Setting PEEP in ARDS: Special focus on esophageal pressure monitoring

20/02/2015

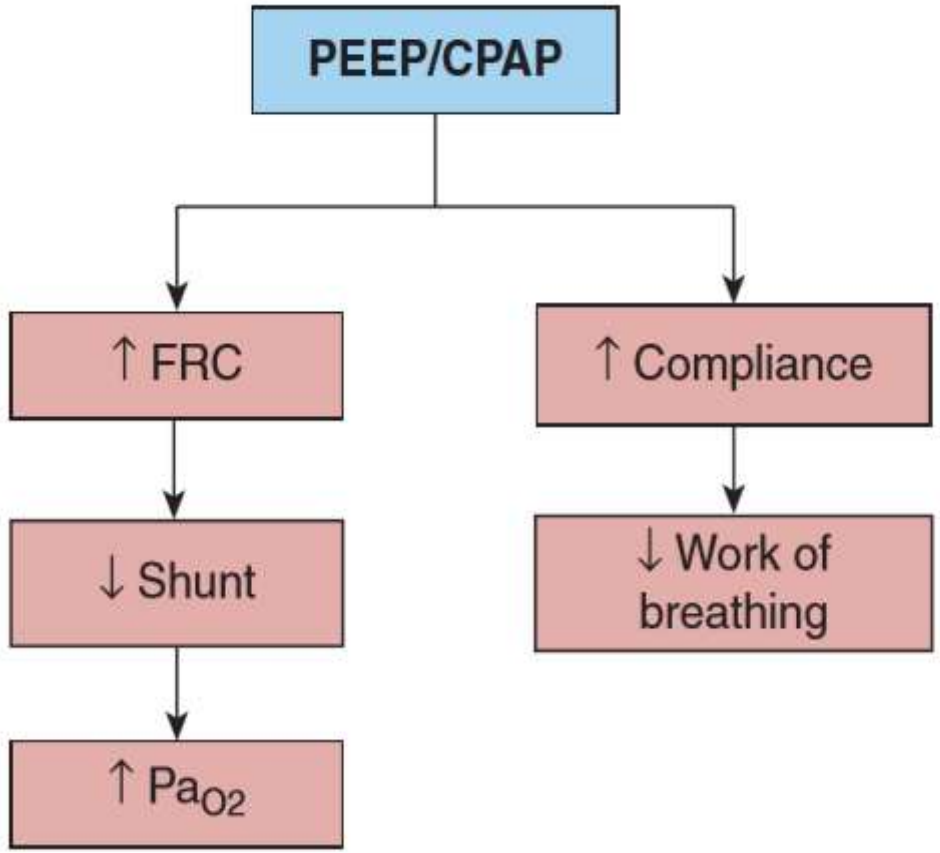
Overview of the seminar

- Introduction
- Optimal strategy for PEEP
- Meta analysis comparing higher vs lower levels of PEEP
- Open lung strategy(LIP approach)
- Physiology of esophageal pressure measurements
- Mechanical ventilation guided by esophageal pressure

The Berlin definition of acute respiratory distress syndrome	
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities — not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]	
Mild	200 mmHg < PaO_2/FIO_2 ≤300 mmHg with PEEP or CPAP ≥5 cmH_2O[c]
Moderate	100 mmHg < PaO_2/FIO_2 ≤200 mmHg with PEEP ≥5 cmH_2O
Severe	PaO_2/FIO_2 ≤100 mmHg with PEEP ≥5 cmH_2O

Abbreviations: CPAP, continuous positive airway pressure; F_IO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure; [a]Chest radiograph or computed tomography scan; [b]If altitude is higher than 1,000 m, the correction factor should be calculated as follows: [PaO_2/FIO_2_(barometric pressure/760)]; [c]This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

Respiratory effects of PEEP in acute respiratory failure



Adverse effects of PEEP

- In patients with ARDS, PEEP may recruit nonaerated regions, but also distend normally aerated regions, contributing to barotrauma through increase in end-inspiratory plateau pressure.
- High levels of PEEP also have been shown to augment the physiologic dead space, and worsen gas exchange and tissue perfusion.
- Potential extrapulmonary side effects of PEEP include decreased cardiac output, increased intracranial pressure, renal dysfunction and decreased splanchnic perfusion and oxygenation

- In the last decade, prevention of VILI through protective lung treatment, by adjusting either tidal volume or PEEP, has become the major goal of mechanical ventilatory support for ARDS.
- With regard to tidal volume, this line of reasoning and research was most conclusively supported by the National Heart, Lung, and Blood Institute ARDS Network trial demonstrating an improvement in survival for patients with ARDS who were ventilated with low tidal volumes (6 mL/kg of predicted body weight) compared with those ventilated with higher tidal volumes(12 ml/kg of PBW)

Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342(18):1301-1308

Optimal strategy for PEEP

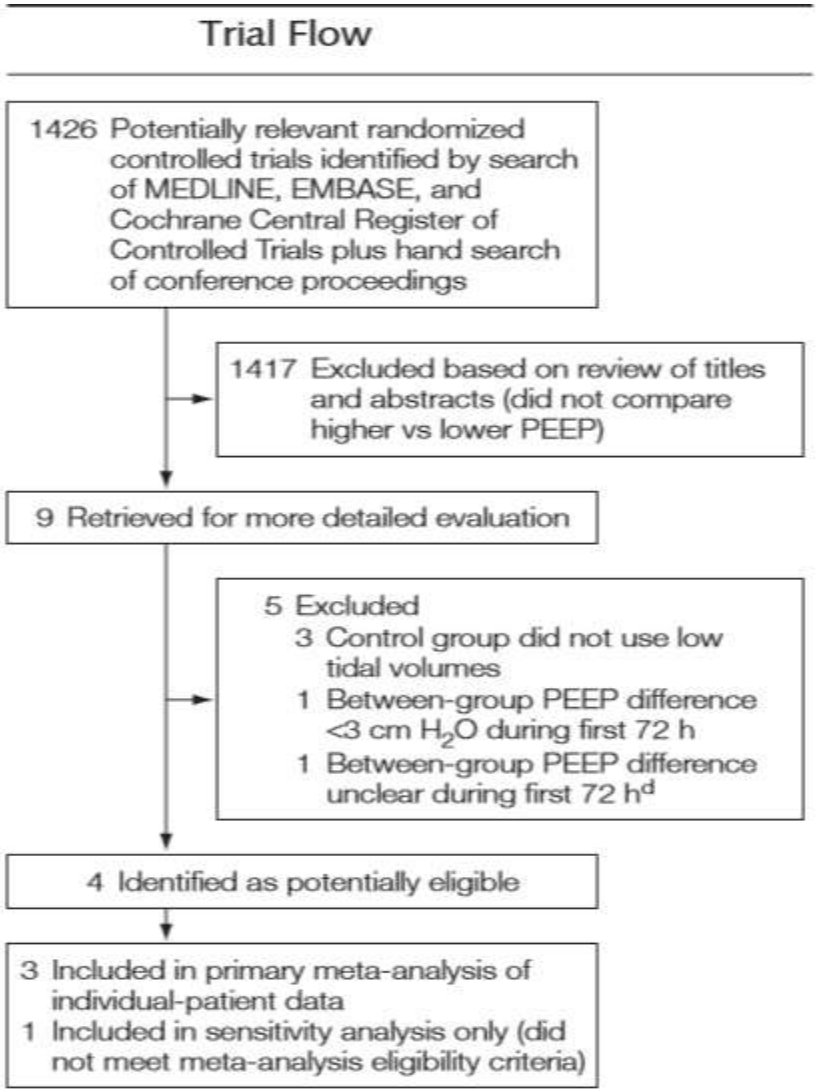
- Experimental data: PEEP levels exceeding traditional values of 5 to 12cm H2O can minimize cyclical alveolar collapse and corresponding shearing injury to the lungs in patients with considerable edema and alveolar collapse
- However, for patients with relatively mild acute lung injury, potential adverse consequences of higher PEEP levels, including circulatory depression or lung overdistension, may outweigh the benefits

DreyfussD,SaumonG.Ventilator-inducedlunginjury: lessons from experimental studies. Am J Respir Crit Care Med. 1998;157(1):294-32

- Ultimate goal of PEEP therapy: Enhanced tissue oxygenation.
- There must be adequate perfusion of the tissues coupled with adequate arterial oxygenation to achieve this goal.
- Inappropriate PEEP levels provide adequate arterial oxygenation while simultaneously decreasing perfusion.
- This results in an improvement in PaO_2 while tissue oxygenation is actually decreased. Therefore, PaO_2 as the sole determinant of appropriate PEEP level is very misleading.

- Optimal PEEP determination: Process focusing on providing the patient the correct amount of therapy for their clinical state
- Primary emphasis in optimal PEEP determination :Preventing ventilator-induced lung injury from overdistention
- Optimal PEEP in ARDS should recruit as much nonaerated lung as possible, while avoiding lung overdistension, hemodynamic impairment, and global and regional disturbances of O_2 balance

Metaanalysis



Briel M et al. Higher vs lower PEEP in patients with ALI and ARDS,Systematic review and metaanalysis. JAMA, Mar 2010;303(9): 865-873

Trial selection

- Randomized trials eligible for this review compared higher with lower levels of PEEP (mean difference of at least 3 cm H2O between groups during first 3 days following randomization)in critically ill adults (>16 years) with a diagnosis of acute lung injury or ARDS as defined by the American-European Consensus Conference.
- 12 Eligible trials incorporated a target tidal volume of less than 8mL/kg of predicted body weight in both the experimental and the control ventilation strategies and provided patient follow-up to death or for at least 20 days.

- **Primary outcome**: Hospital mortality, measured to at least 60 days in all eligible trials
- **Prespecified secondary outcomes**:
  - Death before discharge from the intensive care unit
  - Pneumothorax with need for chest tube drainage in the first 28 days
  - Death following pneumothorax with need for chest tube drainage
  - Time-to-unassisted breathing within the first 28days
  - Days with unassisted breathing between day 1 and day 28
  - Use of rescue therapy
  - Death following rescue therapy
  - use of neuromuscular blockers, vasopressors, and corticosteroids

Table 1. Characteristics of Included Trials

Characteristic	Trial		
	ALVEOLI,[9] 2004	LOVS,[8] 2008	EXPRESS,[10] 2008
Inclusion criteria	Acute lung injury with PaO_2-FIO_2 ≤300[a]	Acute lung injury with PaO_2-FIO_2 ≤250[a]	Acute lung injury with PaO_2-FIO_2 ≤300[a]
Recruitment period	1999-2002	2000-2006	2002-2005
Recruiting hospitals (country)	23 (United States)	30 (Canada, Australia, Saudi Arabia)	37 (France)
Patients randomized to higher vs lower PEEP	276 vs 273	476 vs 509[b]	385 vs 383[c]
Validity			
Concealed allocation	Yes	Yes	Yes
Follow-up for primary outcome, %	100	100	100
Blinded data analysis	Yes	Yes	Yes
Stopped early	Stopped for perceived futility	No	Stopped for perceived futility
Experimental intervention	Higher PEEP according to FIO_2 chart, recruitment maneuvers for first 80 patients	Higher PEEP according to FIO_2 chart, required plateau pressures ≤40 cm H_2O, recruitment maneuvers	PEEP as high as possible without increasing the maximum inspiratory plateau pressure >28-30 cm H_2O
Control intervention	Conventional PEEP according to FIO_2 chart, required plateau pressures ≤30 cm H_2O, no recruitment maneuvers	Conventional PEEP according to FIO_2 chart, required plateau pressures ≤30 cm H_2O, no recruitment maneuvers	Conventional PEEP (5-9 cm H_2O) to meet oxygenation goals
Ventilator procedures	Target tidal volumes of 6 mL/kg of predicted body weight; plateau pressures ≤30 cm H_2O (with exception as above); respiratory rate ≤35/min, adjusted to achieve arterial pH 7.30-7.45; ventilator mode: volume-assist control (except higher PEEP group in LOVS required pressure control); oxygenation goals: PaO_2 55-80 mm Hg and SPO_2 88%-95%; standardized weaning		

Baseline charecteristics of included patients

Characteristic	Higher PEEP (n = 1136)	Lower PEEP (n = 1163)
Age, mean (SD), y	56 (17) [n = 1136]	56 (17) [n = 1163]
Women, No. (%)	437 (38) [n = 1136]	455 (39) [n = 1163]
Body mass index, mean (SD)[a]	27.1 (6.3) [n = 1024]	26.9 (6.6) [n = 1038]
Days in ICU prior to randomization, median (IQR), d	1 (1-3) [n = 1136]	2 (1-3) [n = 1163]
Days intubated prior to randomization, median (IQR), d	1 (1-2) [n = 1136]	1 (1-2) [n = 1163]
Probability of death from APACHE II or SAPS II scores, median (IQR)	49 (29-70) [n = 1133]	49 (29-70) [n = 1160]
No. of organ failures in addition to respiratory failure, median (IQR)[b]	1 (1-2) [n = 1123]	1 (1-2) [n = 1149]
Respiratory measures, mean (SD)		
Pao_2:Fio_2, mm Hg[c]	146 (56) [n = 1135]	148 (60) [n = 1161]
Pao_2:Fio_2 ≤200 mm Hg, No. (%)	951 (84) [n = 1135]	941 (81) [n = 1161]
Oxygenation index, median (IQR)[d]	11.4 (8.2-16.8) [n = 989]	11.1 (7.7-17.0) [n = 1009]
Set PEEP, cm H_2O	9.9 (4.0) [n = 1135]	9.7 (3.8) [n = 1160]
Plateau pressure, cm H_2O	26.7 (6.4) [n = 915]	26.3 (6.6) [n = 899]
Respiratory rate, breaths/min	23.1 (6.6) [n = 1133]	23.2 (6.7) [n = 1160]
Minute ventilation, L/min	11.6 (3.2) [n = 1122]	11.7 (3.6) [n = 1151]
Tidal volume, mL/kg of predicted body weight	8.0 (1.9) [n = 1107]	8.0 (2.0) [n = 1135]
Estimated respiratory system compliance, mL/cm H_2O[e]	32.7 (14.9) [n = 909]	32.6 (13.7) [n = 892]
Cause of lung injury, No. (%)[f]		
Pneumonia	567 (50)	578 (50)
Aspiration	214 (19)	247 (21)
Severe sepsis, including septic shock	595 (52)	628 (54)
Multiple transfusions	71 (6.3)	74 (6.4)
Acute pancreatitis	37 (3.3)	48 (4.1)
Multiple trauma	60 (5.3)	73 (6.3)
Other[g]	146 (13)	119 (10)

ALVEOLI Study Group

Table 1. Summary of Ventilator Procedures in the Lower- and Higher-PEEP Groups.*

Procedure	Value													
Ventilator mode	Volume assist/control													
Tidal-volume goal	6 ml/kg of predicted body weight													
Plateau-pressure goal	≤30 cm of water													
Ventilator rate and pH goal	6–35, adjusted to achieve arterial pH ≥7.30 if possible													
Inspiration:expiration time	1:1–1:3													
Oxygenation goal														
PaO_2	55–80 mm Hg													
SpO_2	88–95%													
Weaning	Weaning attempted by means of pressure support when level of arterial oxygenation acceptable with PEEP ≤8 cm of water and FiO_2 ≤0.40													
Allowable combinations of PEEP and FiO_2†														
Lower-PEEP group														
FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18–24
Higher-PEEP group (before protocol changed to use higher levels of PEEP)														
FiO_2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5	0.5	0.5–0.8	0.8	0.9	1.0	
PEEP	5	8	10	12	14	14	16	16	18	20	22	22	22–24	
Higher-PEEP group (after protocol changed to use higher levels of PEEP)														
FiO_2	0.3	0.3	0.4	0.4	0.5	0.5	0.5–0.8	0.8	0.9	1.0				
PEEP	12	14	14	16	16	18	20	22	22	22–24				

* Complete ventilator procedures and eligibility criteria are listed in the Supplementary Appendix (available with the full text of this article at www.nejm.org) and at www.ardsnet.org. PaO_2 denotes partial pressure of arterial oxygen, SpO_2 oxyhemoglobin saturation as measured by pulse oximetry, FiO_2 fraction of inspired oxygen, and PEEP positive end-expiratory pressure.

† In both study groups, additional increases in PEEP to 34 cm of water were allowed but not required after the FiO_2 had been increased to 1.0 according to the protocol. The combinations of PEEP and FiO_2 used with PEEP values of less than 12 cm of water were eliminated in the higher-PEEP group after 171 patients had been enrolled in this group.

Lung Open Ventilation group

Table 1. Protocol Components

Component Variables	Control Ventilation Strategy	Lung Open Ventilation Strategy
Ventilator mode	Volume-assist control	Pressure control
Tidal volume target, mL/kg predicted body weight	6	6
Tidal volume range, mL/kg predicted body weight	4-8	4-8
Plateau airway pressure, cm H_2O	≤30	≤40
Positive end-expiratory pressure, cm H_2O	See Table 2	See Table 2
Partial pressure of oxygen, arterial, mm Hg	55-80	55-80
Oxygen saturation as measured by pulse oximetry, %	88-93	88-93
pH	≥7.30	≥7.30
Ventilator rate, breaths/min	≤35	≤35
Inspiration:expiration time	1:1-1:3	1:1-1:3
Recruitment maneuvers	Not permitted	After ventilator disconnects

Table 2. Allowable PEEP Ranges at Specified Levels of FIO_2[a]

	Fraction of Inspired Oxygen (FIO_2)							
	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Control PEEP ranges, cm H_2O	5	5-8	8-10	10	10-14	14	14-18	18-24
Lung open ventilation PEEP ranges, cm H_2O								
Before protocol change	5-10	10-14	14-20	20	20	20	20	20-24
After protocol change	5-10	10-18	18-20	20	20	20-22	22	22-24

Abbreviation: PEEP, positive end-expiratory pressure.

[a] Both ventilation strategies included a protocol for reducing PEEP when plateau pressure exceeded the assigned plateau pressure limit or when mean arterial pressure decreased to less than 60 mm Hg, whether or not this occurred in the setting of an increase in PEEP.

Express study group

Ventilation Characteristics in the Minimal Distension and Increased Recruitment Groups

Ventilator Mode	Volume-Assist Control
Tidal volume goal	6 mL/kg of predicted body weight[a]
Plateau pressure limit	≤30 cm H_2O
Ventilation rate and pH goals	≤35; adjusted for a pH between 7.30 and 7.45
Oxygenation goals	
Pa_{O_2}	55-80 mm Hg
Sp_{O_2}	88%-95%
PEEP[b]	
Minimal distension group[c]	Total PEEP between 5 and 9 cm H_2O
Increased recruitment group[d]	Plateau pressure between 28 and 30 cm H_2O
Recruitment maneuvers	Allowed but not recommended
Adjunctive therapies (prone position or inhaled nitric oxide or almitrine bismesylate)	Allowed when the oxygenation goal was not met despite F_{IO_2} ≥0.8
PEEP weaning test	
In patients with Pa_{O_2}:F_{IO_2} >150 mm Hg with F_{IO_2} ≤0.6 daily from day 4 onward; F_{IO_2} of 0.5 and PEEP of 5 cm H_2O for 20-30 min	Successful if Pa_{O_2} ≥100 mm Hg; subsequent ventilation with PEEP of 5 cm H_2O, tidal volume <10 mL/kg predicted body weight, and plateau pressure <30 cm H_2O

Respiratory variables during first week of treatment

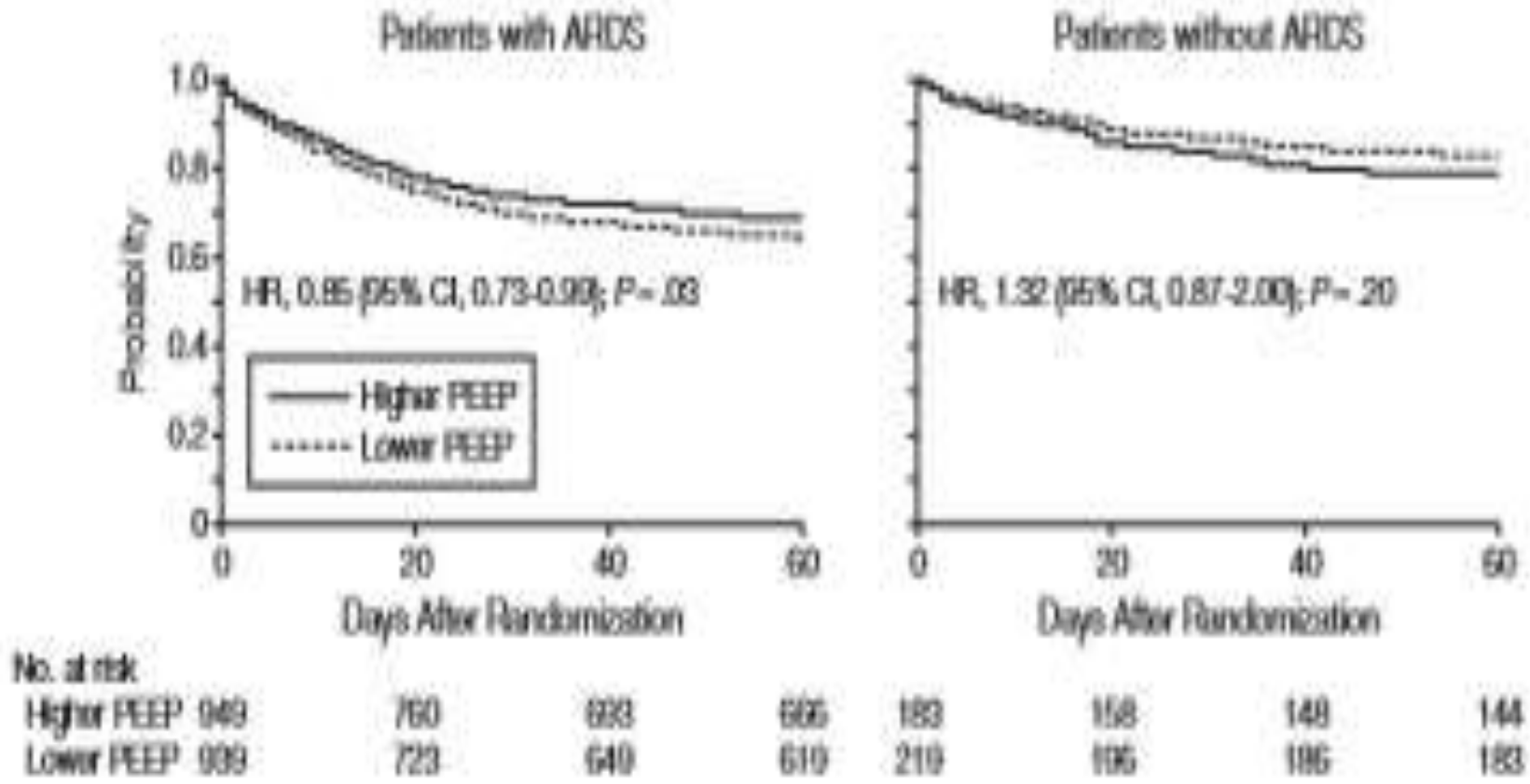
Variable	Mean (SD)								
	Day 1			Day 3			Day 7		
	Higher PEEP	Lower PEEP	*P* Value	Higher PEEP	Lower PEEP	*P* Value	Higher PEEP	Lower PEEP	*P* Value
Tidal volume, mL/kg of predicted body weight	6.3 (1.0) [n = 1051]	6.3 (0.8) [n = 1051]	.33	6.3 (1.0) [n = 793]	6.3 (1.0) [n = 852]	.47	6.5 (1.4) [n = 443]	6.4 (1.3) [n = 494]	.25
Plateau pressure, cm H_2O	29 (5.4) [n = 1043]	23 (5.6) [n = 991]	<.001	27 (5.6) [n = 781]	23 (5.9) [n = 825]	<.001	27 (6.2) [n = 408]	24 (6.9) [n = 443]	<.001
FIO_2	0.51 (0.18) [n = 1053]	0.61 (0.19) [n = 1051]	<.001	0.44 (0.15) [n = 812]	0.56 (0.18) [n = 862]	<.001	0.45 (0.15) [n = 502]	0.54 (0.19) [n = 550]	<.001
PEEP, cm H_2O	15.3 (3.4) [n = 1053]	9.0 (3.1) [n = 1051]	<.001	13.3 (4.3) [n = 812]	8.2 (3.0) [n = 863]	<.001	10.8 (5.0) [n = 503]	7.8 (3.3) [n = 548]	<.001
Oxygenation index[a]	13.2 (8.7) [n = 949]	12.7 (7.8) [n = 944]	.16	11.2 (7.0) [n = 705]	11.6 (7.1) [n = 755]	.29	11.2 (7.1) [n = 392]	11.8 (8.4) [n = 421]	.34
PaO_2, mm Hg	96 (38) [n = 1024]	83 (29) [n = 1026]	<.001	87 (31) [n = 792]	82 (28) [n = 835]	<.001	84 (25) [n = 484]	83 (26) [n = 532]	.41
$PaCO_2$, mm Hg	44 (11) [n = 1025]	44 (11) [n = 1026]	.42	44 (9.9) [n = 792]	44 (11) [n = 835]	.68	45 (12) [n = 485]	46 (12) [n = 532]	.06
Arterial pH	7.35 (0.09) [n = 1025]	7.36 (0.09) [n = 1026]	.02	7.38 (0.08) [n = 793]	7.38 (0.08) [n = 836]	.49	7.41 (0.08) [n = 485]	7.40 (0.08) [n = 532]	.08

Abbreviations: FIO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure.
[a]Calculated as mean airway pressure × FIO_2 × 100/PaO_2.

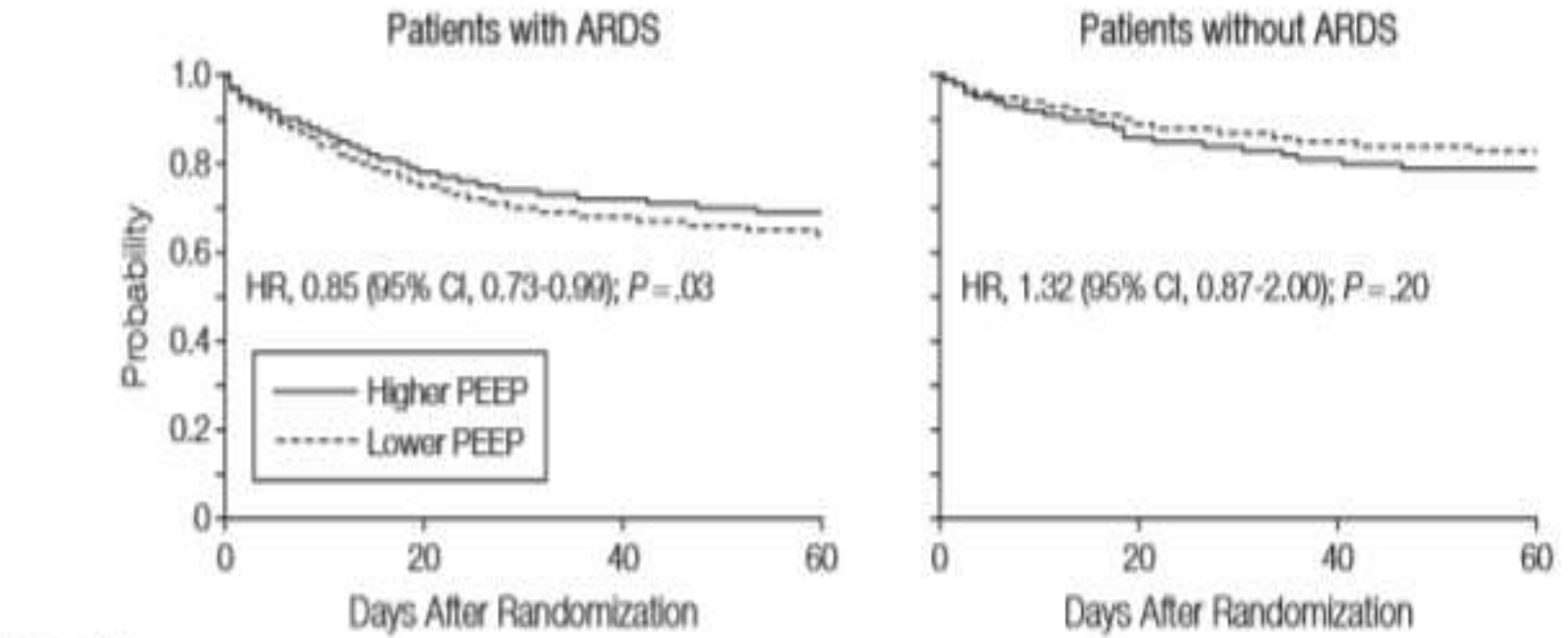
Clinical outcomes in all patients and stratified by presence of ARDS at baseline

Outcomes	All Patients				With ARDS				Without ARDS			
	No. (%)				No. (%)				No. (%)			
	Higher PEEP (n = 1136)	Lower PEEP (n = 1163)	Adjusted RR (95% CI)[a]	P Value	Higher PEEP (n = 951)	Lower PEEP (n = 941)	Adjusted RR (95% CI)[a]	P Value	Higher PEEP (n = 184)	Lower PEEP (n = 220)	Adjusted RR (95% CI)[a]	P Value
Death in hospital	374 (32.9)	409 (35.2)	0.94 (0.85 to 1.04)	.25	324 (34.1)	368 (39.1)	0.90 (0.81 to 1.00)	.049	50 (27.2)	44 (19.4)	1.37 (0.98 to 1.92)	.07
Death in ICU[b]	324 (28.5)	381 (32.8)	0.87 (0.78 to 0.97)	.01	288 (30.3)	344 (36.6)	0.85 (0.76 to 0.95)	.001	36 (19.6)	37 (16.8)	1.07 (0.74 to 1.55)	.71
Pneumothorax between day 1 and day 28[c]	87 (7.7)	75 (6.5)	1.19 (0.89 to 1.60)	.24	80 (8.4)	64 (6.8)	1.25 (0.94 to 1.66)	.13	7 (3.8)	11 (5.0)	0.72 (0.37 to 1.39)	.33
Death after pneumothorax[c]	43 (3.8)	40 (3.5)	1.11 (0.73 to 1.69)	.63	41 (4.3)	35 (3.7)	1.20 (0.79 to 1.81)	.39	2 (1.1)	5 (2.3)	0.44 (0.08 to 2.35)[d]	.34
Days with unassisted breathing between day 1 and day 28, median (IQR)[d]	13 (0 to 22)	11 (0 to 21)	0.64 (−0.12 to 1.39)[e]	.10	12 (0-21)	7 (0-20)	1.22 (0.39 to 2.05)[e]	.004	17 (0-23)	19 (5.5-24)	−1.74 (−3.60 to 0.11)[e]	.07
Total use of rescue therapies[f]	138 (12.2)	216 (18.6)	0.64 (0.54 to 0.75)	<.001	130 (13.7)	200 (21.3)	0.63 (0.53 to 0.75)	<.001	8 (4.4)	16 (7.3)	0.60 (0.25 to 1.43)[d]	.25
Death after rescue therapy[f]	85 (7.5)	132 (11.3)	0.65 (0.52 to 0.80)	<.001	82 (8.6)	124 (13.2)	0.66 (0.52 to 0.82)	<.001	3 (1.6)	8 (3.6)	0.37 (0.10 to 1.46)[d]	.15
Use of vasopressors	722 (63.6)	759 (65.3)	0.93 (0.75 to 1.14)[d]	.49	627 (65.9)	647 (68.8)	0.90 (0.72 to 1.13)[d]	.37	95 (51.6)	111 (50.5)	0.92 (0.56 to 1.50)[d]	.72

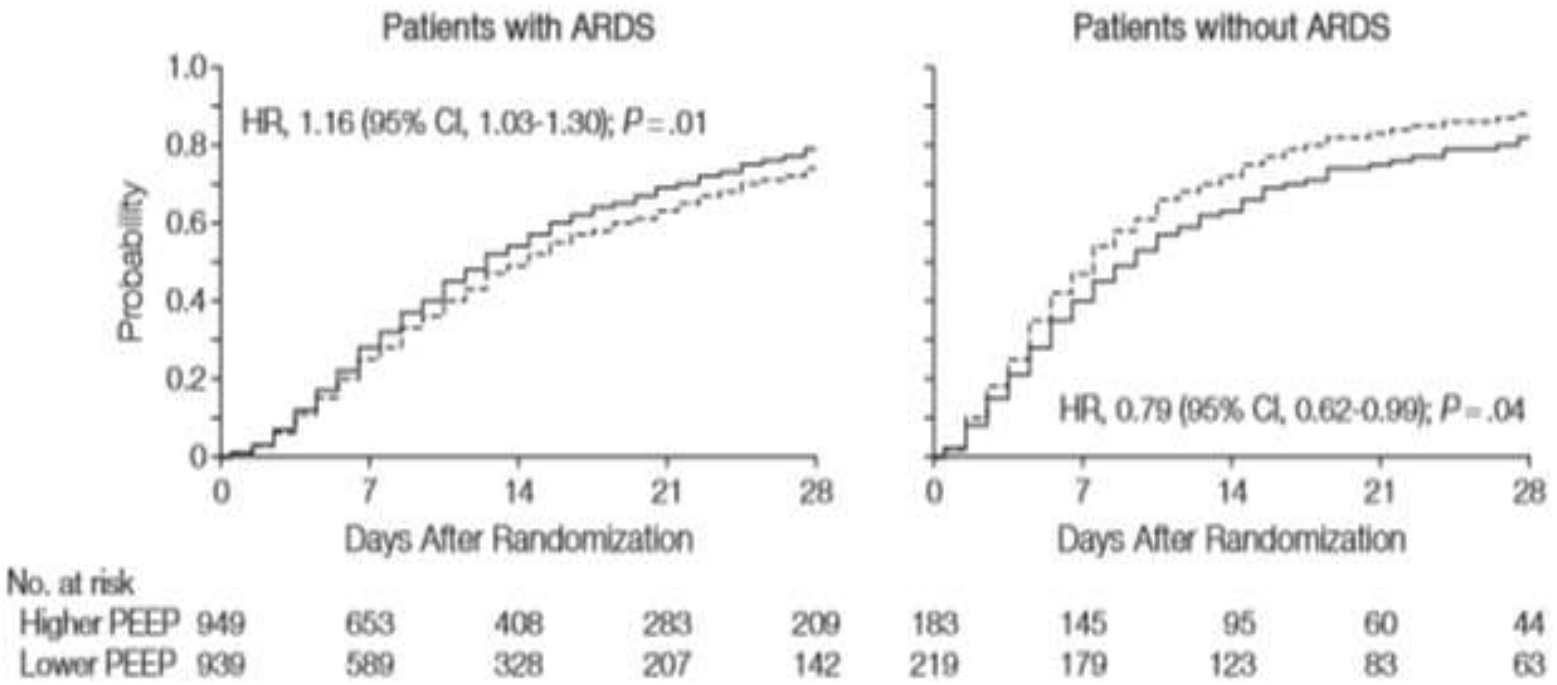
In-hospital time to death

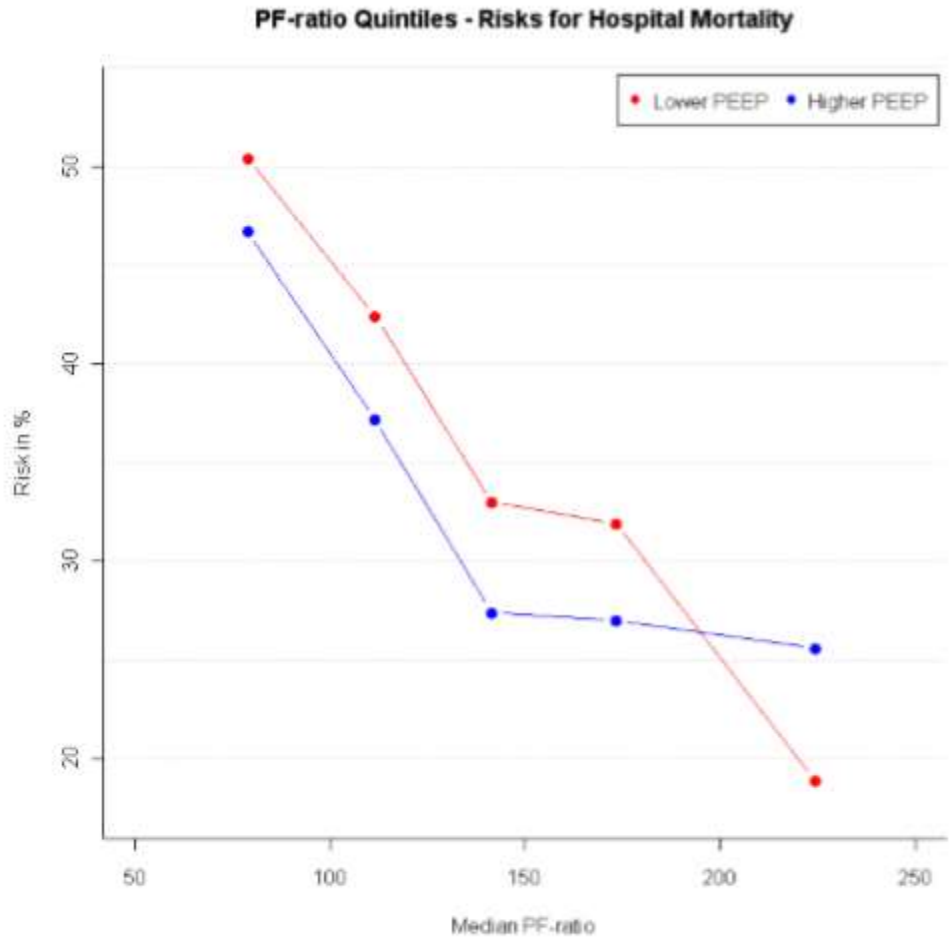


In-hospital time to death



Time to unassisted breathing





Limits defining quintiles of PaO_2/FiO_2 ratio: Quintile 1: 30.0 to 95.0 mmHg; Quintile 2: >95.0 to 126.7 mmHg; Quintile 3: >126.7 to 156.2 mmHg; Quintile 4: >156.2 to 194 mmHg; Quintile 5: >194.0 mmHg.
Abbreviations: PF-ratio, PaO_2/FiO_2 ratio (FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen).

Strengths of this meta-analysis

- An explicit study protocol and analysis plan
- Access to trial protocols, case report forms, and complete, unedited data sets
- Standardized outcome definitions across trials (except for rescue therapies)
- Analyses based on the intention-to-treat principle.

Limitations of this meta-analysis

- Limited statistical power: A post hoc calculation estimated that the primary analysis had a power of 72% to detect a 5% absolute risk reduction in hospital mortality(2-sided α=0.05)
- Caregivers were not blinded to allocated PEEP strategies. Differing thresholds for rescue therapy in the high and low PEEP groups could explain the lower use of rescue therapies and mortality following rescue therapy in the higher PEEP group
- Rescue therapies were not standardized across the trials
- Analyses involving lung compliance are limited by missing data

Clinical implications of the study

- The potentially lower hospital mortality and the absence of increased serious adverse events associated with higher PEEP levels in patients with moderate and severe ARDS support the safety of higher PEEP in these patients. For this purpose, clinicians could titrate PEEP as described in the 3 major trials in this review
- For patients with mild ARDS, the results lack statistical power; still, the 95% CI of 0.98-1.92 for hospital mortality in patients with mild ARDS indicates that a RR reduction of 2%(0.4% absolute reduction) associated with higher PEEP is plausible but that larger, important risk reductions are unlikely

Open lung strategy (LIP approach): Amato NEJM 1998

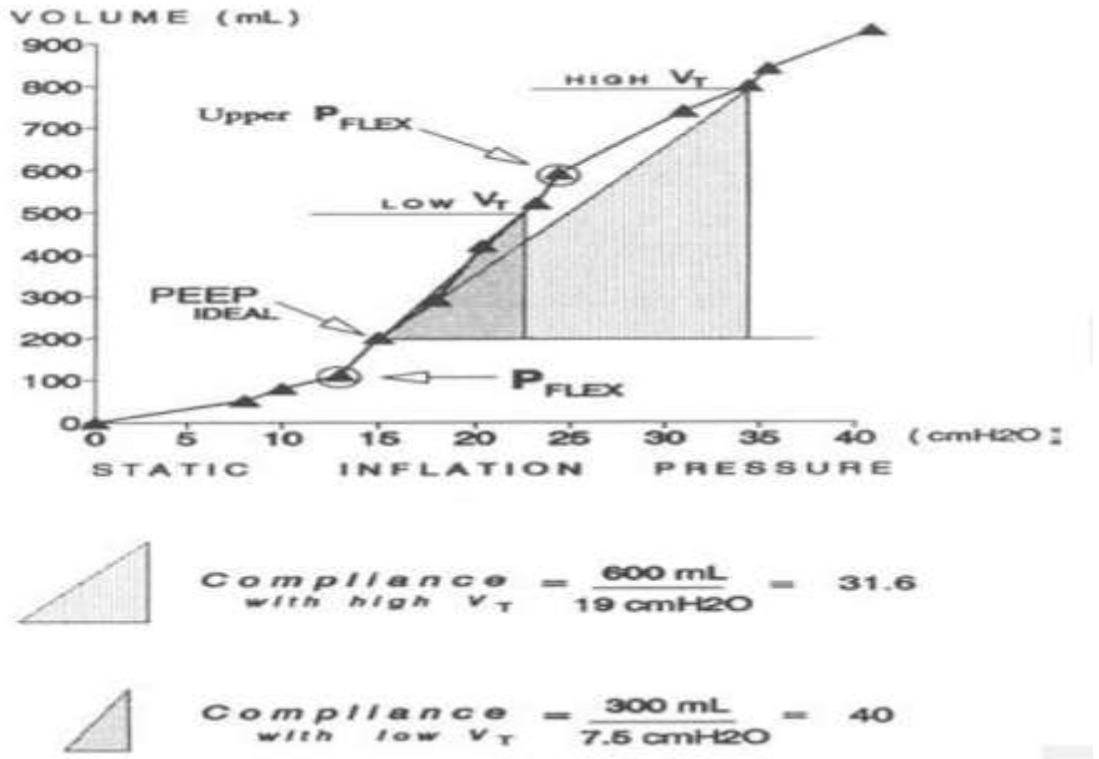
BASE-LINE CHARACTERISTICS OF THE STUDY GROUPS.

CHARACTERISTIC	PROTECTIVE VENTILATION (N=29)	CONVENTIONAL VENTILATION (N=24)
Age (yr)	33±13	36±14
Duration of mechanical ventilation before entry (days)	1.9±1.8	2.2±2.6
Extrapulmonary organ failure	2.6±1.3	2.7±1.5
APACHE II†		
Standard score	28±7	27±6
Standard risk of death (%)	65±18	60±19
Adjusted score	24±7	24±6
Adjusted risk of death (%)	54±23	52±21
Critical-care score	19±6	17±6
Lung-injury score	3.4±0.4	3.2±0.4
Ventilator score	87±12	84±14
Respiratory tract infection (%)	52	63
Sepsis (%)	86	79
PaO_2:FiO_2	112±51	134±67
P_{FLEX}	14.7±3.9	14.0±3.7
Static compliance (ml/cm of water)	28.2±8.3	30.0±6.5
Primary diagnosis (no.)		
Leptospirosis	4	4
Bacterial pneumonia	1	3
Aspirative pneumonia	4	0
Atypical pneumonia	2	4
Pneumocystis pneumonia	4	1
Puerperal sepsis and disseminated intravascular coagulation	4	2
Systemic lupus erythematosus and sepsis or pneumonia	2	2
Acute pancreatitis	1	1
Soft-tissue infection with sepsis	1	3
Abdominal sepsis	1	2
Intracranial hemorrhage	1	0
Pulmonary contusion	1	0
Near-drowning	2	0
Disseminated tuberculosis	1	0
Immune alveolar hemorrhage	0	1
Polytransfusion	0	1

Stabilizing procedures and randomization

- All patients underwent a standardized regimen of ventilatory–hemodynamic procedures for at least 30 minutes (control period), during which time their initial clinical condition was evaluated and stabilized
- Subsequently, a bedside procedure was performed to calculate the inspiratory and static pressure–volume curve without disconnecting the ventilator
- A well-defined P_{FLEX} (corresponding to an upward shift in the slope of the curve and signaling an increment in lung compliance) could be determined for 49 patients, but the corresponding value was used to adjust PEEP only in the group assigned to protective mechanical ventilation

Inspiratory static P-V curve of the respiratory system obtained from a patient



Amato et al.Beneficial Effects of the "Open Lung Approach" with Low Distending Pressures in Acute Respiratory Distress Syndrome. AM J RESPIR CRIT CARE MED 1995;152:1835-46

- **Conventional ventilation:** Strategy of maintaining the lowest PEEP for acceptable oxygenation, with a tidal volume of 12 ml per kilogram of body weight and normal arterial carbon dioxide levels (35 to 38 mm Hg)
- **Protective ventilation:** End-expiratory pressures above the lower inflection point on the static pressure–volume curve, a tidal volume of less than 6 ml per kilogram, driving pressures of less than 20 cm of water above the PEEP value, permissive hypercapnia, and preferential use of pressure-limited ventilatory modes.

Effect of a Protective-Ventilation Strategy on Mortality in the ARDS. Amato NEJM 1998

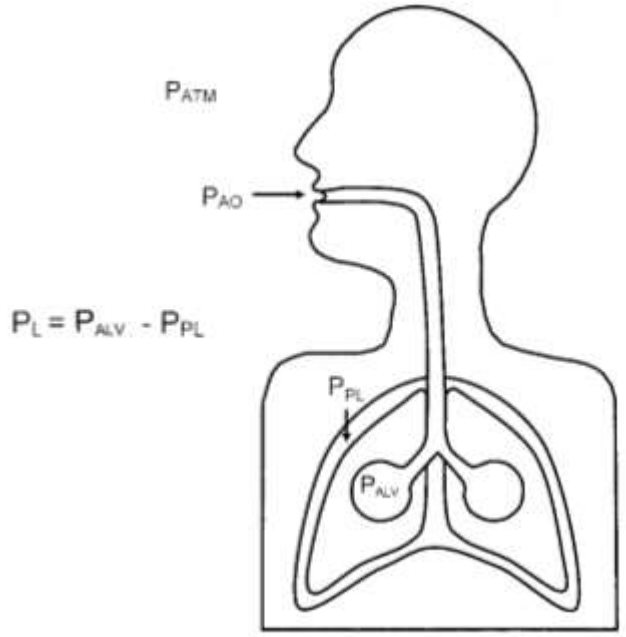
- PEEP was preset at 2 cm of water above P_{FLEX}. When auto-PEEP was present, the total PEEP (external PEEP plus auto-PEEP) was considered and adjusted to equal P_{FLEX} plus 2 cm of water.
- If a sharp P_{FLEX} could not be determined on the pressure–volume curve, an empirical total PEEP value of 16 cm of water was used.
- Recruiting maneuvers were frequently used, especially after inadvertent disconnections from the ventilator. Continuous positive airway pressures of 35 to 40 cm of water were applied for 40 seconds, followed by a careful return to previous PEEP levels

Study outcomes according to intention to treat analysis

OUTCOME	PROTECTIVE VENTILATION (N=29)	CONVENTIONAL VENTILATION (N=24)	P VALUE	
			ISOLATED COMPARISONS	COMPARISONS CORRECTED FOR MULTIPLE TESTING*
Primary end point — no. (%)				
Mortality at 28 days	11 (38)	17 (71)	<0.001†	<0.001
Secondary end points — no. (%)				
In-hospital death	13 (45)	17 (71)	0.09‡	0.37
Barotrauma	2 (7)§	10 (42)¶	0.004‡	0.02
Weaning at 28 days	19 (66)	7 (29)	0.001†	0.005
Other outcomes				
Death in the intensive care unit — no. (%)	11 (38)	17 (71)	0.03‡	
Death after weaning — no.	4	0	>0.10‡	
Nosocomial pneumonia — no.	17	11	>0.10‡	
Use of paralyzing agents for >24 hr — no.	17	8	0.10‡	
Neuropathy after extubation — no.	2	0	>0.10‡	
Dialysis required — no.	7	5	>0.10‡	
Packed red cells infused — ml/patient/day	230	309	0.25‖	
Cause of in-hospital death — no.**				
Progressive respiratory failure	1	6		
Refractory septic shock	6	7		
Accidental extubation	2	1		
Gastric hemorrhage	2	1		
Cerebral nocardiosis	1	0		
Accidental hemothorax	1	0		
Ventricular fibrillation	0	1		
Intracranial hemorrhage	0	1		

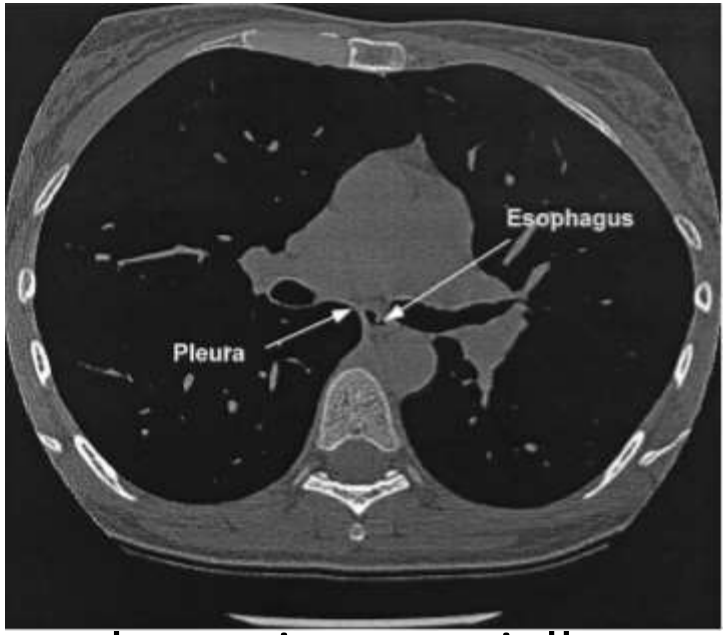
Esophageal pressure measurements

- Physiologic background:



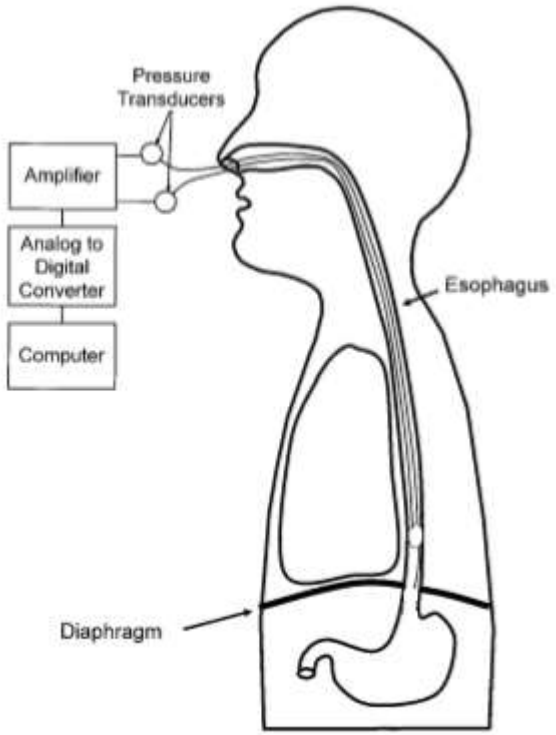
- At the end of a relaxed exhalation (to functional residual capacity) and with the mouth open,the alveolar pressure(Palv),the pressure at the airway opening (P_{AO}), and the atmospheric pressure (Patm) are equal

How to measure pleural pressure in clinical practice?



- Because the body of the esophagus is essentially a passive structure (except during a swallow), able to transmit pressure from the adjacent pleural space (Ppl) to the measurement catheter in the esophagus, Pes in lower 1/3rd of esophagus is a reasonably close surrogate for Ppl in a human being in the upright posture

Equipments required for recording pressure from esophageal balloon catheter



- The device consists of a thin polyethylene catheter with multiple small holes in the distal 5–7 cm of its length
- The distal end of the catheter is placed in a 10-cm latex balloon that prevents the holes in the catheter from being occluded by esophageal tissue and maintains a column of air within and around the catheter, in order to measure pressure in the surrounding structures
- The proximal end of the catheter is attached to the pressure transducers and recording equipment

Benditt JO.Esophageal and gastric pressure measurements.Respir Care Jan 2005;50(1):70-71

Hypothesis of using esophageal pressure to set PEEP

- Calculated transpulmonary pressure is often a negative value at end-expiration. This is presumed to reflect closed airways.
- In the presence of closed airways and flooded or atelectatic lung, the Paw measured proximally(the set PEEP) may underestimate alveolar pressure, resulting in a negative calculated transpulmonary pressure.
- Raising PEEP until transpulmonary pressure becomes positive at end expiration could assure that airways remain open

- Wide variation in pleural pressure in patients of ARDS due to factors like ascites, intra-abdominal hypertension, resuscitation with large fluid volumes, obesity
- Estimating pleural pressure to calculate transpulmonary pressure may allow better control of both end inspiratory and end expiratory lung volume, and thereby reduce VILI caused by overdistension or atelectrauma
- Optimizing inflating pressures to the mid lung may prevent over distension of the upper, nondependent portions of the aerated lung while preventing collapse of the lower, dependent portions

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Mechanical Ventilation Guided by Esophageal Pressure in Acute Lung Injury

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- RCT involving patients of ARDS comparing mechanical ventilation directed by esophageal pressure measurements with mechanical ventilation managed according to the ARDSNet recommendations
- **Methods**: trial performed in the medical and surgical ICUs of Beth Israel Deaconess Medical Center in Boston
- **Inclusion criteria**: Patients with acute lung injury or ARDS according to the American–European Consensus Conference definitions
- **Exclusion criteria**: Recent injury or other pathologic condition of the esophagus, major bronchopleural fistula, and solid organ transplantation

Experimental protocol

- Subjects were supine, with head of bed elevated to 30 degrees
- An esophageal balloon catheter was passed to a depth of 60 cm from the incisors for measurement of gastric pressure and then withdrawn to a depth of 40 cm to record esophageal pressure during mechanical ventilation
- Mixed expired partial pressure of carbon dioxide was measured to allow calculation of physiological dead space
- Patients were randomly assigned with the use of a block-randomization scheme to the control or esophageal pressure–guided group

- Each patient underwent a recruitment maneuver under heavy sedation or paralysis, in which airway pressure was increased to 40 cm of water for 30 seconds
- **Esophageal pressure guided group**:

  Tidal volume= 6 ml/kg of predicted body weight

  PEEP set to achieve a transpulmonary pressure of 0 to 10 cm of water at end expiration according to a sliding scale based on PaO_2 and FiO_2

  Tidal volume limited to keep end inspiratory transpulmonary pressure

  at less than 25cm of water

- **Control group**:

  Treated according to the low tidal volume strategy reported by the ARDSNet study

  Tidal volume= 6 ml/kg of predicted body weight

  PEEP based on patient's PaO2 and FiO2

- **Goals of mechanical ventilation(Both groups**):

  PaO2: 55-120 mmHg or pulse oximetry reading of 88-98%

  Arterial pH: 7.30- 7.45

  PaCO2: 40-60 mmHg

Ventilator settings according to the protocol

- Esophageal pressure guided group

FiO2	0.4	0.5	0.5	0.6	0.6	0.7	0.7	0.8	0.8	0.9	0.9	1.0
P_{Lep}	0	0	2	2	4	4	6	6	8	8	10	10

- Control group

FiO2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	20-24

- All measurements were repeated 5 minutes after initiation of mechanical ventilation, at 24, 48 and 72 hours and whenever changes were made in ventilator settings
- **Primary end point**: Arterial oxygenation as measured by PaO2: FiO2 ratio, 72 hours after randomization
- **Secondary end points**:

  Respiratory system compliance and the ratio of physiological dead space to tidal volume

  the number of ventilator-free days at 28 days

  length of stay in the ICU

  death within 28 days and 180 days after treatment

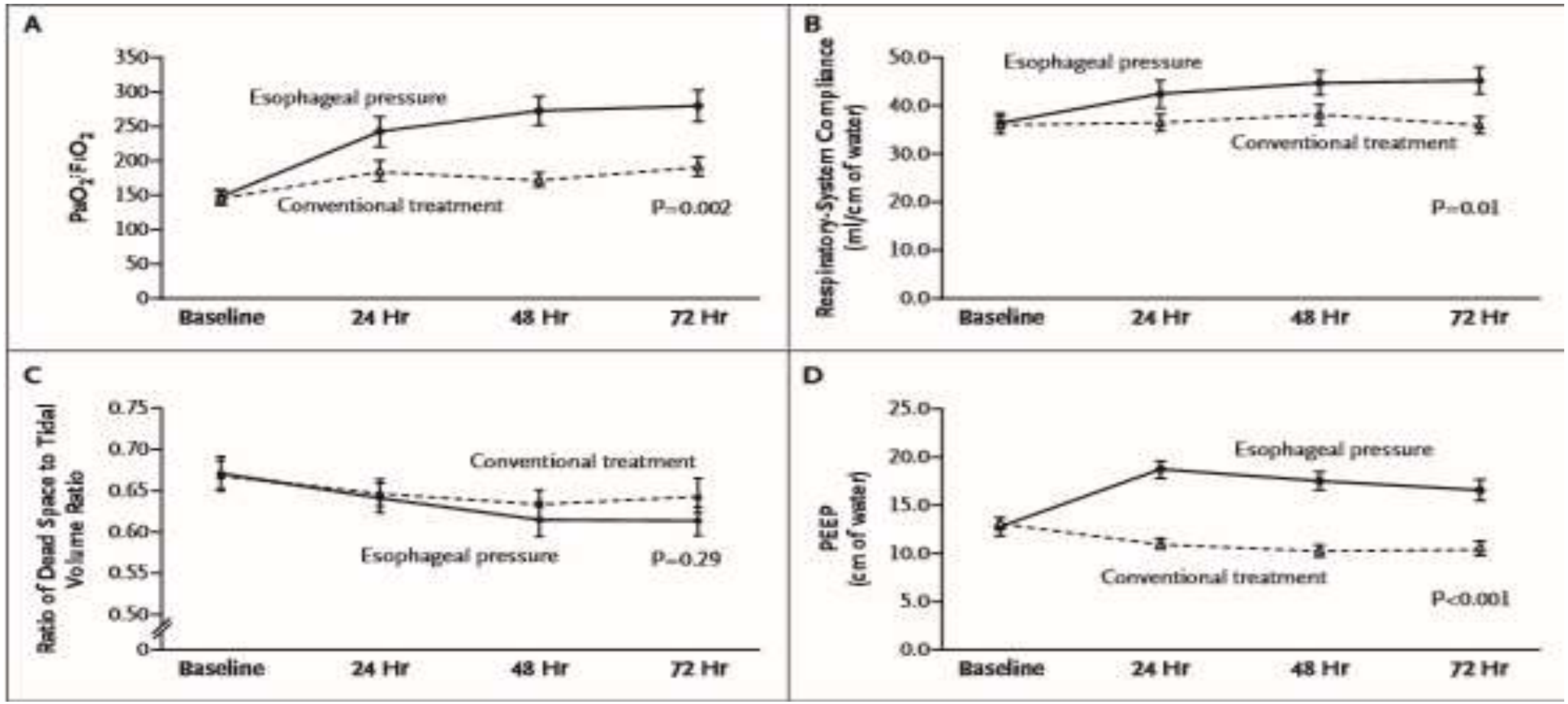
Table 1. Baseline Characteristics of the Patients.*

Characteristic	Esophageal-Pressure–Guided (N=30)	Conventional Treatment (N=31)	P Value
Male sex — no. (%)	19 (63)	17 (55)	0.44
Age — yr	54.5±16.1	51.2±23.0	0.52
White race — no. (%)†	26 (87)	27 (87)	0.96
Predicted body weight — kg	67.1±8.9	63.2±11.1	0.14
APACHE II score at admission	26.3±6.4	26.8±6.5	0.76
Primary physiological injury — no. (%)‡			0.54
Pulmonary	7 (23)	5 (16)	
Abdominal	13 (43)	11 (35)	
Trauma	6 (20)	9 (29)	
Sepsis	3 (10)	2 (6)	
Other	1 (3)	4 (13)	
Organ failure at baseline — no. (%)			
Cardiac	10 (33)	10 (32)	0.93
Renal	19 (63)	16 (52)	0.36
Neurologic	12 (40)	12 (39)	0.92
Hepatic	11 (37)	10 (32)	0.72
Hematologic	7 (23)	5 (16)	0.48
Arterial blood gases at baseline			
pH	7.34±0.09	7.32±0.08	0.34
$PaCO_2$ — mm Hg	42±8	40±8	0.23
PaO_2 — mm Hg§	91±25	107±44	0.09
Bicarbonate — mmol/liter	24±5	22±4	0.05
Hemodynamic variables at baseline			
Lactate — mg/dl	3.1±3.5	3.4±3.3	0.83
Heart rate — beats/min	98±26	100±19	0.71
Systolic blood pressure — mm Hg	108±18	107±18	0.80
Diastolic blood pressure — mm Hg	58±11	54±11	0.20
Central venous pressure — mm Hg	16±5	16±4	0.96

Table 2. Measurements of Ventilatory Function at Baseline and 72 Hours.*

Measurement	Baseline			72 Hr†		
	Esophageal-Pressure–Guided (N=30)	Conventional Treatment (N=31)	P Value	Esophageal-Pressure–Guided (N=29)	Conventional Treatment (N=29)	P Value
PaO_2:FiO_2	147±56	145±57	0.89	280±126	191±71	0.002
Respiratory-system compliance (ml/cm of water)	36±12	36±10	0.94	45±14	35±9	0.005
Ratio of physiological dead space to tidal volume	0.67±0.11	0.67±0.09	0.95	0.61±0.09	0.64±0.10	0.27
PaO_2 (mm Hg)	91±25	107±44	0.09	124±44	101±33	0.03
FiO_2	0.66±0.17	0.77±0.18	0.02	0.49±0.17	0.57±0.18	0.07
PEEP (cm of water)	13±5	13±3	0.73	17±6	10±4	<0.001
Tidal volume (ml)	484±98	491±105	0.80	472±98	418±80	0.03
Tidal volume (ml per kg of predicted body weight)	7.3±1.3	7.9±1.4	0.12	7.1 ±1.3	6.8±1	0.31
Respiratory rate (breaths/min)	26±6	24±6	0.32	26±6	28±5	0.20
Inspiratory time (sec)	0.8±0.1	0.9±0.2	0.19	0.8±0.1	0.8±0.1	0.27
$PEEP_{total}$ (cm of water)	14±5	15±4	0.67	18±5	12±5	<0.001
Peak inspiratory pressure (cm of water)	35±8	35±7	0.85	32±8	28±7	0.007
Mean airway pressure (cm of water)	20±6	20±4	0.88	22±6	16±5	0.001
Plateau pressure (cm of water)	29±7	29±5	0.79	28±7	25±6	0.07
Transpulmonary end-inspiratory pressure (cm of water)	7.9±6.0	8.6±5.4	0.61	7.4±4.4	6.7±4.9	0.58
Transpulmonary end-expiratory pressure (cm of water)	−2.8±5.0	−1.9±4.7	0.49	0.1±2.6	−2.0±4.7	0.06
Esophageal end-inspiratory pressure (cm of water)	21.2±4.9	20.7±5.1	0.68	21.7±7.2	17.9±5.2	0.03
Esophageal end-expiratory pressure (cm of water)	17.2±4.4	16.9±5.0	0.79	18.4±5.9	14.3±4.9	0.008

* Plus–minus values are means ±SD. FiO_2 denotes the fraction of inspired oxygen, PaO_2 the partial pressure of arterial oxygen, PEEP positive end-expiratory pressure applied by the ventilator, and $PEEP_{total}$ airway pressure measured during end-expiratory occlusion.
† The values are given for the 29 surviving patients in each treatment group.


A
$PaO_2:FiO_2$
350
300
250
200
150
100
50
0
Esophageal pressure
Conventional treatment
P=0.002
Baseline
24 Hr
48 Hr
72 Hr
B
Respiratory-System Compliance (ml/cm of water)
50.0
40.0
30.0
20.0
10.0
0.0
Esophageal pressure
Conventional treatment
P=0.01
Baseline
24 Hr
48 Hr
72 Hr
C
Ratio of Dead Space to Tidal Volume Ratio
0.75
0.70
0.65
0.60
0.55
0.50
0
Conventional treatment
Esophageal pressure
P=0.29
Baseline
24 Hr
48 Hr
72 Hr
D
PEEP (cm of water)
25.0
20.0
15.0
10.0
5.0
0.0
Esophageal pressure
Conventional treatment
P<0.001
Baseline
24 Hr
48 Hr
72 Hr

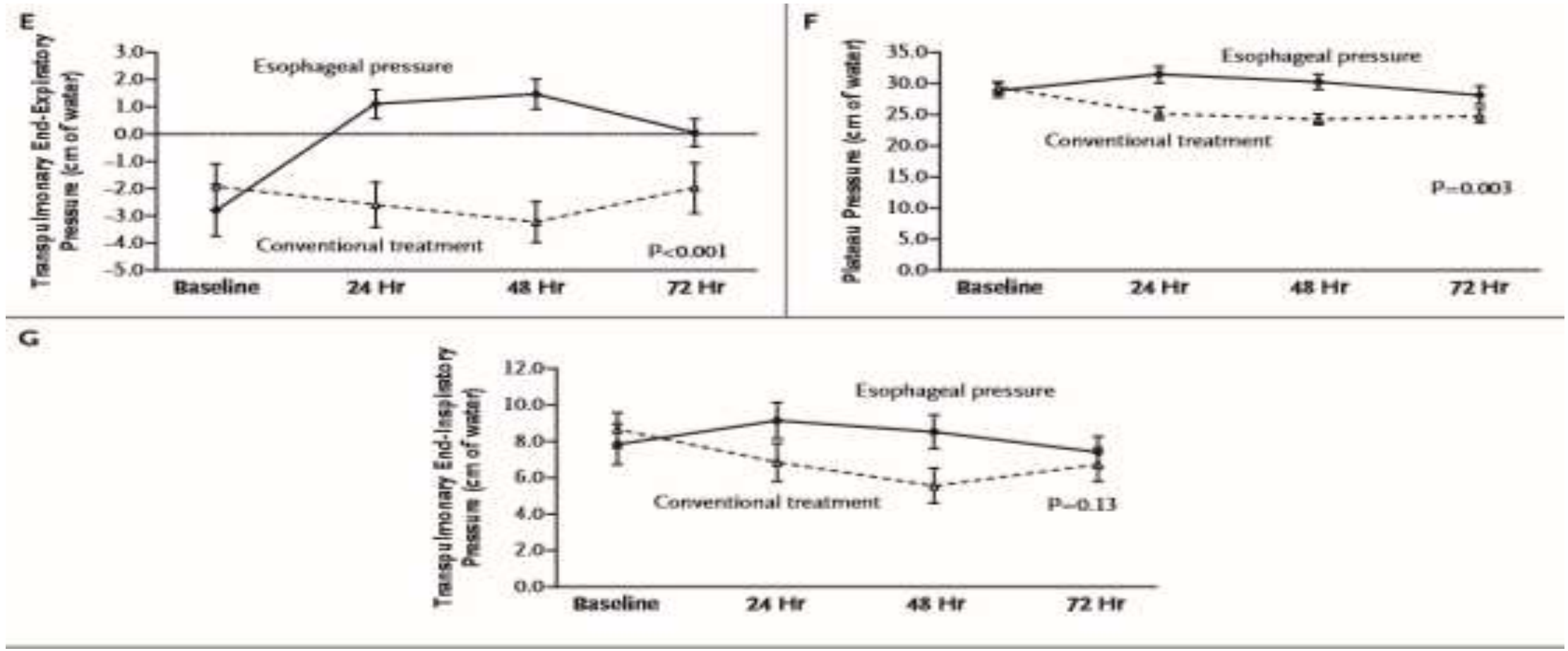

E
Transpulmonary End-Expiratory Pressure (cm of water)
3.0
2.0
1.0
0.0
-1.0
-2.0
-3.0
-4.0
-5.0
Esophageal pressure
Conventional treatment
P<0.001
Baseline
24 Hr
48 Hr
72 Hr
F
Plateau Pressure (cm of water)
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
Esophageal pressure
Conventional treatment
P=0.003
Baseline
24 Hr
48 Hr
72 Hr
G
Transpulmonary End-Inspiratory Pressure (cm of water)
12.0
10.0
8.0
6.0
4.0
2.0
0.0
Esophageal pressure
Conventional treatment
P=0.13
Baseline
24 Hr
48 Hr
72 Hr

Table 3. Changes in PEEP at the Initiation of Ventilation According to the Protocol.

Treatment Group	Change in PEEP				
	−1 to −6 cm of Water	0 to 5 cm of Water	6 to 10 cm of Water	11 to 15 cm of Water	16 to 20 cm of Water
			no. of patients		
Esophageal-pressure–guided group	3	9	12	4	2
Control group	12	18	1	0	0

Table 4. Clinical Outcomes.*

Outcome	Esophageal-Pressure–Guided (N=30)	Conventional Treatment (N=31)	P Value
28-Day mortality — no. (%)	5 (17)	12 (39)	0.055
180-Day mortality — no. (%)	8 (27)	14 (45)	0.13
Length of ICU stay — days			0.16
Median	15.5	13.0	
Interquartile range	10.8–28.5	7.0–22.0	
No. of ICU-free days at 28 days			0.96
Median	5.0	4.0	
Interquartile range	0.0–14.0	0.0–16.0	
No. of ventilator-free days at 28 days			0.50
Median	11.5	7.0	
Interquartile range	0.0–20.3	0.0–17.0	
No. of days of ventilation among survivors			0.71
Median	12.0	16.0	
Interquartile range	7.0–27.5	7.0–20.0	

* For patients who were deceased at day 28, a value of 0 days was assigned. ICU denotes intensive care unit.

Criticism of study

- Mean PaO2 was 122±44 mmHg in the esophageal pressure guided group at 72 hours.
- More than half of patients in the esophageal pressure guided group had a PaO2 above the range stipulated by the protocol.
- Poor protocol compliance
- Profound artifact on PaO2: FiO2 at the critical time of assessment for the primary outcome

- Effects on important clinical outcomes such as long term mortality, ventilator free days, and length of stay in ICU remain unanswered
- Improved oxygenation need not result in clinical improvement.
- Only large trial to show a lowering of mortality rates in association with a particular method of ventilation also found that group with improved oxygenation had higher mortality rates

The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301-8.

Other potential sources of error

- Balloon placement was inadequate in 1/3rd of patients
- A correction factor of 5 cm of water was subtracted from the esophageal pressure in an attempt to compensate for the known artifacts of mediastinal weight and balloon air volume on the observed pressures

? Too many assumptions

- the balloon pressure reflects the esophageal pressure
- the transmural pressure in the esophagus is 0 cm of water
- the esophagus is not compressed by intrathoracic structures such as the heart
- the pressures in the periesophageal area are the same as the pleural pressure
- pleural pressure is relatively uniform throughout the thorax

Comparison of changes in PEEP and PaO2:FiO2 From baseline to day 3 in the study by Talmor et al. and in the ARDSNet ALVEOLI Trial

Table 2. Changes in PEEP and PaO_2:FiO_2 from Baseline to Day 3 in the Study by Talmor et al. and in the ARDSNet ALVEOLI Trial.*

Variable	Talmor et al.		ALVEOLI Trial	
	Esophageal-Pressure–Guided Group (N=30)	Conventional-Treatment Group (N=31)	Higher PEEP (N=276)	Lower PEEP (N=273)
PEEP (cm of water)				
Baseline	13±5	13±3	10±4	9±4
Day 3	17±6	10±4	13±5	9±4
PaO_2:FiO_2				
Baseline	147±56	145±57	151±67	165±77
Day 3	280±126	191±71	206±76	169±69

- Improvements in oxygenation in the study by Talmor et al. were reflective of generally higher level of PEEP, rather than a unique response to PEEP titration method