Management of refractory ARDS

Saurabh maji

Refractory hypoxemia as

- PaO_2/FIO_2 is less than 100 mm Hg,
- inability to keep plateau pressure below 30 cm H_2O despite a VT of 4 mL/kg
- development of barotrauma
- oxygenation index 30

Chest 2013;137(5): 1203-1216

- In another study it has been defined as
- ARDS patient with Pao2/Fio2 is less than 100 mm Hg for 12 to 24 hrs on a PEEP more than 10 cm H2O and FiO2 greater than 0.5

Am J Respir Crit Care Med. 2012 Nov 15;172(10):1241-5

- Lung-Recruitment Maneuvers
- Prone Positioning
- Extracorporeal Membrane Oxygenation
- Inhaled Vasodilators: Nitric Oxide and Prostacyclin

Lung-Recruitment Maneuvers

- There are three 'compartments' in ARDS-affected lungs:

1. aerated normal lung susceptible to barotrauma induced by inappropriate ventilation;
2. air spaces that are filled with exudate and not recruitable;
3. areas that are collapsed due to interstitial infiltration and are potentially recruitable

- There is an increasing perception that mechanical ventilation may further compromise the sick lung. Compromise may be due to:
- Overinflation of normal lung tissue, due to high transpulmonary pressures, causing increased permeability, worsening compliance, and a vicious cycle of progressive lung injury;
- Inadequate levels of positive end-expiratory pressure (PEEP), promoting regional collapse of lung tissue (atelectasis), and also causing alveolar injury due to cyclical closing and opening of airways with ventilation.

Recruitment Manoeuvres

- An administration of high ventilation pressure to a patient for a brief period of time
- Aim is to reinflate collapsed lung tissue, thus “recruiting” that tissue
- Aim is also to prevent “de-recruitment” by applying PEEP after the manoeuvre
- The desired outcome is improved oxygenation

Indications for RM

- ARDS / Acute Lung Injury

Patients with “secondary ARDS” (eg from abdominal sepsis) seem to respond better than those with “primary” ARDS eg. from pneumonia

- Bilateral pulmonary infiltrates
- PaO2/FiO2* <300 = ALI
- PaO2/FiO2 <200 = ARDS
- Atelectasis during general anaesthesia
- Desaturation After suctioning the ETT

Annals of Intensive Care 2011, 1:9

Contraindications for RM

- Hemodynamic compromise:

  recruitment manoeuvres cause a transient loss of venous return, compromising cardiac output.

- Existing barotrauma
- Increased intracranial pressure
- Predisposition to barotrauma:

  Apical bullous lung disease

  Focal lung pathology eg. lobar pneumonia

Crit Care Med 2010,38:2207-2214.

Types of Recruitment Manoeuvres

- CPAP with increased pressures
- Pressure-controlled ventilation on high PEEP

- Advanced recruitment manoeuvres:
- Prone ventilation to recruit dorsal lung units
- High frequency oscillatory ventilation (lung protective)
- Airway pressure release ventilation, low PEEP and low tidal volume, with I:E of 4:1

Some basic RM protocols

- CPAP 40cmH2O for 40 seconds Crit Care Med 2005,33:54-61
- CPAP 40cmH2O for 30 seconds Anesth Analg.2007 Feb;104(2):384-90
- Pressure controlled ventilation with Pplat 45cm H2O, PEEP of 5, I:E 1:1 and rate of 10

  Anesthesiology 2002, 96:795-802

PEEP after recruitment

- Generally, it is recommended (Hickling 2001) to gradually decrease PEEP until there is a fall in PO2; this is a "decremental PEEP trial"
- PEEP is decreased by 2cmH2O every 4 minutes
- A fall in PO2 by over 10% indicates that there is derecruitment
- PEEP is then set to just above the level at which derecruitment occurs

Am J Respir Crit Care Med. 2001 Jan;163(1):69-78

Consequences of Recruitment Manoeuvres

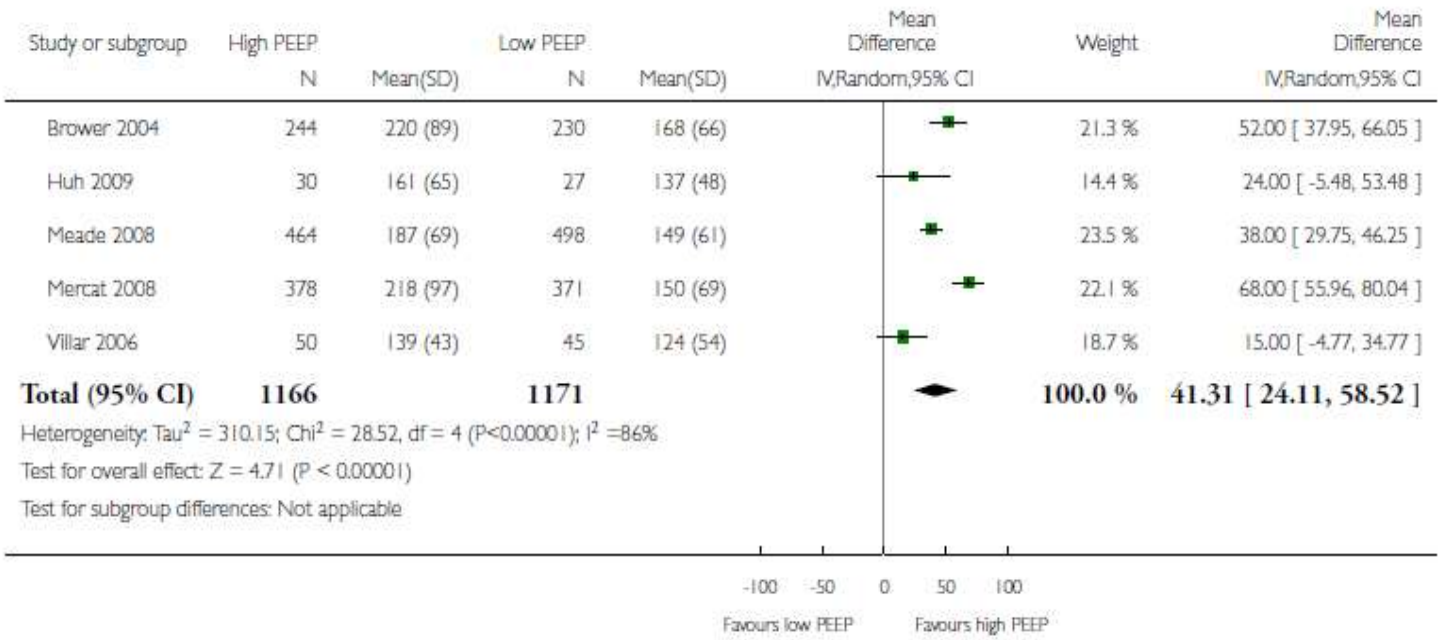
- Increased oxygenation
- Stretch reflex of the alveoli, which causes Type II respiratory cells to release more surfactant
- Increased intrapulmonary shunt
- Barotrauma; overdistension of already well-ventilated lung regions
- VILI due to the above
- Increased pulmonary arterial pressure
- Decreased cardiac output
- Increased intracranial pressure
- The hemodynamic consequences seem to normalise 10-20mintues after the manoeuvre

Analysis 1.2. Comparison 1 High versus low levels of PEEP, Outcome 2 Oxygen efficiency (PaO2/FIO2). Day 1.

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

Comparison: 1 High versus low levels of PEEP

Outcome: 2 Oxygen efficiency (PaO_2/FIO_2). Day 1



Analysis 1.12. Comparison 1 High versus low levels of PEEP, Outcome 12 Mortality within 28 days of randomization.

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

Comparison: 1 High versus low levels of PEEP

Outcome: 12 Mortality within 28 days of randomization

Study or subgroup	High PEEP n/N	Low PEEP n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Amato 1998	11/29	17/24		11.9 %	0.54 [0.31, 0.91]
Huh 2009	12/30	9/27		7.7 %	1.20 [0.60, 2.39]
Meade 2008	135/475	164/508		39.9 %	0.88 [0.73, 1.06]
Mercat 2008	107/385	119/382		35.8 %	0.89 [0.72, 1.11]
Talmor 2008	5/30	12/31		4.6 %	0.43 [0.17, 1.07]
Total (95% CI)	**949**	**972**		**100.0 %**	**0.83 [0.67, 1.01]**

Total events: 270 (High PEEP), 321 (Low PEEP)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 6.30$, df = 4 (P = 0.18); $I^2 = 37\%$

Test for overall effect: Z = 1.83 (P = 0.067)

Test for subgroup differences: Not applicable

Analysis 1.11. Comparison 1 High versus low levels of PEEP, Outcome 11 Mortality before hospital discharge (studies with or without other interventions).

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

Comparison: 1 High versus low levels of PEEP

Outcome: 11 Mortality before hospital discharge (studies with or without other interventions)

Study or subgroup	High PEEP n/N	Low PEEP n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Amato 1998	13/29	17/24		4.0 %	0.63 [0.39, 1.02]
Brower 2004	69/276	75/273		16.1 %	0.91 [0.69, 1.21]
Meade 2008	173/475	205/508		42.3 %	0.90 [0.77, 1.06]
Mercat 2008	136/385	149/382		32.0 %	0.91 [0.75, 1.09]
Villar 2006	17/50	25/45		5.6 %	0.61 [0.38, 0.98]
Total (95% CI)	**1215**	**1232**		**100.0 %**	**0.88 [0.79, 0.98]**

Total events: 408 (High PEEP), 471 (Low PEEP)

Heterogeneity: $Chi^2 = 4.38$, df = 4 (P = 0.36); I^2 =9%

Test for overall effect: Z = 2.43 (P = 0.015)

Test for subgroup differences: Not applicable

Prone ventilation

Effect of prone ventilation:

Prone positioning improves gas exchange via its effect on pleural pressure and lung compression

Increased functional residual capacity (FRC) has also been proposed, but changes in FRC have not been a dominant finding in most studies of prone ventilation

Am Rev Respir Dis. 1977;115(4):559
Am J Respir Crit Care Med. 1998;157(2):387

Trans pulmonary pressure (Ptp) is defined as the difference between the airway pressure (Paw) and pleural pressure (Ppl):

$$Ptp = Paw - Ppl$$

In supine position, the dorsal pleural pressure is greater than ventral pleural pressure

So , the ventral trans pulmonary pressure exceeds the dorsal transpulmonary pressure and greater expansion of the ventral alveoli than the dorsal alveoli

Eur Respir J. 2008;20(4):1017.
Intensive Care Med. 1986;12(3):137

- Exaggerated in supine patients with acute respiratory distress syndrome (ARDS), probably because the difference between the dorsal and ventral pleural pressures is increased by the excess lung weight

- The result is a tendency towards overinflation of the ventral alveoli and atelectasis of the dorsal alveoli

- Prone positioning reduces the difference between the dorsal and ventral pleural pressures
- Making ventilation more homogeneous
- Leading to a decrease in alveolar overinflation and alveolar collapse.
- Minimize stress and strain on alveoli, limiting ventilator-associated lung injury from overdistention and cyclic atelectasis

Anesth Analg. 2009;83(6):1206

- **Compression**:
- in supine position: Heart compresses the medial posterior lung parenchyma and the diaphragm compresses the posterior-caudal lung parenchyma

- Compression by either the heart or the diaphragm may exaggerate dependent lung collapse in the supine position, increasing hypoxemia and ventilator-associated lung injury

Am J Respir Crit Care Med. 2008;158(5 Pt 1):1644

- During prone ventilation, the heart becomes dependent, decreasing medial posterior lung compression
- The diaphragm is displaced caudally (especially in non-obese patients and when the abdomen is left unsupported), decreasing compression of the posterior-caudal lung parenchyma

Improve ventilation and oxygenation

- Cardiac output: Increase in lung recruitment and reduction in hypoxic pulmonary vasoconstriction

- Increases in cardiac output by Increases in right ventricular preload, and decreased right ventricular afterload

Am J Respir Crit Care Med. 2007;157(2):387

- Perfusion: In ARDS, there is substantial ventilation-perfusion mismatch in the supine position, since blood flow and alveolar collapse are both greatest in the dependent portions of the lung

- In prone position as the previously dependent lung continues to receive the majority of the blood flow (independent of the gravitational gradient) as alveoli reopen, while the newly dependent lung continues to receive the minority of the blood flow as alveoli begin to collapse

Clinical outcome

- prone ventilation increases arterial oxygen tension (PaO2)
- a reduction in the fraction of inspired oxygen (Fio2)
- Among patients whose oxygenation improves during prone ventilation, some continue to have improved oxygenation for hours after they return to the supine position and many improve each time prone ventilation is repeated

N Engl J Med. 2013;368(23):2159

Predictor

- The best predictor of a sustained increase in PaO2 during prone ventilation is 10 mmHg increase in PaO2 over the first 30 minutes of prone ventilation predicted a sustained increase in PaO2 over the next two hours

- Patients whose PaO2 did not increase during the first 30 minutes of prone ventilation showed no subsequent improvement in their oxygenation

Chest. 1988;94(1):103

CHEST
Official publication of the American College of Chest Physicians

The prone position in ARDS patients. A clinical study.

M Langer, D Mascheroni, R Marcolin and L Gattinoni

Chest 1988;94:103-107
DOI 10.1378/chest.94.1.103

Table 1—*Patient Population**

Patient No.	Diagnosis	Sex/Age	Outcome
1	Bacterial pneumonia	F/43	S
2	Sepsis, pulmonary embolism (?)	F/74	D
3	Aspiration pneumonia	F/1	D
4	Viral pneumonia	F/11	S
5	Bacterial pneumonia	M/30	S
6	Blunt chest trauma, pneumonia	M/53	S
7	Sepsis, aspiration pneumonia	F/42	D
8	Blunt chest trauma	M/44	D
9	Viral pneumonia	M/44	D
10	Sepsis, restrictive lung disease	F/25	S
11	Blunt chest trauma	M/24	S
12	Bacterial pneumonia	M/29	S
13	Viral pneumonia	F/46	D

*S is survivor; D, dead.

Trend of principal parameter throughout the study

		Baseline Supine	30 Min Prone	120 Min Prone	240 Min Supine
PaO_2, mm Hg	A	70±8	90±8‡	112±20‡§	92±16†
	B	81±22	67±13†	71±17†	85±22†
$PaCO_2$, mm Hg	A	40±4	38±6	39±6	38±4
	B	36±2	36±2	38±6	37±4
Qs/Qt, %	A	27±6	20±6	20±9	17±6
	B	30±7	35±8	33±8	32±9
CI, L/min/m²	A	3.6±1.0	3.6±1.0	3.6±1.0	3.6±1.2
	B	4.4±1.4	4.7±1.4	5.3±2	5.2±1.6
PAP, mm Hg	A	25±5	24±6	24±5	20±7
	B	26±3	25±4	25±3	23±4

*A is responders; B, nonresponders.
†Significantly different from A ($p<0.01$).
‡Significantly different from baseline ($p<0.01$).
§Significantly different from 30 min ($p<0.01$).

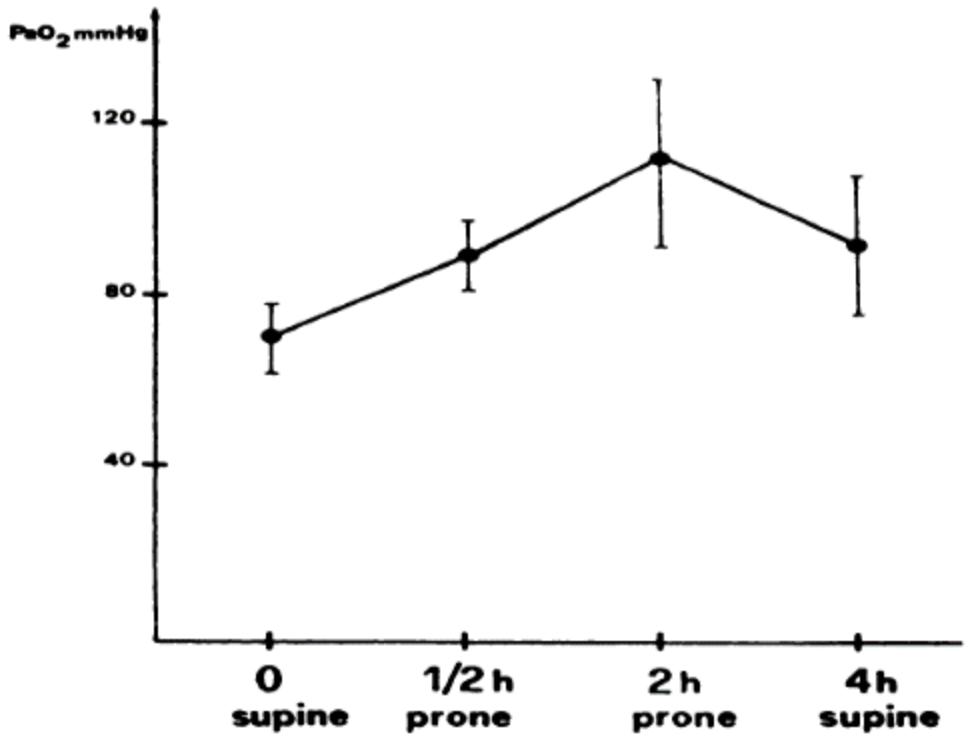


FIGURE 2. PaO_2 trend throughout the study in the responders group. PaO_2 significantly improved 30 minutes after prone position ($p<0.01$). Further improvement was observed at the end of the prone position period ($p<0.01$ vs 30 minutes). The PaO_2 remained higher than baseline ($p<0.01$) two hours after returning in supine position.

- Patients with diffuse pulmonary edema and dependent alveolar collapse appear more likely to improve their PaO2 during prone ventilation than patients with predominantly anterior abnormalities, marked consolidation, and/or fibrosis

- Extrapulmonary cause for their ARDS seem more likely to increase their PaO2 during prone ventilation than patients with a pulmonary cause

Am J Respir Crit Care Med. 2012;157(6 Pt 1):1785

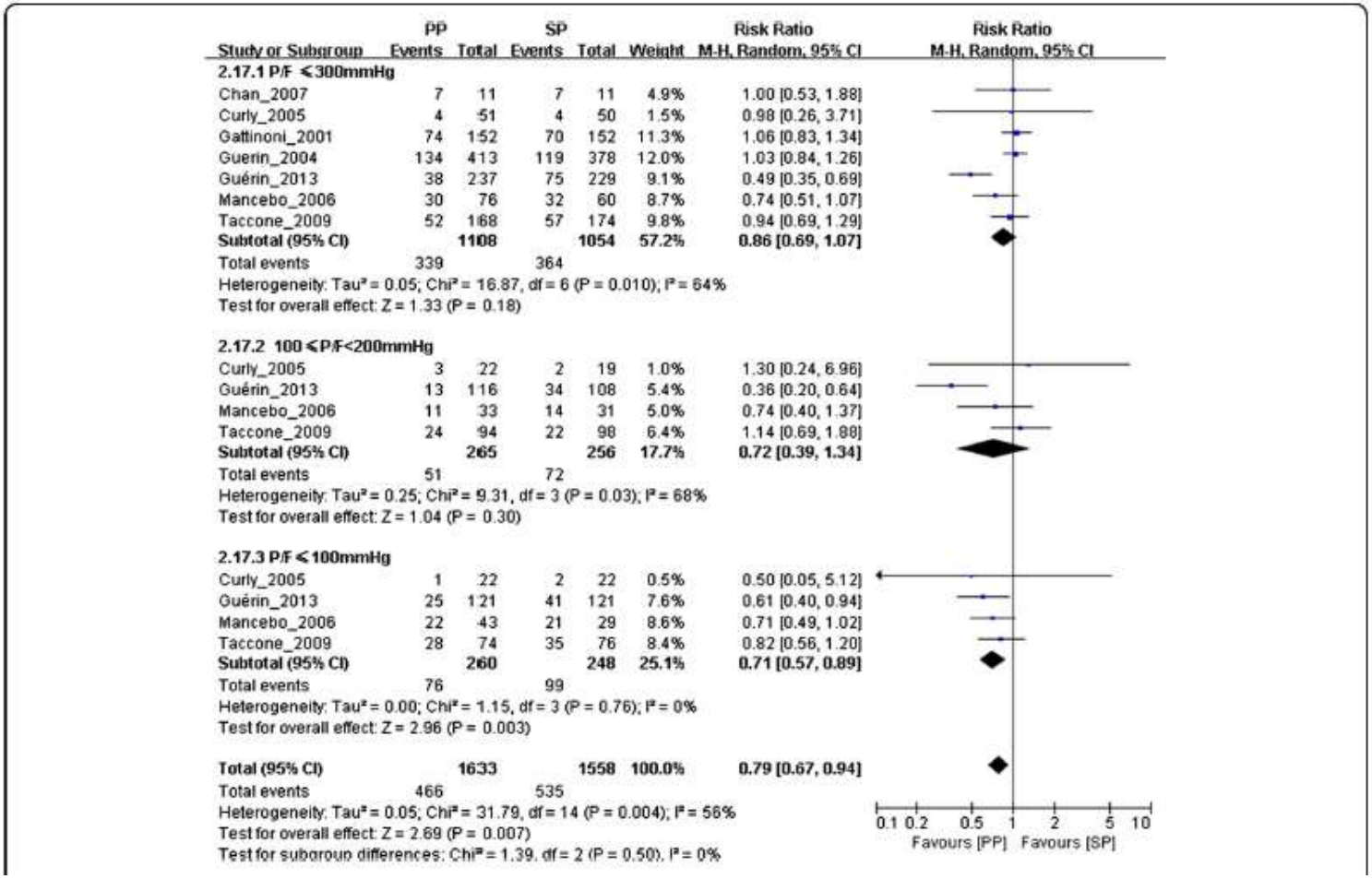
- Patients with elevated intraabdominal pressure appear more likely to increase their PaO2 during prone ventilation than patients with normal intraabdominal pressure

- Patients whose chest wall compliance decreases when moving from the supine to the prone position are likely to improve their PaO2 during prone ventilation

Trial	Gattinoni *et al.*, 2001 [19]	Guerin *et al.*, 2004 [14]	Voggenreiter *et al.*, 2005 [20]	Curley *et al.*, 2005 [18]	Mancebo *et al.*, 2006 [21]	Chan *et al.*, 2007 [22]	Fernandez *et al.*, 2008 [23]	Taccone *et al.*, 2009 [24]	Guérin *et al.*, 2013 [13]
Design	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT
P/F for enrollment (mmHg)	300	300	300	300	200	300	300	200	150
Total number of included patients	304	791	40	101	136	22	40	342	466
PEEP level (cmH_2O)	9	7	11	9	12	13	11	11	10
Duration of PP (h/day)	7.0	8.5	11	20	17	24	≥20	≥20	17
V_t (ml/kg)	10	8	6-8	7	8	7	7	7	6
28- to 30-day mortality in P/F ≤ 100 mmHg group (P (*n*/*N*), S (*n*/*N*))	NA[b]	NA	NA	NA	22/43, 21/29	NA	NA	28/74, 35/76	25/121, 41/121
28- to 30-day mortality in 100 ≤ P/F < 200 mmHg group (P (*n*/*N*), S (*n*/*N*))	NA	NA	NA	NA	11/33, 14/31	NA	NA	24/94, 22/98	13/116, 34/108
28- to 30-day mortality in P/F ≤ 300 mmHg group (P (*n*/*N*), S (*n*/*N*))	74/152, 70/152	134/413, 119/378	NA	4/51, 4/50	30/76, 32/60	7/11, 7/11	NA	52/168, 57/174	38/237, 75/229
60-day mortality in P/F ≤ 300 mmHg group (P (*n*/*N*), S (*n*/*N*))	95/152, 89/152	NA	NA	NA	22/76, 28/60	NA	8/21, 10/19	79/168, 91/174	NA
90-day mortality in P/F ≤ 300 mmHg group (P (*n*/*N*), S (*n*/*N*))	89/152, 84/152	179/413, 159/377	1/21, 3/19	NA	NA	NA	NA	NA	56/237, 94/229
ICU mortality in P/F ≤ 300 mmHg group (P (*n*/*N*), S (*n*/*N*))	77/152, 73/152	NA	NA	NA	33/76, 35/60	NA	NA	64/168, 73/174	NA

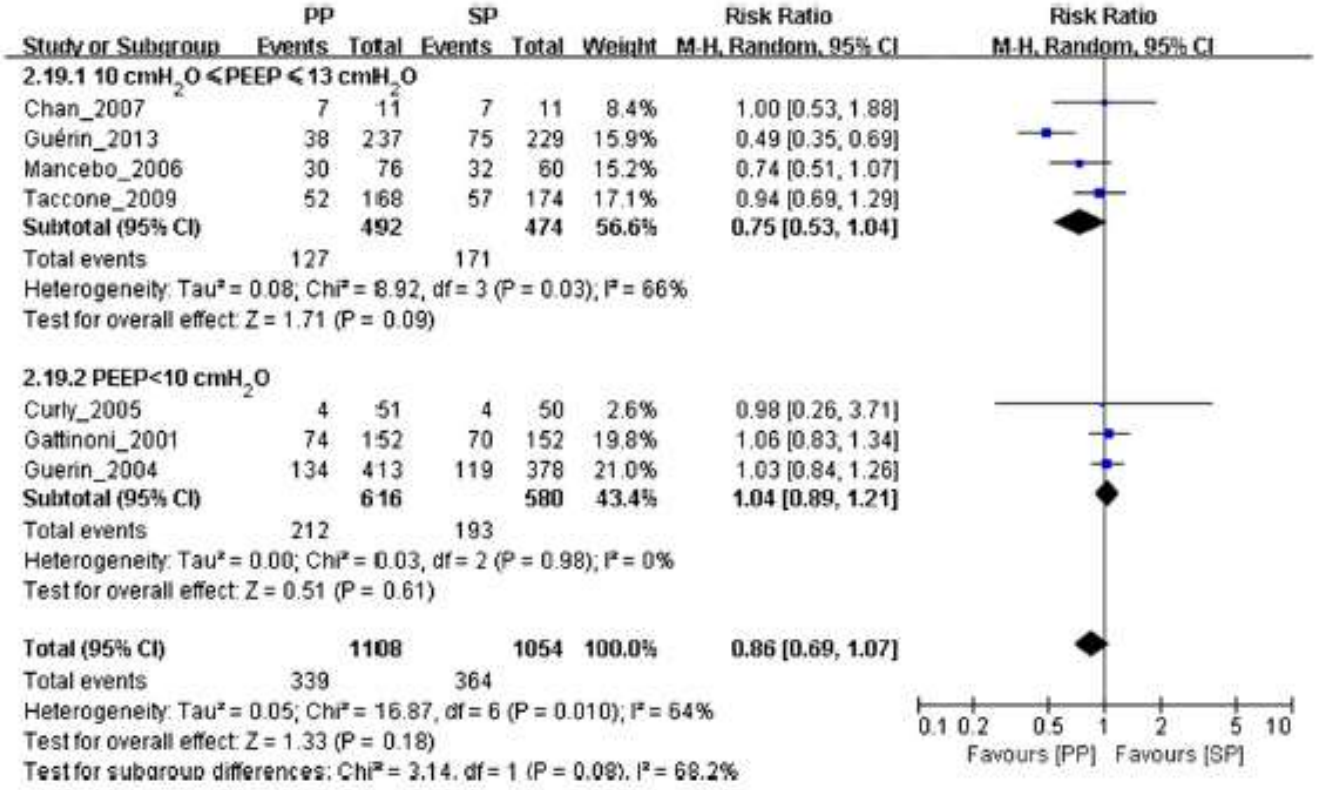
[a]ARDS, Acute respiratory distress syndrome; MV, Mechanical ventilation; *N*, Total number in group; *n*, Number of deaths; NA, Not available; P, Prone; P/F, Ratio of partial pressure of arterial oxygen to fraction of inspired of oxygen; PEEP, Positive end-expiratory pressure; S, Supine; V_t, Tidal volume. [b]Data not supplied in primary article.

Hu et al. Critical Care 2014, 18:R109

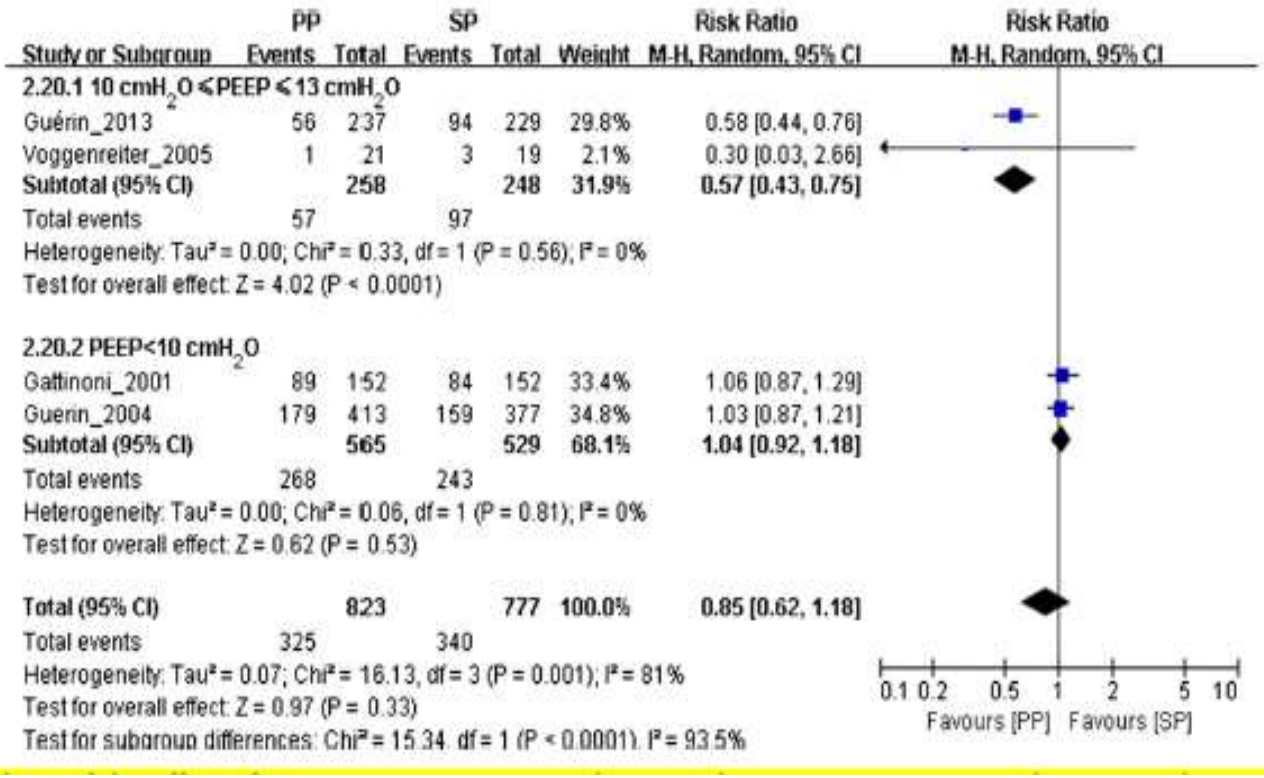


Meta-analysis of the effect of prone positioning on 28- to 30-day mortality in acute respiratory distress syndrome patients related to the ratio of partial pressure of arterial oxygen/fraction of inspired oxygen

Prone position with high peep and mortality



Meta-analysis of the effect of prone positioning on 28- to 30-day mortality related to positive end-expiratory pressure in acute respiratory distress syndrome patients



Meta-analysis of the effect of prone positioning on 90-day mortality in acute respiratory distress syndrome patients related to positive end-expiratory pressure

The NEW ENGLAND JOURNAL of MEDICINE

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Prone Positioning in Severe Acute Respiratory Distress Syndrome

- Multicenter, prospective, randomized, controlled trial
- 466 patients with severe ARDS to undergo prone-positioning sessions of at least 16 hours or to be left in the supine position
- Severe ARDS was defined as Pao2/Fio2 is less than150 mm Hg, with an Fio2 of at least 0.6, a PEEP of at least 5 cm of water, and a tidal volume close to 6 ml per kilogram of predicted body weight
- After stabilization period of 12 to 24 hours patients were proned for at least 16 hours
- The primary outcome was the proportion of patients who died from any cause within 28 days after inclusion

Table 1. Characteristics of the Participants at Inclusion in the Study.*

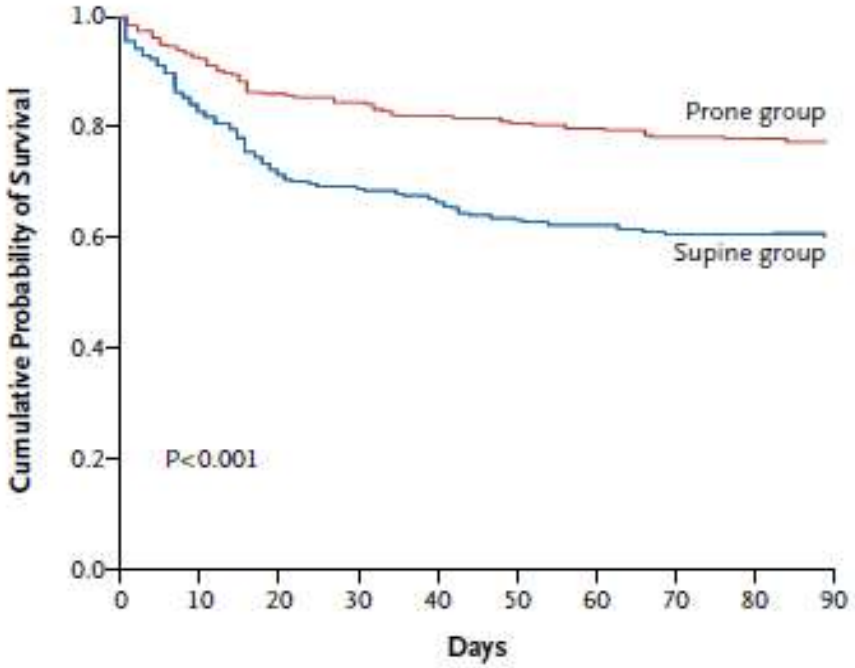
Characteristic	Supine Group (N = 229)	Prone Group (N = 237)
Age — yr	60±16	58±16
Male sex — no. (%)	152 (66.4)	166 (70.0)
Setting from which patient was admitted to ICU — no. (%)		
Emergency room	98 (42.8)	101 (42.6)
Acute care facility	87 (38.0)	86 (36.3)
Home	26 (11.4)	31 (13.1)
ICU	9 (3.9)	11 (4.6)
Other	9 (3.9)	8 (3.4)
McCabe score — no. (%)†		
A	183 (79.9)	197 (83.1)
B	45 (19.7)	39 (16.5)
C	1 (0.4)	1 (0.4)
Coexisting conditions — no. (%)		
Diabetes	39 (17.0)	50 (21.1)
Renal failure	12 (5.2)	10 (4.2)
Hepatic disease	16 (7.0)	15 (6.3)
Coronary artery disease	24 (10.5)	24 (10.1)
Cancer	30 (13.1)	24 (10.1)
COPD	29 (12.7)	23 (9.7)
Immunodeficiency — no. (%)	38 (16.6)	32 (13.5)
SAPS II‡	47±17	45±15
Sepsis — no./total no. (%)§	195/229 (85.2)	194/236 (82.2)
SOFA score¶	10.4±3.4	9.6±3.2
ARDS due to pneumonia	133 (58.1)	148 (62.4)
Body-mass index‖	29±7	28±6
Other interventions — no./total no. (%)		
Vasopressors	190/229 (83.0)	172/237 (72.6)
Neuromuscular blockers	186/226 (82.3)	212/233 (91.0)
Renal-replacement therapy	39/228 (17.1)	27/237 (11.4)
Glucocorticoids	101/225 (44.9)	91/230 (39.6)

Table 2. Ventilator Settings, Respiratory-System Mechanics, and Results of Arterial Blood Gas Measurements at the Time of Inclusion in the Study.*

Variable	Supine Group (N = 229)	Prone Group (N = 237)
Tidal volume (ml)	381±66	384±63
Tidal volume (ml per kg of PBW)	6.1±0.6	6.1±0.6
Respiratory frequency (breaths per min)	27±5	27±5
PEEP (cm of water)	10±4	10±3
F_{IO_2}	0.79±0.16	0.79±0.16
$Pplat_{RS}$ (cm of water)	23±5	24±5
Cst_{RS} (ml per cm of water)	35±15	36±23
Pao_2 (mm Hg)	80±18	80±19
Pao_2:F_{IO_2} (mm Hg)	100±20	100±30
$Paco_2$ (mm Hg)	52±32	50±14
Arterial pH	7.30±0.10	7.30±0.10
Plasma bicarbonate (mmol per liter)†	25±5	25±5

- First prone-positioning done within 55±55 minutes after randomization
- The average number of sessions was 4±4 per patient
- Mean duration per session was 17±3 hours
- All the patients in this group underwent at least one prone-positioning session
- patients were ventilated in the prone position for 73% of the 22,334 patient-hours spent in the ICU from the start of the first session to the end of the last session

Result



No. at Risk					
Prone group	237	202	191	186	182
Supine group	229	163	150	139	136

Figure 2. Kaplan–Meier Plot of the Probability of Survival from Randomization to Day 90.

Result

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

Multicenter, randomized trial compared

conventional treatment (in the supine position) of patients with acute lung injury or the acute respiratory distress syndrome with a predefined strategy of placing patients in a prone position for six or more hours daily for 10 days

Enrolled 304 patients, 152 in each group

JAMA. 2006;302(18):1977-1984

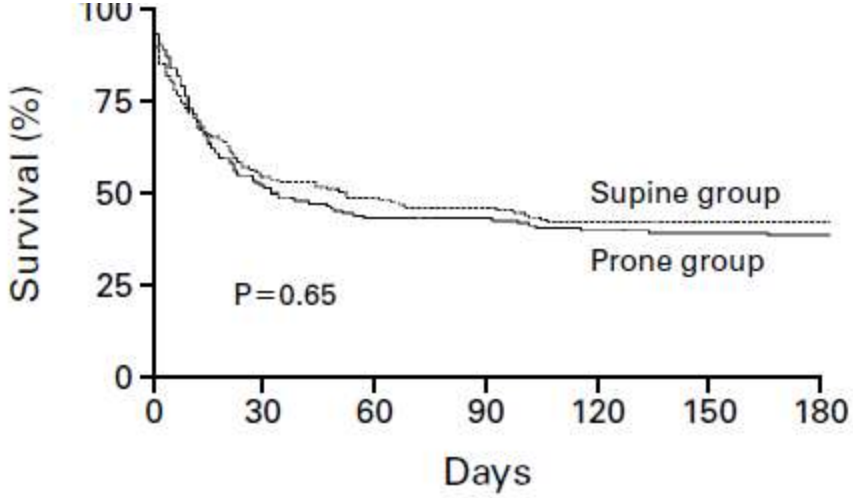
- The primary end point was death at 10 days
- At the time of discharge from the intensive care unit
- 6 months mortality after randomization Secondary end points were
- Improvement in respiratory failure and improvement in organ dysfunction at 10 days

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	SUPINE GROUP (N=152)	PRONE GROUP (N=152)
Age (yr)	57±16	59±17
Female sex (%)	25.0	34.2
SAPS II†	40±16	40±14
Acute lung injury (%)‡	6.6	5.3
Acute respiratory distress syndrome (%)§	93.4	94.7
No. of nonpulmonary organ or system failures	1.4±1.0	1.3±1.0
Cause of lung injury (%)¶		
Pneumonia	48.3	48.3
Aspiration	4.6	1.3
Other types of respiratory disease	16.6	11.9
Respiratory tract infection after surgery	11.9	9.9
Sepsis	8.6	9.9
Trauma	1.3	3.3
Other causes	8.6	15.2

TABLE 2. CHANGES IN RESPIRATORY VARIABLES DURING THE 10-DAY TREATMENT PERIOD.*

VARIABLE	BASE-LINE VALUE			AVERAGE CHANGE†		
	SUPINE GROUP	PRONE GROUP	P VALUE	SUPINE GROUP	PRONE GROUP	P VALUE
PaO_2 (mm Hg)	88.3±25.9	85.7±24.6	0.38	8.5±26.8	15.0±26.4	0.04
FiO_2 (%)	72.7±18.7	73.4±18.3	0.72	−7.6±17.6	−12.7±18.7	0.02
PaO_2:FiO_2	129.5±47.5	125.3±48.8	0.45	44.6±68.2	63.0±66.8	0.02
PEEP (cm of water)	9.6±3.2	9.7±2.9	0.79	0.0±2.9	−0.1±2.5	0.81
Peak inspiratory pressure (cm of water)	32.6±7.4	32.4±7.5	0.86	−0.6±5.3	−0.1±6.6	0.85
Tidal volume						
Milliliters	658±192	652±177	0.80	−11±138	25±128	0.02
Milliliters per kilogram of predicted body weight‡	10.3±2.9	10.3±2.7	0.92	−0.1±2.2	0.4±2.1	0.03
Respiratory rate (breaths/min)	17.2±5.1	17.1±5.3	0.91	1.3±4.5	0.7±4.2	0.20
Minute ventilation (liters/min)	10.4±3.3	10.4±3.2	0.96	0.5±2.6	0.5±2.3	0.96
$PaCO_2$ (mm Hg)	44.2±11.8	45.1±11.0	0.50	2.5±9.9	0.6±11.2	0.11



No. at Risk							
Supine group	152	82	72	68	62	62	62
Prone group	152	78	63	63	58	57	56

complication

Complication	Patients, %[a]				Events/100 Days of Study[b]				Events During Positional Changes, %[c]
	All	Prone	Supine	*P* Value[c]	All	Prone	Supine	*P* Value[c]	
Entire Population									
Need for increased sedation/muscle relaxants	68.1	80.4	56.3	<.001	15.2	17.9	12.5	<.001	26.9
Airway obstruction	42.1	50.6	33.9	.002	8.4	10.3	6.6	<.001	20.4
Transient desaturation	57.0	63.7	50.6	.01	13.4	15.4	11.3	<.001	21.3
Vomiting	20.8	29.1	12.6	<.001	3.0	4.4	1.7	<.001	35.1
Hypotension, arrhythmias, increased vasopressors	63.2	72.0	54.6	<.001	15.2	18.0	12.4	<.001	22.0
Loss of venous access	9.9	16.1	4.0	<.001	0.7	1.23	0.25	<.001	36.6
Displacement of endotracheal tube	7.6	10.7	4.6	.03	0.6	0.87	0.40	.02	40.0
Displacement of thoracotomy tube	2.9	4.2	1.7	.21	0.2	0.25	0.11	.23	30.0
Moderate Hypoxemia									
Need for increased sedation/muscle relaxants	69.3	79.8	59.2	.002	13.3	15.8	10.9	<.001	26.5
Airway obstruction	40.6	44.7	36.7	.26	7.4	8.5	6.3	<.001	23.3
Transient desaturation	51.0	54.3	48.0	.38	11.2	12.0	10.4	<.001	16.5
Vomiting	19.8	26.6	13.3	.02	2.3	2.8	1.8	<.001	21.9
Hypotension, arrhythmias, increased vasopressors	57.8	64.9	51.0	.05	13.7	17.5	10.2	<.001	18.6
Loss of venous access	10.9	17.0	5.1	.008	0.7	1.1	0.3	.02	27.3
Displacement of endotracheal tube	9.4	12.8	6.1	.11	0.7	0.9	0.5	.18	36.4
Displacement of thoracotomy tube	2.1	3.2	1.0	.36	0.1	0.2	0.1	.35	50.0
Severe Hypoxemia									
Need for increased sedation/muscle relaxants	66.7	81.1	52.6	<.001	17.9	20.5	14.9	.001	27.4
Airway obstruction	44.0	58.1	30.3	<.001	9.9	12.6	7.0	<.001	17.4
Transient desaturation	64.7	75.7	54.0	.005	16.4	19.7	12.8	<.001	25.8
Vomiting	22.0	32.4	11.8	.002	4.1	6.5	1.5	<.001	45.3
Hypotension, arrhythmias, increased vasopressors	70.0	81.1	59.2	.004	17.2	18.6	15.7	.07	25.6
Loss of venous access	8.7	14.7	2.6	.008	0.8	1.4	0.2	<.001	47.4
Displacement of endotracheal tube	5.3	8.1	2.6	.16	0.6	0.8	0.3	.04	46.2
Displacement of thoracotomy tube	4.0	5.4	2.6	.44	0.3	0.3	0.2	.09	16.7

JAMA. 2009;302(18):1977-1984

ECMO

- Extracorporeal lung support technologies [i.e., Interventional Lung Assist (ILA) and extracorporeal membrane oxygenation (ECMO)] have been advocated for use in the treatment of patients with respiratory failure

- These techniques do not treat the underlying lung condition; rather, they improve gas exchange while enabling the implantation of a protective ventilation strategy to prevent further damage to the lung tissues imposed by the ventilator

Am J Emerg Med. 2014;32(10):1300 e1–2.
doi:10.1016/j.

- “ECMO” has become a general term encompassing a range of methods for extracorporeal blood oxygenation and CO2 removal

- In the 1970’s, ECMO referred to a high-flow venoarterial bypass system aimed primarily at blood oxygenation.

- By the 1980’s, the term ‘extracorporeal CO2 removal (ECCO2R) was used to cover a low-flow venovenous bypass technique and replaced ECMO

- Later in the mid-1980’s, ‘partial extracorporeal CO2 removal’ (PECO2R) emerged with the development of a technique used to eliminate only part of the body’s CO2 for patients with chronic lung disease.

- In 1987, a Japanese working group then introduced the term‘extracorporeal lung assist (ECLA)’ to describe a venovenous low-flow bypass system.
- ‘Extracorporeal life support’ was then introduced to describe techniques that provide prolonged but temporary support for the lungs and heart

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- The ECMO system consists of a centrifugal pump, a membrane oxygenator, inlet and outlet cannulas, and tubing

- The exchange of oxygen and CO2 then takes place in the oxygenator, which delivers the reoxygenated blood back into one of the patient's veins or arteries

- Additional ports may be added for haemodialysis or ultrafiltration

- Two different techniques may be used to introduce ECMO
- venoarterial and venovenous
- venoarterial technique, cannulation is through either the femoral artery and the femoral vein, or through the carotid artery and the internal jugular vein

- venovenous technique cannulation is through both femoral veins or a femoral vein and internal jugular vein

- Venovenous ECMO will not provide adequate support if a patient has pulmonary hypertension or right heart failure

- Venovenous ECMO can be either two site approach or single site approach

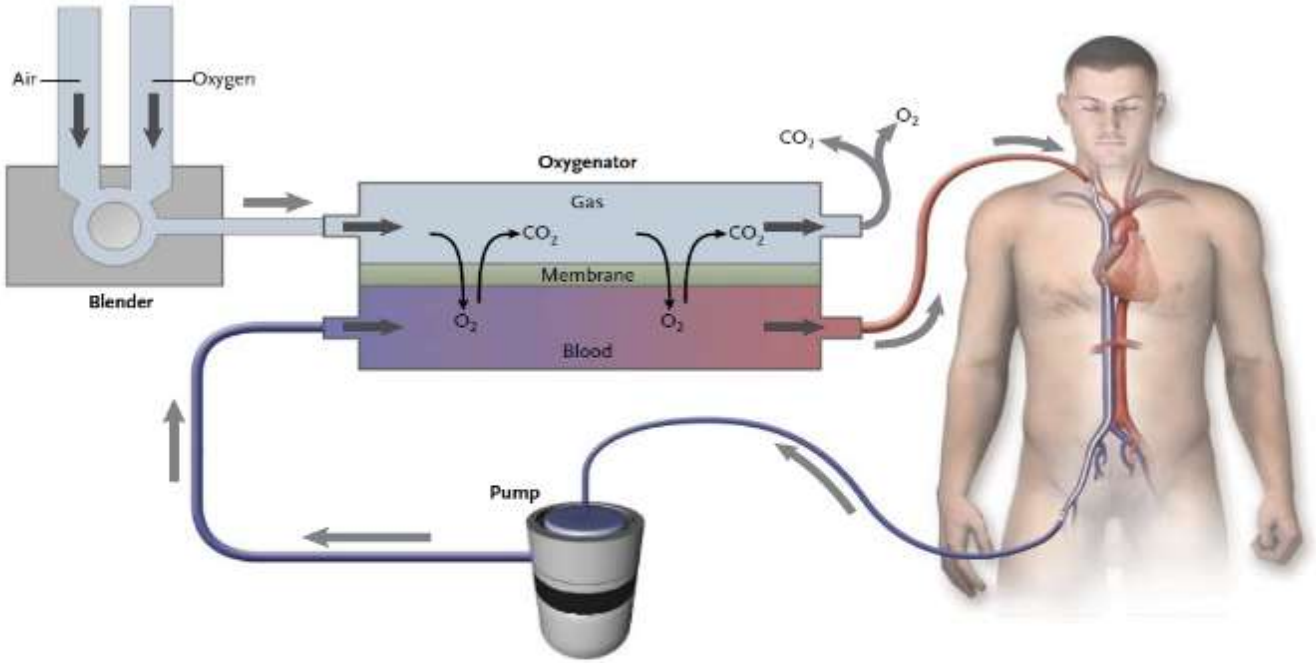
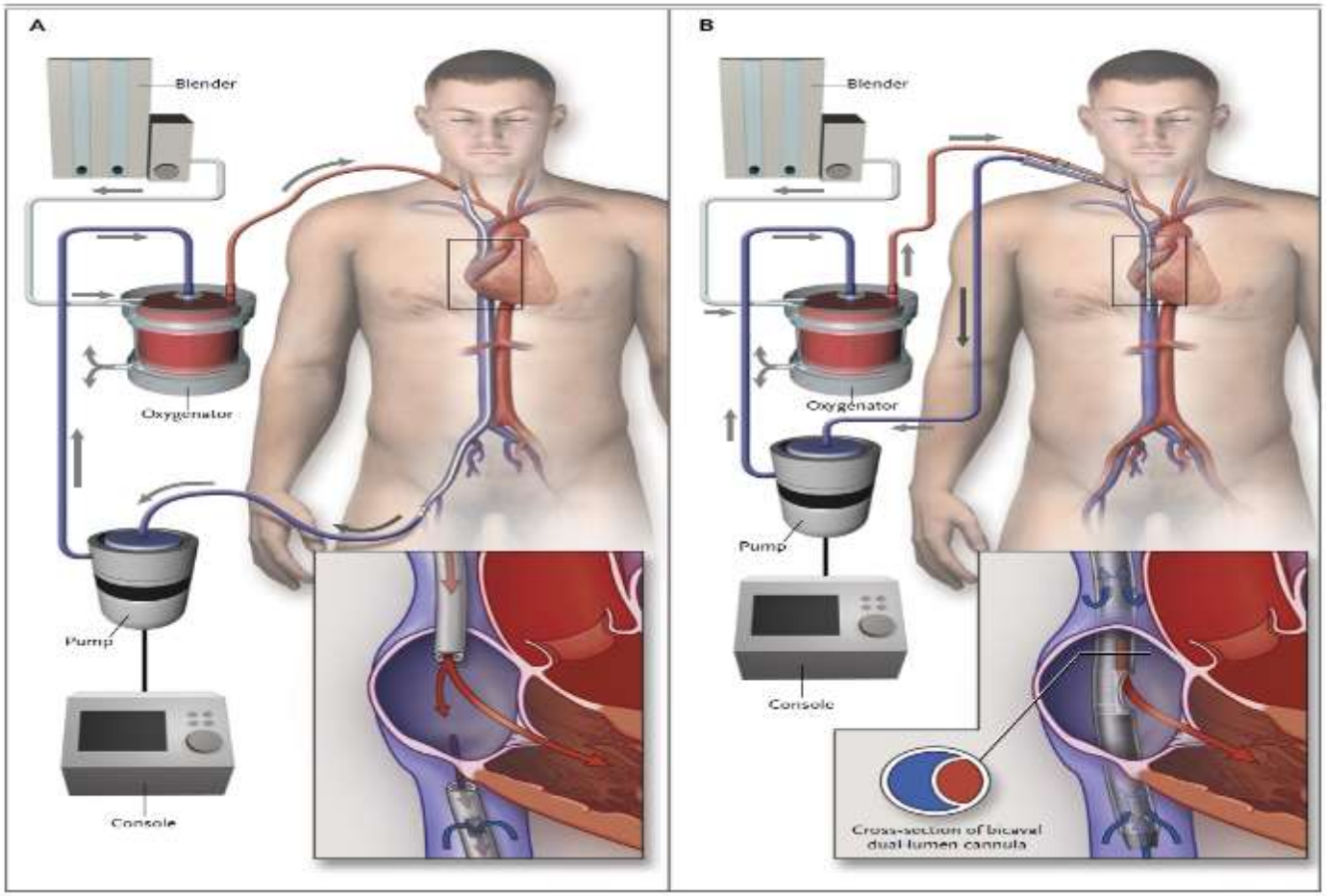


Figure 2. The Oxygenator in Venovenous ECMO.

The extracorporeal membrane oxygenation pump delivers venous blood to the oxygenator. This device is divided into two chambers by a semipermeable membrane. The venous blood enters the oxygenator and travels along one side of the membrane (the blood side), while fresh gas, known as sweep gas, is delivered to the other side (the gas side). Gas exchange (oxygen uptake and carbon dioxide elimination) takes place across the membrane. The oxygenated blood is then reinfused into the patient's venous system. The composition of the gas on the gas side of the oxygenator membrane is determined by adjustment of a blender that mixes room air with oxygen for delivery into the oxygenator.



Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine (2015) 23:30

- Problems associated with cannulation during the procedure include bleeding around the cannulation site and limb ischemia distal to the cannulation site

- The system is characterized by a novel, low-resistance gas exchange device with a diffusion membrane composed of polymethylpentene (PMP) fibres

- These fibres are woven into a complex configuration that maximizes the exchange of oxygen and CO2 by simple diffusion
- system is also designed to operate without the help of an external pump, though one can be added if higher blood flow is required
- Depending on the size of the cannula used and the mean systemic venous pressure, a blood flow of up to 2.5 L/min can be achieved (up to 5.5 L/min with an external pump).

Intensive Care Med 2009;35:2105-14.

pros and cons of double lumen cannula and femoro-jugular cannulation

Veno-venous ECMO	
femoral-jugular cannulation	double lumen cannula
PROs	**PROs**
High blood flow 6–7 L/min possible, No fluoroscopy needed for cannulation, Bedside cannulation possible, Heparin free run possible, Suitable for patients with high risk of bleeding	More comfortable for awake patients, Less or no sedation and less pain medication necessary, Fully mobilization, sitting and walking possible
CONTRAs	**CONTRAs**
Risk of femoral cannula kinking during mobilization, Less comfortable for patients, More pain medication, eventually sedation necessary	Fluoroscopy recommended for cannulation, less risk of malposition, bed-side cannulation with high risk with echocardiography possible, pTT 50–60 s needed, not suitable for bleeding patients, patients with severe brain injury or high bleeding risk patients, maximal blood flow about 5 L/min with 31 F cannula

N Engl J Med 2011;365:1905-14.

Table 2: Characteristics of the Studies Included in the Review: Case Series Studies on ILA

*Author, Year	Country/City	Study Design	No. Patients	Male/ Female	Mean Age ± SD, Years (Range)	Indication	Mean Days on ILA ± SD (Range)
Müller et al. 2009 (20)	Germany Regensburg	Prospective	96	NR	22.8 ± 5.6	Brain injury and chest trauma due to traffic accidents	8.2 ± 3.2
Zimmermann et al. 2009 (21)	Germany Regensburg	Prospective	51	43/8	52 (40-59)	ARDS due to pneumonia, trauma, or sepsis (51)	Survivors: 8 (6-10) Non-survivors: 8 (4-16)
Weber-Carstens et al. 2009 (22)	Germany Berlin	Retrospective	10	6/4	54 ± 10.75	Pulmonary fibrosis due to medication (3) Pneumonia of different types (6) Invasive aspergillosis after renal transplantation (1)	31.5 (7-77)
Florchinger et al. 2008 (23)	Germany Regensburg	Prospective	159	121/38	44 ± 17 (7-78)	ARDS (112) Pneumonia (45) End stage cystic fibrosis waiting for lung transplantation (2)	7±6.2 (0-33)
Muellenbach et al. 2008 (24)	Germany Wuerzburg	Retrospective	22	20/2	31 ± 15	Trauma (11) Pneumonia (6) Aspiration (4) COPD (1)	Survivors: 6 (4.8-7.3) Non-survivors: 4.5 (1.5-9)
Fisher et al. 2006 (25)	Germany Hannover	Prospective	12	NR	NR	ARDS as bridge to LTx	15 ± 8 (4-32)
Bein et al. 2005 (26)	Germany Regensburg	Retrospective	5	4/1	22.8 ± 5.6	ARDS and brain injury	8.2 ± 3.2

ILA, interventional lung assist; ARDS, Acute respiratory distress syndrome; COPD, Chronic obstructive pulmonary disease; LTx, Lung transplantation

* Include one study as bridge to LTx;

OHTAS 2010; 10(5)

Removal of CO_2 and Correction of Respiratory Acidosis

Most studies reported a significant reversal of hypercapnea and severe respiratory acidosis within 2 to 6 hours of initiating ILA. Partial pressure of CO_2 in arterial blood and arterial blood pH remained in the normal range until termination of ILA (see Figure 3).

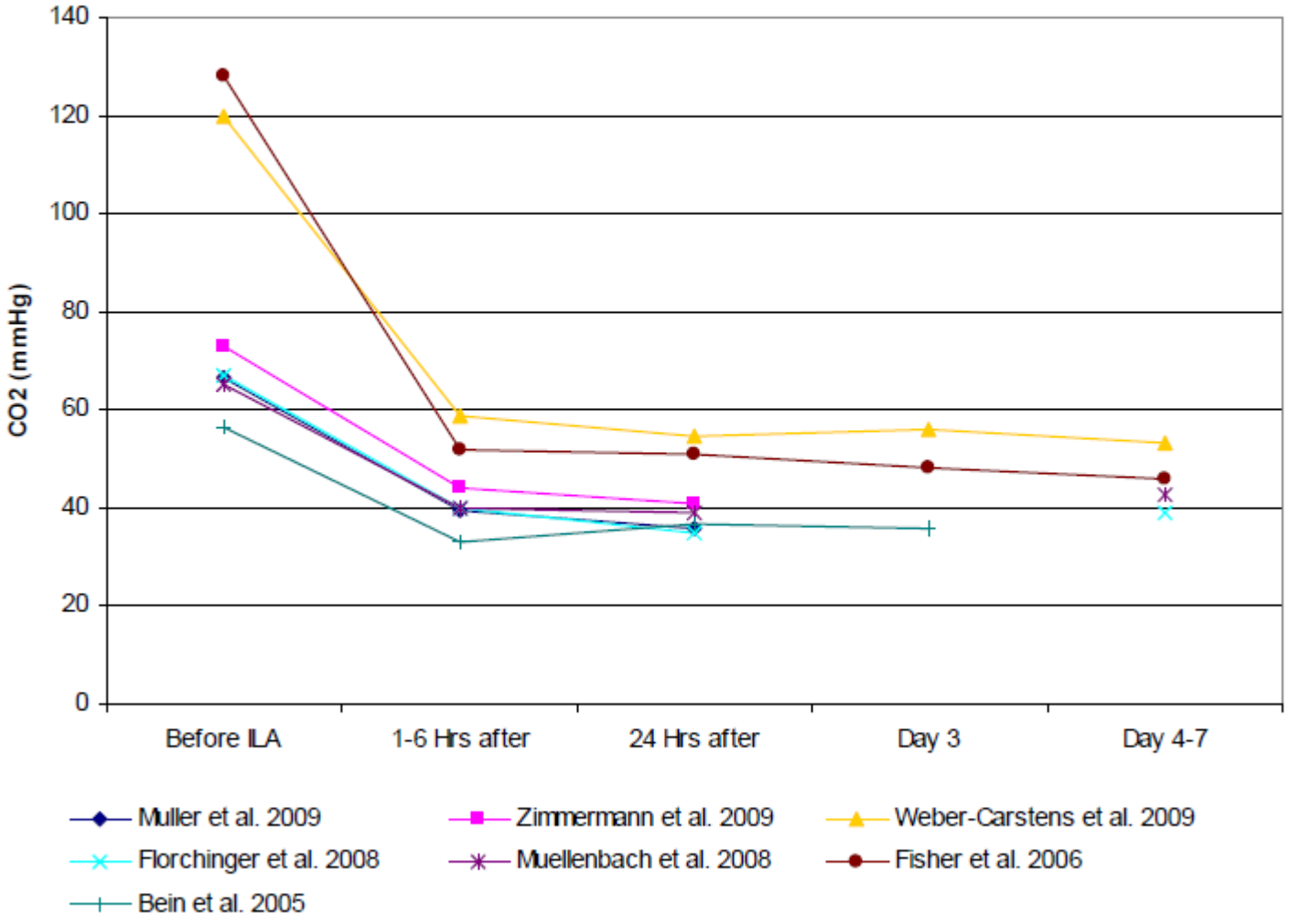


Figure 3: Reduction in partial pressure of CO_2 in arterial blood

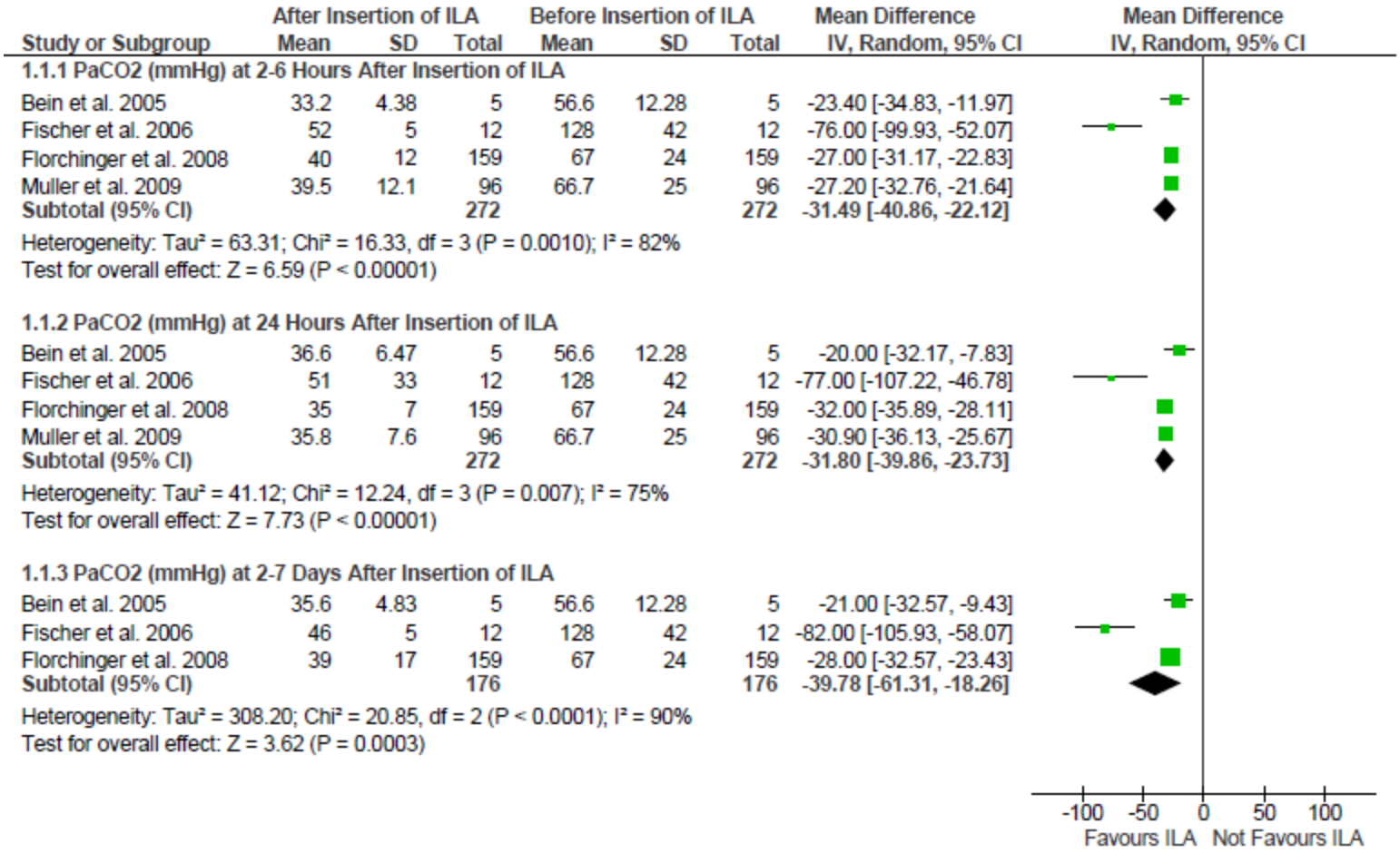


Figure 4: Reduction in Partial Pressure of CO_2 in Arterial Blood

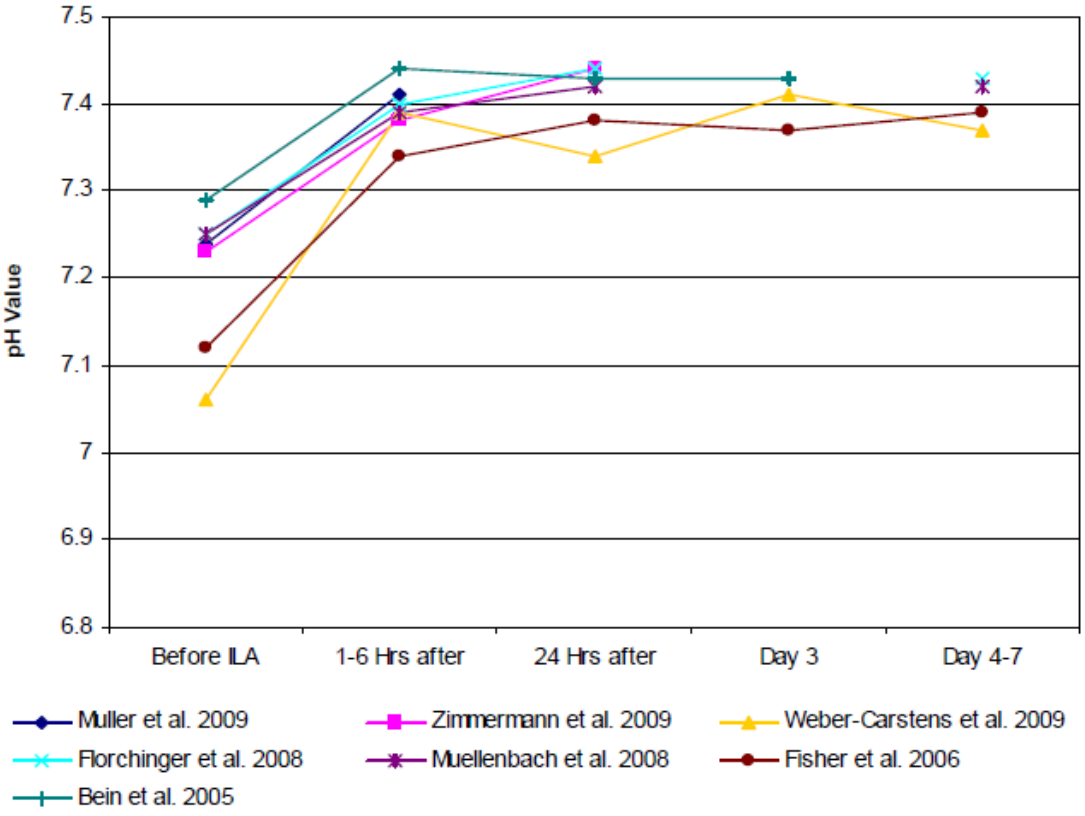


Figure 5: Changes in arterial blood pH and correction of respiratory acidosis

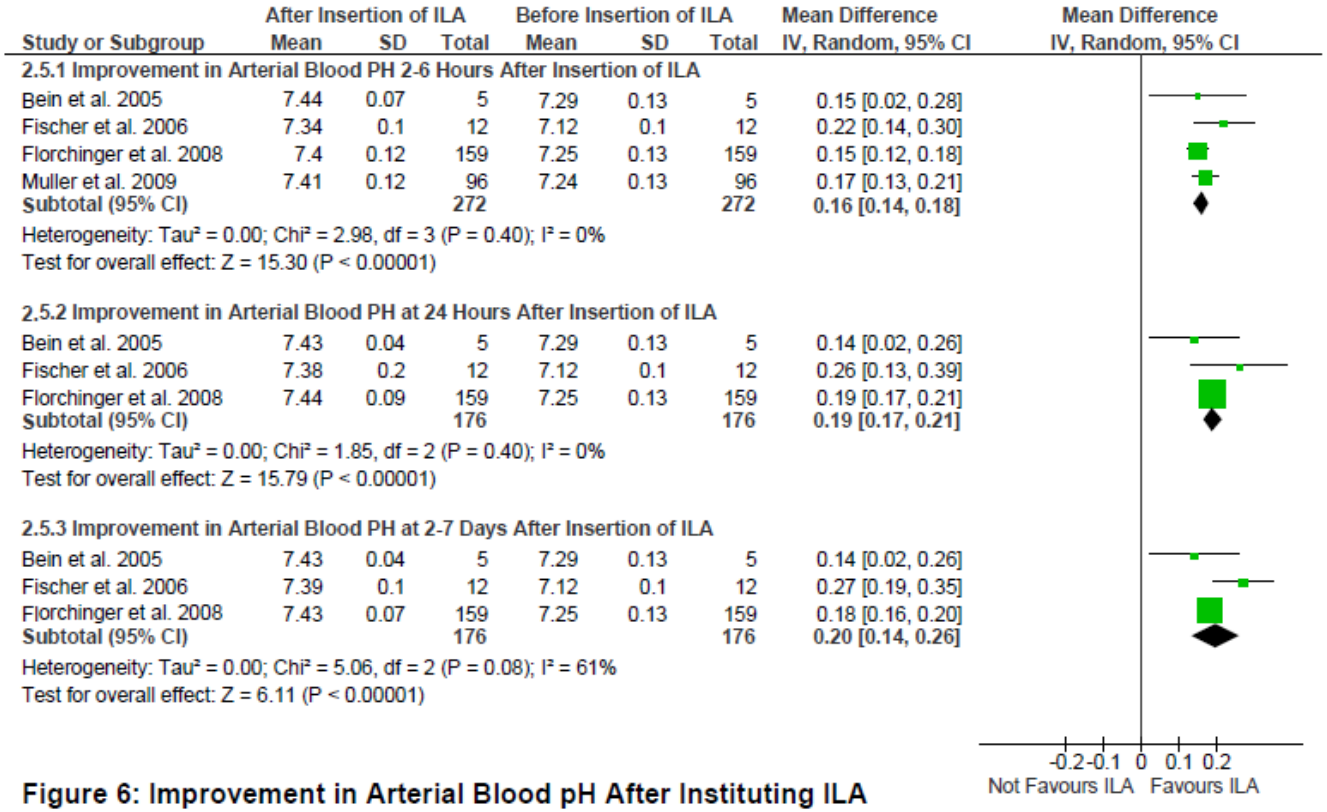


Figure 6: Improvement in Arterial Blood pH After Instituting ILA

Figure 7: Improvement in Ratio of PaO_2/FiO_2 After Instituting ILA

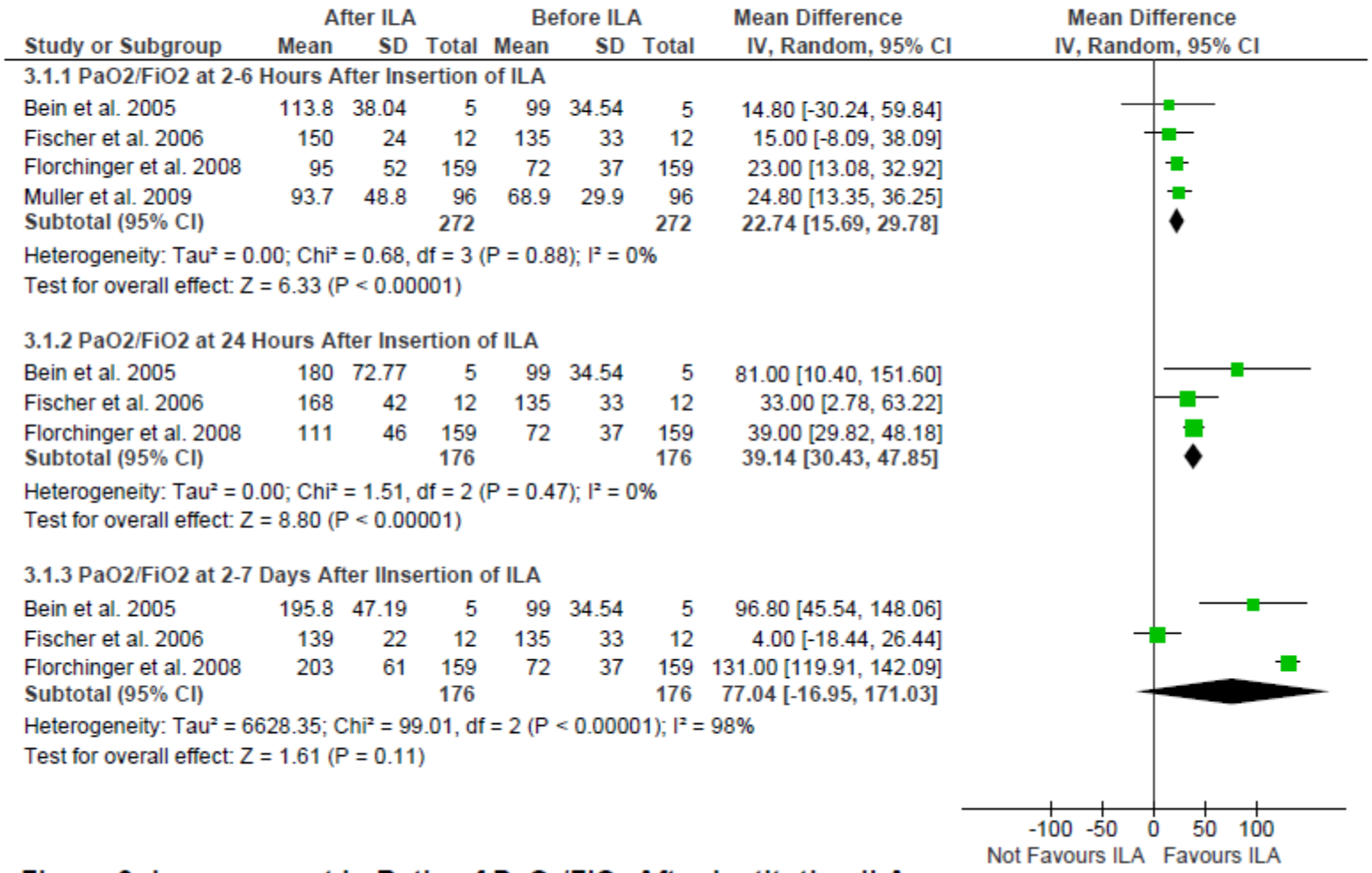


Figure 8: Improvement in Ratio of PaO_2/FiO_2 After Instituting ILA

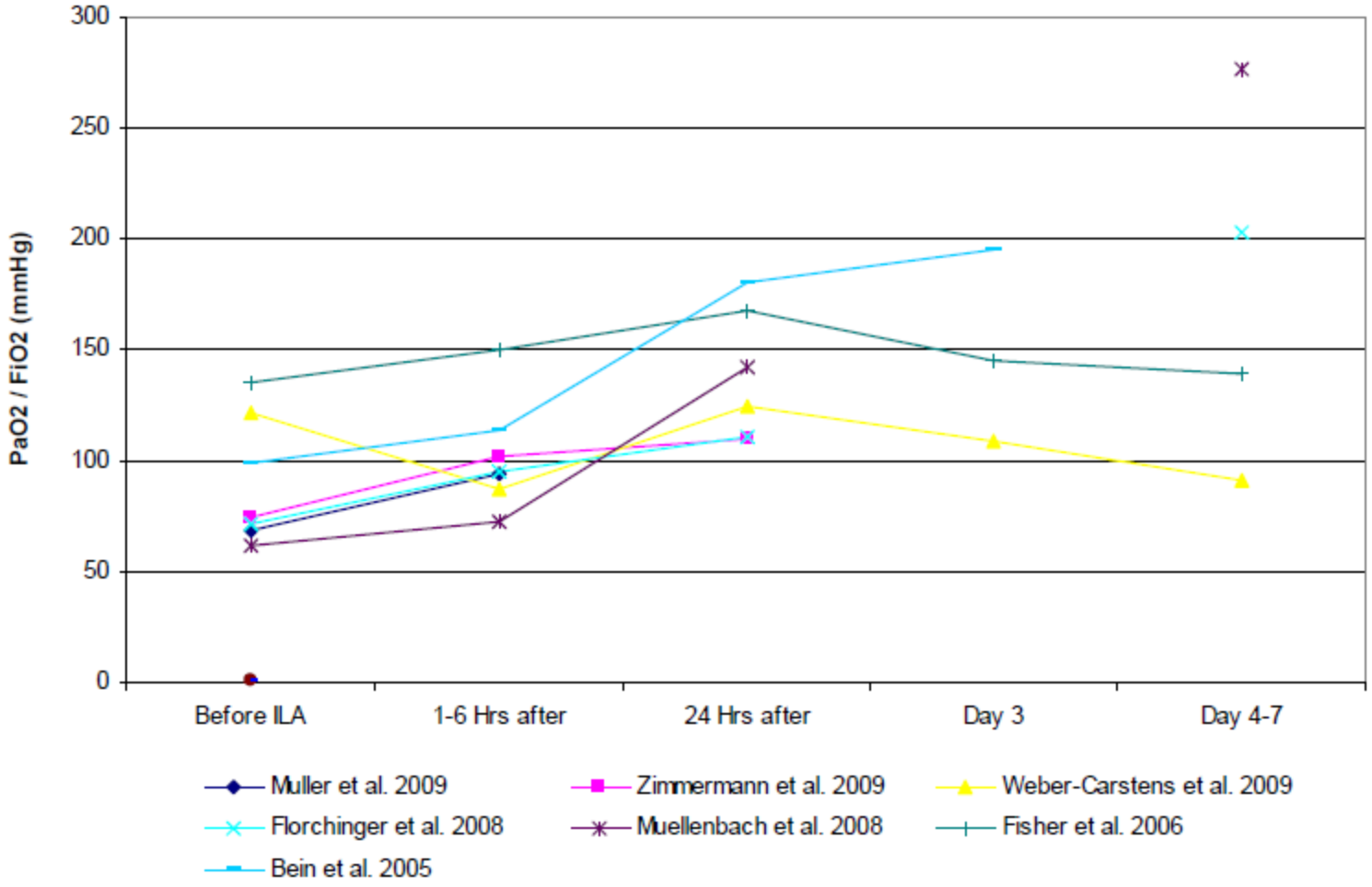


Figure 7: Improvement in Ratio of PaO_2/FiO_2 After Instituting ILA

Table 1. Indications and Contraindications for ECMO in Severe Cases of ARDS.*

Indications
Severe hypoxemia (e.g., ratio of Pao_2 to Fio_2 <80, despite the application of high levels of PEEP [typically 15–20 cm of water]) for at least 6 hr in patients with potentially reversible respiratory failure†
Uncompensated hypercapnia with acidemia (pH <7.15) despite the best accepted standard of care for management with a ventilator
Excessively high end-inspiratory plateau pressure (>35–45 cm of water, according to the patient's body size) despite the best accepted standard of care for management with a ventilator
Relative contraindications
High-pressure ventilation (end-inspiratory plateau pressure >30 cm of water) for >7 days
High Fio_2 requirements (>0.8) for >7 days
Limited vascular access
Any condition or organ dysfunction that would limit the likelihood of overall benefit from ECMO, such as severe, irreversible brain injury or untreatable metastatic cancer
Absolute contraindication
Any condition that precludes the use of anticoagulation therapy‡

N Engl J Med 2011;365:1905-14.

Table 2. Adverse Events Associated with ECMO in Adults with Respiratory Failure.*

Event	Rate
	%
Directly related to the ECMO circuit	
Oxygenator failure	17.5
Blood clots	
Oxygenator	12.2
Other circuit	17.8
Cannula-related problems	8.4
Other mechanical complications	7.9
Not directly related to the ECMO circuit†	
Bleeding	
Surgical-site bleeding	19.0
Cannulation-site bleeding	17.1
Pulmonary hemorrhage	8.1
Gastrointestinal hemorrhage	5.1
Intracranial hemorrhage	3.8
Hemolysis	6.9
Disseminated intravascular coagulation	3.7
Culture-confirmed infection at any site (related or unrelated to ECMO)‡	21.3

N Engl J Med 2011;365:1905-14.

CESAR trial was conducted to assess the effectiveness and cost of ECMO therapy for severe, acute respiratory failure.

The trial protocol were published in 2006 and details of the methods used for the economic evaluation were published in 2008.

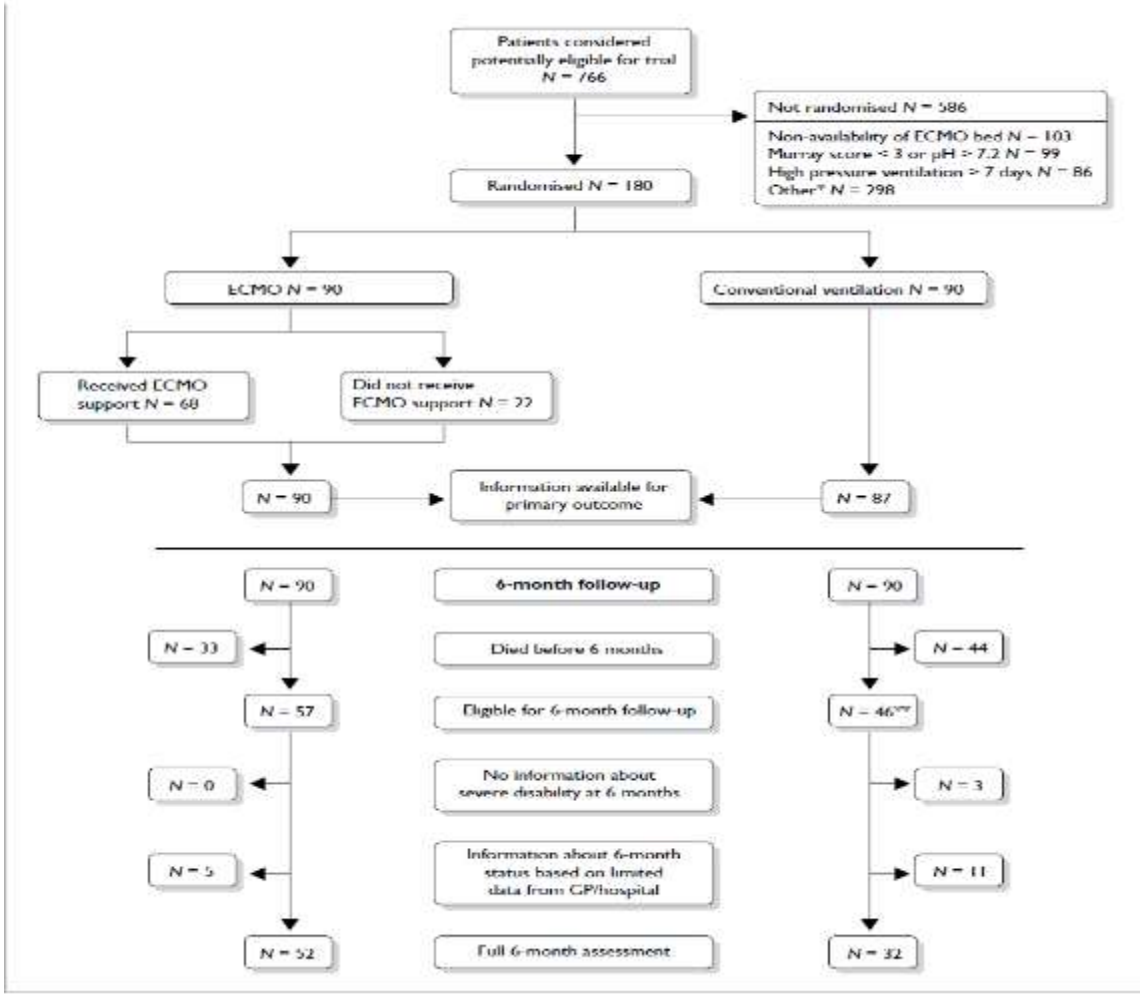
The study itself was a pragmatic trial (similar to a UK trial of neonatal ECMO), in which best standard practice was compared with an ECMO protocol.

- The trial involved 180 patients with acute but potentially reversible respiratory failure, with each also
- Murray score of ≥ 3.0 or uncompensated hypercapnia at a pH of < 7.2.
- Randomized in a 1:1 ratio to receive either conventional ventilation treatment or ECMO while on
- Conventional management included intermittent positive pressure ventilation, high frequency oscillatory ventilation, or both. As a pragmatic trial, a specific management protocol was not followed; rather the treatment centres were advised to follow a low volume low pressure ventilation strategy. A tidal volume of 4 to 8 mL/kg body weight and a plateau pressure of < 30 cm H2O were recommended

Out come measurement

- The primary outcome measure was death or severe disability at 6 months
- The secondary outcomes included a range of hospital indices: duration of ventilation, use of high frequency/oscillation/jet ventilation, use of nitric oxide, prone positioning, use of steroids, length of ICU stay, and length of hospital stay

  and (for ECMO patients only) mode (VV/VA), duration of ECMO.


Patients considered potentially eligible for trial N = 766
Not randomised N = 586
Non-availability of ECMO bed N = 103
Murray score < 3 or pH > 7.2 N = 99
High pressure ventilation > 7 days N = 86
Other* N = 298
Randomised N = 180
ECMO N = 90
Conventional ventilation N = 90
Received ECMO support N = 68
Did not receive ECMO support N = 22
N = 90
Information available for primary outcome
N = 87
N = 90
6-month follow-up
N = 90
N = 33
Died before 6 months
N = 44
N = 57
Eligible for 6-month follow-up
N = 46**
N = 0
No information about severe disability at 6 months
N = 3
N = 5
Information about 6-month status based on limited data from GP/hospital
N = 11
N = 52
Full 6-month assessment
N = 32

	Random allocation	
	ECMO ($N=90$)	CM ($N=90$)
Hospital of trial entry[a]		
CTC	73	75
RH	17	15
Gender		
Male	51	53
Age (years)[a]		
18–30	25	23
31–45	29	32
46–65	36	35
Mean (SD)	39.9 (13.4)	40.4 (13.4)
Primary diagnosis at entry[a]		
Pneumonia	56	53
Obstetric ARDS	0	0
Other ARDS	25	26
Trauma including surgery within 24 hours	5	7
Other	4[b]	4[c]
Number of organs failed[a]		
1–2	62	63
≥ 3	28	27
Duration of IPPV at entry (hours)		
0–48	46	51
49–168	36	32
> 168	6	7
Median (IQR)	35.0 (17.3 to 104.5)	37.0 (15.5 to 101.5)
Missing	2	0
Duration of high-pressure ventilation and/or high FiO2 at entry (days)[a]		
0–48	56	59
49–168	34	31
Median (IQR)	28.5 (17.0 to 69.3)	28.0 (12.0 to 88.0)
Entry based on		
a) Hypoxia[a]	85	87
If yes, Murray score mean (SD)	3.5 (0.6)	(0.3)
Components of Murray score		
PaO_2/FiO_2 mean (SD)	75.9 (29.5)	75.0 (35.7)
PaO_2/FiO_2 median (IQR)	73 (57.5 to 87.0)	70.5 (60 to 88)
PEEP mean (SD)	13.7 (9.6)	14.2 (9.4)
Lung compliance mean (SD)	27.4 (12.2)	25.3 (8.0)
Chest radiograph mean (SD)	3.5 (0.7)	3.7 (0.6)
b) Uncompensated hypercapnoea[a]	5	3
If yes, pH mean (SD)	7.1 (0.1)	7.1 (0.1)

a Minimisation criteria.
b Asthma; Weil's disease; dermatomyositis; pancreatitis.
c Asthma; aspiration; asthma/bronchospasm; acute miliary tuberculosis.

TABLE 4 *Actual management after randomisation*

Actual management	Random allocation	
	ECMO (*N* = 90)	CM (*N* = 90)
ECMO received	68[a]	0
Type of transport to ECMO centre		
Air (+ ground)	24	
Ground	38	
Not transferred	6[b]	
Time between randomisation and starting (hours) – median (IQR)	6.1 (4.0 to 7.1)[c]	
Duration of ECMO (days) – median (IQR)	9.0 (6.0 to 16.0)[d]	
Conventional management (IPPV)		
Transferred for conventional management after randomisation	22[a]	11
Type of transport to conventional centre		
Air (+ ground)	5	2
Ground	14	9
Not transferred	3	79
Duration of IPPV after randomisation (days) – median (IQR)	10 (4.8 to 22.8)	11 (4.0 to 20.3)
Other managements after randomisation		
Missing all data	2	
High frequency/oscillation or jet ventilation	6	13
Nitric oxide	9	6
Prone position	32	38
Steroids	76	58
MARS	15	
Continuous venovenous haemofiltration	72	76
Low volume ventilation strategy at any time	84	63
Proportion of days under low volume ventilation strategy[e] – mean (SD)	0.86 (0.17)	0.67 (0.32)

a Of those who did not receive ECMO, 16 improved with conventional care, three died before transfer to Glenfield, two died in transit and one patient required amputation and could therefore not be heparinised.
b Already in the ECMO centre receiving conventional treatment.
c *N* = 66. Includes one patient whose condition improved on arrival at the ECMO centre so was managed conventionally but then 10 days later deteriorated and ECMO was started.
d *N* = 67. Includes three patients who had a second course of ECMO.
e Based on those under low volume ventilation strategy at all.

Primary outcome

	Allocation		
	ECMO (*N*=90)	CM (*N*=90)	RR (95% CI)
Death or severe disability at 6 months			
No	57	41	
Yes	33	46	0.69 (0.05 to 0.97) (p=0.03)[a]
No information about severe disability at 6 months	0	3	
Died ≤6 months or died before discharge			
No	57	45	
Yes	33	45	0.73 (0.52 to 1.03) (p=0.07)
Severe disability			
Yes	0	1	
No	57	41	
Died ≤6 months before discharge	33	45	
No information about severe disability at 6 months	0	3	
Cause of death			
Respiratory failure	8	24	
Multi-organ failure	14	15	
Neurological	4	2	
Cardiovascular	1	3	
ECMO related	1	0	
Other	1	0	
Unknown	4	1	
Randomisation to death interval (days)			
Median (IQR)	15 (3.0 to 40.5)	5 (2 to 14)	

a Based on 187 patients with known primary outcome. The three patients in the CM group for whom the severe disability status at 6 months was unknown had all been discharged from hospital 1–3 months post randomisation and were known to be alive at 6 months. Sensitivity analyses assuming that these three patients had all been or not been severely disabled change these figures to RR=0.67 (95% CI 0.48 to 0.94), p=0.017, and RR=0.72 (95% CI 0.51 to 1.01), p=0.051 respectively.

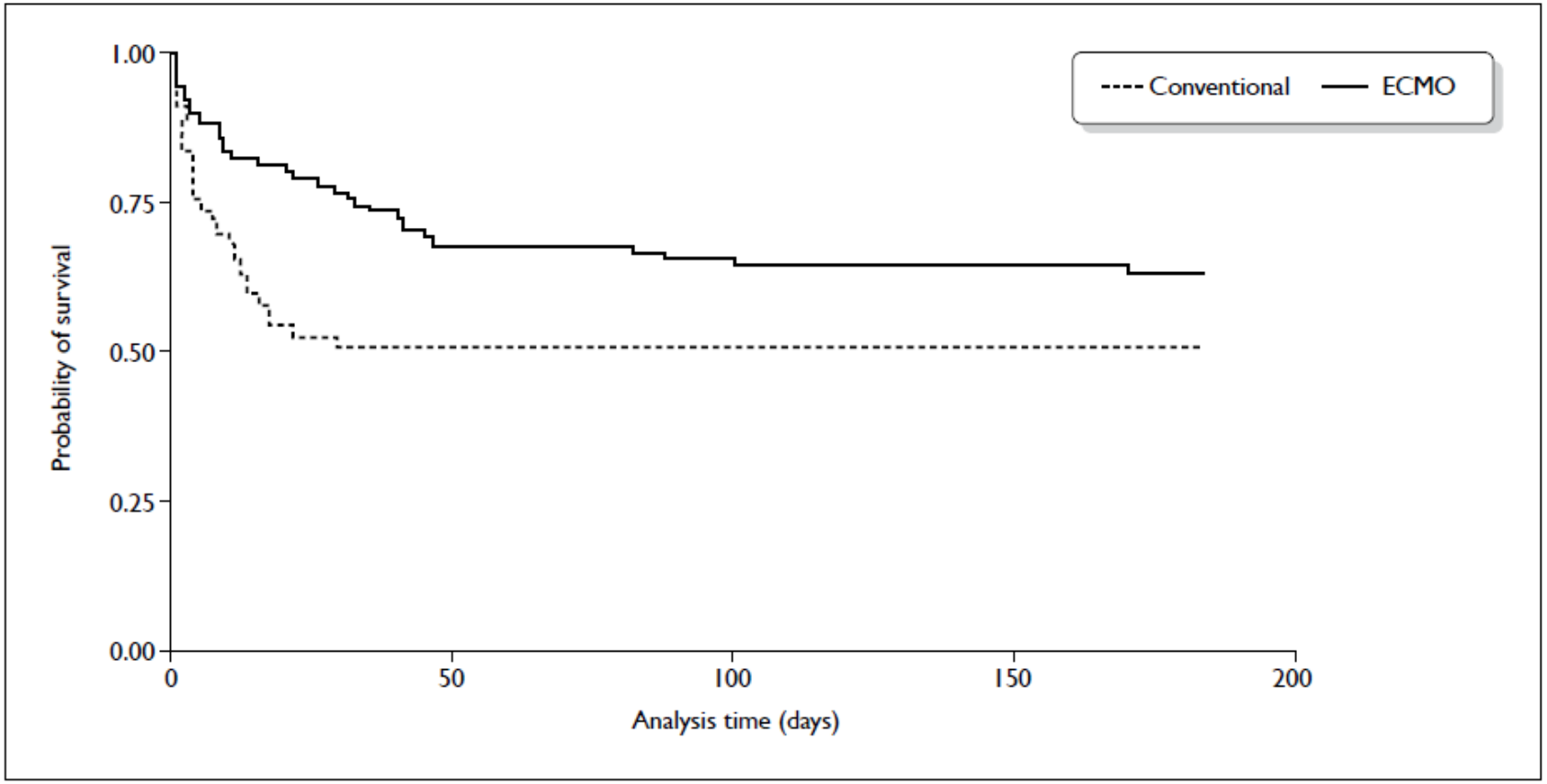


FIGURE 2 *Kaplan–Meier survival estimates, by allocation.*

Inhaled vasodialator

- Inhaled vasodilator can result in important physiologic benefits (eg, improved hypoxemia, lower pulmonary arterial pressure, and improved right-ventricular function and cardiac output) without systemic hemodynamic effects.
- Inhaled nitric oxide (INO) and aerosolized prostacyclins are currently the most frequently used inhaled vasodilators. Inhaled prostacyclins are as effective physiologically as INO and cost less.
- Randomized controlled trials of INO in the treatment of ARDS have shown short-term physiologic benefits, but no benefit in long-term outcomes.
- No outcome studies have been reported on the use of prostacyclin in patients with ARDS.
- There is no role for the routine use of inhaled vasodilators in patients with ARDS. Inhaled vasodilator as a rescue therapy for severe refractory hypoxemia in patients with ARDS may be reasonable, but is controversial

Respir Care2014;Feb;55(2):144-5

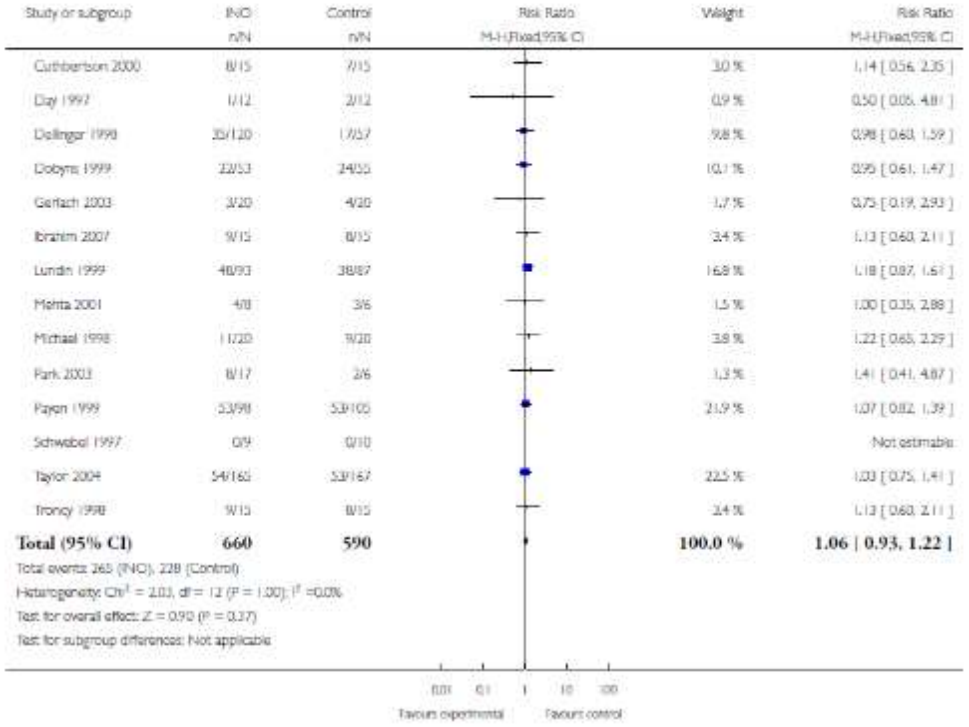
Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) and acute lung injury in children and adults (Review)

Analysis 1.1. Comparison 1 Mortality: INO versus control group, Outcome 1 Longest follow up mortality (complete case analysis): INO vs. control.

Review: Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) and acute lung injury in children and adults

Comparison: 1 Mortality: INO versus control group

Outcome: 1 Longest follow up mortality (complete case analysis): INO vs. control



Analysis 1.2. Comparison 1 Mortality: INO versus control group, Outcome 2 28-30 day mortality: INO vs. control.

Review: Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) and acute lung injury in children and adults

Comparison: 1 Mortality: INO versus control group

Outcome: 2 28-30 day mortality: INO vs. control

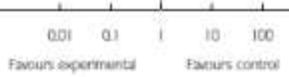
Study or subgroup	INO n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cuthbertson 2000	8/15	7/15		4.1 %	1.14 [0.56, 2.35]
Dellinger 1998	35/120	17/57		13.4 %	0.98 [0.60, 1.59]
Lundin 1999	41/93	35/87		21.1 %	1.10 [0.78, 1.55]
Mehta 2001	4/8	2/6		1.3 %	1.50 [0.40, 5.65]
Michael 1998	11/20	9/20		5.2 %	1.22 [0.65, 2.29]
Park 2003	8/17	2/6		1.7 %	1.41 [0.41, 4.87]
Payen 1999	48/98	46/105		25.9 %	1.12 [0.83, 1.50]
Taylor 2004	44/192	39/193		22.6 %	1.13 [0.77, 1.66]
Troncy 1998	9/15	8/15		4.7 %	1.13 [0.60, 2.11]
Total (95% CI)	**578**	**504**		**100.0 %**	**1.12 [0.95, 1.31]**

Total events: 208 (INO), 165 (Control)

Heterogeneity: $Chi^2 = 0.72$, df = 8 ($P = 1.00$); $I^2 = 0.0\%$

Test for overall effect: $Z = 1.32$ ($P = 0.19$)

Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1 Mortality: INO versus control group, Outcome 3 Mortality: subgroup analysis, paediatric vs. adult population.