

# Physiological Effects of the Open Lung Approach in Patients with Early, Mild, Diffuse Acute Respiratory Distress Syndrome

## An Electrical Impedance Tomography Study

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### ABSTRACT

**Background:** To test the hypothesis that in early, mild, acute respiratory distress syndrome (ARDS) patients with diffuse loss of aeration, the application of the open lung approach (OLA) would improve homogeneity in lung aeration and lung mechanics, without affecting hemodynamics.

**Methods:** Patients were ventilated according to the ARDS Network protocol at baseline (pre-OLA). OLA consisted in a recruitment maneuver followed by a decremental positive end-expiratory pressure trial. Respiratory mechanics, gas exchange, electrical impedance tomography (EIT), cardiac index, and stroke volume variation were measured at baseline and 20 min after OLA implementation (post-OLA). Esophageal pressure was used for lung and chest wall elastance partitioning. The tomographic lung image obtained at the fifth intercostal space by EIT was divided in two ventral and two dorsal regions of interest ( $ROI_{\text{ventral}}$  and  $ROI_{\text{dorsal}}$ ).

**Results:** Fifteen consecutive patients were studied. The OLA increased arterial oxygen partial pressure/inspired oxygen fraction from  $216 \pm 13$  to  $311 \pm 19$  mmHg ( $P < 0.001$ ) and decreased elastance of the respiratory system from  $29.4 \pm 3$  cm H<sub>2</sub>O/l to  $23.6 \pm 1.7$  cm H<sub>2</sub>O/l ( $P < 0.01$ ). The driving pressure (airway opening plateau pressure – total positive end-expiratory pressure) decreased from  $17.9 \pm 1.5$  cm H<sub>2</sub>O pre-OLA to  $15.4 \pm 2.1$  post-OLA ( $P < 0.05$ ). The tidal volume fraction reaching the dorsal ROIs increased, and consequently the  $ROI_{\text{ventral/dorsal}}$  impedance tidal variation decreased from  $2.01 \pm 0.36$  to  $1.19 \pm 0.1$  ( $P < 0.01$ ).

**Conclusions:** The OLA decreases the driving pressure and improves the oxygenation and lung mechanics in patients with early, mild, diffuse ARDS. EIT is useful to assess the impact of OLA on regional tidal volume distribution. (**ANESTHESIOLOGY 2015; 123:1113-21**)

CURRENT guidelines recommend the use of low tidal volume ( $V_T$ ), 6 to 8 ml/kg predicted body weight, for patients with acute respiratory distress syndrome (ARDS).<sup>1-3</sup> The approach to positive end-expiratory pressure (PEEP) and lung recruitment maneuver (LRM) is more controversial. The ARDS Network protocol<sup>2,4</sup> matches a “safe” minimal oxygenation target with the lowest possible PEEP and inspired oxygen fraction ( $F_{iO_2}$ ) according to a PEEP/ $F_{iO_2}$  combination table and does not prescribe LRMs. This may result in incomplete lung recruitment (permissive atelectasis).<sup>4</sup> Three large clinical trials<sup>5-7</sup> compared low and high PEEP in association with low  $V_T$ s and were not conclusive. However, in those trials, PEEP-setting criteria and LRMs were not standardized. Recently the more physiologically oriented “open lung” approach (OLA), aiming at maximal alveolar recruitment, has been proposed.<sup>3</sup> During OLA, relatively high distending pressures are applied to overcome the critical “opening pressure” (lung recruitment phase). Subsequently, PEEP is titrated on the expiratory limb of the

### What We Already Know about This Topic

- Recruitment maneuvers aim to open atelectatic regions of the lung, thereby increasing lung compliance and improving gas exchange. However, in established acute respiratory distress syndrome, such maneuvers can overdistend already opened lungs.

### What This Article Tells Us That Is New

- In 15 patients with early, mild, diffuse acute respiratory distress syndrome, application of an open lung approach (vs. a standard management protocol that does not target an “open” lung) resulted in lower driving pressure, improved oxygenation, and more homogeneous distribution of ventilation (assessed by electric impedance tomography).

volume–pressure curve (decremental PEEP trial) to match the best compliance (or the best oxygenation) compatible with the lowest PEEP level.<sup>4,8</sup>

Optimal recruitment is a key factor for minimizing ventilator-induced lung injury (VILI), and it may potentially affect outcome.<sup>9,10</sup> This explains the research focus on OLA

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in ARDS. However, to the best of our knowledge, the OLA has not been tested in less severe ARDS forms (mild ARDS according to the Berlin definition). Indeed, a meta-analysis by Briel *et al.*<sup>11</sup> supports the hypothesis that high PEEP may be indifferent (or even harmful) in mild ARDS. However, none of the studies taken into account for that meta-analysis was based on the OLA strategy. Mild ARDS has a mortality rate of 27%,<sup>1</sup> and it is conceivable that optimal lung recruitment could further reduce this figure.

We reasoned that the OLA would be particularly appropriate for patients with early, mild, diffuse ARDS who are good recruiters.<sup>12,13</sup> In this study, we assessed the physiological effects of the ARDS Network protocol *versus* the OLA in patients with early, mild, diffuse ARDS. Our hypothesis was that when compared with the ARDS Network protocol, the OLA would improve lung aeration without affecting hemodynamics. Thoracic computed tomography (CT) is the “definitive standard” to assess PEEP- and LRM-induced alveolar recruitment.<sup>14,15</sup> However, it has serious limitations in clinical practice (transportation to CT scan facility and exposure to radiations). In this bedside study, we used electrical impedance tomography (EIT) for online assessment of regional changes in lung aeration in response to OLA.<sup>16</sup>

## Materials and Methods

### Study Population

After obtaining approval from the ethics committee of the “Azienda Ospedaliero Universitaria-Ospedali Riuniti” of Foggia, Italy, and written informed consent from each patient’s next of kin, the study was performed in patients with early (within 72 h from the onset), mild, diffuse ARDS<sup>1</sup> admitted to the general intensive care unit of the “Azienda Ospedaliero Universitaria-Ospedali Riuniti” of Foggia, Italy, from January to December 2013. Patient’s demographic data, medical history, ARDS etiology, days spent on mechanical ventilation, and intensive care outcome were recorded on a dedicated database.

Inclusion criteria were as follows: mild ARDS defined according to the Berlin definition<sup>1</sup> (*i.e.*, with an arterial oxygen partial pressure ( $P_{aO_2}$ )/ $F_{IO_2}$  ratio between 200 and 300), invasive mechanical ventilation for clinical decision (for those who underwent thoracic chest radiograph and CT scan for clinical reasons), qualitative analysis of CT scan showing diffuse involvement of the lung parenchyma (according to the definition of the CT scan ARDS study group),<sup>13</sup> age older than 18 yr, and continuous intravenous sedation and analgesia, with a Ramsay score between 3 and 4 for clinical decision.<sup>17</sup>

Exclusion criteria were as follows: hemodynamic instability, defined as systolic artery pressure 90 mmHg or less or mean artery pressure 60 mmHg or less; pneumothorax; intracranial hypertension or other conditions in which hypercapnia is contraindicated; burns greater than 30% total body surface area; pregnancy; contraindication to

EIT use (presence of pacemaker or automatic implantable cardioverter defibrillator); impossibility in placing the EIT belt in the right position for the presence of surgical wound dressing; malignancy or other irreversible disease or conditions; bone marrow or lung transplant; severe chronic or acute liver disease and vasculitis with diffuse alveolar hemorrhage; and refusal to participate in the study.

### Respiratory Mechanics and Hemodynamic Measurements

All patients were orotracheally intubated and ventilated using SERVO-i-ventilator (Maquet Holding GmbH & Co. Kg, Germany). Airflow was measured with a heated pneumotachograph (Fleisch no. 2; Fleisch, Switzerland) connected to a differential pressure transducer (Diff-Cap,  $\pm 1$  cm  $H_2O$ ; Special Instruments, Germany) inserted between the Y-piece of the ventilator circuit and the endotracheal tube. The pneumotachograph was linear over the experimental range of flow. Volume was obtained by numerical integration of the flow signal. Airway opening pressure ( $P_{AO}$ ) was measured proximal to the endotracheal tube with a pressure transducer (Special Instruments Digima-Clic  $\pm 100$  cm  $H_2O$ , Germany). To measure esophageal pressure ( $P_{ES}$ ), an esophageal thin latex balloon-tipped catheter (Compliance catheter; Microtek Medical B.V., The Netherlands) was inserted through the mouth, advanced into the esophagus, and connected by means of a polyethylene catheter to a pressure transducer (Digima-Clic). The esophageal balloon was filled with 1 to 1.5 ml of air, and its correct positioning in the lower third of the esophagus was verified by the presence of appropriate esophageal pressure deflections induced by mechanical ventilation and moderate push on the abdomen.<sup>18,19</sup>

The difference between the PEEP set on the ventilator (read as the  $P_{AO}$  value at the end of a regular breath) ( $PEEP_{EXT}$ ) and the  $P_{AO}$  during a 3- to 5-s end-expiratory occlusion ( $PEEP_{TOT,RS}$ ) was measured and regarded as the static intrinsic PEEP of the respiratory system ( $PEEP_{i,RS}$ ) according to Pepe and Marini.<sup>20</sup> The end-expiratory occlusion was performed through the expiratory hold button of the Servo-i-ventilator.

Static elastance of the respiratory system ( $E_{RS}$ ) was calculated using the following:

$$E_{RS} = (P_{PLAT,RS} - PEEP_{TOT,RS}) / VT, \quad (1)$$

where  $P_{PLAT,RS}$  is the value of  $P_{AO}$  read at the end of an end-inspiratory pause of 2 to 3 s (appropriate hold button of the ventilator).

Static elastance of the chest wall ( $E_{CW}$ ) was calculated as follows:

$$E_{CW} = (P_{PLAT,CW} - PEEP_{TOT,CW}) / VT, \quad (2)$$

where  $P_{PLAT,CW}$  and  $PEEP_{TOT,CW}$  are the values of  $P_{ES}$  during an end-inspiratory and end-expiratory pause, respectively. Lung static elastance ( $E_L$ ) was calculated as follows:

$$E_L = E_{RS} - E_{CW}. \quad (3)$$

Transpulmonary end-inspiratory pressure ( $P_{\text{PLAT,L}}$ ) was computed<sup>1,5,20,21</sup> as follows:

$$P_{\text{PLAT,L}} = P_{\text{PLAT,RS}} \times E_L / (E_L + E_{\text{CW}}). \quad (4)$$

The driving pressure was calculated as follows:

$$\text{Driving pressure} = P_{\text{PLAT,RS}} - \text{PEEP}_{\text{TOT,RS}}. \quad (5)$$

The transpulmonary driving pressure was calculated as follows:

$$P_{\text{PLAT,L}} - P_{\text{EE,L}},$$

where  $P_{\text{EE,L}}$  is the transpulmonary pressure measured at end-expiration, which is given as follows:

$$P_{\text{EE,L}} = \text{PEEP}_{\text{TOT,RS}} \times E_L / (E_L + E_{\text{CW}}).$$

Blood pressure was measured through a radial catheter connected to the pressure transducer of the MP40 monitor (Intellivue MP40 monitor; Philips, Germany). Hemodynamic parameters obtained through the Vigileo™ monitor (software version 03.10, Edwards Life Sciences LLC, USA) included stroke volume (SV), cardiac output, and SV variation (SVV), whereas SV index and cardiac index (CI) were calculated using standard formulae. Intravascular pressure measurements were adjusted to zero at atmospheric pressure and leveled to the mid-axillary line.

Analysis of arterial blood gases was performed (ABL 330; Radiometer, Denmark). Parameters pertaining to hemodynamics and respiratory mechanics were recorded, digitized, and collected on a personal computer for subsequent analysis through a 12-bit analog-to-digital converter board (DAQ-Card 700; National Instrument, USA) at a sample rate of 200 Hz (ICU-Lab; KleisTEK Engineering, Italy).

### EIT Monitoring and Data

The EIT system (PulmoVista 500®; Draeger Medical GmbH, Germany) was used to monitor patients' regional tidal ventilation.<sup>22–24</sup> A rubber belt containing 16 electrodes was placed around the thorax at the level of the fifth intercostal space and connected to the EIT monitor (Draeger/GoemFII EIT Evaluation Kit 2, Draeger Medical GmbH). In brief, an alternating electrical current (5 mA, 50 kHz) is applied in turn to every pair of electrodes and the resulting surface potentials are measured in the remaining 13 electrode pairs. Voltage differences between different electrode pairs are related to air impedance in different lung regions. One complete rotation of injection and measuring electrodes allows reconstruction of a cross-sectional bidimensional EIT image.

For the purposes of the current study, the EIT image was divided into four quadrants to obtain two ventral and two dorsal regions of interest (ROIs),  $\text{ROI}_{\text{Ventral}}$  and  $\text{ROI}_{\text{Dorsal}}$ , respectively. The following parameters were subsequently obtained<sup>24</sup>:

1.  $\text{ROI}_{\text{Ventral}}$  and  $\text{ROI}_{\text{Dorsal}}$  impedance tidal variation (*i.e.*, the difference between the minimum and maximum value of impedance for each breath) expressed as percentage of global tidal variation (*i.e.*, the difference between maximum and minimum value of global impedance for each breath, which is always 100%, regardless of the  $V_T$ , and is uniquely used as a reference for regional tidal variations).
2.  $\text{ROI}_{\text{Ventral/Dorsal}}$  ratio: A ratio = 1 indicates homogeneity of the anteroposterior distribution of tidal variations. Levels greater than 1 indicate that tidal ventilation is prevalent in ventral lung regions and *vice versa*.
3.  $V_{T\text{Ventral}}$  and  $V_{T\text{Dorsal}}$ : These indicate the regional tidal variations, expressed in milliliter, reaching  $\text{ROI}_{\text{Ventral}}$  and  $\text{ROI}_{\text{Dorsal}}$ , respectively. These were obtained by multiplying the expiratory  $V_T$  for  $\text{ROI}_{\text{Ventral}}$  and  $\text{ROI}_{\text{Dorsal}}$ , respectively.  $V_{T\text{Ventral}}$  and  $V_{T\text{Dorsal}}$  were normalized for patients' predicted body weight to obtain  $V_{T\text{Ventral}}/\text{kg}$  and  $V_{T\text{Dorsal}}/\text{kg}$  values.

### Study Protocol

A physician not involved in the study was always present for patient care. The lungs were ventilated with a square flow waveform according to the ARDS Network protocol.<sup>2</sup>

A standardized protocol for hemodynamic management was applied to ensure fluid volume optimization. In brief, if SVV was less than 13%, no additional fluids were given, whereas if SVV was greater than 13%, additional boluses of 250 ml of crystalloids were infused for 15 to 20 min. After each bolus, SVV was reevaluated, and a further bolus was administered if SVV increased by more than 10%, until reaching an SVV less than 13%.<sup>25</sup>

Our study consisted in the following steps:

1. A set of data on baseline respiratory mechanics, EIT, hemodynamics, and blood gases was recorded (pre-OLA) during ventilation according to the ARDS Network protocol.<sup>2</sup>
2. OLA was achieved according to the Alveolar Recruitment for ARDS Trial (ART).<sup>3</sup> In brief, after checking for hemodynamic stability (see above in this paragraph the standardized protocol for hemodynamic management), patients were sedated and paralyzed with short-acting neuromuscular agents. The ventilator was set to pressure control ventilation with driving pressure 15 cm  $\text{H}_2\text{O}$ , inspiratory-to-expiratory ratio 1:1, respiratory rate 10 breaths/min,  $\text{FIO}_2$  1, and PEEP 25 cm  $\text{H}_2\text{O}$  for 1 min; PEEP was then increased to 35 cm  $\text{H}_2\text{O}$  for 1 min and finally to 45 cm  $\text{H}_2\text{O}$  for 2 min. Afterward, the ventilator was switched to volume control ventilation without changing the remaining parameters, and PEEP was reduced to 23 cm  $\text{H}_2\text{O}$  and then progressively decreased in steps of 3 cm  $\text{H}_2\text{O}$  every 5 min. At each step,  $E_{\text{RS}}$  was calculated until lung closing pressure, that is, the lowest  $E_{\text{RS}}$ , was reached. A

second recruitment maneuver was then applied, and the final PEEP (open lung PEEP) was corresponding to closing pressure + 2 cm H<sub>2</sub>O.<sup>3</sup>

3. A second set of measurements was obtained after 20 min (post-OLA) while patients were ventilated with a square flow waveform.

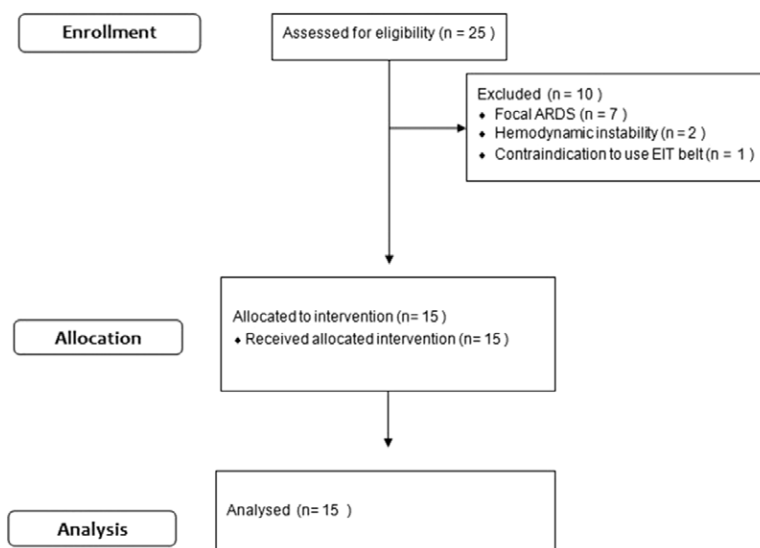
After the study period, the ventilation setting was turned back to the ARDS Network protocol according to our current clinical guidelines for ventilation of patients with mild ARDS.

### Statistical Analysis

A sample size calculation was performed using data from the study by Mauri *et al.*<sup>24</sup> Based on these data, the significant recruitment was designated as a 5% increase in dependent ROI V<sub>T</sub> with an SD of 15. By using a one-sample, one-sided test, the sample size calculated was of 11 patients; this number was increased to 15 to allow for an expected dropout of around one third of patients and was used for patient enrollment. The  $\alpha$  and  $\beta$  errors for the sample size were chosen as 0.05 and 90%, respectively. Statistical comparison of respiratory mechanics, ROI<sub>dorsal</sub>, ROI<sub>Ventral/Dorsal</sub> ratio, V<sub>T,Ventral</sub>/kg and V<sub>T,Dorsal</sub>/kg, hemodynamics, and gas exchange data was performed between the two study steps: data were tested for normal distribution by the Kolmogorov–Smirnov goodness-of-fit test and presented as mean  $\pm$  SD. Data analysis was performed by means of Wilcoxon test for paired samples. A *P* value less than 0.05 was considered statistically significant. Statistical analysis was performed using Statistica 10.0 (Statsoft Italia srl 2011; available at: www.statsoft.com).

### Results

Fifteen of 25 patients with mild ARDS evaluated for enrollment entered the study. The enrollment flow diagram is



**Fig. 1.** Flow diagram of the progress through the phases of the trial. ARDS = acute respiratory distress syndrome; EIT = electrical impedance tomography.

reported in figure 1. The study was completed successfully in each patient without early or late (*i.e.*, occurring after the study period) OLA-related complications. Patients' demographic data are listed in table 1. Of the four nonsurvivor patients, one (patient 5) died because of a dehiscence of intestinal anastomosis and the remaining three (patients 2, 8, and 14) because of supervening severe sepsis. The PEEP level resulting from the OLA ( $15.7 \pm 2.4$  cm H<sub>2</sub>O) was significantly higher than the PEEP level resulting due to the PEEP/FiO<sub>2</sub> combination table of the ARDS Net protocol ( $8.3 \pm 1.8$  cm H<sub>2</sub>O; *P* < 0.001).

### Effects of the OLA on Gas Exchange, Respiratory Mechanics, and Hemodynamics

Switching from the ARDS Network protocol to the OLA decreased the driving pressure by 14% (from  $17.9 \pm 1.5$  cm H<sub>2</sub>O pre-OLA to  $15.4 \pm 2.1$  post-OLA; *P* < 0.0008). The *transpulmonary* driving pressure decreased from  $13 \pm 1.3$  (pre-OLA) to  $12.6 \pm 1.1$  (post-OLA) (*P* < 0.064). E<sub>L</sub> significantly decreased by 19.7% (*P* < 0.05). The PaO<sub>2</sub>/FiO<sub>2</sub> ratio increased from  $216 \pm 13$  to  $311 \pm 19$  mmHg (*P* < 0.00001) (table 2). P<sub>PLAT,L</sub> increased by 18.4% (from  $21.7 \pm 1.9$  to  $25.7 \pm 1.9$  cm H<sub>2</sub>O; *P* < 0.00002) (table 2). During the OLA recruiting phase, the CI decreased by approximately 10% compared with that in the pre-OLA and returned to pre-OLA values immediately and remained stable thereafter. Mean CI, blood pressure, and HR remained stable, and SVV was below the 13% threshold in all patients throughout the experimental procedure (table 2).

### Effects of OLA on Dorsal-to-ventral Ventilation Distribution

Figure 2 is an experimental record showing the effects of the OLA on regional distribution of lung aeration in a representative patient (patient 3). Table 3 shows that the V<sub>T,Dorsal</sub> increased from  $33 \pm 4.3\%$  (pre-OLA) to

**Table 1.** Patients' Main Characteristics

Subjects	Age (yr)	Sex	ARDS Etiology	PaO <sub>2</sub> /Fio <sub>2</sub> Ratio	PEEP before RM (cm H <sub>2</sub> O)	Days of MV before Inclusion	Outcome
1	72	M	Aspiration pneumonia	226	6	1	Survivor
2	53	M	Thoracic trauma	225	5	3	Nonsurvivor
3	44	F	Thoracic trauma	215	8	2	Survivor
4	76	F	Bacterial pneumonia	203	8	2	Survivor
5	81	F	Postoperative respiratory failure	220	5	1	Nonsurvivor
6	75	M	Postoperative respiratory failure	237	5	1	Survivor
7	74	F	Pneumonia	192	12	2	Survivor
8	40	M	Thoracic trauma	210	9	2	Nonsurvivor
9	83	F	Bacterial pneumonia	224	8	2	Survivor
10	77	F	Postoperative respiratory failure	221	8	2	Survivor
11	69	F	Postoperative respiratory failure	217	5	2	Survivor
12	39	M	Hemorrhagic shock	201	9	1	Survivor
13	85	M	Postoperative respiratory failure	219	7	1	Survivor
14	43	F	Thoracic trauma	229	6	3	Nonsurvivor
15	76	M	Aspiration pneumonia	201	9	1	Survivor

ARDS = adult respiratory distress syndrome; F = female; M = male; MV = mechanical ventilation; PaO<sub>2</sub>/Fio<sub>2</sub> = ratio of arterial oxygen partial pressure to fractional inspired oxygen; PEEP = positive end-expiratory pressure; RM = recruitment maneuver.

**Table 2.** Breathing Pattern and Hemodynamics before and after the OLA

	Pre-OLA	Post-OLA	Wilcoxon, P Value
Vt (ml/kg PBW)	6.4±0.6	6.9±0.7	<0.65
RR (breaths/min)	12±2.3	12±1.9	<0.99
PEEP <sub>TOT,RS</sub> (cm H <sub>2</sub> O)	8.3±1.8	15.7±2.4	<0.000012
PEEP <sub>EXT</sub> (cm H <sub>2</sub> O)	7.3±1.1	14.9±2.1	<0.000005
PEEP <sub>i,RS</sub> (cm H <sub>2</sub> O)	1.1±1	0.8±1.1	<0.44
P <sub>PLAT,RS</sub> (cm H <sub>2</sub> O)	26.2±1.4	31.1±1.2	<0.00002
P <sub>PLAT,CW</sub> (cm H <sub>2</sub> O)	11.1±0.9	8.9±0.9	<0.0005
P <sub>PLAT,L</sub> (cm H <sub>2</sub> O)	19.1±1.9	25.6±1.9	<0.00002
Driving pressure (cm H <sub>2</sub> O)	17.9±1.5	15.4±2.1	<0.0008
Transpulmonary driving pressure (cm H <sub>2</sub> O)	13±1.3	12.6±1.1	<0.064
E <sub>RS</sub> (cm H <sub>2</sub> O/l)	29.3±2.2	23.4±2.5	<0.00004
E <sub>CW</sub> (cm H <sub>2</sub> O/l)	7.8±2.2	4.1±3.1	<0.06
E <sub>L</sub> (cm H <sub>2</sub> O/l)	21.5±3	19.4±1.7	<0.05
PaO <sub>2</sub> /Fio <sub>2</sub> ratio (mmHg)	216±13	311±19	<0.00001
Paco <sub>2</sub> (mmHg)	43±2.2	38.6±3.1	<0.00001
Etco <sub>2</sub> (mmHg)	38.3±3.9	35.8±3.9	<0.06
pH	7.43±0.3	7.4±0.4	<0.83
MAP (mmHg)	93.7±20.9	92.5±12.3	<0.84
HR (beats/min)	76.1±16.1	76.8±14.2	<0.09
CI (l min <sup>-1</sup> m <sup>-2</sup> )	2.8±0.7	2.6±0.5	<0.37

Wilcoxon test for paired samples.

CI = cardiac index; E<sub>CW</sub> = chest wall elastance; E<sub>L</sub> = lung elastance; E<sub>RS</sub> = elastance of the respiratory system; Etco<sub>2</sub> = end-tidal carbon dioxide; Fio<sub>2</sub> = inspired oxygen fraction; HR = heart rate; MAP = mean arterial pressure; OLA = open lung approach; PaCO<sub>2</sub> = arterial carbon dioxide partial pressure; PaO<sub>2</sub> = arterial oxygen partial pressure; PBW = predicted body weight; PEEP<sub>EXT</sub> = positive end-expiratory pressure external; PEEP<sub>i,RS</sub> = static intrinsic positive end-expiratory pressure of the respiratory system; PEEP<sub>TOT,RS</sub> = total positive end-expiratory pressure; P<sub>PLAT,CW</sub> = chest wall plateau pressure; P<sub>PLAT,L</sub> = transpulmonary pressure plateau airways pressure; P<sub>PLAT,RS</sub> = respiratory system plateau pressure; RR = respiratory rate; VT = tidal volume.

45 ± 2% (post-OLA) when ventilating according to the ARDS Network protocol. Accordingly, the ROI<sub>Ventral/Dorsal</sub> impedance tidal variation ratio was 2.01 ± 0.36 on

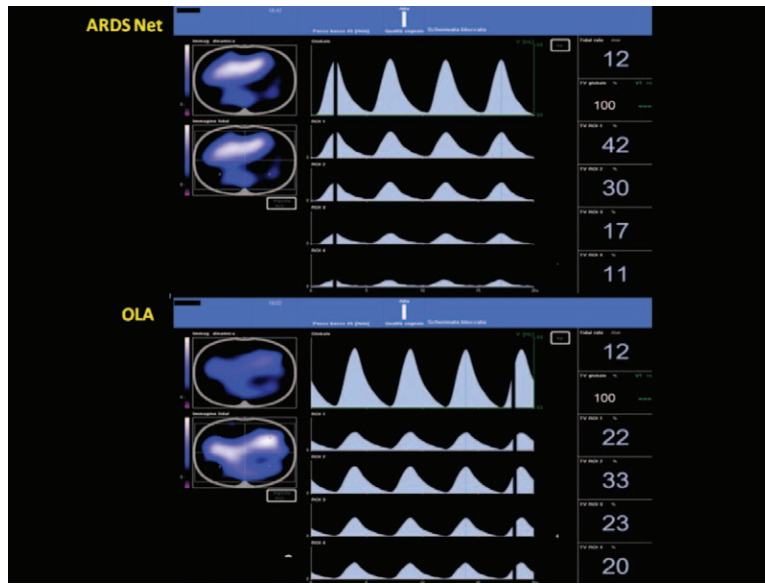
pre-OLA and decreased to 1.19 ± 0.1 on post-OLA ( $P < 0.00003$ ). In every patient, the OLA-related increase in PaO<sub>2</sub>/Fio<sub>2</sub> was associated to a decrease in ROI<sub>Ventral/Dorsal</sub> ratio (fig. 3).

## Discussion

In a small cohort of patients with early, mild ARDS and a diffuse pattern of loss of aeration, the OLA, when compared with the ARDS Network protocol, improved oxygenation and decreased global lung elastance, without inducing hemodynamic impairment. Furthermore, EIT monitoring revealed that the OLA favored a more homogeneous V<sub>T</sub> distribution by recruiting dorsal lung regions.

In patients with a high potential for alveolar recruitment, the PEEP dramatically improves oxygenation and prevents tidal alveolar opening collapse, a key mechanism of VILI.<sup>26,27</sup> However, in poor recruiters, the predominant effect of higher PEEP and “classical” LRMs (*i.e.*, applied pressure of 40 to 45 cm H<sub>2</sub>O)<sup>28</sup> is alveolar hyperinflation.<sup>29</sup> In those patients, excessive PEEP levels may even generate VILI.<sup>30</sup> Furthermore, the morphological pattern of loss of aeration (focal *vs.* diffuse) and the ARDS stage (early *vs.* late) have an impact on lung recruitment. Several reports showed that patients with early, diffuse ARDS are very good recruiters and *vice versa*.<sup>4,5,13,29</sup> The variable PEEP effect could explain why three large clinical trials testing lower *versus* higher PEEP strategies were not conclusive.<sup>5-7,11</sup> Of note, in these trials, PEEP-setting criteria and LRMs were not standardized.<sup>28</sup> Alveolar recruitment is a pan-inspiratory phenomenon.<sup>9,31</sup> Accordingly, PEEP should be titrated on the expiratory limb of the respiratory system volume–pressure curve after obtaining full-lung recruitment. This is the theoretical background of the OLA strategy.

Lacking definitive evidences,<sup>3</sup> the OLA is at present deemed as a rescue strategy for patients with refractory hypoxemia.<sup>32</sup>



**Fig. 2.** Experimental record in a representative patient (no. 3). *Upper panel:* pre-open lung approach (OLA) (acute respiratory distress syndrome [ARDS] Network ventilation); *lower panel:* post-OLA. *Left:* electrical impedance tomography (EIT) scan: ventilated lung areas are in light blue; *middle:* tidal ventilation distribution over time; *from top to bottom:* global region of interest (ROI) 1, ROI 2 (ventral ROIs), ROI 3, and ROI 4 (dorsal ROIs); *right:* numerical value indicating respiratory rate (top), global impedance (*i.e.*, always 100%), and relative impedance of every ROI in percent (*from third to sixth line* ROI 1 to 4, respectively). On post-OLA, dorsal ventilated areas are broader, and ventilation was distributed more homogeneously.

**Table 3.** Patient Electrical Impedance Tomography Data before and after Recruiting Maneuvers and Positive End-expiratory Pressure Titration

	Pre-OLA	Post-OLA	Wilcoxon, <i>P</i> Value
ROI <sub>Ventral</sub> (%)	66 ± 4.3	54 ± 2	<0.00001
ROI <sub>Dorsal</sub> (%)	33 ± 4.3	45 ± 2	<0.00001
ROI <sub>Ventral/Dorsal</sub>	2.01 ± 0.36	1.19 ± 0.1	<0.00003
VT <sub>Ventral</sub> /kg (ml/kg)	4.22 ± 0.64	4.26 ± 0.43	NS
VT <sub>Dorsal</sub> /kg (ml/kg)	2.11 ± 0.3	3.55 ± 0.41	<0.00001

Wilcoxon test for paired samples.

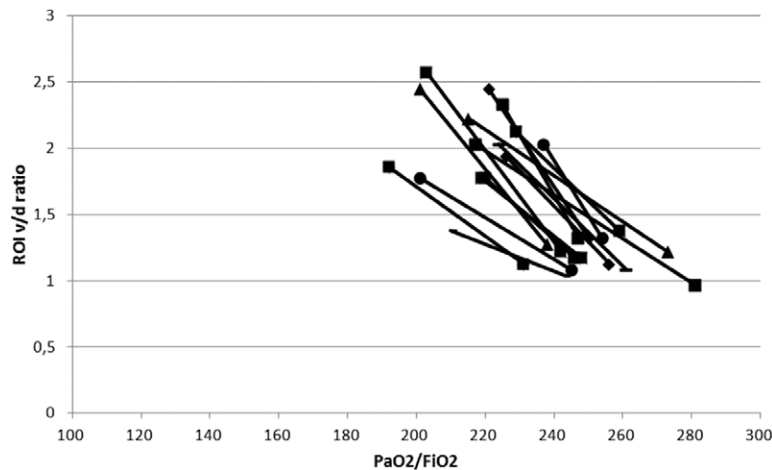
NS = no significance; OLA = open lung approach; ROI = region of interest; ROI<sub>dorsal</sub> = VT% dorsal, *i.e.*, end-inspiratory fraction of tidal ventilation reaching dorsal (dependent) lung region; ROI<sub>ventral</sub> = VT% ventral, *i.e.*, end-inspiratory fraction of tidal ventilation reaching ventral (nondependent) lung region; VT<sub>dorsal</sub> = tidal volume reaching dorsal (dependent) lung region, obtained by multiplication of VT% dorsal × expiratory VT measured by the ventilator; VT<sub>ventral</sub> = tidal volume reaching ventral (nondependent) lung region, obtained by multiplication of VT% ventral × expiratory VT measured by the ventilator.

Nevertheless, in patients with moderate ARDS, the OLA stabilizes lung units and protects them from atelectrauma.<sup>33–35</sup> Hopefully, the ongoing “ART” clinical trial will elucidate the impact, if any, of the OLA on outcome in patients with moderate and severe ARDS.<sup>3</sup> The novelty of our study is that we applied the OLA in patients with mild ARDS, which, of note, is not included in the ART.<sup>3</sup> Our data convincingly show that the OLA may be highly effective in these patients in physiological terms, but we point out that we studied a small cohort of highly selective patients and that our study design does not allow to draw any conclusion on the impact of the OLA on clinically meaningful outcome parameters. Nevertheless, we

speculate that OLA could prevent worsening of ARDS by preventing VILI, and we hope that our pilot observation will fuel further research in this field.

In 2006, a “cornerstone” CT scan study by Gattinoni *et al.*<sup>36</sup> showed that the potential for alveolar recruitment is correlated to ARDS severity: the most severe ARDS forms present the highest potential and *vice versa*. These results are only apparently in contradiction with ours. Indeed, in a recent study,<sup>37</sup> the Gattinoni group reanalyzed the 2006 data and showed that the correlation between the potential for alveolar recruitment and ARDS severity is significant only if the severity of ARDS is classified at a standard PEEP level of 5 cm H<sub>2</sub>O. In contrast, at “clinical” PEEP, the potential for alveolar recruitment does not correlate with ARDS classification. Accordingly, at “clinical” PEEP, thanks to the PEEP-induced alveolar recruitment, some ARDS forms that would have been classified as “moderate” or even “severe” at PEEP 5 cm H<sub>2</sub>O shift to “mild.” Our patients were studied at “clinical” PEEP (*i.e.*, the PEEP level resulting from the ARDS Network PEEP/FiO<sub>2</sub> combination table), and therefore, some of our patients would have been probably classified as “moderate” or “severe” at PEEP 5 cm H<sub>2</sub>O. Thus, our results are not in contradiction with the results presented in 2006 Gattinoni’s article. Overall, our and Gattinoni’s data clearly suggest that it is important to take into account the effects of PEEP on ARDS classification when applying the “Berlin” definition.

One major concern when applying the OLA is to assess the balance between alveolar recruitment and overinflation. Patients with higher potential for recruitment experience



**Fig. 3.** Arterial oxygen partial pressure/inspired oxygen fraction ( $\text{PaO}_2/\text{FiO}_2$ ) and region of interest ( $\text{ROI}_{\text{Ventral/Dorsal}}$ ) ratio time course in individual patients.

dramatic improvement in oxygenation and lung mechanics without significant hemodynamic derangement, provided that the volemic status is optimized before the lung recruitment phase.<sup>4,9,10,27,29</sup> However, overdistension and hemodynamic impairment make the OLA unsafe in nonresponders. Typical responders are patients with early ARDS and diffuse loss of aeration.<sup>8,10,12,38</sup> EIT is a noninvasive, radiation-free bedside tool that produces images by computing lung conductivity from electrodes placed on the body surface.<sup>22,23,39</sup> Because air has a large conductivity contrast compared with lung tissue, EIT dynamically shows the  $V_T$  distribution during ventilation.<sup>24,40</sup> Our data confirm the usefulness of EIT to continuously assess “regional” lung aeration.<sup>24,41–43</sup> In patients recovering from ARDS, recently Mauri *et al.*<sup>24</sup> showed a more homogeneous ventral-to-dorsal ventilation distribution with assisted ventilation (PSV) plus high PEEP than with control ventilation. Furthermore, experimental and clinical studies show that EIT-derived regional  $V_T$  distribution is useful to evaluate PEEP- or LRM-induced regional recruitment.<sup>42–46</sup> Camporota *et al.*<sup>21</sup> report two cases of patients with severe ARDS in which EIT allowed to estimate the potential for alveolar recruitment. Karsten *et al.*<sup>46</sup> used EIT to study  $V_T$  distribution on a regional basis in patients undergoing general anesthesia for laparoscopic cholecystectomy.

Electrical impedance tomography data should be interpreted in conjunction with the physiological ones. Indeed, EIT detects only tidal variations in impedance, and both closed lung areas and areas that are opened but not ventilated are not sensed. Our patients presented a diffuse loss of aeration pattern at CT scan and responded to the OLA with a significant decrease in lung elastance and driving pressure. The  $\text{PaO}_2/\text{FiO}_2$  ratio increased, and  $\text{PaCO}_2$  remained stable (table 2). Accordingly, we interpret the OLA-induced decrease in  $\text{ROI}_{\text{Ventral/Dorsal}}$  impedance tidal variation ratio as a clear sign of OLA-induced lung recruitment, which occurs mostly in the dorsal lung regions. We must point out that a limitation of our study was that by design we did not plan to assess the

impact of OLA on lung aeration with the definitive standard CT scan. We took into account the risks of transporting critically ill patients to the CT scan facility and of repeated CT scan radiation exposure. Thus, further studies are required to confirm our interpretation of EIT.

Grasso *et al.*<sup>12</sup> recently demonstrated that titrating PEEP to a  $P_{\text{PLATL}}$  level close to the upper physiological limit (25 cm  $\text{H}_2\text{O}$ ) optimizes oxygenation and lung mechanics in patients with early, severe ARDS and refractory hypoxemia. In this study, we replicated these findings in patients with early, mild, diffuse ARDS. Indeed, in our patients, the OLA strategy increased  $P_{\text{PLATL}}$  from  $21.7 \pm 1.9$  to  $25.7 \pm 1.9$  cm  $\text{H}_2\text{O}$ . Furthermore, driving pressure decreased from  $17.9 \pm 1.5$  to  $15.4 \pm 2.1$  cm  $\text{H}_2\text{O}$ , suggesting a reduction of tidal mechanical stress.

Our study has some limitations: (1) we studied a relatively small number of highly selective patients, and therefore, our data need further confirmation to be extrapolated to clinical practice; and (2) patients with mild, early, diffuse ARDS and normal chest wall mechanics are easily recruitable.<sup>47,48</sup> Our results may not apply to patients with more severe, late, and/or nondiffuse ARDS forms.

In conclusion, our pilot study shows that the OLA improves oxygenation and lung mechanics in patients with early, mild, diffuse ARDS. It also confirms the usefulness of EIT as an online tool subsidiary to periodic CT scans in assessing the regional effects of lung-protective ventilation in ARDS. Further studies are required to define the clinical impact of the OLA in mild ARDS.

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### Competing Interests

The authors declare no competing interests.

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