ARDS
Proning, ECMO , NO which works

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- I have nothing to disclose other than I like the challenge to treat ARDS patients

Berlin definition of ARDS

- Timing : Within 1 week of a known clinical insult or new or worsening respiratory symptoms.

- Chest radiography : Bilateral opacities – not fully explained by effusions, lobar/lung collage, or nodules.

- Origin of edema : Respiratory failure not fully explained by cardiac failure or fluid overload.

- Severity : Mild : PO2/ FiO2 200-300

    Moderate : PO2/ FiO2 200-100

    Severe : PO2/ FiO2 less than 100

With PEEP equal or more than 5cm H20

Pathogenesis of ARDS

- Lung stiffness :non cradiogenic pulmonary edema.

    Surfactant depletion and resultant atelectasis.

    DAD

- All these processes are more pronounced in the dependent areas of the lung (usually dorsal).

- ARDS lungs are baby lungs , fragile and need rest (protective mechanical ventilation).

- Mortality in ARDS is mainly driven by VILI , MOF and hypoxia.

- Refractory hypoxia per se is associated with poor prognosis in ARDS even though it accounts for 10% mortality.

Proning in ARDS

- First suggested in 1974 for pediatric group.
- Studies in ARDS started in late 1990s.

Proning
Pathophysiological concept

Gattinoni et al AJRCCM 2013
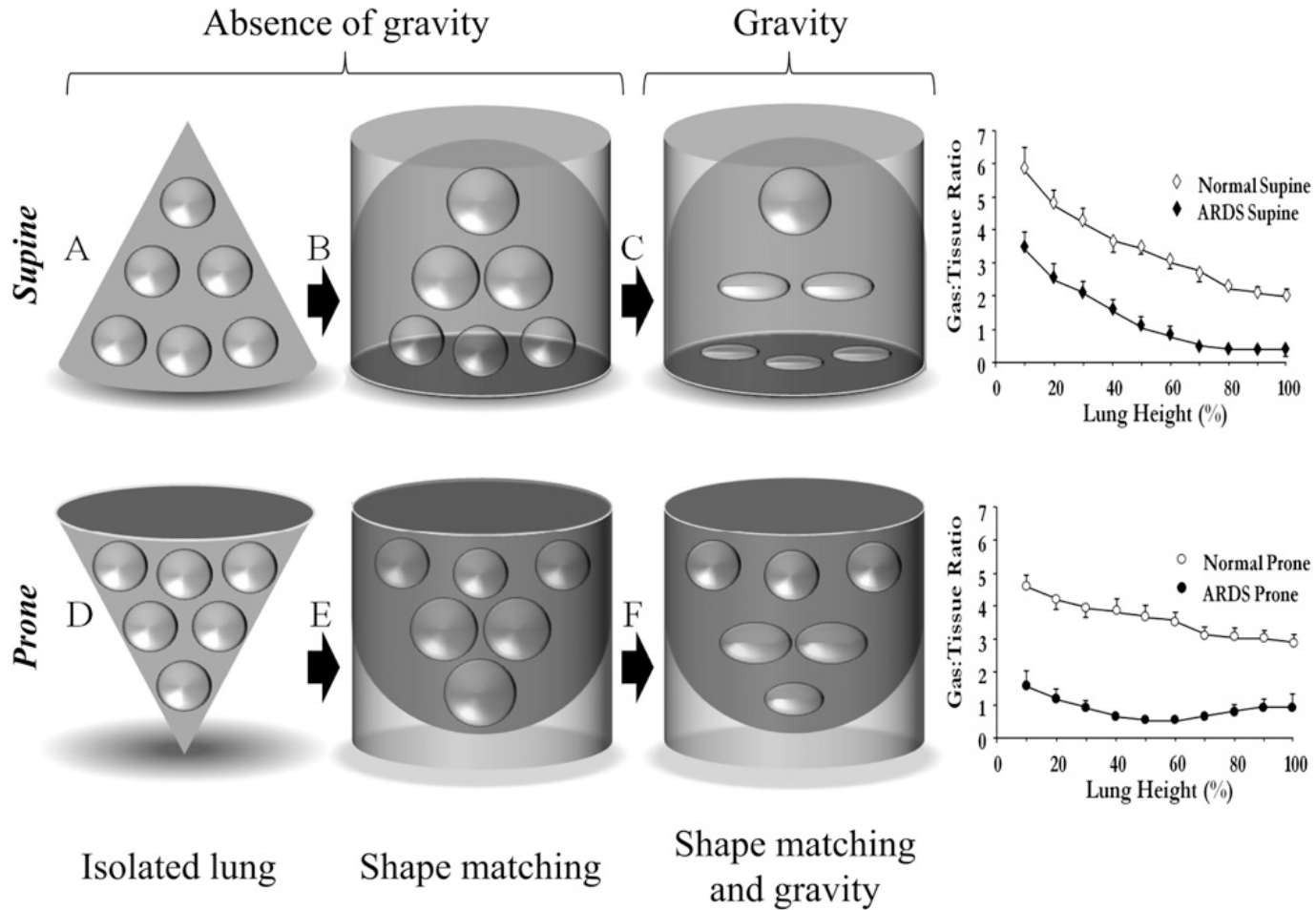
- In ARDS lung weight increases 4-5 times compressing more the dorsal part and potentiating the abdominal and heart weight eventually aggravating the compression atelectasis.

- Atelectetic lung adds to lung stiffness and eventually ARDS.

- Ventral lung gets hyperinflated in supine position predisposing to barotrauma and volutrauma.

Gattinoni et al AJRCCM 2013

Pathophysiologic benefits of proning

- Chest wall compliance decrease initially elevating peak and plateau pressures (mechanical restriction).

- Transpulmonary pressure and so stress and strain is more evenly distributed across the lung zones in prone position.

- Gas-to-tissue ratio gets more uniform and eventually dorsal lung recruits more than the ventral derecruitment improving compliance.

- Other benefits: improved lymphatic drainage, improved secretion drainage by the repositioning and drop in FiO2 requirement attenuating oxygen toxicity and surfactant depletion.

Gattinoni et al AJRCCM 2013

Gases in prone position

- All studies showed significant improvement in oxygenation in prone position.

- This effect is mainly due to recruitment of the dorsal lung rather than redistribution of blood flow to better aerated areas.

- Improved CO_2 clearance in prone position isn't necessarily related to improvement of oxygenation.

- CO_2 clearance correlates more with less (VILI in ventral lung) and recruitment of dorsal lung improving lung compliance, eventually minute ventilation , so reflecting improvement of prognosis.

Gattinoni et al AJRCCM 2013

Contraindications

- Mainly adopted from studies : facial trauma or spinal instability ,pelvic fractures , increased intracranial pressure, anterior chest tubes with air leak ? , ? Hemodynamic instability, life threatening dysrythmias , massive hemoptysis , chronic hypoxemic respiratory failure, ? DVT, ?inhaled nitric oxide and pregnancy.

- ? ECMO

Complications

- Accidental extubation , tube obstruction , line displacement , feeding issues , hemodynamic instability , bed sores.

How to prone

- Manual or mechanical.
- Manual : easy to apply , the most experienced person takes care of the ETT and CVC, patient pulled to the edge and rolled as a block by the team with the arm of the side to turn to below the hip.
- Pillows applied below face , shoulders and hip.
- Face turned toward the ventilator.
- Mechanical bed rotation offers less labor, shorter duration to turn and ease of turning back in case of arrest to do CPR.
- Issues : facial edema and family concern, nutrition, bed sores.

When to stop proning

- PO2 more than 150 with FiO2 less than 60% and PEEP less than 10 in supine session after 4 hours of the last prone session.

- Interruption of Proning : drop in PO2/FiO2 ratio of more than 20% compared to supine , mechanical complication , O2 sat less than 85% , bradycardia , hemodynamic instability.

Clinical evidence for proning

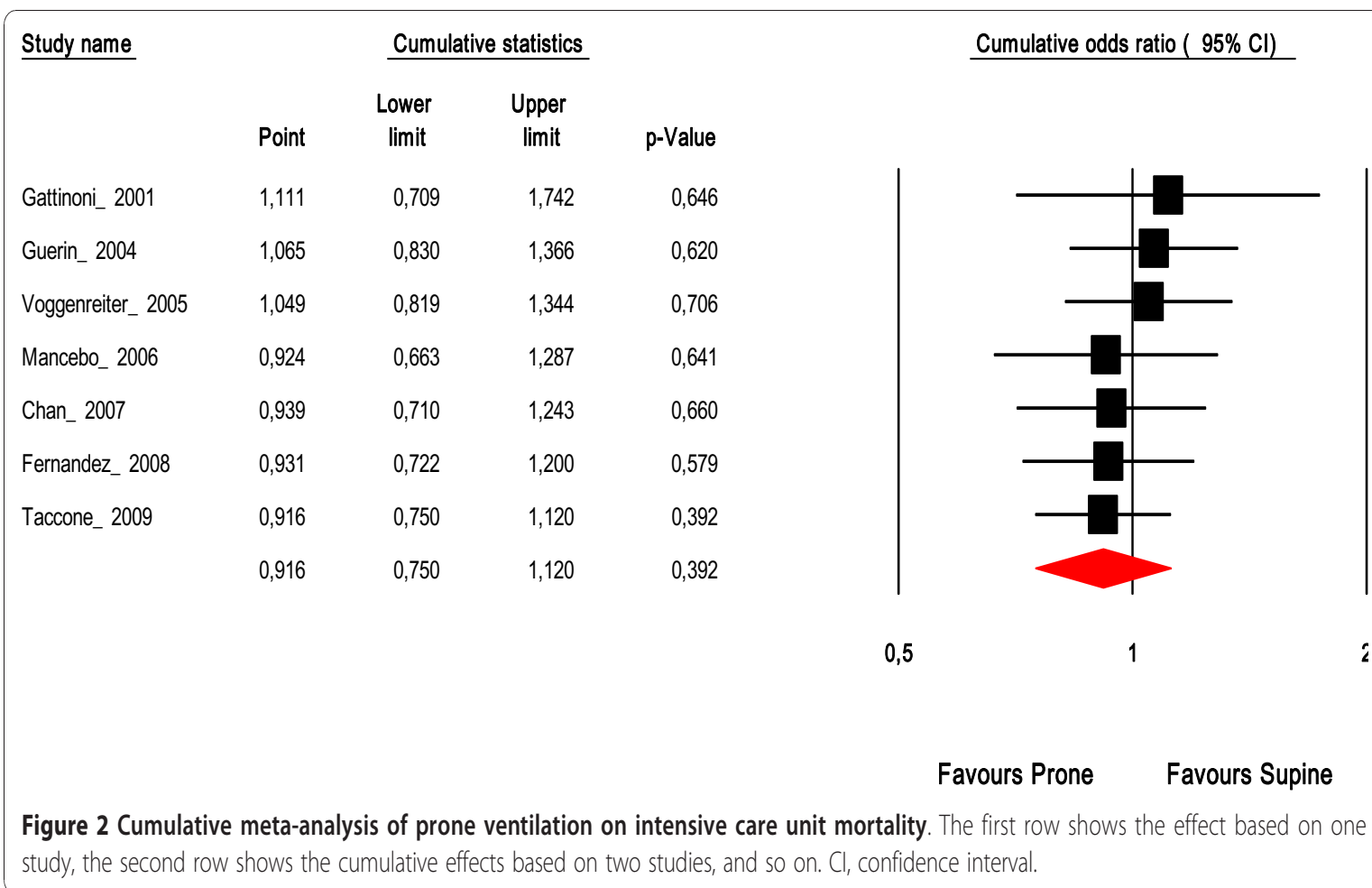- Earlier metanalysis by Abroug in 2008 didn't show significant survival benefit , while showed significant improvement of oxygenation , marginal benefit concerning VAP while ICU lenght of stay was marginally increased with proning.

- Studies included patiens with mainly mild disease, proned for short duration and didn't use lung protective ventilation strategy.

Abroug et al intensive care medicine 2008

Updated Metanalysis by Abroug 2014

Trial	Disease	PaO$_2$/ FiO$_2$ ratio	SAPS II	Population	Prone (n)	Supine (n)	Actual prone duration/ day (hours)	Crossover allowed	Protective lung ventilation	Jadad score
Gattinoni_2001 [1]	ALI/ARDS (6%/94%)	127	40	304	152	152	7	Yes	No	3
Guerin_2004 [2]	ALI/ARDS (21%/31%) and other causes of ARF (pneumonia; acute on chronic ARF; CPE, coma)	153	46	791	413	378	8	Yes	No	3
Voggenreiter_2005 [3]	ALI/ARDS (45%/55%) (trauma)	222	NA	40	21	19	11	No	Yes	3
Mancebo_2006 [16]	ARDS	145	41	136	76	60	17	Yes	Yes	3
Chan_2007 [21]	ARDS	109	NA	22	11	11	24	No	Yes	1
Fernandez_2008 [17]	ARDS	120	38	40	21	19	20	Yes	Yes	3
Taccone_2009 [10]	ARDS	113	40	342	168	174	18	Yes	Yes	3
Total/mean		141 ± 39		1,675	862	813	15 ± 6			

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; ARF, acute respiratory failure; CPE, cardiogenic pulmonary oedema; SAPS II, Simplified Acute Physiology Score II.

Abroug et al. Critical Care 2014

9% nonsignificant drop in mortality in overall

Study name	Cumulative statistics				Cumulative odds ratio (95% CI)
	Point	Lower limit	Upper limit	p-Value	
Gattinoni_ 2001	1,111	0,709	1,742	0,646	
Guerin_ 2004	1,065	0,830	1,366	0,620	
Voggenreiter_ 2005	1,049	0,819	1,344	0,706	
Mancebo_ 2006	0,924	0,663	1,287	0,641	
Chan_ 2007	0,939	0,710	1,243	0,660	
Fernandez_ 2008	0,931	0,722	1,200	0,579	
Taccone_ 2009	0,916	0,750	1,120	0,392	
	0,916	0,750	1,120	0,392	

0,5   1   2

Favours Prone   Favours Supine

Figure 2 Cumulative meta-analysis of prone ventilation on intensive care unit mortality. The first row shows the effect based on one study, the second row shows the cumulative effects based on two studies, and so on. CI, confidence interval.
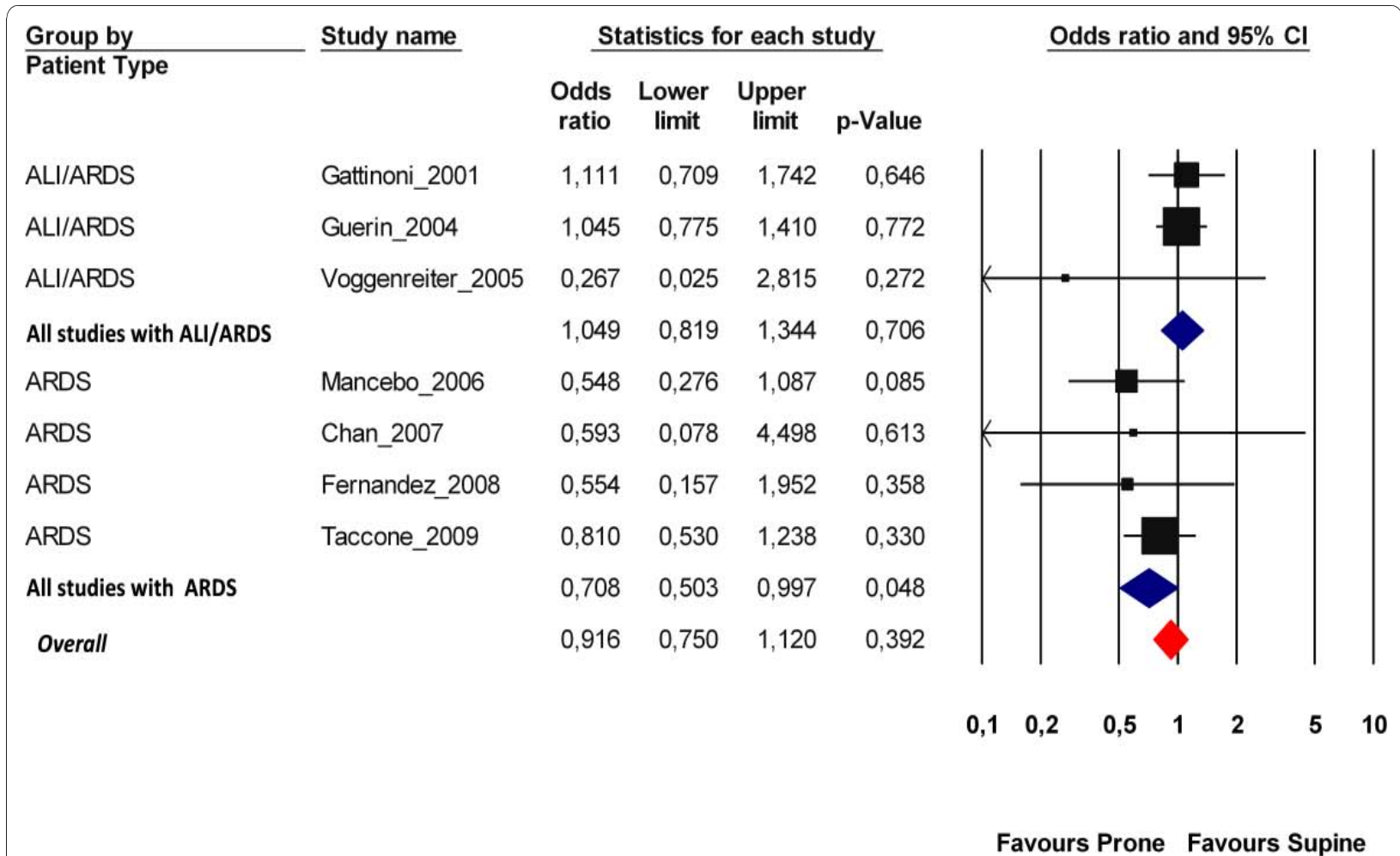
Abroug et al. Critical Care 2014

Figure 3 Effects of prone ventilation on intensive care unit mortality. Point estimates (by random-effects model) are reported separately for the groups of studies that included both acute lung injury (ALI) and acute respiratory distress syndrome patients (ARDS), those that included only ARDS patients, and the pooled overall effects of all meta-analysis-included patients. CI, confidence interval.

Hu et al. Critical Care 2014
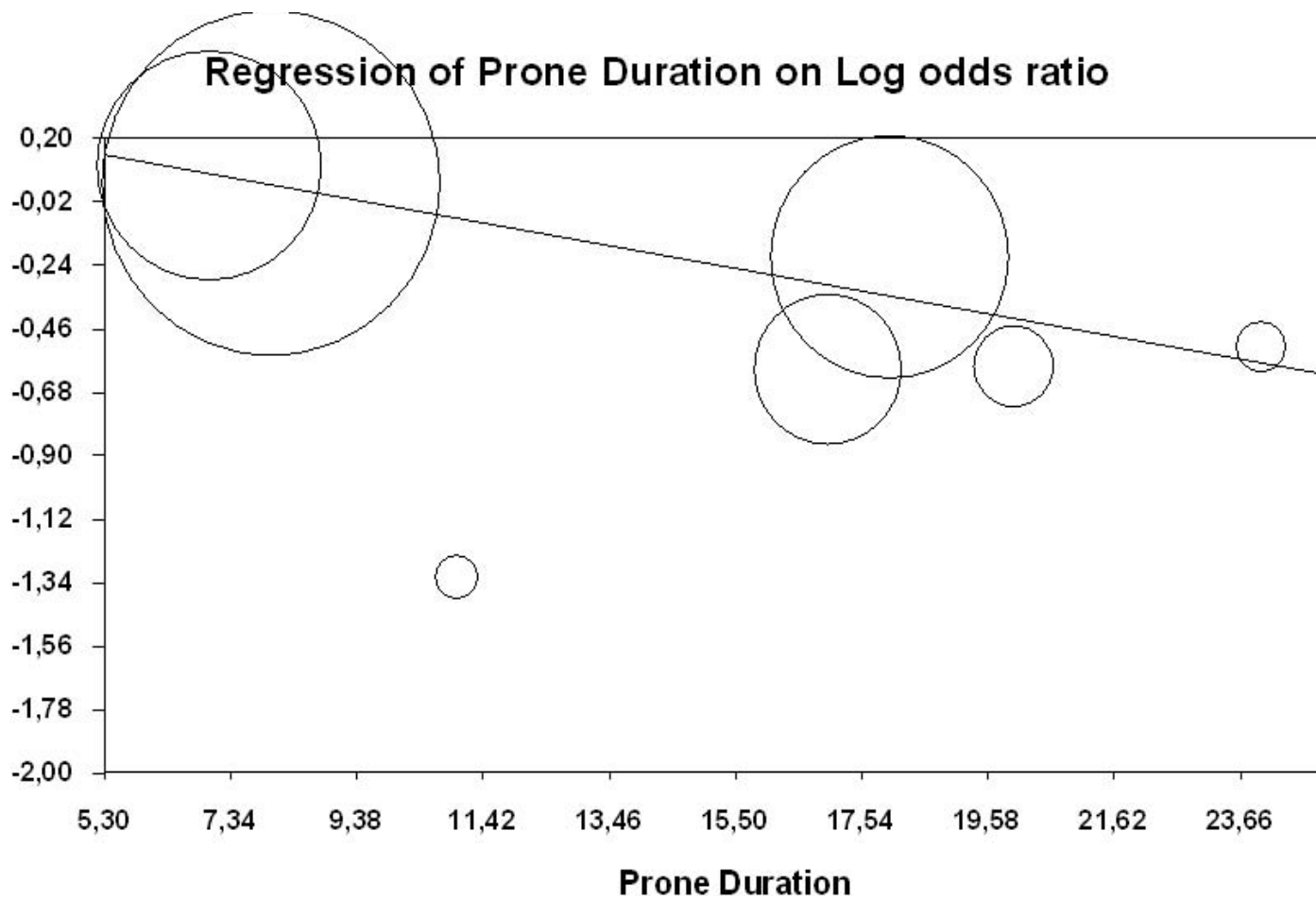
Adverse events

- Non significant increase in accidental extubation in prone group.

- Sud et al 2014 conducted a systematic review analyzing patients with ARDS according to the recent definition.

- Analyzed studies based on use of lung protective ventilation strategy.

| Study | Deaths, *n*/*N* | | RR (95% CI) | |
	Prone	Supine		
Protective lung ventilation mandated				
Curley et al.,[37] 2005	4/51	4/51	1.00 (0.26–3.78)	
Voggenreiter et al.,[38] 2005	1/21	3/19	0.30 (0.03–2.66)	
Chan et al.,[35] 2007	5/11	6/11	0.83 (0.36–1.94)	
Fernandez et al.,[34] 2008	8/21	10/19	0.72 (0.36–1.45)	
Taccone et al.,[14] 2009	79/166	91/172	0.90 (0.73–1.11)	
Guerin et al.,[17] 2013	57/240	95/234	0.58 (0.44–0.77)	
Subtotal Heterogeneity: I^2 = 29%	154/510	209/506	0.74 (0.59–0.95)	
Protective lung ventilation not mandated				
Gattinoni et al.,[15]* 2001	92/148	87/149	1.06 (0.88–1.28)	
Beuret et al.,[39] 2002	1/4	0/3	2.40 (0.13–44.41)	
Guerin et al.,[16] 2004	98/230	81/183	0.96 (0.77–1.20)	
Mancebo et al.,[36] 2006	38/76	37/60	0.81 (0.60–1.10)	
Subtotal Heterogeneity: I^2 = 0%	229/458	205/395	0.98 (0.86–1.12)	
Overall Heterogeneity: I^2 = 42%	383/968	414/901	0.86 (0.73–1.00)	

Favours prone ← | → Favours supine
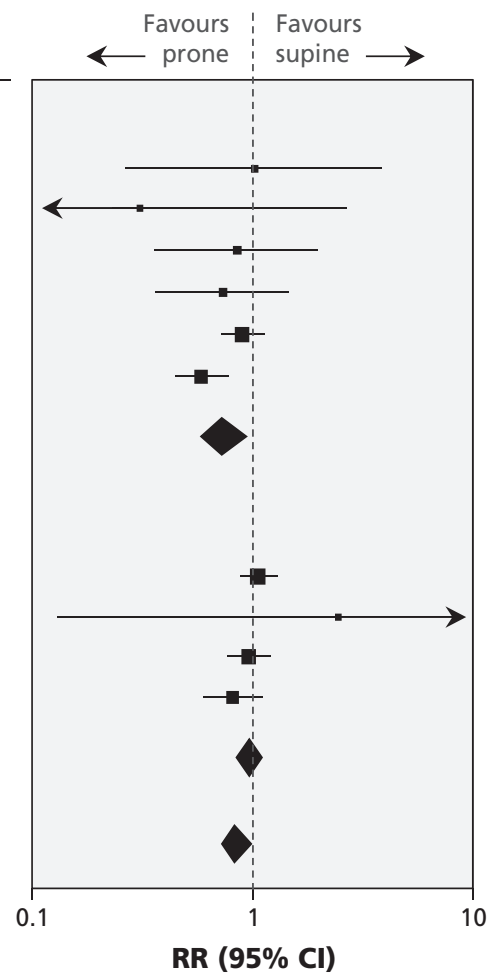
RR (95% CI)

0.1   1   10

Table 3: Results of primary and sensitivity analyses for the effect of prone positioning during mechanical ventilation on mortality among patients with acute respiratory distress syndrome (ARDS)

Analysis*	No. of trials	No. of deaths, n/N	Risk ratio (95% CI)	I^2 value, %
Primary				
Trials mandating protective ventilation†	6	363/1016	0.74 (0.59–0.95)	29
Sensitivity				
Included all trials‡	10	797/1869	0.86 (0.73–1.00)	42
Assumed patients lost to follow-up lived	6	363/1020	0.74 (0.59–0.95)	28
Assumed patients lost to follow-up died	6	366/1020	0.74 (0.59–0.94)	26
Excluded trial in which allocation was not concealed[35]	5	352/994	0.73 (0.55–0.98)	43
Excluded trial with pediatric population[37]	5	355/914	0.73 (0.56–0.96)	42
Included trial that used moderate tidal volume (< 10 mL/kg)[36]	7	438/1152	0.77 (0.65–0.91)	16
Fixed-effects model	6	363/1016	0.74 (0.63–0.87)	29

Note: CI = confidence interval.
*Random-effects models were used for all analyses except in the final sensitivity analysis.
†Tidal volume < 8 mL/kg of predicted or actual body weight.
‡For the 2 trials that enrolled some patients without ARDS,[16,39] we included only patients whose condition met the authors' definition of ARDS; when the analysis was redone to include all patients in these trials, the risk ratio changed minimally (0.87, 95% CI 0.74–1.02; I^2 = 48%).

| Variable	No. of trials	Deaths, n/N		RR (95% CI)	I² value, %	Favours prone ← → Favours supine
		Prone	Supine			
Protective lung ventilation						
Mandated	6	154/510	209/506	0.74 (CI 0.59–0.95)	29	
Not mandated	4	229/458	205/395	0.98 (CI 0.86–1.12)	0	p = 0.05
Duration of prone positioning						
≥ 16 h/d	6	191/565	243/547	0.77 (CI 0.64–0.92)	21	
< 16 h/d	4	192/403	171/354	1.02 (CI 0.88–1.17)	0	p = 0.02
Level of hypoxemia*						
Severe	6	75/210	102/209	0.76 (CI 0.61–0.94)	0	
Moderate	6	75/274	102/268	0.74 (CI 0.48–1.16)	42	
Mild	4	3/22	3/23	0.98 (CI 0.18–5.24)	0	p > 0.9

RR (95% CI)

Sud et al, CMAJ , 2014
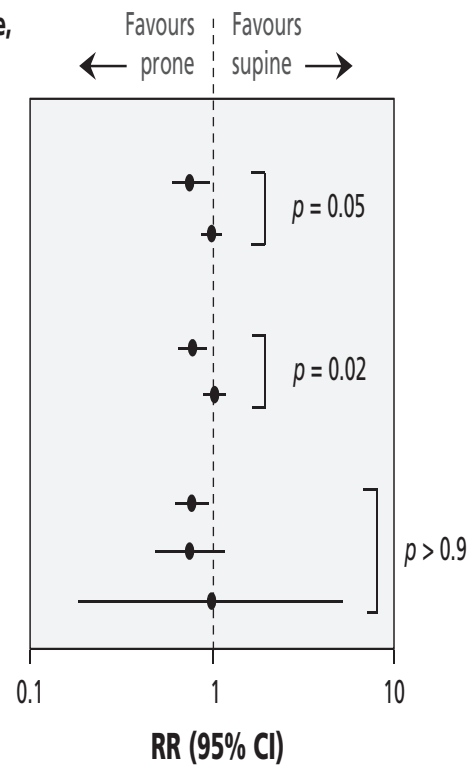
Table 4: Physiologic, clinical and safety outcomes associated with prone positioning during mechanical ventilation

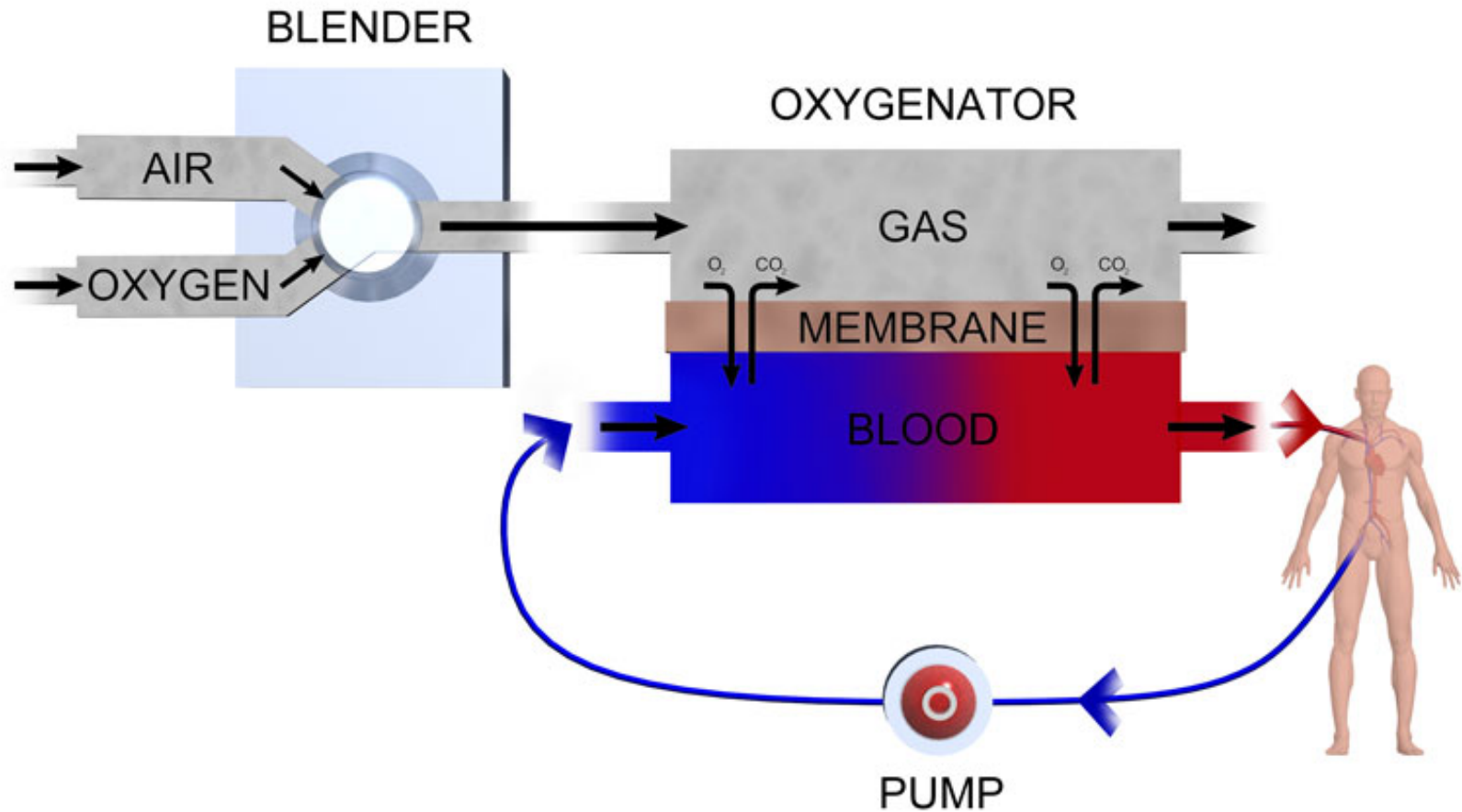| Outcome	No. of patients or events	Measure of effect*	I^2 value, %
Oxygenation (PaO₂/FIO₂ ratio)†	No. of patients	Ratio of means (95% CI)	
Day 1	1283	1.36 (1.25–1.47)	49
Day 2	1171	1.29 (1.21–1.37)	27
Day 3	933	1.25 (1.18–1.31)	0
Clinical and safety outcomes	No. of events, n/N	Risk ratio (95% CI)	
Ventilator-associated pneumonia	368/1561	0.89 (0.71–1.13)	0
Pressure ulcers	818/1765	1.27 (1.16–1.40)	0
Obstruction of endotracheal tube	200/1847	1.60 (1.27–2.02)	0
Unplanned extubation or dislodgement of endotracheal tube‡	211/2309	1.08 (0.78–1.48)	16
Unplanned removal of central or arterial lines	59/886	1.49 (0.42–5.27)	67
Dislodgement of thoracostomy tube	17/886	3.14 (1.02–9.69)	0
Pneumothorax	95/1663	0.84 (0.57–1.25)	0
Cardiac arrest	211/1527	0.73 (0.39–1.38)	76

Conclusion

- Proning improves outcome if applied concurrently with lung protective strategy ,enough duration (more than 16 hours/day) and in moderate to severe hypoxemia , ? all spectrum of the disease severity.

- Adverse effects as endotracheal tube dislodgment or obstruction, pressure ulcer and others are more common with Proning, therefor it is advised to refer these patients to centers specialized with prone ventilation and to create protocols for Proning with emphasis on nursing care items.

- Data is still not definite concerning optimal duration of sessions but at least it should be more than 16 hours per day.

- Larger study including different disease severity is still needed.

Why don't we give full rest for the lungs

ECMO

- 1968 Kolobow invented the first prolonged ECMO, in 1972 it was used successfully for first time for respiratory failure (75 hours) in polytrauma patient. Hill et al Mt Saini Med J 1973

- First RCT by NIH published in JAMA 1979 (90 patients heterogeneous group of respiratory failure , had high mortality rate in both arms)

- Since 2006 it became more popular especially with H1N1 pandemic and technological advances.

- ECMO has been subject to technical advances including more biocompatible membranes , heparin coated circuits and better cannulas.

Illustration: Lara Durrant and Peter Kuempel

BLENDER

AIR

OXYGEN

OXYGENATOR

GAS

O_2 CO_2 O_2 CO_2

MEMBRANE

BLOOD

PUMP

How ECMO Works:

The oxygenator in venovenous ECMO. The ECMO pump delivers venous blood to the oxygenator. This device is divided into two separate 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 CO_2 elimination) take 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.

- Usually if there is no left ventricular dysfunction venovenous ECMO is used (less hypoxia to the heart and brain) rather than venoarterial.

- Different ways to drain blood and return it to the patients.

- The key point to avoid recirculation and improve efficiency of the oxygenation is draining from the vena cava and return blood to the right atrium.

- Target is to keep PO2 in the arterial blood more than 55mm Hg or O2 sat more than 88%.

Ventilator settings
(Ultraprotective mechanical ventilation)

- High PEEP , more than 10 to keep lung recruited.

- As much as low FiO2 to keep arterial O2 sat about 85%.

- Ultralow tidal volume (give lung rest) , targeting plateau less than 25 ideally (tidal volume less than 50ml had been used)

- Benefit from ECMO not only by treating hypoxia ,improving perfusion and clearing hypercapnia, probably most important benefit is by giving lung rest avoiding VILI with its systemic drastic effects.

Clinical evidence
CESAR trial
lancet 2009

- 90 patients in each arm .
- Almost 60% in each group had pneumonia as a cause of ARDS.
- Patients were referred to a tertiary center specialized in ECMO.
- 68 patients actually received ECMO out of the 90 allocated to this arm while 22 improved with lung protective ventilation.
- Primary endpoint was death or severe disability after 6 months.
- 63% had the primary endpoint in ECMO arm versus 47% in control group (relative risk 0·69; 95% CI 0·05–0·97)
- ? Primary end point (Survival without disability at end of 6 months) was mainly driven by disability rather than survival.

Peek et ala, the lancet 2009

|	ECMO group (n=90)*	Conventional management group (n=90)	Relative risk (95% CI, p value)
Death or severe disability at 6 months	NA	NA	0·69 (0·05–0·97, 0·03)†
No	57 (63%)	41 (47%)‡	NA
Yes	33 (37%)	46 (53%)‡	NA
No information about severe disability	0	3 (3%)§	NA
Died at ≤6 months or before discharge	NA	NA	0·73 (0·52–1·03, 0·07)
No	57 (63%)	45 (50%)	NA
Yes	33 (37%)	45 (45%)	NA

Flaws

- External validity: (almost 300 excluded due to unavailability of beds for ECMO)
- selection bias: referring physician refusal to enroll, ? Reversible ARDS
- High rate of lost follow up in control arm.
- Calculation of sample size issues (anticipated mortality of 70% in control group)
- No standardization for mechanical ventilation in control group.
  70% in control group vs 95% in ECMO group had lung protective ventilation.
- 16 patients in the intervention group actually improved without ECMO but just with protective mechanical ventilation.
- 60% of deaths in control group due to respiratory failure (? Mortality driven by VILI)
- Significant difference in steroids use in ECMO arm ? affects mortality
- No clear data about hemodynamics in both arms.
- Unclear conditioned cost effectiveness.
- 5 patients died pre or during transfer ? Transport issues

H1N1 population
UK experience with H1N1

- 80 patients with H1N1 and severe ARDS.

- Case control study.

- Young population 35-40

Noah et al , JAMA 2009

Individual matching
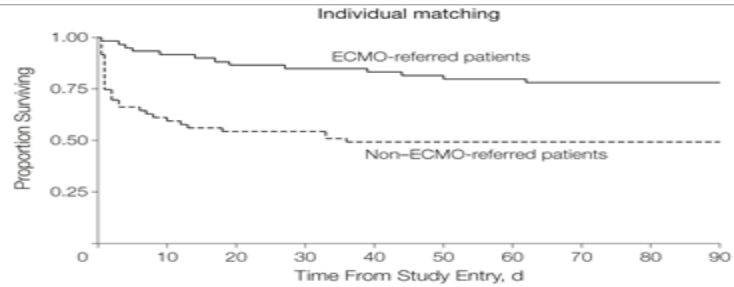
No. at risk

ECMO-referred patients	59	54	51	50	49	48	47	46	46	46
Non–ECMO-referred patients	59	36	32	32	29	29	29	29	29	29
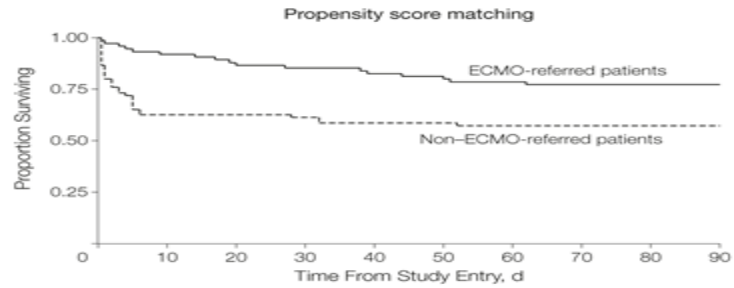
Propensity score matching

No. at risk

ECMO-referred patients	75	69	66	64	62	61	59	58	58	58
Non–ECMO-referred patients	75	47	47	46	44	44	43	43	43	43
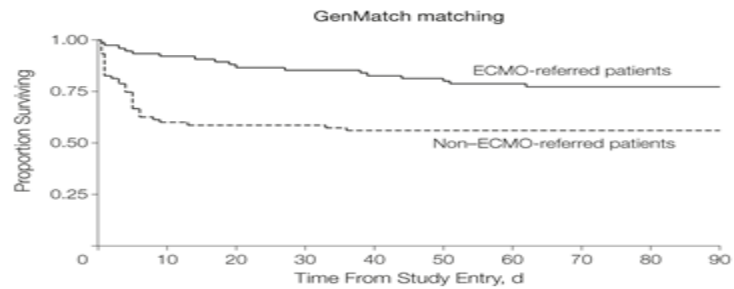
GenMatch matching

No. at risk

ECMO-referred patients	75	69	66	64	62	61	59	58	58	58
Non–ECMO-referred patients	75	45	44	44	42	42	42	42	42	42

- Zampieri metanalysis in critical care medicine 2013.
- 5 studies (3 RCT and 2 case control)
- 2 studies of RCT didn't use lung protective strategy.
- 3 used protective ventilation 2 case control and one RCT (CESAR)
- Population were mainly young (mean age 40-45)

Odds Ratio

Study	ECMO Events	Total	Control Events	Total	OR	95%-CI	W(random)
Peek, 2009	25	68	45	90	0.58	[0.31; 1.11]	37.8%
Noah, 2011	14	59	14	32	0.40	[0.16; 1.00]	28.8%
Pham, 2012	26	52	21	52	1.48	[0.68; 3.21]	33.3%
Random effects model		179		174	0.71	[0.34; 1.47]	100%

Heterogeneity: I-squared=62.1%, tau-squared=0.2543, p=0.0714

0.2 0.5 1 2 5
Favors ECMO   Favors control

Without replacement

Odds Ratio

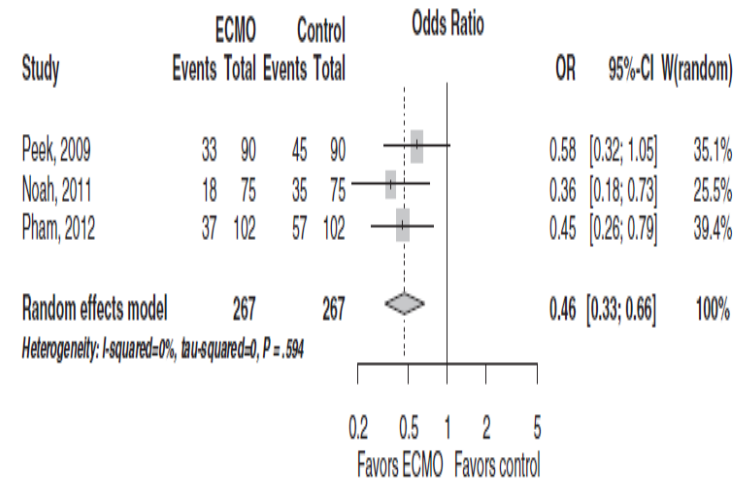| Study	ECMO Events	Total	Control Events	Total	OR	95%-CI	W(random)
Peek, 2009	25	68	45	90	0.58	[0.31; 1.11]	35.4%
Noah, 2011	10	58	15	58	0.60	[0.24; 1.47]	18.1%
Pham, 2012	37	102	57	102	0.45	[0.26; 0.79]	46.4%
Random effects model		228		250	0.52	[0.35; 0.76]	100%

Heterogeneity: I-squared=0%, tau-squared=0, P = .7924

0.5 1 2
Favors ECMO   Favors control

With replacement

Odds Ratio

Study	ECMO Events	Total	Control Events	Total	OR	95%-CI	W(random)
Peek, 2009	33	90	45	90	0.58	[0.32; 1.05]	35.1%
Noah, 2011	18	75	35	75	0.36	[0.18; 0.73]	25.5%
Pham, 2012	37	102	57	102	0.45	[0.26; 0.79]	39.4%
Random effects model		267		267	0.46	[0.33; 0.66]	100%

Heterogeneity: I-squared=0%, tau-squared=0, P = .594

0.2 0.5 1 2 5
Favors ECMO   Favors control

With replacement and intention to treat

Zampieri et al journal of Critical are 2013

Park, 2012 (n = 10) [9]
Allen, 2012 (n = 10) [46]
Albuquerque , 2012 (n = 10) [23]
Bonastre, 2012 (n = 9) [26]
Beurtheret, 2012 (n = 12) [28]
Patroniti, 2011 (n = 60) [24]
Nair, 2011 (n = 12) [25]
Ciapetti, 2011 (n = 4) [27]
Forrest, 2011 (n = 40) [32]
Roch, 2010 (n = 9) [22]
Hoelzgraefe, 2010 (n = 20) [29]
Freed, 2010 (n = 6) [30]
Chan, 2010 (n = 7) [31]
Mikelsen, 2009 (n = 24) [33]
Muller, 2009 (n = 60) [34]
Brogan, 2009 (n = 1143) [36]
Davies, 2009 (n = 68) [37]
Beiderlinden, 2006 (n = 17) [38]
Frenckner, 2002 (n = 38) [35]
Linden, 2000 (n = 17) [40]
Bartlett, 2000 (n = 146) [41]
Mols, 2000 (n = 62) [42]
Peek, 1997 (n = 47) [39]
Lewandowski, 1997 (n = 49) [43]
Gattinoni, 1986 (n = 43) [44]
Zapol, 1977 (n = 6) [45]

Observed
Expected

Mortality (%)

Zampieri et al journal of Critical are 2013

Conclusion

- Young patients with worst hypoxemia and high plateau pressure (worst disease) had lowest mortality (H1N1) but couldn't have been matched properly in the french study by Pham.

- Still no definite answer.

Whom to refer for ECMO
PRESERVE score

Design and Population: Retrospective, middle aged , 70% had pneumonia as a cause, 26% H1N1, all had severe ARDS, 2/3 had Proning pre ECMO, ECMO initiated (5-11) days post onset.

Most common cause of death was multiorgan failure and septic shock. Overall mortality rate was 40% at 6 months. While H1N1 patient had mortality of 17%

Characteristic	All patients ($n = 140$)
Ventilation parameters	
PaO_2/FiO_2	53 (43–60)
FiO_2	100 (100–100)
Plateau pressure, cm H_2O	32 (30–35)
Compliance, mL/cm H_2O	18 (14–21)
Prone positioning	82 (59)
Vasopressors	98 (70)
SAPS II	59 (49–71)
SOFA score	12 (10–15)
ARDS etiology	
Peri-/post-operative	24 (17)
2009 A(H_1N_1) influenza	36 (26)
Bacterial infection	63 (45)
Others	17 (12)

Schmidt et al , intesive care Med 2013

Parameter	Score
Age (years)	
<45	0
45–55	2
>55	3
Body mass index >30	−2
Immunocompromised	2
SOFA >12[a]	1
MV >6 days	1
No prone positioning before ECMO	1
PEEP < 10 cm H_2O	2
Plateau pressure >30 cm H_2O	2
Total score[c]	0–14
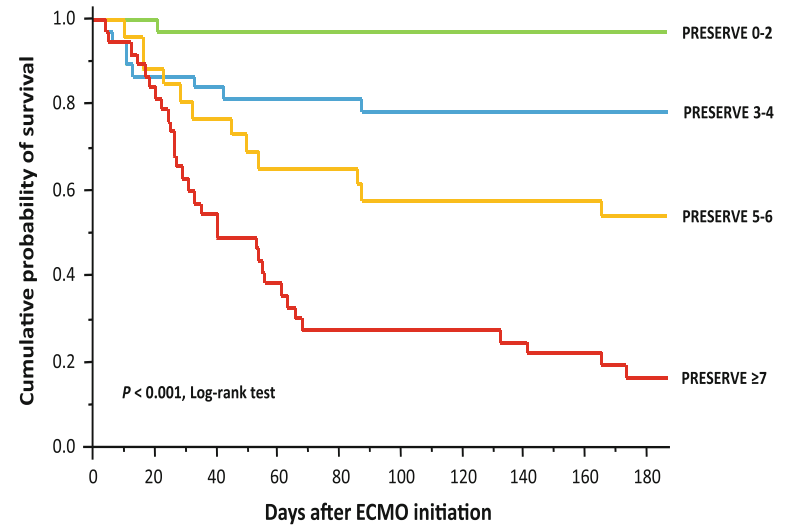
Cumulative probabilities of survival by 6 months following ECMO initiation were 97, 79, 54 and only 16 % for PRESERVE score classes 0–2 ($n = 34$), 3–4 ($n = 38$), 5–6 ($n = 26$) and ≥7 ($n = 38$), respectively

- Early referral within less than 6 days was protective.

- Severity of hypoxemia didn't affect outcome while parameters of lung mechanics were significantly associated with survival.

- Proning had survival benefit despite no improvement of hypoxemia.

- Obesity was protective (?reflecting unrealistic plateau pressure)

ECMOnet score

- Assessed prospectively 60 patients all with H1N1 who had ECMO.

- Overall Survival was 71%.

Variable	Total ($n = 60$)
Pronation	16 (26.7)
Vasoactive and inotropic drugs	37 (64.9)
Plateau airway pressure (cmH_2O)	33.3 ± 4.6
MV (h)	26.9 ± 20.5

Pappalardo et al , intensive care Med 2013

- Cutoff value of 4.5 was associated with drastic effect on survival.
- No ventilatory parameters were predictive of outcome?

26% of the patients had proning preECMO in this study versus 59% in the PRESERVE study.

- Score was validated even into other ARDS causes cases and into patients not referred to ECMO even.

Parameter	Partial score
PreECMO hospital length of stay (days)	
≤3	0.5
4–7	1
8–11	1.5
>11	2
Bilirubin (mg/dl)	
≤0.15	0
0.16–0.65	0.5
0.66–1.15	1
1.16–1.65	1.5
1.66–2.15	2
>2.15	2.5
Creatinine (mg/dl)	
≤0.5	0
0.51–0.80	0.5
0.81–1.10	1
1.11–1.40	1.5
1.41–1.70	2
1.71–2.00	2.5
2.01–2.30	3
>2.30	3.5
Hematocrit (%)	
>40	0.5
36–40	1
31–35	1.5
≤30	2.0
Mean arterial pressure (mmHg)	
>90	0
61–90	0.5
≤60	1

Conclusion

- ?Tow kinds of population : viral pneumonia H1N1 ? Easily reversible pulmonary process, benefit from ECMO and their outcome depends mainly on other organ involvement.

    Others with ARDS due to systemic insult and their outcome mainly depends on ARDS severity reflected by preECMO ventilatory settings (VILI) mainly.

- Early ECMO is a main predictor of outcome , but how much early (before VILI and organ failure), while still could be premature referral for a easily reversible disease.

- Indications for referral (lung mechanics and blood gases)? Is it a good criteria ?

- VV ECMO seems a reasonable and realistic option , VA seems to be invasive and well studied so far.

Future study design

- Bigger sample and subgroup analysis.
- Protocolized standardized protective mechanical ventilation in both arms.
- Transfer issues, complications , specialized teams to start ECMO and do cannulation.
- Unanswered questions hopefully will be answered by the international, randomized, controlled trial, ECMO to Rescue Lung Injury in Severe ARDS .
- So far it should be individualized option of treatment and based on center experience in addition to predicted risk outcome to prioritize this valuable method of treatment.

Inhaled nitric oxide

Pathophysiology

- Hypoxemia in ARDS is driven mainly by the V/Qmismatch, vasoconstriction in normal lung and vasodilatation in diseased lung.

- ARDS is associated with pulmonary hypertension due to in situ thrombosis and lung tissue destruction.

- PAH further exacerbates pulmonary edema and leads to right heart dysfunction.

- NO has selective pulmonary vasodilator of relatively normal lung tissue.

- 3 metanalysis showed no survival benefit but rather increased renal impairment risk.

- Although these studies showed significant transient improvement of oxygenation.

Adhikari et al BMJ 2007
Kumar et al JAMA 2009
Ashfari et al cochrane database syst rev 2010

- Adhikari metanalysis 2014 assessed the differential effect of NO based on ARDS severity.
- Reviewed individual patient data.
- Children and adults but not neonates.
- Included studies that used comparable other ARDS therapies including ventilation strategies among both groups.
- Excluded studies that had more than 50% cross over.
- mortality in severe ARDS was 1.01; 95% CI, 0.78–1.32; n=329 patients (small sample to detect a difference).
- Mortality in mild – moderate ARDS was 1.12; 95%CI, 0.89–1.42; n=740 patients .
- No PO2/FiO2 beneficial threshold was identified by Subgroup analysis .
- NO dose used in included trials was physiologically sufficient to treat hypoxia.

Future study

- It is difficult to conduct a study from cost point , considering previous disappointing results and risk of renal impairment of NO in severe ARDS patients especially with the marginal expected benefit.

- NO might be used in special circumstances where hypoxia is the main risk of death as a rescue measure with doubtful survival benefit.

Thanks for attendance