Mechanical Ventilation Guided by Esophageal Pressure in Acute Lung Injury/ARDS

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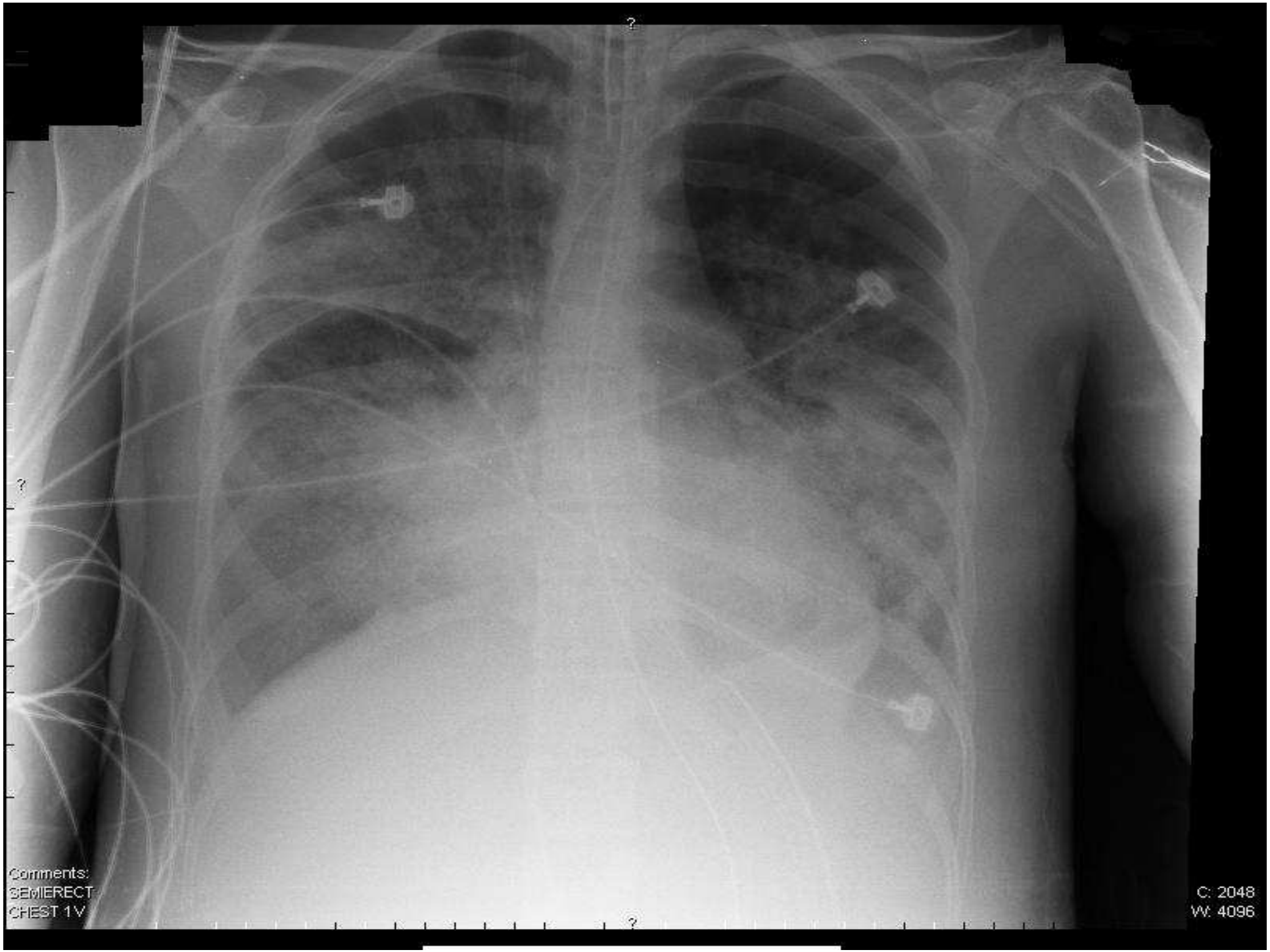
Journal Club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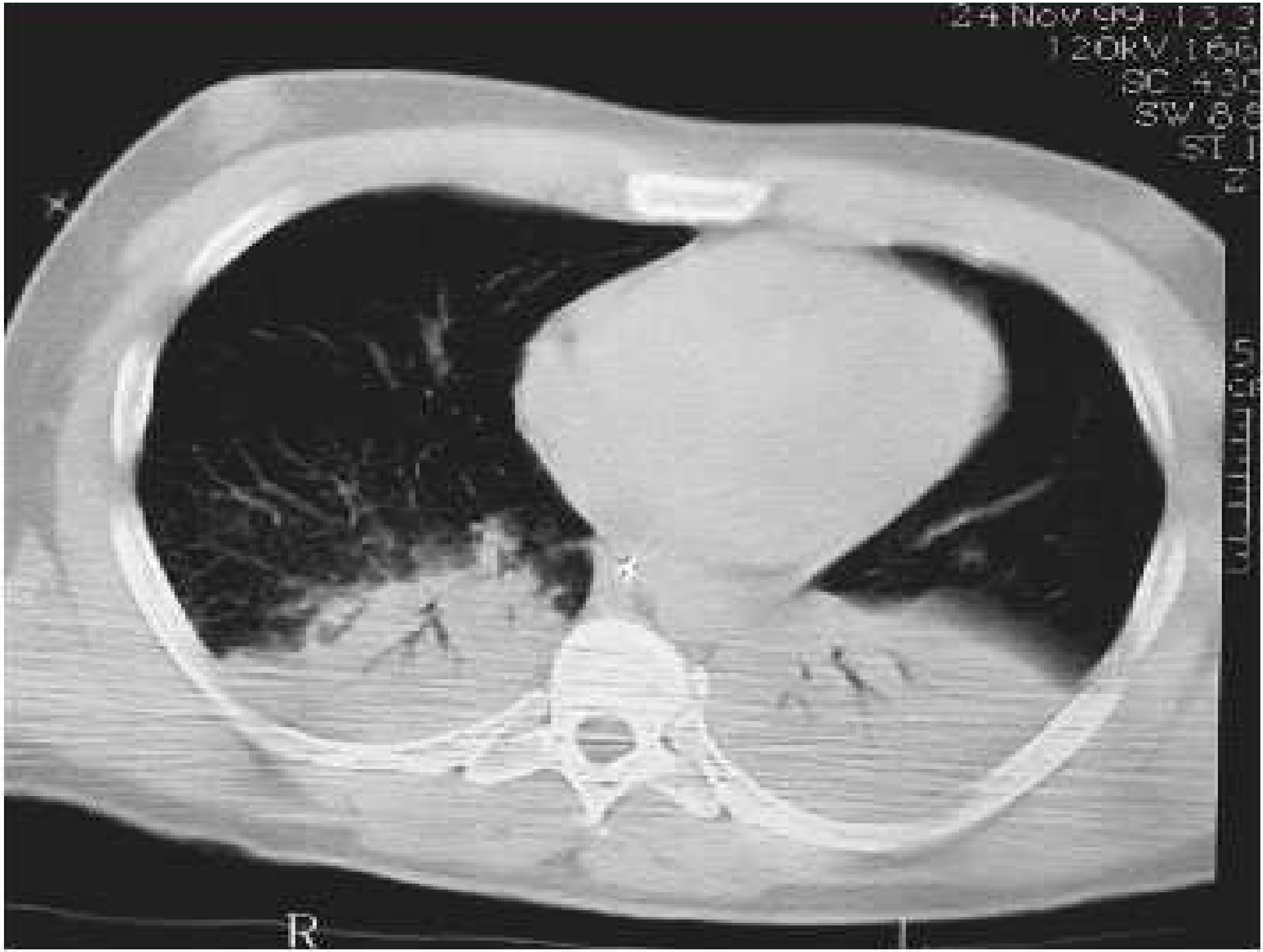
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Introduction

- Recent advances in mechanical ventilation have improved survival in ALI/ARDS but mortality remains high.
- Low tidal volumes (6ml/kg) beneficial in ARDS.
- Optimal PEEP remains uncertain.
- Ideal mechanical ventilation should provide sufficient transpulmonary pressure (airway pressure – pleural pressure) to maintain oxygenation while:
  - Minimising repetitive alveolar collapse
  - Minimising alveolar overdistension/volutrauma
- In critically ill patients however, for any given PEEP, transpulmonary pressures can vary between patients.

Hypothesis

- Pleural pressure can be estimated with esophageal balloon catheter – validated in healthy humans but not ICU patients.

- Study plan: adjust/tailor PEEP to individual patient's needs/lung and chest wall mechanics.

- Speculated that in patients with high estimated pleural pressure undergoing mechanical ventilation, underinflation may cause hypoxia => raising PEEP to maintain +ve transpulmonary pressure could improve oxygenation without causing overdistension.

- Speculated conversely that in pts. with low pleural pressures, lowering PEEP would keep transpulmonary pressure low, minimising volutrauma/overdistension and also minimise hemodynamic effects of high PEEP.

Methods

- Randomised controlled pilot trial involving patients with ALI or ARDS.
- Aim: compare mechanical ventilation directed by eosophageal-pressure measurements with mechanical ventilation managed according to ARDSnetwork recommendations.
- Hypothesis: Oxygenation in patients can be improved by adjusting PEEP to maintain positive transpulmonary pressures as guided by oesophageal-pressure measurements.
- Patients enrolled from both SICU & MICU
- Patients included in study if they had ALI/ARDS according to the American-European Consensus Conference definitions.
- Exclusion criteria: recent injury of oesophageal pathology, major bronchopleural fistula, and solid organ transplantation recipients.

Methods

- While undergoing treatment, patients were supine with head of bed elevated to 30 degrees.
- Airway pressure, tidal volume and airflow were recorded.
- Esophageal balloon to depth of 40cm placed to record esophageal pressure during mechanical ventilation.
- Balloon position confirmed by cardiac artifact and changes in transpulmonary pressure during tidal ventilation.
- Mixed expired partial pressure of CO2 measured to allow calculation of physiological dead space.
- After these measurements, pts. randomised to control or esophageal-pressure-guided group.

Methods

- Each pt, while under heavy sedation or curare, underwent a recruitment manoeuvre to standardise history of long volume .

- Airway pressure increased to 40cmH2O for 30sec. +/- PEEP to keep transpulmonary pressure [airway pressure – esophageal pressure] <25cmH2O ie. physiological range.

- After lung volume recruitment manoeuvre, pt underwent mechanical ventilation according to randomised treatment assignment.

- For both groups:
  - Either pressure or volume-controlled mechanical ventilation acceptable
  - I:E ratio between 1:1 and 1:3
  - Target tidal volume 6ml +/- 2ml per kg, RR<35 breaths per minute
  - PaO2 between 55 and 120mmHg, sats between 88-98%

Methods

- In esophageal-pressure guided group, mechanical ventilation settings determined by initial esophageal pressure measurements.

- Tidal volume set at 6ml per kg predicted body weight.

- PEEP set to achieve a transpulmonary pressure of 0-10cm H_2O at end expiration, according to a sliding scale based on PaO_2 and FiO_2 – see figure 1.

- Also limited tidal volume to keep transpulmonary pressure <25cmH_2O at end-inspiration (limit rarely approached during study and tidal volume was never reduced for this purpose).

Figure 1. *Ventilator Settings According to the Protocol.*
For the intervention group, keep the partial pressure of arterial oxygen (PaO_2) between 55 and 120 mm Hg by using the ventilator settings in one column at a time. **Set the positive end-expiratory pressure (PEEP) at such a level that transpulmonary pressure during end-expiratory occlusion (P_{Lexp}) stays between 0 and 10 cm of water, and keep transpulmonary pressure during end-inspiratory occlusion at less than 25 cm of water**. For the control group: Set the PEEP and tidal volume at such levels that the airway pressure during end-inspiratory occlusion stays at less than 30 cm of water.

Esophageal-Pressure–Guided Group

FiO_2	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_{Lexp}	0	0	2	2	4	4	6	6	8	8	10	10

Control 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	20–24

Methods

- Pts in control group treated according to low-tidal volume strategy reported in ARDSnetwork;
  - Tidal volume set at 6ml/kg
  - PEEP based on patient's PaO_2 + FiO_2 – see Figure 1.

- In both groups, as previously stated, target PaO_2 55 – 120mmHg or sats 88-98% (measured by pulse oximetry), pH 7,30 – 7,45, and a $PaCO_2$ between 40 – 60mmHg.

- All measurements repeated 5 minutes after initiation of experimental or controlled ventilation and again at 24, 48, and 72 hrs.

Methods

- Primary end-point of study was arterial oxygenation, as measured by PaO2:FiO2 [P:F] ratio 72 hours after randomisation.

- Secondary end points included:
  - Indexes of lung mechanics (eg.compliance, ratio of dead space to tidal volume)
  - Indexes of gas exchange
  - No. of ventilator-free days at 28days
  - Length of ICU stay
  - Death within 28 days and 180 days after treatment

Statistical Analysis

- In evaluating P:F ratio at 72 hours, decided a priori that clinically important change in ratio would be approximately 20% - chose minimal average of 40 in P:F ratio to determine sample size.

- 100 pts required to detect difference of 40 in ratio with 80% power and two-tailed alpha value of 0.05.

- Interim analysis after 60 patients enrolled +/- recommendation by safety board to stop trial if overwhelming effect detected on basis of critical significance level as defined by p value </= 0.02.

RESULTS

- Baseline characteristics well matched between groups.
- Mean APACHE II score of 26.6 +/- 6.4 and a median of 2 failed organs – see Table 1.
- Unable to sedate 1 patient in the esophageal-pressure-guided group sufficiently to obtain stabel measurements; patient included in analysis on basis of intention-to-treat principle.
- No adverse events reported or incidents of barotrauma in either group.

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

* Plus–minus values are means ±SD. APACHE denotes Acute Physiology and Chronic Health Evaluation, $PaCO_2$ the partial pressure of arterial carbon dioxide, and PaO_2 the partial pressure of arterial oxygen.
† Race was determined by the investigators.
‡ Pulmonary injury included pneumonia (nine patients), aspiration pneumonitis (two), and smoke inhalation (one). Abdominal injury included bowel obstruction (four patients), abdominal surgery (four), pancreatitis (four), cholangitis (two), small-bowel perforation (three), ruptured aortic aneurysm or surgery for aortic aneurysm (two), gastrointestinal bleeding

RESULTS

- Study stopped after 61 patients enrolled.
- Planned interim analysis showed that study had reached the prespecified stopping criterion.
- **P:F ratio at 72 hours was 88mmHg higher in patients treated with mechanical ventilation with esophageal balloons than in control group (95% CI 78.1 – 98.3; P=0.002)**

RESULTS – Physiological measurements

- Ventilator settings and physiological measurements similar between 2 groups at baseline – see table 2.
- 49 pts (80%) met definition for ARDS as defined by P:F <200mmHg.
- No significant difference in P:F ratio between 2 groups at baseline.
- Average tidal volume during first 24h reduced by 67ml in control group and 44ml in pressure-guided group.
- **Oxygenation and respiratory-system compliance significantly improved in the esophageal-pressure-guided group as compared with control group – see Figure 2 a + b.**

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.

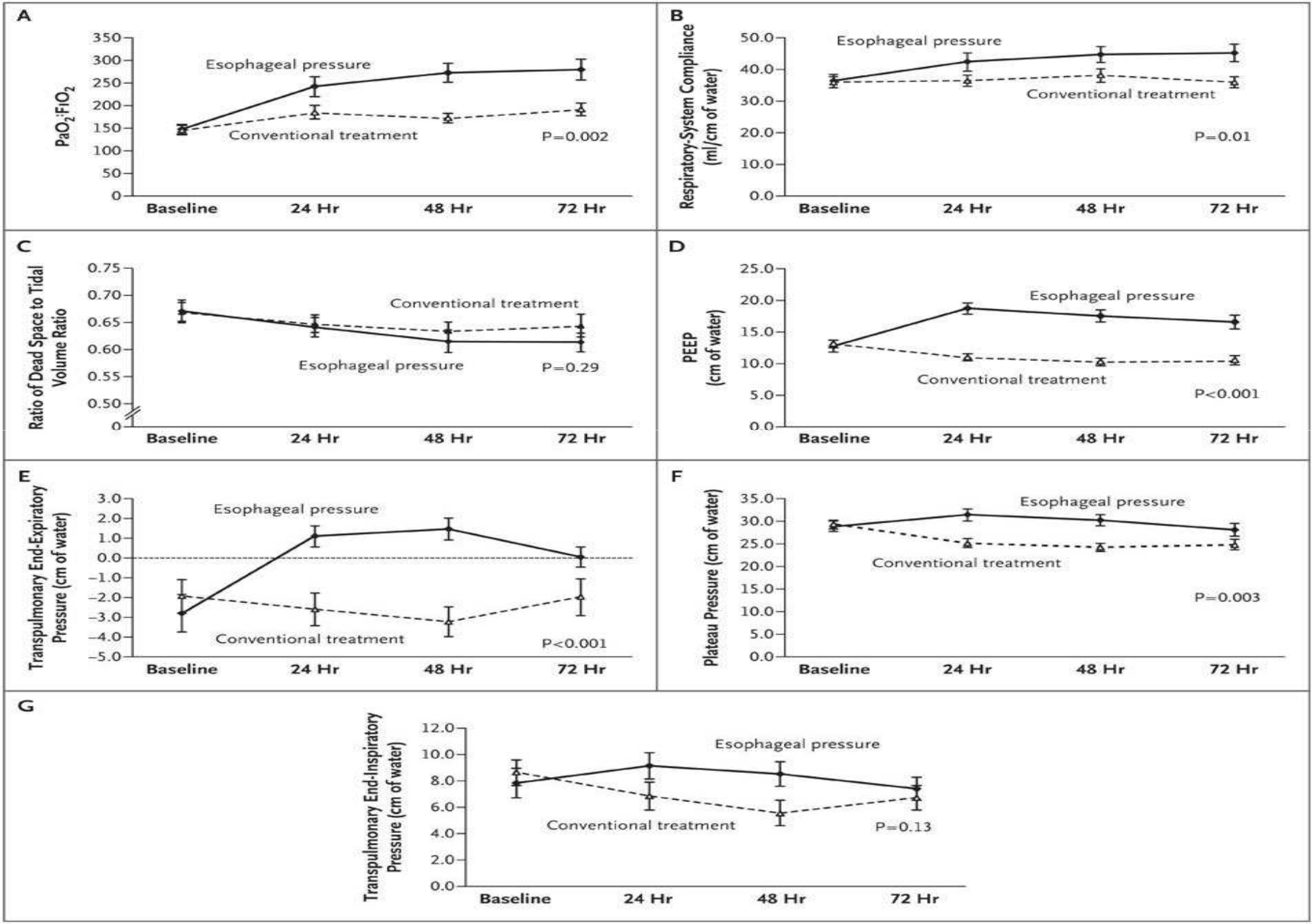
RESULTS – Physiological measurements

- Ratio of dead-space to tidal volume did not significantly differ between groups within 72h.

- P:F improved during first 72h by 131mmHg in esophageal-pressure-guided group and by 49mmHg in the control group p=0.002 – evident at 24h – see Table 2

- Compliance significantly better/improved in pressure-guided group p=0.01 at 24, 48 and 72h.

Respiratory measurements at baseline, 24, 48 and 72 hours in esophageal-pressure guided group and control group



RESULTS – Physiological measurements

- Patients in pressure-guided group had significantly higher PEEP at 24, 48 and 72h $p < 0.001$
- Difference in PEEP at 24h 7.7cmH2O with mean PEEP of 18.7 +/- 5.1 cm in esophageal-pressure-guided group.
- At 24, 48 and 72h, mean transpulmonary end-expiratory pressure remained > 0cmH2O in pressure-guided group, whereas remained negative in control group $p<0.001$.
- Plateau airway pressure during end-inspiratory occlusion was higher in pressure-guided group $p=0.003$ **however** transpulmonary pressures during end-inspiratory inclusion never exceeded 24cmH2O and did not statistically differ between 2 groups.

RESULTS – Clinical outcomes

- **No significant difference between groups in ventilator-free days at day 28 or length of ICU stay.**

- 28-day mortality in entire study cohort was 28% (17 of 61 pts).

- Baseline APACHE score higher in pts who died 31.5 versus 24.7 $p<0.001$ but baseline P:F ratio similar among survivors and non-survivors $p=0.56$.

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.

RESULTS – Clinical outcomes

- Mortality rate (unadjusted)at 28days lower in esophageal-pressure-guided group than control group but difference not significant (RR 0.43; 95% CI 0.17-1.07;p=0.06)

- **Mulitvariate analysis showed that after adjustment for baseline APACHE II score, the esophageal-pressure-guided protocol was associated with significant reduction in 28-day mortality compared to control/conventional treatment group (RR 0.46;95% CI 0.19-1.0;p=0.049)**

- Mortality rate at 180days did not differ between two groups

Discussion

- Several large trials (ALVEOLI trial, Lung Open Ventilation Study) failed to demonstrate benefit of increased PEEP as compared with standard PEEP in pts with ARDS.

- Lack of observed benefit due to inclusion of pts with elevated abdominal pressure or plural pressure?

- Lungs of such patients may collapse due to such high ‘extrinsic’ pressures at end-expiration despite levels of PEEP that may be adequate in other patients.

- By using/monitoring esophageal pressure (and hence transpulmonary pressure), possible to adjust PEEP according to patient’s dynamics/physiological flux thereby preventing repeated alveolar collapse or over-distension.

Discussion

- Technically feasible to make repeated accurate measurements of esophageal pressures that may be of use in management of mechanically-ventilated patients.
- Pts with ALI/ARDS treated in this way had significantly improved oxygenation/P:F ratio.
- Also demonstrated significantly improved lung compliance.
- Improvements achieved without elevating transpulmonary pressure at end-inspiration above physiologic range (never >24cmH2O)
- Non-statistically significant trend toward improved 28-day survival.

Negative aspects of study

- Small pilot study
- Single center study
- Technical expertise required for esophageal pressure monitoring – reproducibility/practicality?
- Primary outcome defined as improved P:F ratio which in turn determined by PEEP.
- Improved oxygenation ,when obtained at cost of higher airway presures, not associated with significantly improved survival outcomes (or maybe even worse outcome!)