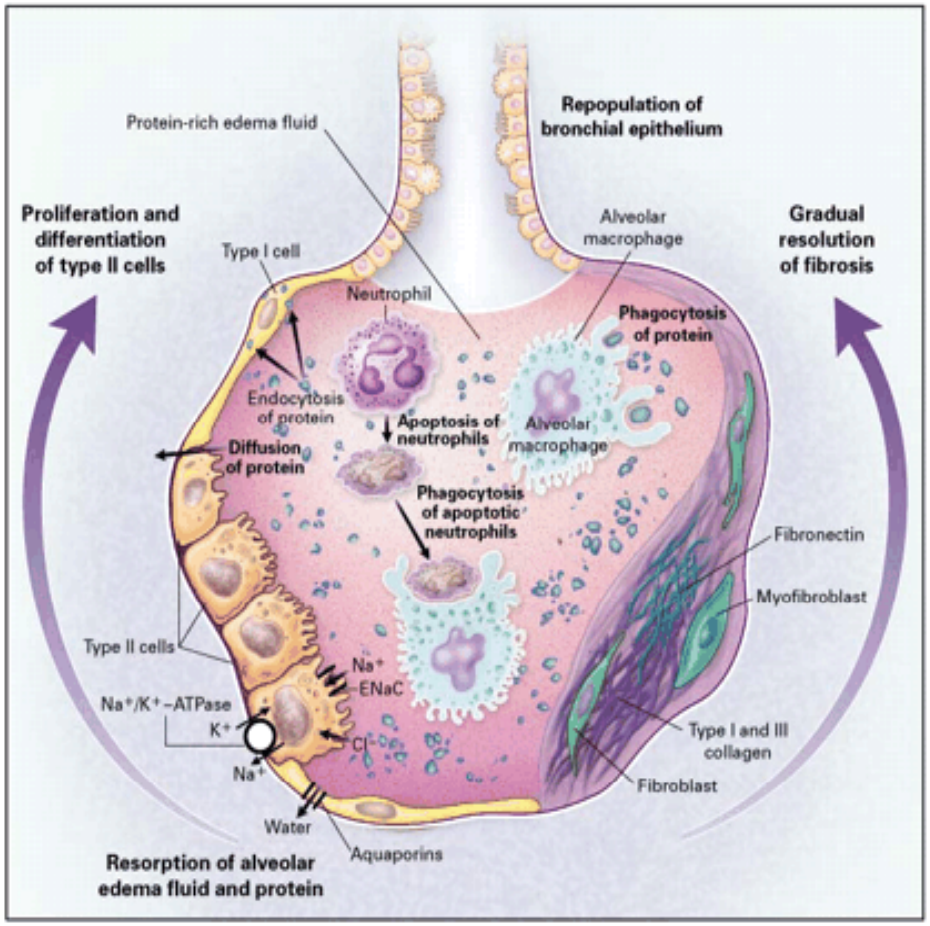
(CHEST 2006; 130:724–729)

Can we do anything more?

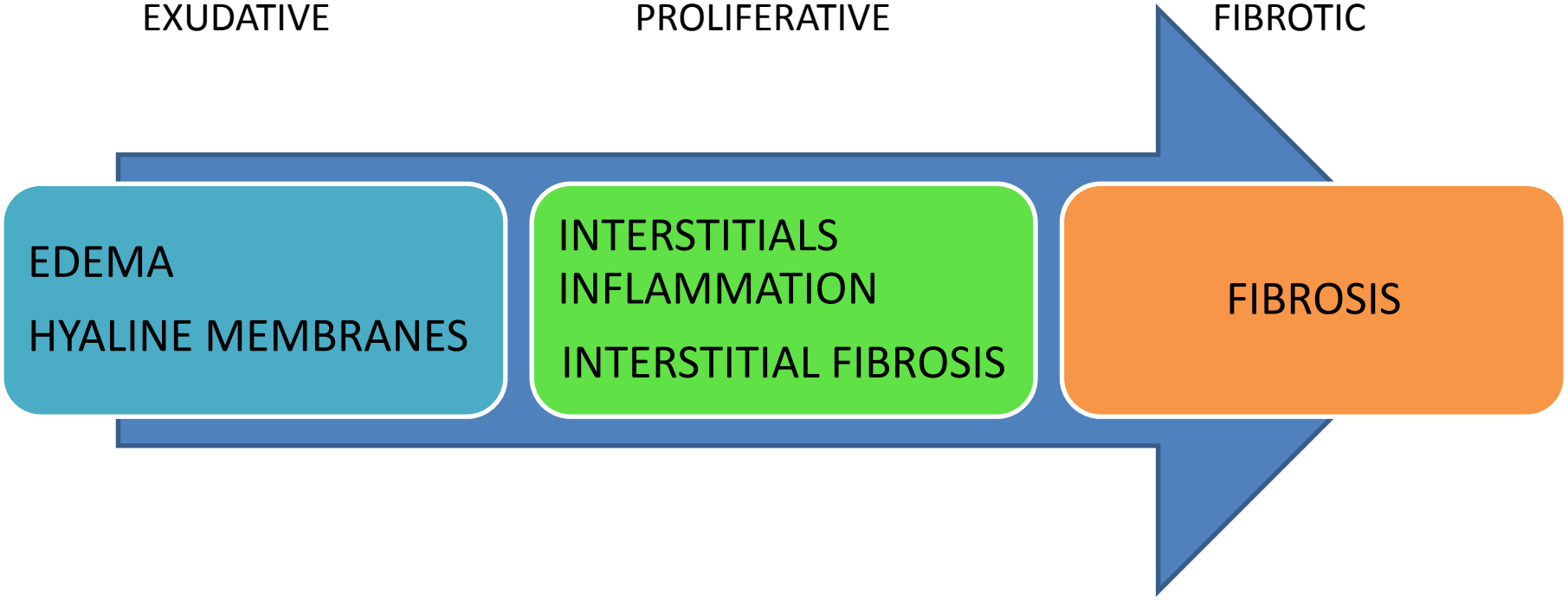
- Non ventilatory
  - Drugs
  - Fluid management
  - Nutritional supplementation
- Ventilatory
  - Understanding & implementing respiratory mechanics
  - Newer & exotic modes

Pathophysiology





The NEJM 5/2000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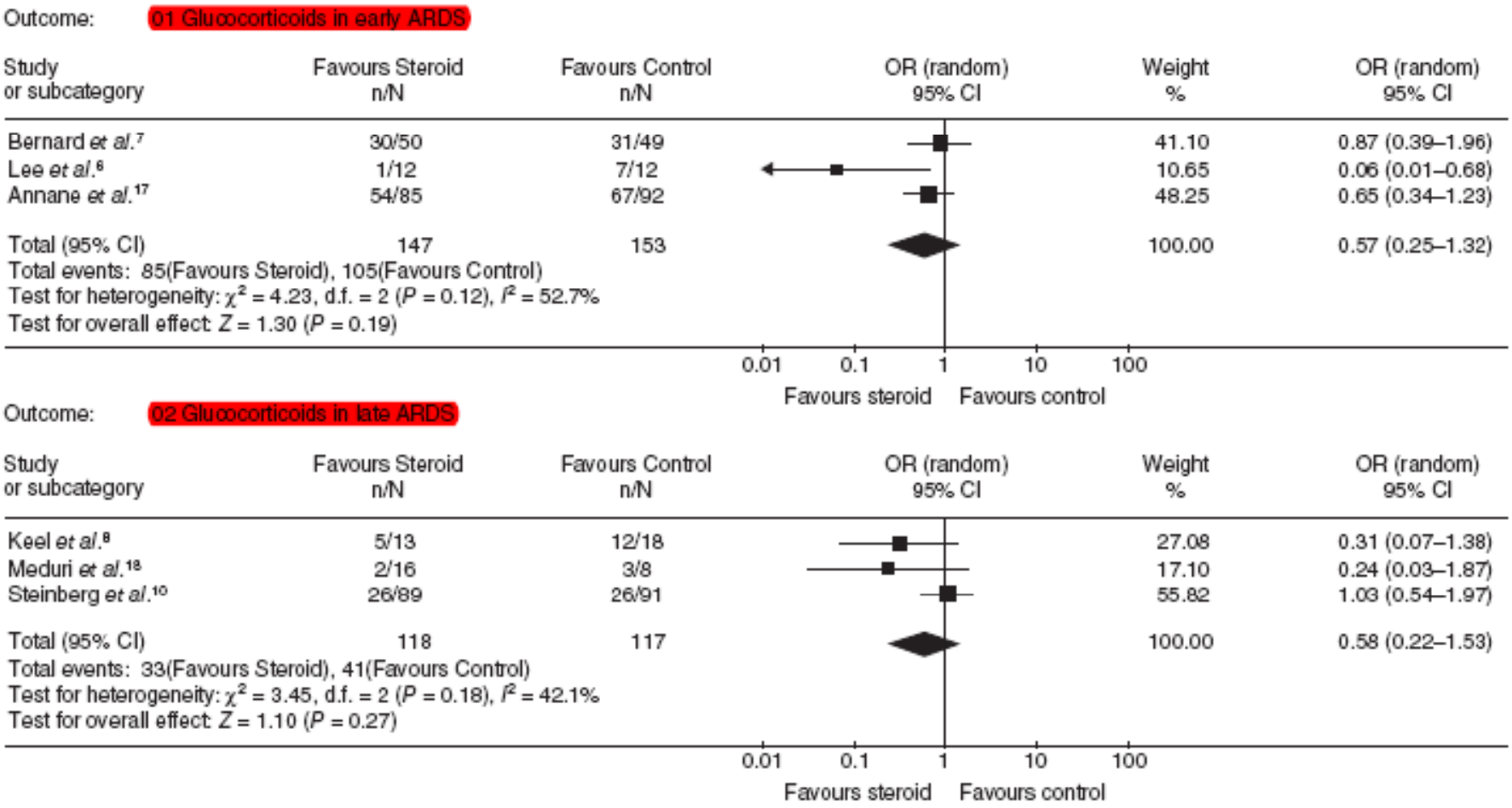


Figure 2 Forest plots showing that glucocorticoids do not decrease the mortality in patients with early and late ARDS (odds ratio (OR), 95% confidence intervals (CI); random effects model).

Methylprednisolone Infusion in Early Severe ARDS*

Results of a Randomized Controlled Trial

Objective: To determine the effects of low-dose prolonged methylprednisolone infusion on lung function in patients with early severe ARDS.
Design: Randomized, double-blind, placebo-controlled trial.
Setting: ICUs of five hospitals in Memphis.
Participants: Ninety-one patients with severe early ARDS (≤ 72 h), 66% with sepsis.
Interventions: Patients were randomized (2:1 fashion) to methylprednisolone infusion (1 mg/kg/d) vs placebo. The duration of treatment was up to 28 days. Infection surveillance and avoidance of paralysis were integral components of the protocol.
Main outcome measure: The predefined primary end point was a 1-point reduction in lung injury score (LIS) or successful extubation by day 7.
Results: In intention-to-treat analysis, the response of the two groups (63 treated and 28 control) clearly diverged by day 7, with twice the proportion of treated patients achieving a 1-point reduction in LIS (69.8% vs 35.7%; p = 0.002) and breathing without assistance (53.9% vs 25.0%; p = 0.01). Treated patients had significant reduction in C-reactive protein levels, and by day 7 had lower LIS and multiple organ dysfunction syndrome scores. Treatment was associated with a reduction in the duration of mechanical ventilation (p = 0.002), ICU stay (p = 0.007), and ICU mortality (20.6% vs 42.9%; p = 0.03). Treated patients had a lower rate of infections (p = 0.0002), and infection surveillance identified 56% of nosocomial infections in patients without fever.
Conclusions: Methylprednisolone-induced down-regulation of systemic inflammation was associated with significant improvement in pulmonary and extrapulmonary organ dysfunction and reduction in duration of mechanical ventilation and ICU length of stay.

(CHEST 2007; 131:954–963)

Conclusions

- Current evidence does not support routine use steroids in early or late ARDS

- Sub-group of early ARDS with septic shock, between 7 – 14 days of ventilation may benefit but further studies needed before routine use can be recommended

N -acetylcystiene

- NAC is a precursor for glutathione (GSH), an antioxidant present in significant levels in the normal lung
- Lavage from patients with ALI/ARDS is deficient in GSH
- NAC also has direct anti-oxidant properties
- Experimental animal studies had shown significant improvement

NAC in ALI/ARDS

Study, yr	No. of Patients	Therapy	Outcome
Jepsen, 1992	66	Placebo, NAC	No effect – Pao_2/Fio_2 time to improve LIS. Improve – compl.*NS. **Mortality – No diff**
Suter 1994	61	Placebo, NAC	Improve – Pao_2/Fio_2; Lis; need for M.V. **Mortality – No diff**
Bernard 1997	48	Placebo, NAC OTZ	Improve – ALI free days & cardiac index ↓ new organ failure. **Mortality – No diff**
Domenighetti 1997	42	Placebo, NAC	Improved – LIS **No effect – Pao_2/Fio_2, mortality**

Effect of NO on Oxygenation

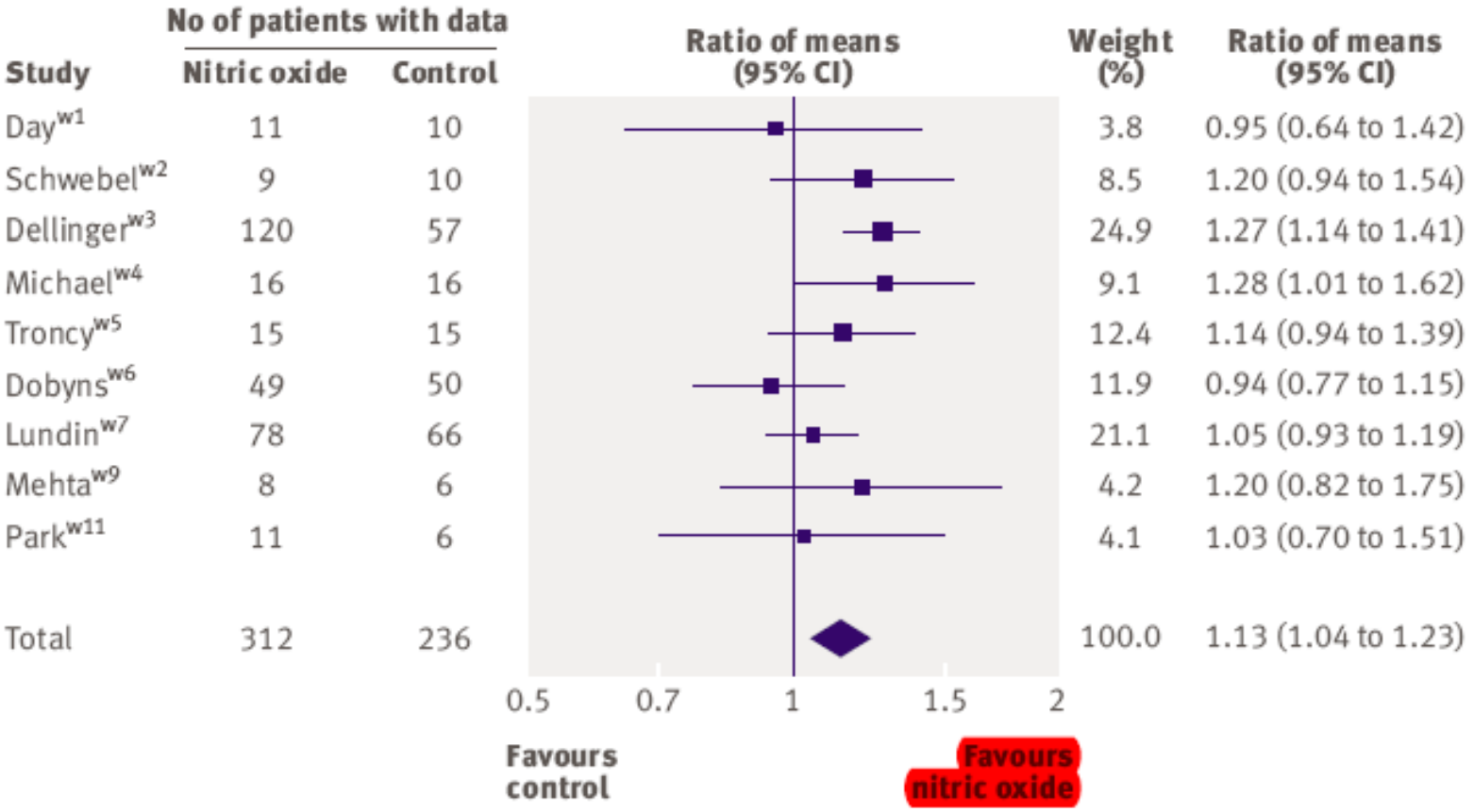


Fig 4 | Effect of nitric oxide on PaO_2/FiO_2 ratio at 24 hours. Weight is the relative contribution of each study to overall estimate of treatment effect (ratio of means, nitric oxide relative to control) on log scale assuming a random effects model. For some trials, number of patients with data is less than number randomised

BMJ 2007;334;779

Effect on mortality

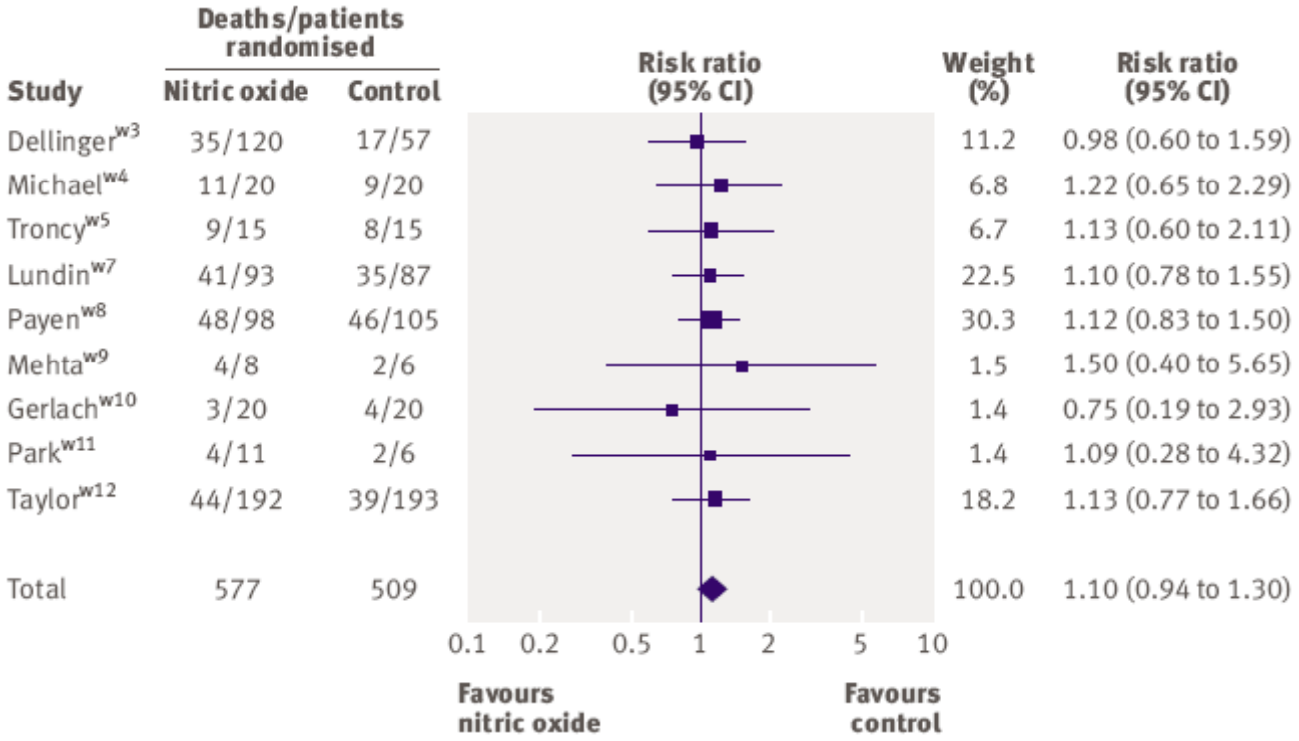
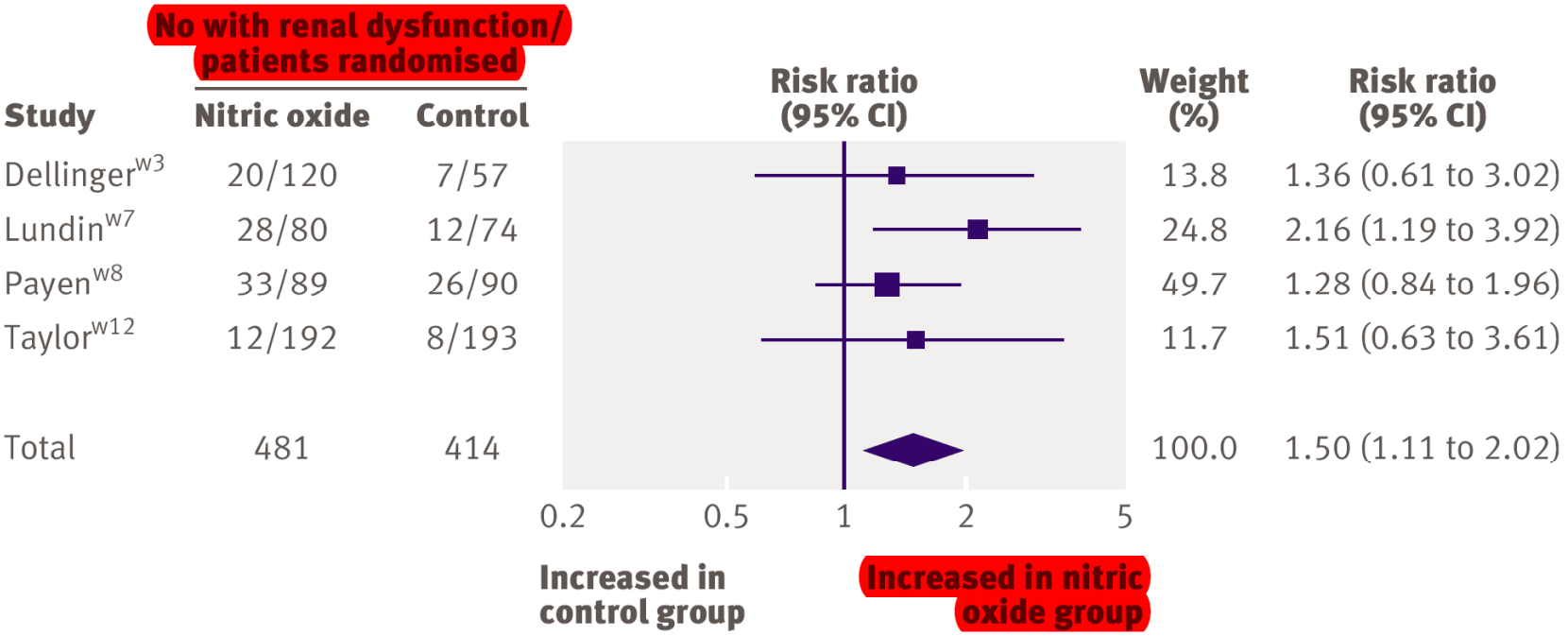


Fig 2 | Effect of nitric oxide on mortality. Weight is the relative contribution of each study to the overall estimate of treatment effect on a log scale assuming a random effects model. Two trials with ≥50% of control patients crossing over to nitric oxide also reported mortality data.[w2 w6] Inclusion of these trials did not alter summary mortality estimate (risk ratio 1.09, 0.94 to 1.27)

BMJ 2007;334;779

Adverse events

- Renal dysfunction



- No significant increase in methhemoglobinaemia

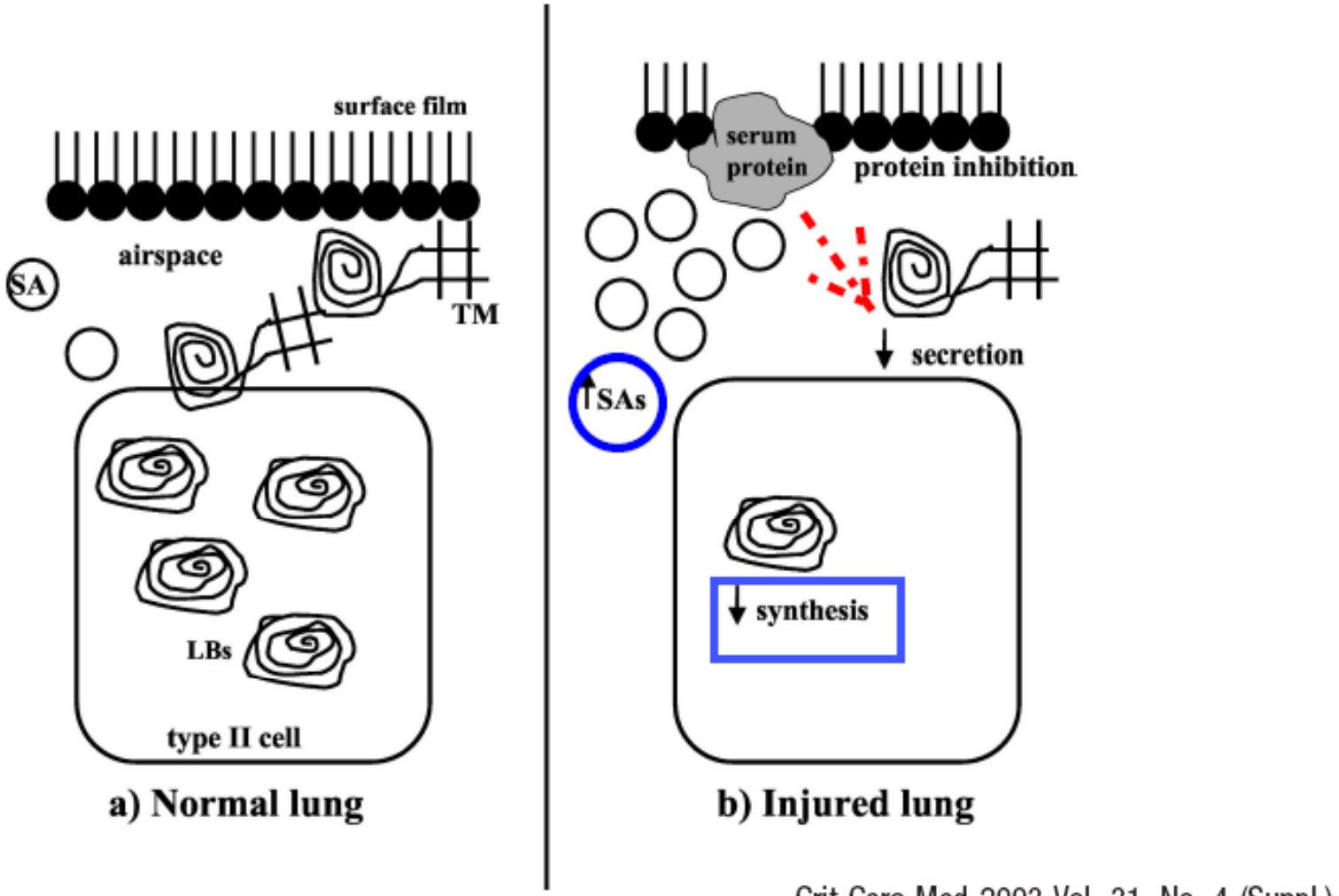
BMJ 2007;334;779

Summary

- Consistent improvement in oxygenation
- No effect on mortality
- Potential for acute renal shutdown

Not recommended for routine use in ARDS Mx

Surfactant



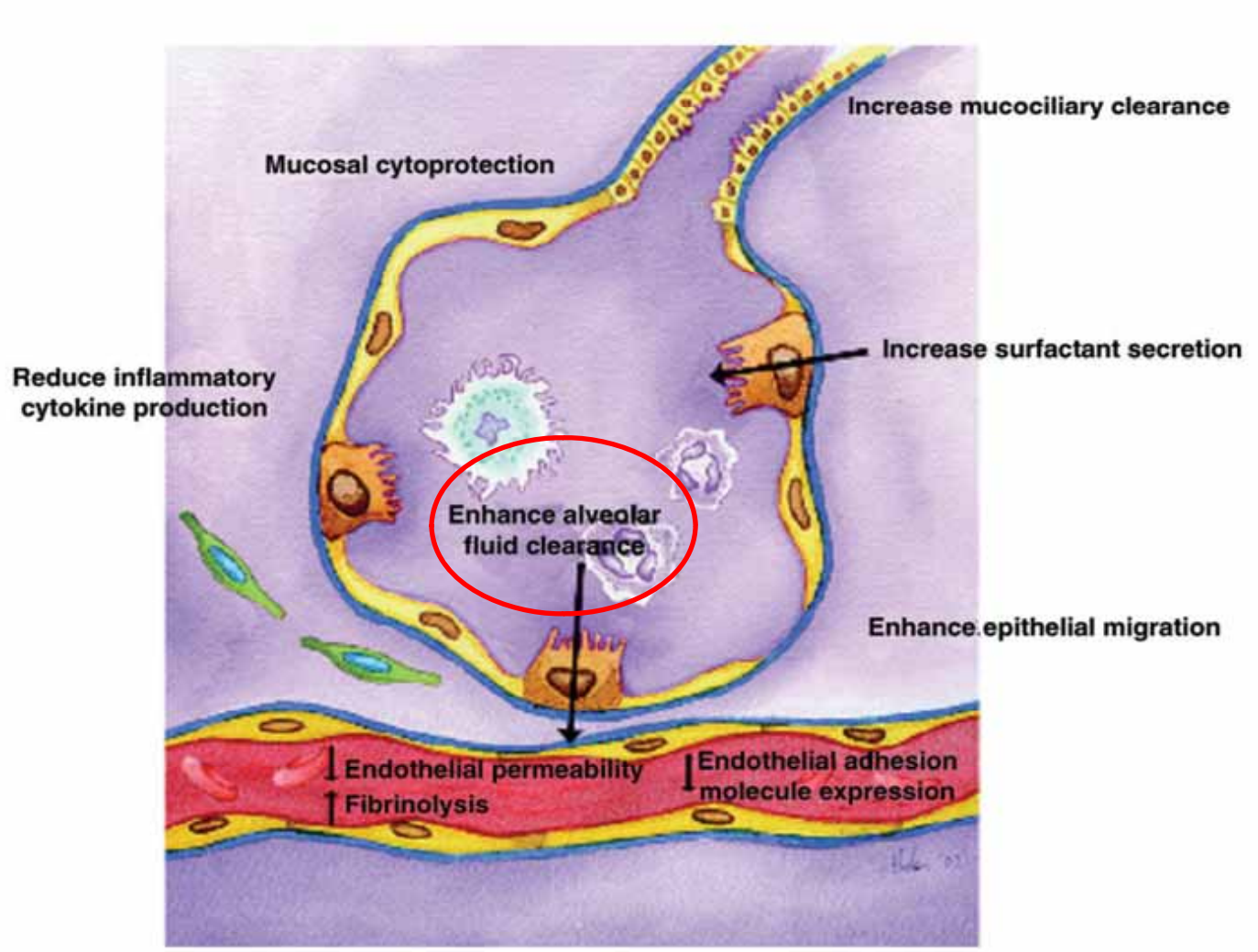
Crit Care Med 2003 Vol. 31, No. 4 (Suppl.)

Evidence from clinical trials

Study, yr	No. of Patients	Therapy	Outcome
Anzueto A,1996	725	Placebo, aerosolized surf - 5 days	No effect vent free days, **Mortality – No diff**
Gregory TJ, 1997	59	Placebo, inhaled survanta diff doses - 28 days	**Mortality – decreased in mid dose group**
Spragg R,2001	448	Placebo, aerosolised venticure	Improve – oxygenation, no change vent free days **Mortality – No diff**

Not recommended for routine use, but is safe

B agonist in ARDS



The effects of β-agonists on epithelial and endothelial function.

Critical Care 2004, **8**:25-32

Selected studies of alveolar fluid clearance by beta agonists

Study	Model	Beta-2 agonist	Effect
Sartori and colleagues, 2002 [43]	High-altitude edema in humans	Salmeterol	+
Ware and colleagues, 2002 [61]	Human donor lung	Terbutaline	+
Sakuma and colleagues, 1994 [29]	Resected human lung	Terbutaline	+
Atabai and colleagues, 2002 [45]	Ventilated patients (ARDS)	Albuterol	+
Sakuma and colleagues, 1997 [62]	*Ex vivo* human and rat	Salmeterol	+
Suzuki and colleagues, 1995 [63]	Cultured rat alveolar type II	Terbutaline	+
Minakata and colleagues, 1998 [36]	Cultured rat alveolar type II	Terbutaline	+
Planes and colleagues, 2002 [37]	Cultured rat alveolar type II	Terbutaline	+
Icard and Saumon, 1999 [64]	Mice	Terbutaline	+
Tibayan and colleagues, 1997 [27]	Rats	Dobutamine	+
Barnard and colleagues, 1997 [28]	Rats	Dopamine	+
Charron and colleagues, 1999 [65]	Rats	Epinephrine	+
Saldias and colleagues, 1999 [34]	Rats	Isoproterenol	+
Morgan and colleagues, 2002 [39]	Rats	Prolonged isoproterenol	–
Lasnier and colleagues, 1996 [66]	Rats	Terbutaline	+
Norlin and colleagues, 2001 [31]	Rats	Terbutaline	+
Jayr and colleagues, 1994 [30]	Rats	Terbutaline	+
Saldias and colleagues, 2000 [67]	Rats	Terbutaline + isoproterenol	+
Pittet and colleagues, 1994 [12]	Rats	Epinephrine	+
	Rabbit	Epinephrine	–
Smedira and colleagues, 1991 [68]	Rabbit	Terbutaline	–
Effros and colleagues, 1987 [69]	Rabbit	Terbutaline	–
Campbell and colleagues, 1999 [70]	Sheep	Salmeterol	+
Berthiaume and colleagues, 1987 [71]	Sheep	Terbutaline	+
Berthiaume and colleagues, 1988 [72]	Sheep (faster) > dog	Terbutaline	+
Frank and colleagues, 2000 [35]	Sheep and rats	Salmeterol	+
Grimme and colleagues, 1997 [73]	Dogs	Terbutalir	
Sugita and colleagues, 2003 [74]	Transplanted dogs	Terbutaline	–

Selected studies of anti-inflammatory effects of beta agonists in acute lung injury

Study	Model	Treatment	Effect
Perkins and colleagues, 2003 [54]	Human neutrophils	Salbutamol	Inhibited chemotaxis
Sekut and colleagues, 1995 [47]	Lipopolysaccharide-activated THP1 cells	Salmeterol, salbutamol	Inhibited TNF-α
Dhingra and colleagues, 2001 [46]	Murine sepsis	Dobutamine, dopexamine	Attenuated inflammatory cytokine expression and chemokines induction
Van der Poll and colleagues, 1994 [48]	Lipopolysaccharide-stimulated macrophages	Norepinephrine	Decreased TNF-α, IL-6
Van der Poll and Lowry, 1997 [49]	Human endotoxemia	Epinephrine	Increased IL-10

TNF-α, tumor necrosis factor alpha.

Selected studies of bronchodilator effects of beta agonists in acute lung injury

Study	Cohort	Treatment	Effect
Morina and colleagues, 1997 [56]	Human ARDS	Salbutamol	Decreased airway resistance, increased compliance
Pesenti and colleagues, 1993 [55]	Human ARDS	Salbutamol	Decreased airway resistance
Wright and colleagues, 1994 [57]	Human ARDS	Metoproterenol	Decreased airway resistance

ARDS, acute respiratory distress syndrome.

The β-Agonist Lung Injury Trial (BALTI)

A Randomized Placebo-controlled Clinical Trial

Rationale: Experimental data suggest that manipulation of alveolar fluid clearance with β-agonists can accelerate the resolution of alveolar edema and improve survival.

Objective: To determine if a sustained infusion of intravenous salbutamol (albuterol) would accelerate the resolution of alveolar edema in adult patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS).

Methods: This was a single-center, double-blind, randomized controlled trial. Patients with ALI/ARDS were randomized to treatment with intravenous salbutamol (15 $\mu g\ kg^{-1}\ h^{-1}$) or placebo for 7 d. The primary endpoint was extravascular lung water measured by thermodilution (PiCCO) at Day 7.

Measurements and Main Results: Sixty-six patients were screened; of these, 40 met the inclusion criteria and were enrolled during 2001–2003. Patients in the salbutamol group had significantly lower lung water at Day 7 than the placebo group (9.2 ± 6 vs. 13.2 ± 3 ml kg^{-1}; 95% confidence interval difference, 0.2–8.3 ml kg^{-1}; $p = 0.038$). Plateau airway pressure was lower at Day 7 in the salbutamol group (23.9 ± 3.8 cm H_2O) versus placebo (29.5 ± 7.2 cm H_2O; $p = 0.049$). There was a trend toward lower Murray lung injury score at Day 7 in the salbutamol group (1.7 ± 0.9) versus placebo (2.0 ± 0.6; $p = 0.2$). Patients in the salbutamol group had a higher incidence of supraventricular arrhythmias (26 vs. 10%; $p = 0.2$).

Conclusion: Although further research is required to confirm the efficacy and safety of intravenous salbutamol in ALI/ARDS, this trial provides the first proof of principle that, in humans with ALI/ARDS, sustained treatment with intravenous β-agonists reduces extravascular lung water.

Am J Respir Crit Care Med Vol 173. pp 281–287, 2006

Ketoconazole in ARDS

Study, yr	No. of Pat.	Outcome
Slotmann, 1988	71 high risk surgical	Reduced Incidence of ARDS, ICU stay, cost **No mortality benefit**
Yu & Tomasa, 1993	54 sepsis	Reduced incidence of ARDS **lower mortality**
NIH ARDS Network, 1997 Trial	234 ALI/ARDS	**No mortality benefit** No effect on lung function or duration of Ventilation

The list continues…

- More vasodilators
  - Prostacyclin, prostaglandin E_1, Dazoxiben, Pentoxyphylline
- Anti inflammatory agents
  - Indomethacin, Ibuprofen, lisofylline
- Immunomodulators
  - GM- CSF, Recombinant superoxide dismutase
- Immunonutrients
  - Fish oils, Gamma-linolenic acid, Vit C & E

Future beholds…

- Anticoagulants
  - APC, TFPI
- Inhibition of NF-KB
- Endothelin receptor antagonist
  - Tezosentan
- Anti cytokine therapy
  - Anti IL-8, IL 10, IL 1, TNF alpha
- Stem cell therapy

Pharmacotherapy in ARDS

No mortality benefit

Fluid therapy in ARDS

Table 1—*Pulmonary Outcomes and Physiologic Variables in the FACTT

Variables	Fluid Management		p Value†
	Conservative Group	Liberal Group	
Ventilator-free days, No.	14.6 ± 0.5	12.1 ± 0.5	< 0.001
PEEP, cm H_2O	7.5 ± 0.3	8.2 ± 0.2	0.008
Plateau pressure, cm H_2O	24.2 ± 0.6	25.7 ± 0.5	0.002
Pao_2/Fio_2	198 ± 8	183 ± 6	0.07
Oxygenation index‡	10.1 ± 0.8	11.8 ± 0.7	0.003
Lung injury score§	2.03 ± 0.07	2.27 ± 0.06	< 0.001

Table 2—*Simplified Algorithm for Conservative Management of Fluids in Patients With ALI, Based on Protocol Used in the FACTT

CVP, mm Hg (Recommended)	PAOP, mm Hg (Optional)	MAP ≥ 60 mm Hg and Not Receiving Vasopressors for ≥ 12 h	
		Average Urine Output < 0.5 mL/kg/h	Average Urine Output ≥ 0.5 mL/kg/h
≥ 8	> 12	Furosemide†; reassess in 1 h	Furosemide; reassess in 4 h
4–8	8–12	Fluid bolus as fast as possible‡; reassess in 1 h	Furosemide; reassess in 4 h
< 4	< 8	Fluid bolus as fast as possible‡; reassess in 1 h	No intervention; reassess in 4 h

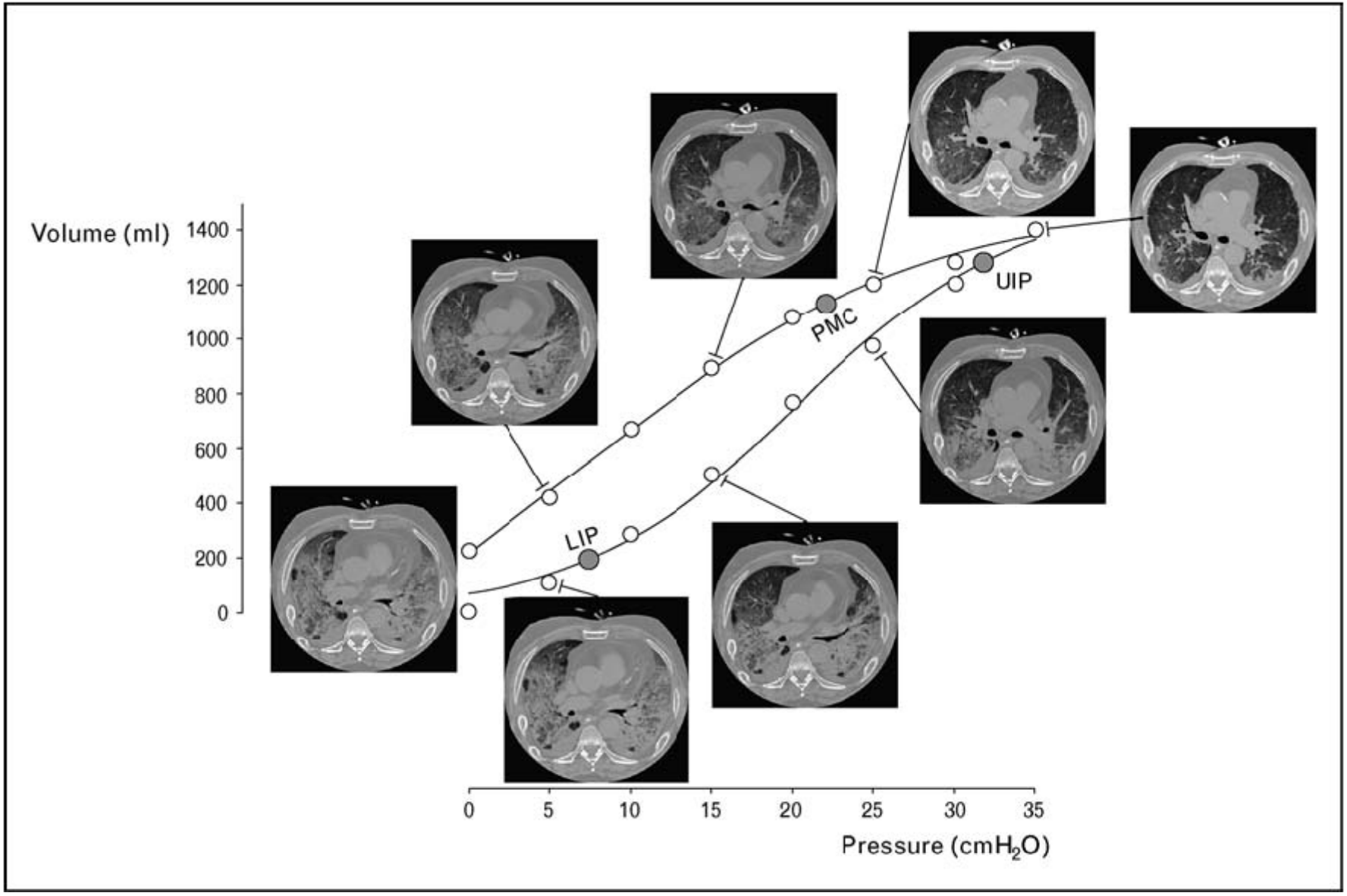
(CHEST 2007; 131:913–920)

Ventilatory strategies

Steps in recruitment

- Attaining recruitment
  - Attaining recruitment is a function of lung inflation
- Providing recruitment maneuver
  - Sigh breath of 1.5 to 2 times the set tidal volume
  - Temporary increase in PEEP
    - Intrinsic PEEP
    - Extrinsic PEEP
  - Temporary increase in tidal volume
  - Application of CPAP – 30-40 cm H_2O for 30-90 seconds
  - Application of pressure controlled ventilation
  - Increasing inspiratory time

- Maintaining recruitment
  - Maintaining recruitment is a function of PEEP
- Monitoring recruitment
  - Visual approach
    - **Computerized tomography scan**
  - Other visual techniques
    - Electrical impedance tomography
    - Breath sound analysis
    - Radiolabelled gas or aerosol analysis
  - Mechanical approach
    - **Static pressure volume curve**
    - Step changes in PEEP to determine the level that gives best compliance



Current Opinion in Critical Care 2008, 14:80–86

High PEEP – is there evidence ?

- ALVEOLI trial
  - No difference in mortality
- LOVS Trial
  - *No significant difference in all-cause hospital mortality or barotraumas*
- Express Trial
  - *No significant difference in all-cause hospital mortality*
  - *Improved lung function*
  - *Reduced the duration of mechanical ventilation & the duration of organ failure*

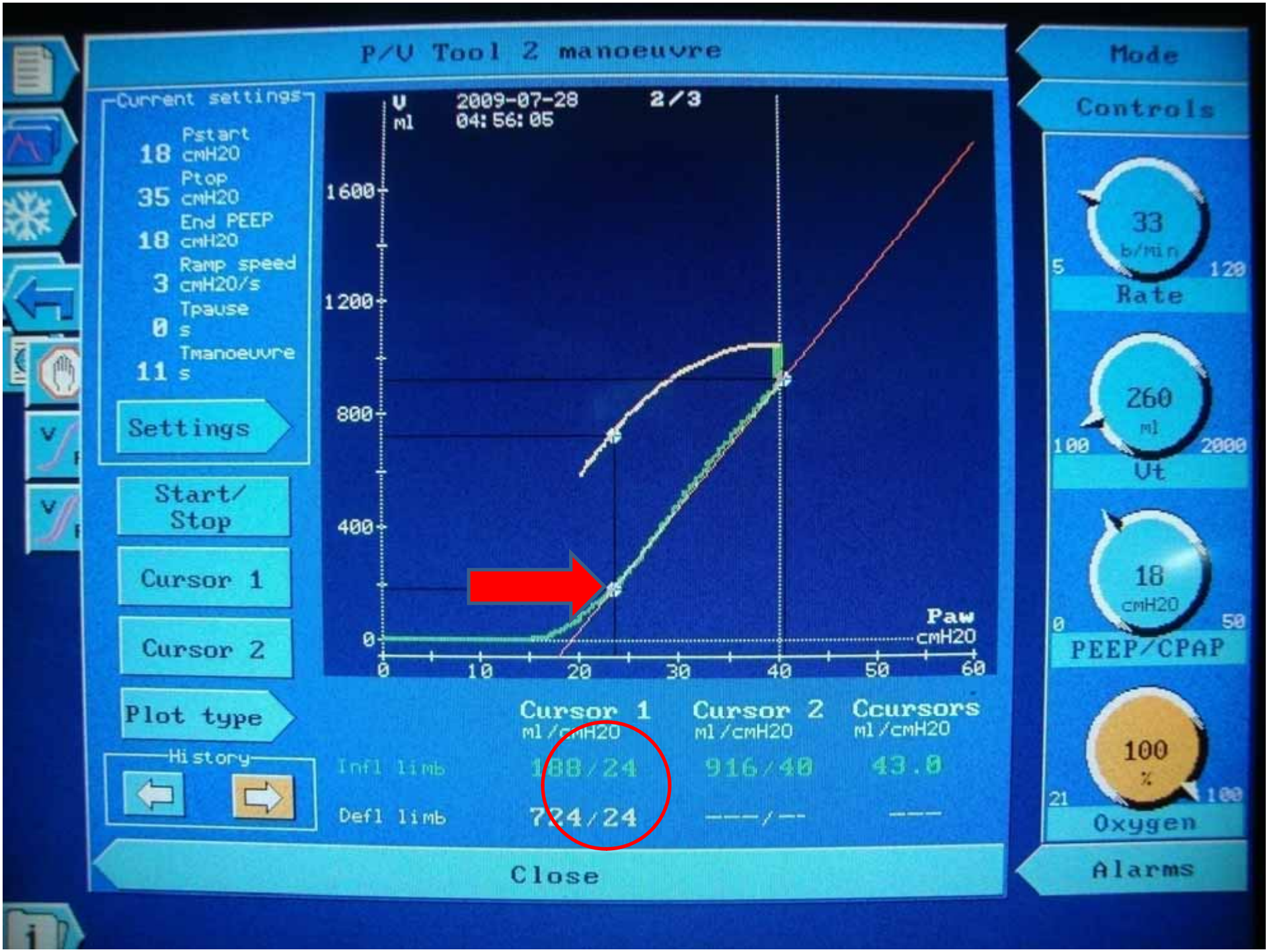
Having said that…

- High PEEP was found to be safe
- Sub group analysis
  - Lesser numbers requiring salvage therapy(10 % vs. 20 %)
  - Alveoli trial was not based on identification of LIP & PEEP was arbitrarily set as per table

Definite role in subset of patients with severe lung injury

What is our experience ?

What next ?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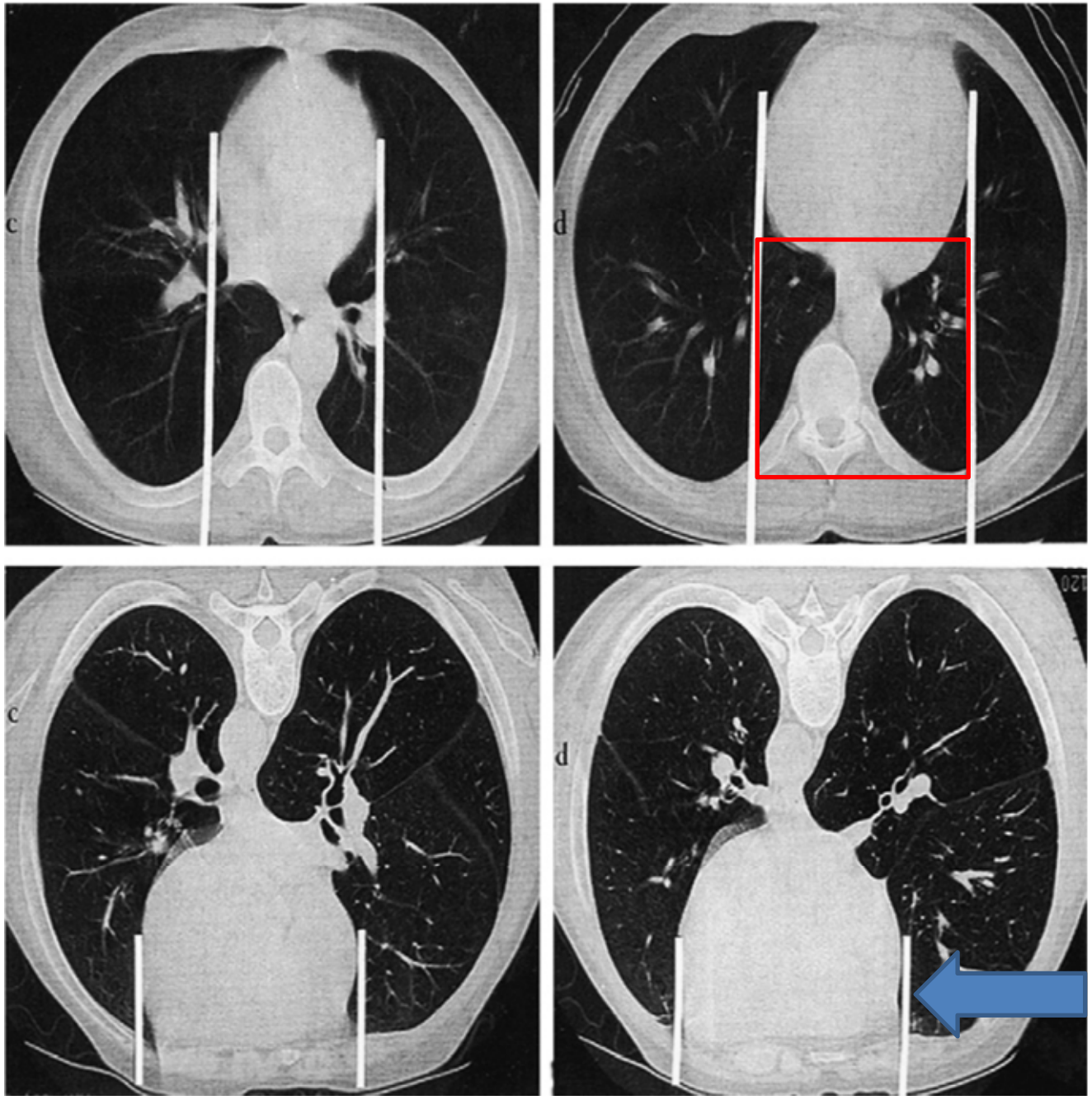
Infl limb 188/24 916/40 43.0
Defl limb 724/24 ---/-- ----
Close
Mode
Controls
33 b/min 5 120 Rate
260 ml 100 2000 Vt
18 cmH20 0 50 PEEP/CPAP
100 % 21 100 Oxygen
Alarms

72 hrs later (31/7/09)

Off inotropes, sat 94 %, @ Fio2 .4

Prone position ventilation



Supine

Prone

Am J Respir Crit Care Med 2000;161:1661–2

Mechanism of action

- Increase in FRC
- Changes in diaphragm position/ movement
- Secretions drainage
- Gravity directed blood flow to less injured areas
- Reduction of heart/ mediastinal compression
- Changes in chest wall compliance

Respir Care Clin 9 (2003) 495–509

What have learnt from trials?

- Oxygenation
  - All trials recorded change
  - Significant increase in most trials (75% of 613 pts)
- Lung mechanics
  - 15 studies recorded C_{stat}
  - 10 showed no change in C_{stat}, 4 increase and 1 decrease
- Hemodynamics
  - Recorded in all
  - All showed no sig hemodynamic instability

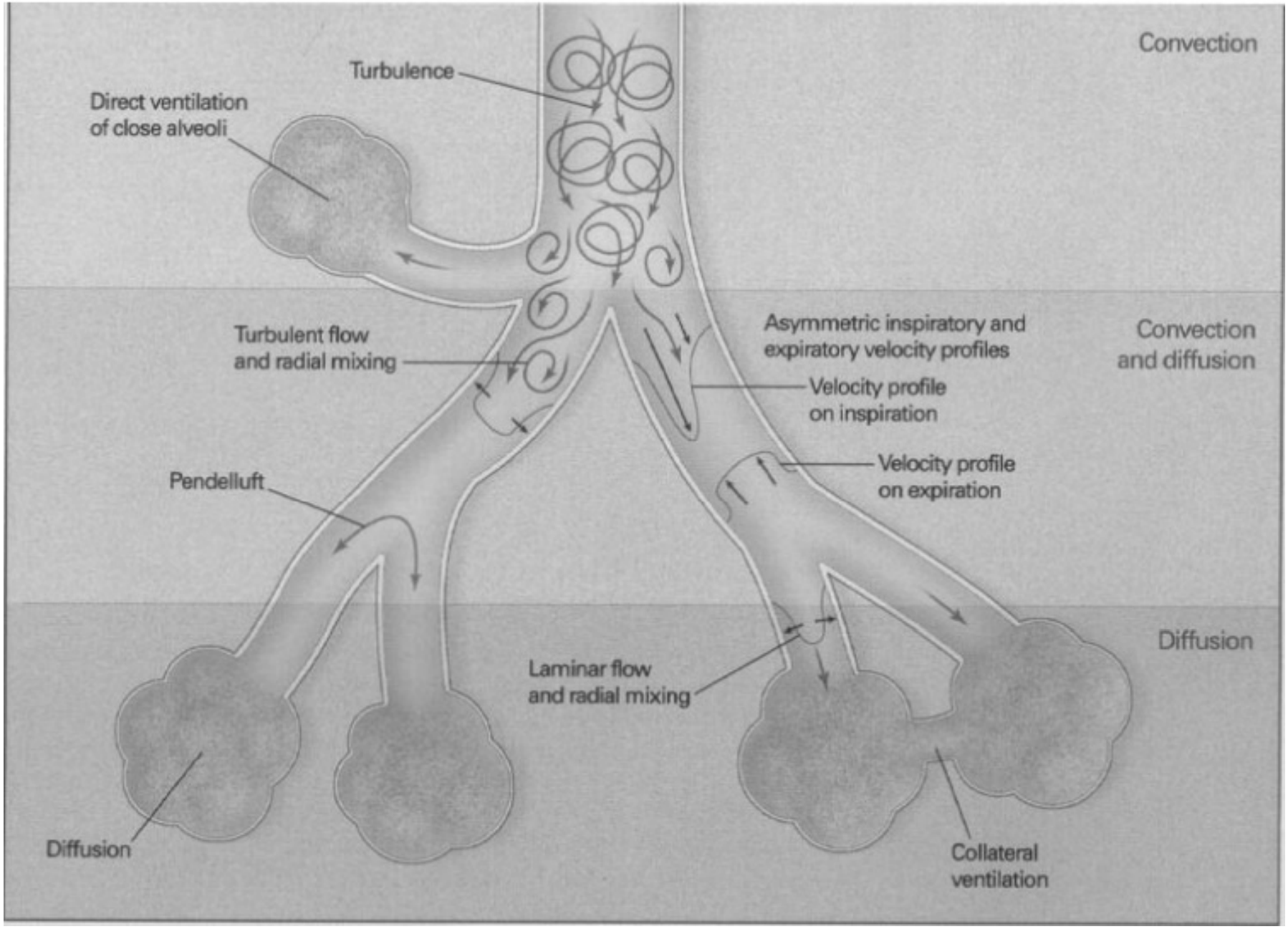
- Predictors of poor response
  - Long duration of ARDS
  - More sev disease
  - No response with first attempt
  - Poor chest wall compliance
- Mortality
  - Only 3 trials looked at mortality
  - Gattinoni et al 50 % decrease at 10 day but no change in ICU mortality
- Complications
  - No sig difference

Uncertainties…

- When ?
- Whom?
- How long ?
- How many times ?

High Frequency Ventilation

- Rapid rate (> 150/min)
- Ultra Low tidal volume (= dead space)
- Maintain open lung (higher mean pr)
- Minimal volume swings



CHEST 2007; 131:1907–1916

Only 2 RCTs comparing HFOV with CMV

HFOV is safe , whether better than ARDSnet protocol remains to be seen

May be considered as a salvage measure in pts not responding to standard Rx

APRV

- A mode of ventilation along with spontaneous ventilation to promote lung recruitment of collapsed and poorly ventilated alveoli
- Continuous positive airway pressure with short, intermittent releases
- The short release along with spontaneous breathing promote CO_2 elimination
- Release time is short to prevent the peak expiratory flow from returning to a zero baseline
- Always implies inverse ratio ventilation

ECMO

- Indications - Lung disease that is
  - Acute
  - Life threatening
  - Reversible
  - Unresponsive to conventional therapy
  - $PO_2 / FiO_2 < 50$ (in spite of standard care)

Evidence

Study, yr	No. of Patients	Therapy	Outcome
Zapol WM,1979	90	ECMO(42) , MV(48)	**Mortality – No diff**
Wallace CJ,1994	40	ECMO (21), MV (19)	**Mortality – No diff**
CESAR TRIAL, 2009	240	CMV vs. ECMO	Preliminary results **Mortality – sig diff**

Partial Liquid Ventilation

Partial Liquid Ventilation in Adult Patients With ARDS

A Multicenter Phase I-II Trial

Objective

To evaluate the safety and efficacy of partial liquid ventilation (PLV) in adult patients with the acute respiratory distress syndrome (ARDS).

Summary Background Data

Previous studies have evaluated gas exchange and the safety of PLV in adult patients with severe respiratory failure whose gas exchange was partially provided by extracorporeal life support (ECLS). This is the first experience with adult patients who were not on ECLS.

Methods

Intratracheal perflubron in a total dose of 30.1 ± 7.1 ml/kg was administered over a period of 45 ± 9 hours to nine adult patients with mean age = 49 ± 4 years and mean PaO_2/FiO_2 ratio = 128 ± 7 as part of a prospective, multicenter, phase I-II noncontrolled trial.

Results

Significant decreases in mean (A-a)DO_2 (baseline = 430 ± 47, 48 hour = 229 ± 17, p = 0.0127 by ANOVA) and FiO_2 (baseline = 0.82 ± 0.08, 48 hour = 0.54 ± 0.06, p = 0.025), along with an increase in mean SvO_2 (baseline = 75 ± 3, 48 hour = 85 ± 2, p = 0.018 by ANOVA) were observed. No significant changes in pulmonary compliance or hemodynamic variables were noted. Seven of the nine patients in this study survived beyond 28 days after initiation of partial liquid ventilation whereas 5 patients survived to discharge. Three adverse events [hypoxia (2) and hyperbilirubinemia (1)] were determined to be severe in nature.

Conclusions

These data suggest that PLV may be performed safely with few related severe adverse effects. Improvement in gas exchange was observed in this series of adult patients over the 48 hours after initiation of PLV.

- Pharma company sponsored study in 2001
  - Phase III trial
  - 311 pts across 56 centers in U.S & Canada
  - Failed to meet end points
  - Never saw the light of day !

Alliance pharma, press release 2001

- Why have these “methods” made no material difference in spite over 40 yrs of research ?

- Especially when most interventions are conceptually sound ?

Causes and Timing of Death in Patients With ARDS*

Background: Since the early 1980s, case fatality of patients with ARDS has decreased, and explanations are unclear.
Design and methods: Using identical definitions of ARDS and organ failure, we analyzed consecutive cohorts of patients meeting syndrome criteria at our institution in 1982 (n = 46), 1990 (n = 112), 1994 (n = 99), and 1998 (n = 205) to determine causes and timing of death.
Results: Overall case fatality has decreased from 68% in 1981–1982 to a low of 29% in 1996, plateauing since the mid-1990s ($p = 0.001$ for trend). Sepsis syndrome with multiple organ failure remains the most common cause of death (30 to 50%), while respiratory failure causes a small percentage (13 to 19%) of deaths. The distribution of causes of death has not changed over time. There was no change in the timing of death during the study periods: 26 to 44% of deaths occurred early (< 72 h after ARDS onset), and 56 to 74% occurred late (> 72 h after ARDS onset). However, the increased survival over the past 2 decades is entirely accounted for by patients who present with trauma and other risk factors for their ARDS, while survival for those patients whose risk factor is sepsis has not changed. Additionally, withdrawal of life support in these patients is now occurring at our institution significantly more frequently than in the past, and median time until death has decreased in patients who have support withdrawn.
Conclusions: While these results do not explain the overall case fatality decline in ARDS, they do indicate that sepsis syndrome remains the leading cause of death and suggest that future therapies to improve survival be targeted at reducing the complications of sepsis.

(CHEST 2005; 128:525–532)

- Are we targeting the wrong organ ?
- Though conceptually sound, variables are too many
- Strength of their individual contribution to problem is unclear
- Most are potentially harmful & some definitely are

Primum non nocere

Novel Rx at best as salvage