Topographic Distribution of Tidal Ventilation in Acute Respiratory Distress Syndrome: Effects of Positive End-Expiratory Pressure and Pressure Support

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Objective: Acute respiratory distress syndrome is characterized by collapse of gravitationally dependent lung regions that usually diverts tidal ventilation toward nondependent regions. We hypothesized that higher positive end-expiratory pressure and enhanced spontaneous breathing may increase the proportion of tidal ventilation reaching dependent lung regions in patients with acute respiratory distress syndrome undergoing pressure support ventilation.

Design: Prospective, randomized, cross-over study.

Setting: General and neurosurgical ICUs of a single university-affiliated hospital.

Patients: We enrolled ten intubated patients recovering from acute respiratory distress syndrome, after clinical switch from controlled ventilation to pressure support ventilation.

Interventions: We compared, at the same pressure support ventilation level, a lower positive end-expiratory pressure (i.e., clinical positive end-expiratory pressure = 7±2 cm H_2O) with a higher one, obtained by adding 5 cm H_2O (12±2 cm H_2O). Furthermore, a pressure support ventilation level associated with increased respiratory drive (3±2 cm H_2O) was tested against resting pressure support ventilation (12±3 cm H_2O), at clinical positive end-expiratory pressure.

Measurements and Main Results: During all study phases, we measured, by electrical impedance tomography, the proportion of tidal ventilation reaching dependent and nondependent lung regions ($Vt\%_{dep}$ and $Vt\%_{nondep}$), regional tidal volumes (Vt_{dep} and Vt_{nondep}), and antero-posterior ventilation homogeneity ($Vt\%_{nondep}/Vt\%_{dep}$). We also collected ventilation variables and arterial blood gases. Application of higher positive end-expiratory pressure levels increased $Vt\%_{dep}$ and Vt_{dep} values and decreased $Vt\%_{nondep}/Vt\%_{dep}$ ratio, as compared with lower positive end-expiratory pressure ($p < 0.01$). Similarly, during lower pressure support ventilation, $Vt\%_{dep}$ increased, Vt_{nondep} decreased, and Vt_{dep} did not change, likely indicating a higher efficiency of posterior diaphragm that led to decreased $Vt\%_{nondep}/Vt\%_{dep}$ ($p < 0.01$). Finally, $Pa_{O_2}/F_{I_{O_2}}$ ratios correlated with $Vt\%_{dep}$ during all study phases ($p < 0.05$).

Conclusions: In patients with acute respiratory distress syndrome undergoing pressure support ventilation, higher positive end-expiratory pressure and lower support levels increase the fraction of tidal ventilation reaching dependent lung regions, yielding more homogeneous ventilation and, possibly, better ventilation/perfusion coupling. (*Crit Care Med* 2013; 41:XX–XX)

Key Words: acute respiratory distress syndrome; electrical impedance tomography; lung collapse; mechanical ventilation; outcome; positive end-expiratory pressure

Acute respiratory distress syndrome (ARDS) is characterized by bilateral lung inflammation, edema, and infiltration of inflammatory cells (1–3). CT studies showed that, in patients with ARDS, inflammatory edema increases lung weight and causes bilateral collapse and loss of aeration in gravitationally dependent lung regions (4–6). Gravitational loss of lung aeration decreases

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the fraction of lung receiving tidal ventilation (i.e., the "baby lung"), thus increasing the risk of "barotrauma" and ventilator-induced lung injury (VILI) (6). Furthermore, regional loss of ventilation is a main determinant of hypoxia in ARDS, as dependent regions receive the most relevant fraction of lung perfusion (7, 8). High positive end-expiratory pressure (PEEP) levels have been shown to promote ventilation of dependent lung regions in ARDS (9); however, elevated PEEP negatively impacts hemodynamics (10) and might promote VILI by increasing plateau pressure (11). Alternatively, active diaphragm contraction increases the proportion of tidal ventilation reaching dependent lung regions in spontaneously breathing healthy subjects in comparison with controlled mechanical ventilation (MV) (12, 13) and with high-assist pressure support ventilation (PSV) (13). In this study, we assessed the effects of different PEEP and support settings on regional ventilation in a group of patients recovering from ARDS undergoing PSV (14). We reasoned that higher PEEP and lower support levels (leading to more intense diaphragm contraction) might increase the fraction of tidal ventilation reaching gravitationally dependent lung regions, thus causing more homogeneous distribution of ventilation. Our results, combined with other clinical data, might help optimize PSV in patients with ARDS.

We assessed regional ventilation distribution by electrical impedance tomography (EIT): a relatively new, noninvasive, radiation-free, bedside lung imaging method (13, 15–17). EIT measures the impedance offered by different imaged lung areas to passage of low-voltage alternate electrical currents (i.e., regional impedance). As air offers the highest impedance within lungs, relative changes in regional lung impedance should reflect changes in air content of that particular region: thus, EIT allows continuous monitoring of the regional distribution of tidal ventilation (17). EIT technology has been studied since long (18), but recently, the focus of investigators has moved toward the clinical meaning of EIT-derived parameters (15).

MATERIALS AND METHODS

Study Population

We enrolled ten consecutive intubated patients with ARDS (19), admitted to the general and neurosurgical ICU of the university-affiliated San Gerardo Hospital, Monza, Italy, after they were switched from controlled MV to PSV, as per clinical decision (i.e., patients recovering from ARDS). Exclusion criteria were age younger than 18 years old, pregnancy, contraindication to EIT use (e.g., presence of pacemaker or automatic implantable cardioverter defibrillator), impossibility to place the EIT belt in the right position (e.g., presence of surgical wounds dressing), altered diaphragm function (e.g., hemidiaphragm paralysis), and severe cardiovascular instability. Diaphragm dysfunction was assessed by ultrasounds (20) when clinically (e.g., low maximal inspiratory pressure) or radiologically (e.g., hemidiaphragm supra-elevation) suspected. Institutional ethical committee approved the study, and informed consent was obtained.

Demographic Data Collection

Sex, age, predicted body weight, body mass index (BMI), Simplified Acute Physiology Score II values, Sepsis-Related Organ Failure Assessment score, ARDS etiology, days spent on MV, and Lung Injury Score (LIS) (21) were recorded at enrolment. We also recorded in-hospital mortality.

EIT Monitoring

Patients were positioned in semirecumbent position during all study phases. EIT dedicated belt, containing 16 equally spaced electrodes, was placed around each patient's thorax at the fifth or sixth intercostal space and connected to a commercial EIT monitor (PulmoVista 500, Dräger Medical GmbH, Lübeck, Germany). During all study phases, EIT data were generated by application of small alternate electrical currents rotating around patient's thorax, registered at 20 Hz, and stored for offline analysis, as previously described (15–17).

Study Protocol

In each patient, we tested three different ventilator settings in random order, each lasting 20 minutes, while leaving F_{IO_2}, PSV inspiratory ramp, and inspiratory and expiratory triggers unchanged:

1. Clinically selected PSV (PSV_{clin}) and PEEP ($PEEP_{clin}$) levels;
2. PSV_{clin} and $PEEP_{high}$ (i.e., $PEEP_{clin}$ + 5 cm H_2O);
3. We aimed to compare a high PSV level (defined as a PSV level associated with p0.1 < 2 cm H_2O) vs. a low PSV level (associated with p0.1 ≥ 2 cm H_2O). To this end, if p0.1 during PSV_{clin} was < 2 cm H_2O, then PSV_{clin} was regarded as PSV_{high}, and a new PSV_{low} was selected during this phase, at least 4 cm H_2O lower than PSV_{clin} and set to obtain p0.1 ≥ 2 cm H_2O. At the opposite, if PSV_{clin} was associated with p0.1 ≥ 2 cm H_2O, then PSV_{clin} was regarded as PSV_{low} and a new PSV_{high} was selected during this step, at least 4 cm H_2O higher than PSV_{clin} to achieve p0.1 < 2 cm H_2O. PEEP was maintained at $PEEP_{clin}$ level in both cases.
4. At the end, patients were switched to volume assist/control ventilation to determine respiratory system compliance (Cst_{rs}) by means of end-expiratory and end-inspiratory occlusions.

Thus, we could compare ten $PEEP_{high}$ (i.e., $PEEP_{clin}$ + 5 cm H_2O) measurements vs. ten $PEEP_{low}$ (i.e., $PEEP_{clin}$), performed at the same PSV_{clin}, and ten PSV_{high} measurements vs. ten PSV_{low}, performed at $PEEP_{clin}$.

EIT Data

We performed offline analyses of raw EIT data recorded at the end of each study phase and immediately prior to the next. We measured the following:

1. Relative distribution of tidal ventilation: we identified two contiguous regions of interest (ROI) (**Fig. 1**): gravitationally

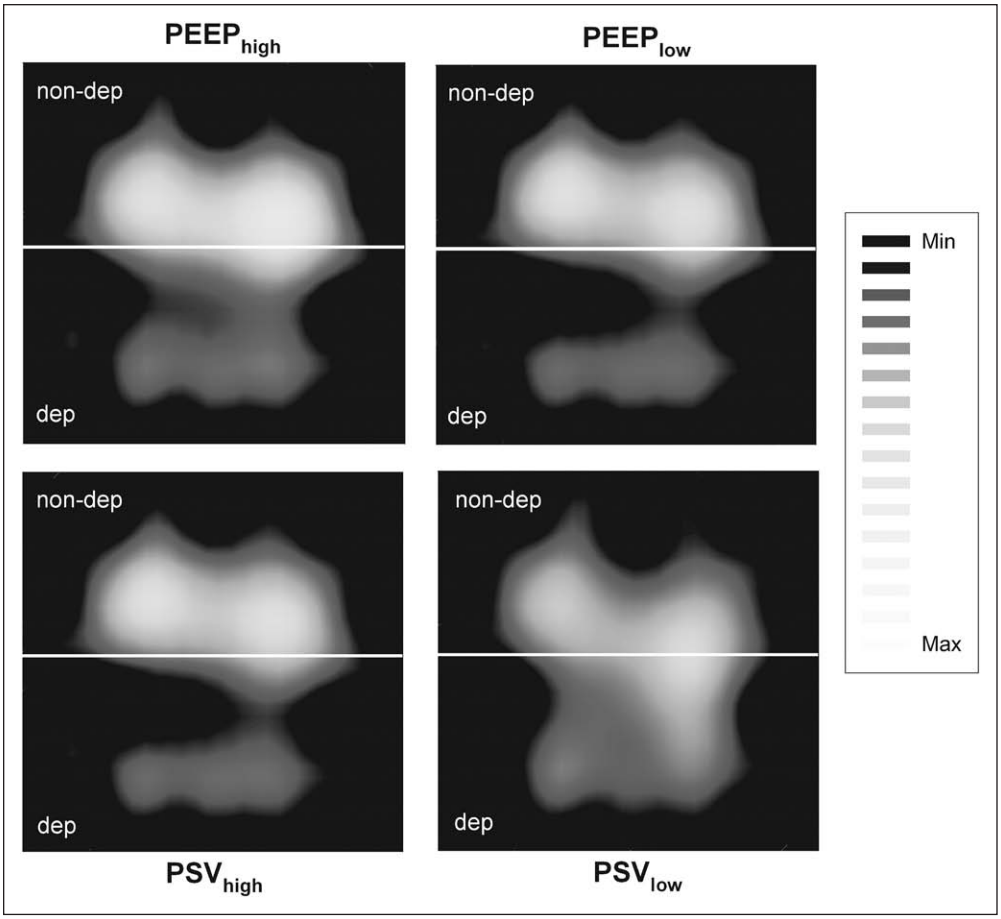

Figure 1. Electrical impedance tomography image reconstruction of regional distribution of changes in impedance between end-inspiration and end-expiration (*black = no change*, *white = max change*) from one representative patient recovering from acute respiratory distress syndrome undergoing pressure support ventilation (PSV) during four different study phases (see text for details). As shown, increased positive end-expiratory pressure (PEEP) (*top* two images) and decreased PSV (*bottom* two images) induced redistribution of tidal impedance changes (i.e., of tidal ventilation) from nondependent (nondep) to dependent (dep) lung regions.

nondependent (nondep) ROI from halfway to the top of the imaging field and dependent (dep) ROI from halfway to the bottom (Fig. 1). We measured the percentage of tidal ventilation ventilating each ROI as the proportion of total tidal impedance variation ventilating each ROI ($Vt\%_{nondep}$ and $Vt\%_{dep}$, respectively).

2. Regional distribution of tidal volume: we calculated an estimate of the absolute value of tidal volume reaching dependent and nondependent lung regions by multiplication of expiratory Vt measured by the ventilator × $Vt\%_{dep}$ and × $Vt\%_{nondep}$ (Vt_{dep} and Vt_{nondep}, respectively).
3. Homogeneity of the antero-posterior distribution of tidal volume: we calculated a regional index of ventilation homogeneity as the ratio of $Vt\%_{nondep}$ and $Vt\%_{dep}$ (that is equal also to Vt_{nondep}/Vt_{dep} ratio). Lower levels indicate more homogenous distribution of tidal ventilation.
4. Pixel-level regional ventilation heterogeneity: pixel-level heterogeneity index (H) was calculated as the standard deviation of the proportion of total tidal impedance variation distributed to each pixel in each ROI (H_{nondep} and H_{dep}, respectively).
5. Relative changes of global end-expiratory lung impedance ($\Delta EELI_{gl}$): defined as the sum of percentage change (at single pixel level) in absolute $EELI_i$ value between one study phase (i.e., baseline) and another (i.e., $PEEP_{low}$ vs. $PEEP_{high}$). $\Delta EELI_{gl}$ values should reflect changes in patient's end-expiratory lung volume.

Physiological Data

At the same time point of EIT data analysis, we also collected ventilator settings and arterial blood gas analysis.

Healthy Controls

By means of the same EIT technique, $Vt\%_{nondep}$ and $Vt\%_{dep}$ values were collected from 15 semirecumbent nonintubated healthy adults (four women and 11 men, aged 45 ± 9 yr old, BMI 27 ± 4 kg/m^2) during spontaneous quiet breathing.

Statistical Analysis

We choose the sample size based on previous similar studies (22). We assessed normal distribution of each variable by Lilliefors test. Nonnormally distributed variables were compared by Mann-Whitney *U* test (two independent samples) or Wilcoxon's test (two paired samples). Normally distributed variables, instead, were analyzed by independent samples or paired *t* test and by one sample *z* test, as appropriate. Association between variables was assessed by Spearman's rho coefficient. A level of *p* value less than 0.05 (two tailed) was considered statistically significant. Normally distributed data are indicated as mean ± SD, while median and interquartile range (IQR) are used to report nonnormally distributed variables. Statistical analyses were performed by SigmaPlot 11.0 (Systat Software, San Jose, CA) and by IBM SPSS Statistics 19 (International Business Machines Corp., Armonk, NY).

RESULTS

Patient Characteristics

Patients' main characteristics are reported in **Table 1**. Patients were 60 ± 10 years old and 5 (50%) were women.

TABLE 1. Patients' Main Characteristics

Patient No.	Age (yr)	Gender	Body Mass Index (kg/m²)	Simplified Acute Physiology Score II	Sequential Organ Failure Assessment Score	Acute Respiratory Distress Syndrome Etiology
1	56	Male	26	40	7	Trauma
2	75	Female	41	54	5	Postoperative respiratory failure
3	44	Female	27	36	2	Pneumonia
4	54	Male	27	46	5	Postoperative respiratory failure
5	53	Male	23	64	8	Septic shock
6	68	Female	33	33	6	Trauma
7	62	Female	23	89	5	Pneumonia
8	66	Female	25	53	5	Pneumonia
9	72	Male	23	40	5	Postoperative respiratory failure
10	53	Male	28	82	19	Pneumonia
Mean ± SD or median (interquartile range)	60 ± 10	5 males/ 5 females	27 (23–29)	54 ± 19	5 (5–7)	–

$PEEP_{clin}$ = clinically set positive end-expiratory pressure (corresponding to study $PEEP_{low}$); Cst_{rs} = static respiratory system compliance; – = descriptive qualitative variable that cannot be summarized by a number.
Data are summarized as mean ± SD or by median (interquartile range) for nonnormally distributed variables.

TABLE 2. Effects of Different Positive End-Expiratory Pressure and Support Levels on Patient Respiratory Parameters

Study Phase[a]	PSV Level (cm H_2O)	PEEP (cm H_2O)	Pa_{O_2}/F_{IO_2} (mm Hg)	F_{IO_2}	Pa_{CO_2} (mm Hg)
$PEEP_{low}$ ($n = 10$)	8 ± 5	7 ± 2*	262 (231–283)[b]	0.42 ± 0.06	39 ± 5
$PEEP_{high}$ ($n = 10$)	8 ± 5	12 ± 2	289 (239–309)	0.42 ± 0.06	41 ± 5
PSV_{low} ($n = 10$)	3 ± 3	7 ± 2	264 (250–290)	0.42 ± 0.06	42 ± 6
PSV_{high} ($n = 10$)	12 ± 3 ^	7 ± 2	257 (225–297)	0.42 ± 0.06	39 ± 4

PSV = pressure support ventilation; PEEP = positive end-expiratory pressure;
Ppeak = peak inspiratory pressure; MVe = expired minute ventilation; p0.1 = pressure generated during the first 100 ms of inspiration.
PSV_{low}, PSV_{high}, $PEEP_{low}$, and $PEEP_{high}$ were performed randomly in each patient for 20 min, leaving F_{IO_2} value, inspiratory ramp, and inspiratory and expiratory triggers unchanged.
[a]$p < 0.01$ vs. $PEEP_{high}$ (paired *t* test).
[b]$p < 0.01$ vs. $PEEP_{high}$ (Wilcoxon's test).
[c]$p < 0.01$ vs. PSV_{low} (paired *t* test).
[d]$p < 0.05$ vs. PSV_{low} (paired *t* test).
Data are expressed as mean ± SD or median (interquartile range) for nonnormally distributed variables.

ARDS etiology was trauma (two patients), septic shock (one patient), pneumonia (four patients), and postoperative respiratory failure (three patients). Nine of ten patients were enrolled within a week from intubation. All patients had ARDS diagnosed at intubation and were recovering from it, being already switched by the attending physician from controlled to assisted MV. Thus, LIS values did not exceed mild-to-moderate severity range. Five patients still fulfilled ARDS criteria when study was performed. Two patients died before hospital discharge.

PEEP Effects on Regional Ventilation

As expected, $PEEP_{high}$ significantly improved oxygenation and increased peak inspiratory pressure, whereas respiratory rate

Days on Mechanical Ventilation	$Pa_{O_2}/F_{I_{O_2}}$ (mm Hg)	$PEEP_{clin}$ (cm H_2O)	Cst_{rs} (mL/cm H_2O)	No. Quadrants Involved	Lung Injury Score	Outcome
1	174	9	80	3	2	Survivor
2	253	5	31	0	1	Survivor
20	250	12	23	3	2.5	Survivor
1	278	5	73	2	1	Survivor
2	244	5	52	1	1	Nonsurvivor
4	271	5	38	0	1	Survivor
2	263	5	48	1	1	Survivor
2	253	9	59	2	1.75	Survivor
4	280	5	70	2	1	Survivor
3	140	8	51	1	1.75	Nonsurvivor
2 (2–4)	253 (226–273)	7 ± 2	52 ± 18	2 ± 1	1 (1–1.75)	8 survivors/2 nonsurvivors

pH	Tidal Volume (mL/kg)	Ppeak (cm H_2O)	Respiratory Rate (b/min)	MVe (L/min)	p0.1 (cm H_2O)
7.42 (7.40–7.44)	8.7 ± 3	16.0 ± 6.1[a]	16 ± 5	8.2 ± 3.4	2.0 ± 1.7
7.43 (7.41–7.44)	8.5 ± 3	21.1 ± 6.2	17 ± 5	8.1 ± 2.7	1.8 ± 1.7
7.42 (7.40–7.42)	6.8 ± 1.7	12.4 ± 4.1	19 ± 5	7.7 ± 2.8	3.0 ± 0.6
7.42 (7.40–7.46)	9.0 ± 2.9^	18.8 ± 5.1[c]	15 ± 4[d]	8.2 ± 3.4	1.0 ± 0.6[c]

and p0.1 were not affected by higher PEEP levels (**Table 2**). $PEEP_{high}$ was associated with increased $Vt\%_{dep}$ and Vt_{dep} ($p < 0.01$ for both) and with decreased $Vt\%_{nondep}$ and Vt_{nondep} ($p < 0.01$) (**Fig. 2**, **Table 3**). Regional ventilation distribution was more homogenous during $PEEP_{high}$, as testified by decreased $Vt\%_{nondep}/Vt\%_{dep}$ values ($p < 0.01$) (Table 3). $Vt\%_{dep}$ and $Vt\%_{nondep}$ during $PEEP_{high}$ did not differ from healthy controls, while during $PEEP_{low}$, both of those two EIT parameters were significantly different from controls ($p < 0.05$ for all comparisons) (Fig. 2, Table 3). During $PEEP_{high}$, H_{nondep} decreased, as compared with $PEEP_{low}$ ($p < 0.01$), while H_{dep} did not change (Table 3). Finally, $PEEP_{high}$ was associated with significant changes in $\Delta EELI_{gl}$ ($p < 0.01$) when $PEEP_{low}$ was considered baseline (Table 3).

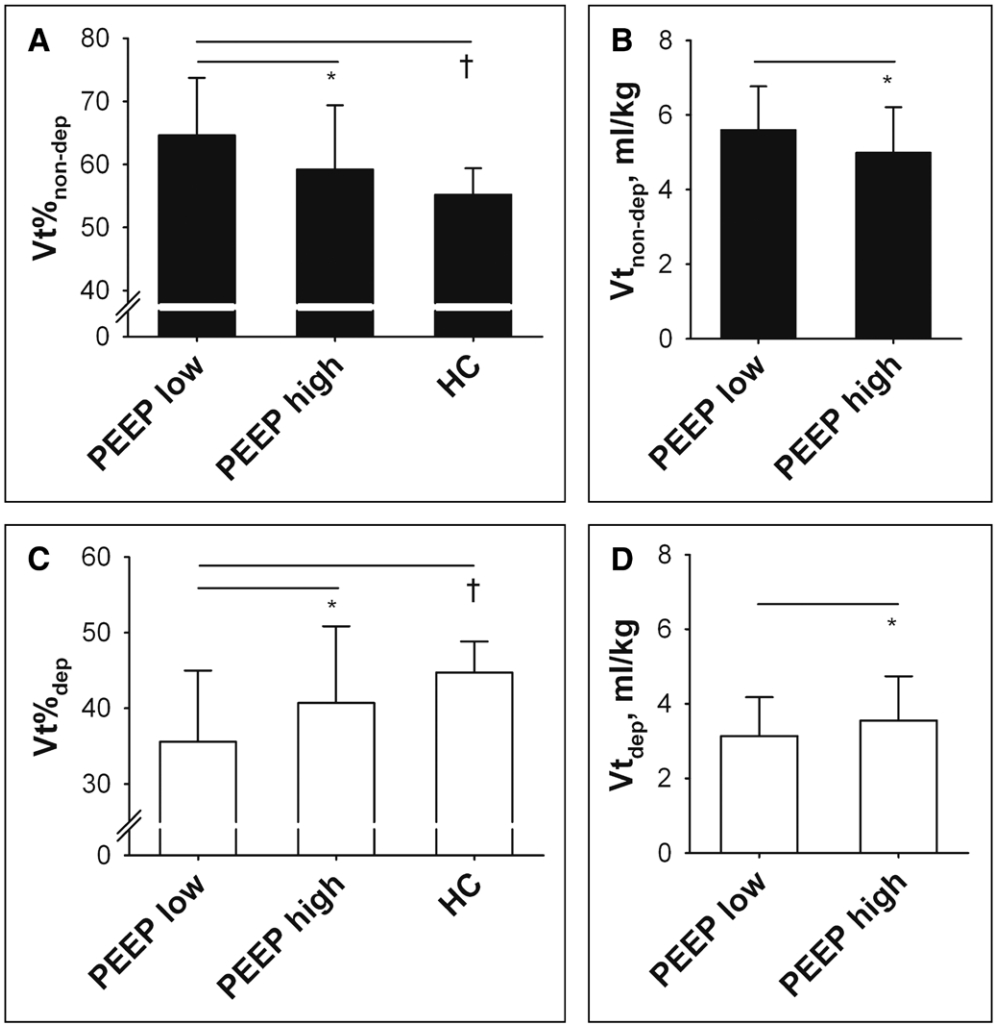

Figure 2. At higher positive end-expiratory pressure (PEEP) levels, in acute respiratory distress syndrome patients undergoing pressure support ventilation, the proportion and the absolute value of tidal volume reaching dependent lung regions ($Vt\%_{dep}$ and Vt_{dep}, respectively) increased (**C** and **D**), whereas relative and absolute ventilation of nondependent regions ($Vt\%_{nondep}$ and Vt_{nondep}, respectively) decreased (**A** and **B**). HC = healthy controls. *$p < 0.01$ and †$p < 0.05$.

Correlation Between Regional Ventilation and Oxygenation

$Pa_{O_2}/F_{I_{O_2}}$ ratios correlated with $Vt\%_{dep}$ during all PEEP and PSV phases (Spearman's rho = 0.629 and 0.487, respectively, $p < 0.05$ for both) (**Fig. 5**).

Association Between Regional Ventilation Distribution and Outcome

When measured at clinically set PSV and PEEP levels (i.e., during $PEEP_{low}$ study phase), $Vt\%_{dep}$ and Vt_{dep} values were significantly higher in survivors in comparison with nonsurvivors (median 40% IQR [28–50]% vs. 17 [16–18]% and 3.4 [2.2–4.9] mL/kg vs. 1.4 [1.3–1.5] mL/kg, $p < 0.05$ for both). Furthermore, $Vt\%_{nondep}/Vt\%_{dep}$ ratios were lower in survivors (1.5 [1.0–2.6] vs. 4.9 [4.7–5.0], $p < 0.05$).

DISCUSSION

The main findings of this study can be summarized as follows: in a population of patients recovering from ARDS undergoing PSV, higher PEEP and lower support levels increase the proportion of tidal ventilation reaching dependent regions and induce more homogenous antero-posterior distribution of ventilation.

Pressure Support Effects on Regional Ventilation

PSV_{low} did not affect gas exchange, in comparison with PSV_{high}. During PSV_{low}, Vt and peak inspiratory pressure were lower, while p0.1 (**Fig. 3**) and respiratory rate increased (Table 2). PSV_{low} was associated with increased $Vt\%_{dep}$ ($p < 0.01$), with decreased $Vt\%_{nondep}$ ($p < 0.01$), and with lower $Vt\%_{nondep}/Vt\%_{dep}$ ratios (i.e., more homogenous lung ventilation) ($p < 0.01$), as compared with PSV_{high} (**Fig. 4,** Table 3). During PSV_{low}, despite lower mechanical ventilatory support, only Vt_{nondep} decreased ($p = 0.01$), while Vt_{dep} did not change (Table 3, Fig. 4). $Vt\%_{dep}$, $Vt\%_{nondep}$, and $Vt\%_{nondep}/Vt\%_{dep}$ during PSV_{low} did not differ from healthy controls' values, whereas at PSV_{high}, they were significantly different from controls' values ($p < 0.05$ for all) (Fig. 4, Table 3). During PSV_{low}, H_{nondep} decreased, as compared with PSV_{high} ($p < 0.01$), while H_{dep} significantly increased ($p < 0.01$) (Table 3). $\Delta EELI_{gl}$ did not vary significantly between the two PSV phases (Table 3).

In this study, we showed that in patients with ARDS clinically switched to PSV, increasing PEEP from 7 ± 2 cm H_2O to 12 ± 2 cm H_2O significantly increased relative and absolute ventilation of dependent lung regions and antero-posterior ventilation homogeneity to values that became more similar to healthy controls. Gattinoni et al (9) already showed that increasing PEEP from 0 to 20 cm H_2O improved the percentage of tidal ventilation reaching dependent lung areas in eight sedated and paralyzed patients with ARDS undergoing two single-slice CT scans at each PEEP level. Gattinoni et al (9) also showed that tidal ventilation redistribution followed recruitment of previously collapsed lung regions. Similarly, in our study, $EELI_{gl}$ increased at higher PEEP levels and paralleled dependent redistribution of tidal ventilation. However, $EELI_{gl}$ increase may reflect both recruitment and overdistension of nondependent regions (20). Thus, our data cannot exclude that increased plateau pressure during $PEEP_{high}$ might have caused nondependent overdistension, worsening regional compliance and redirecting tidal ventilation to more

TABLE 3. Effects of Different Positive End-Expiratory Pressure and Support Levels on Patient Electrical Impedance Tomography Data

Study Phase[a]	$Vt\%_{nondep}$ (%)	$Vt\%_{dep}$ (%)	Vt_{nondep} (mL/kg)	Vt_{dep} (mL/kg)	$Vt\%_{nondep}/Vt\%_{dep}$	H_{nondep}	H_{dep}	$\Delta EELI_{gl}$ (a.u.)
$PEEP_{low}$ ($n=10$)	65 ± 14[a,f]	36 ± 15[a,f]	5.6 ± 1.8[a]	3.1 ± 1.7[a]	2.1 (1.0–3.3)[b]	0.00176 ± 0.00040[a]	0.00117 ± 0.00034	Baseline
$PEEP_{high}$ ($n=10$)	59 ± 16	41 ± 16	5.0 ± 1.9	3.5 ± 1.9	1.6 (0.8–2.8)	0.00157 ± 0.00035	0.00121 ± 0.00031	1485 ± 1755[e]
PSV_{low} ($n=10$)	58 ± 9	42 ± 15	3.9 ± 1.1	2.9 ± 1.0	1.5 (1.0–2.0)	0.00157 ± 0.00032	0.00128 ± 0.00043	−115 ± 1268
PSV_{high} ($n=10$)	68 ± 10[c,f]	32 ± 16[c,f]	6.1 ± 2.0 ^	2.9 ± 1.4	2.4 (1.4–3.3)[d,f]	0.00181 ± 0.00037 ^	0.00103 ± 0.00039[c]	Baseline
Healthy controls ($n=15$)	55 ± 8	45 ± 8	–	–	1.1 (1.0–1.6)	–	–	–

PSV = pressure support ventilation; PEEP = positive end-expiratory pressure; $Vt\%_{nondep}$ = end-inspiratory fraction of tidal ventilation reaching nondependent lung region; $Vt\%_{dep}$ = end-inspiratory fraction of tidal ventilation reaching dependent lung region; Vt_{nondep} = tidal volume reaching nondependent lung region, obtained by multiplication of $Vt\%_{nondep}$ × expiratory Vt measured by the ventilator; Vt_{dep} = tidal volume reaching dependent lung region, obtained by multiplication of $Vt\%_{dep}$ × expiratory Vt measured by the ventilator; H_{nondep} = ventilation heterogeneity in nondependent lung region; H_{dep} = ventilation heterogeneity in dependent lung region; $\Delta EELI_{gl}$ = relative changes of global end-expiratory lung impedance when $PEEP_{low}$ or PSV_{high} was considered baseline (see text for details); – = variables are not available for this study group.

[a]PSV_{low}, PSV_{high}, $PEEP_{low}$, and $PEEP_{high}$ (Table 2) were performed randomly in each patient for 20 min leaving FIO_2 value, inspiratory ramp, and inspiratory and expiratory triggers unchanged.

[a]$p < 0.01$ vs. $PEEP_{high}$ (paired *t* test).

[b]$p < 0.01$ vs. $PEEP_{high}$ (Wilcoxon's test).

[c]$p < 0.01$ vs. PSV_{low} (paired *t* test).

[d]$p < 0.01$ vs. PSV_{low} (Wilcoxon's test).

[e]$p < 0.01$ vs. $PEEP_{low}$ (one sample *z* test).

[f]$p < 0.05$ vs. healthy controls (Mann-Whitney *U* test).

Data are expressed as mean ± SD or median (interquartile range) for nonnormally distributed variables.

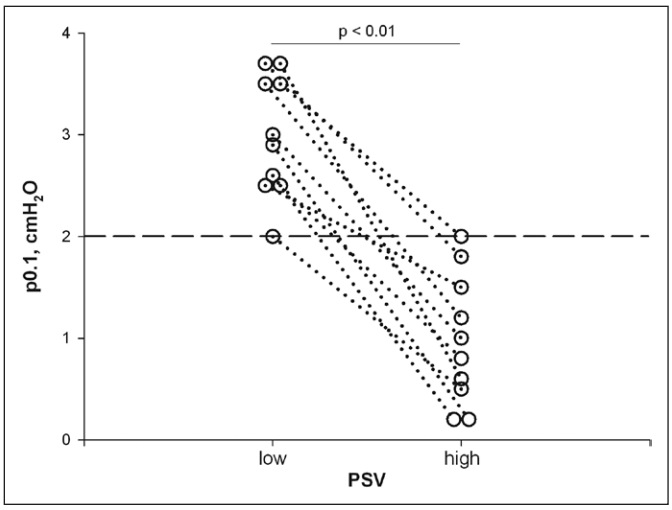

Figure 3. Pressure support ventilation $(PSV)_{low}$ was chosen to obtain pressure generated during the first 100 ms of inspiration (p0.1) values (i.e., a measure of patient's respiratory drive) ≥ 2 cm H_2O, whereas PSV_{high} was selected as a resting condition with p0.1 < 2 cm H_2O. One patient had p0.1 = 2 cm H_2O during PSV_{high}; however, his or her p0.1 was one of the highest during PSV_{low} (3.5 cm H_2O).

dependent lung portions (23). To date, impedance threshold levels able to discriminate normal lung inflation vs. overdistension in human subjects are not yet clearly identified, and our hypotheses should be addressed in formal validation studies.

During controlled or high-assist MV, most diaphragm displacement occurs in nondependent areas, with minimal movement at the most dependent level, at variance with what is observed during spontaneous ventilation (12, 13). We assessed ventilation of dependent lung regions in patients with ARDS during higher resting PSV (associated with minimal active diaphragmatic contribution to ventilation, as shown by lower p0.1 values) vs. lower PSV (associated with substantial diaphragmatic contribution to ventilation and higher p0.1). We observed that lower PSV levels are associated with increased proportion of tidal ventilation reaching gravitationally dependent lung regions, with unchanged tidal volume to dependent areas and with more homogeneous antero-posterior tidal distribution to values more similar to healthy volunteers. The fact that absolute tidal volume reaching dependent lung regions did not vary between the two PSV levels might seem in contrast with ventilation redistribution results. At the opposite, this result is in line with others described in this study. Regional tidal volume, indeed, is a function of regional driving pressure and lung compliance (24). In our study, regional compliance unlikely changed between the two PSV phases as they lasted 20 mins and were performed at the same PEEP level. Thus, regional changes in Vt must have reflected changes in regional driving pressure. Regional driving pressure during PSV is the sum of mechanical ventilatory support (which significantly decreased during PSV_{low}) plus patient's regional inspiratory effort. Therefore, in our study, unchanged values of tidal volume reaching dependent regions likely indicate

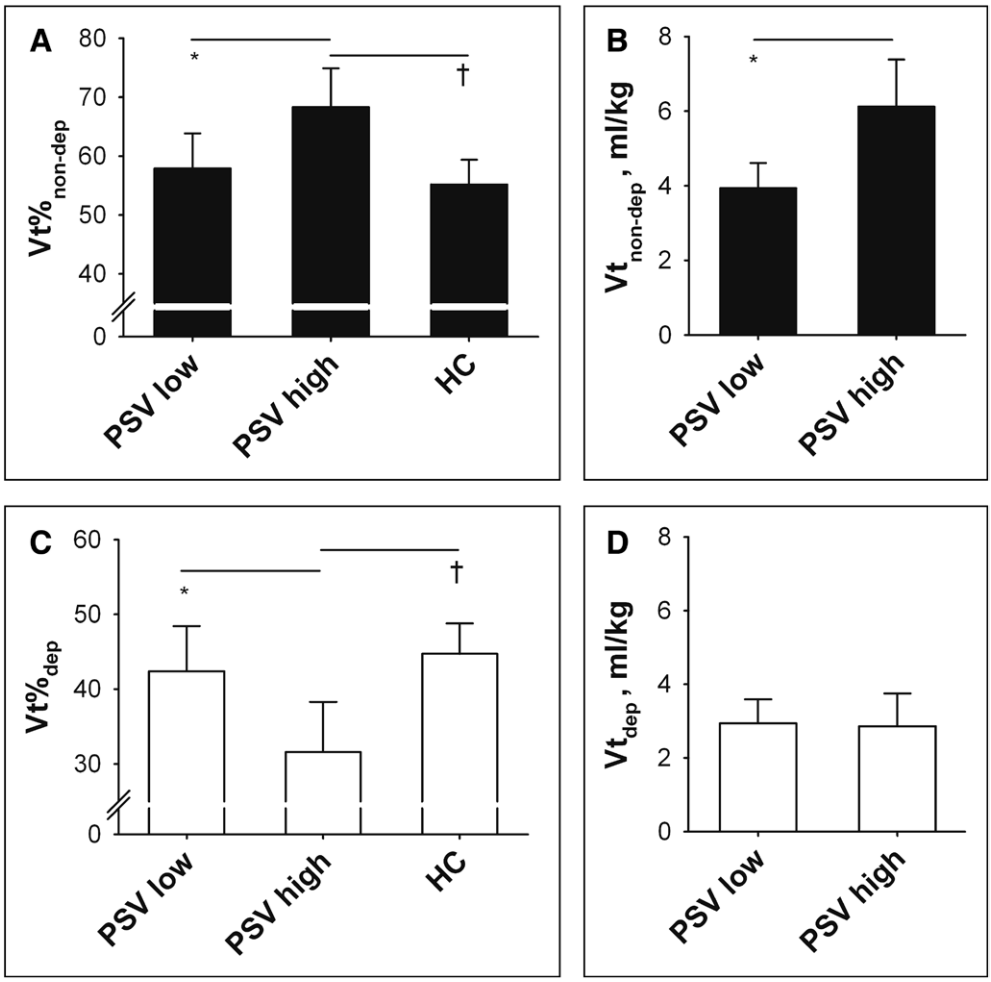

Figure 4. In patients with acute respiratory distress syndrome , lower pressure support ventilation (PSV) was associated with increased ventilation fraction reaching dependent lung regions ($Vt\%_{dep}$) and unchanged regional tidal volume (Vt_{dep}) (**C** and **D**), whereas relative and absolute ventilation of nondependent regions ($Vt\%_{nondep}$ and Vt_{nondep}, respectively) decreased (**A** and **B**) (see text for explanation details). HC = healthy controls. $^{*}p < 0.01$ and $\dagger p < 0.05$.

higher inspiratory force generated by dependent zones of the diaphragm in comparison with nondependent, where, instead, absolute tidal volume decreased. This result is also in line with diaphragm characteristics known since long by respiratory physiologists: more favorable anatomical shape and longer muscular fibers length of dependent regions of the diaphragm make their contraction stronger than nondependent (12). Another possible explanation is that during PSV_{high}, patients' respiratory muscles could have been over-assisted and their diaphragm might have only been triggering the ventilator. During PSV_{low}, instead, diaphragm contraction could have increased globally and along all respiratory cycle, leading to the observed Vt redistribution. As we did not perform direct measures of regional diaphragm contractility, we cannot draw any definitive conclusion on underlying mechanisms. Furthermore, regional tidal volume absolute values must be taken with caution as they combine a "global" respiratory variable (i.e., Vt read by the ventilator) with a regional one (i.e., $Vt\%_{dep}$), and the inference that the behavior of all lung areas is equal to the single slice imaged by EIT may be misleading.

Ventilation heterogeneity of nondependent lung regions decreased both during higher PEEP and lower PSV. During these study phases, tidal volume redistribution reduced the amount of air reaching the baby lung (6) and might have avoided excessive overdistension (barotrauma) (23) and decreased heterogeneity of regional mechanics in nondependent areas (i.e., decreased H_{nondep}), which, by the way, are the most prone to develop barotrauma and VILI (25). At variance, ventilation heterogeneity of dependent lung regions increased during PSV_{low}, while it did not change during $PEEP_{high}$, even in presence of similar proportion of regional ventilation. This might be related to different mechanisms involved in tidal redistribution during $PEEP_{high}$ and PSV_{low}: PEEP-associated tidal ventilation redistribution might have followed increased $EELI_{gl}$ and alveolar recruitment, which increases regional lung mechanics homogeneity (15). During lower PSV, instead, relative redistribution was likely caused by higher force generated by dependent diaphragm regions that might have caused increased regional mechanical stress and heterogeneity (12).

The correlation between oxygenation and the measured fraction of ventilation reaching dependent lung regions is not unexpected. Dependent lung regions receive the highest fraction of lung perfusion (7, 8); thus, it seems rational that higher ventilation fractions in dependent regions shall be associated with oxygenation, as in our results.

Finally, CT scan studies showed that the magnitude of lung aeration loss is related to ARDS severity: in a study on 68 patients with ARDS undergoing lung CT scans, Gattinoni et al (26) found that the ICU mortality was greater among patients with higher proportion of collapsed lung tissue at baseline PEEP, in comparison with that observed among patients with lower proportion of nonaerated lung tissue. A possible explanation for this finding is that in patients with larger collapse of dependent lung regions, MV is mainly distributed to nondependent aerated lung that becomes at higher risk of developing inflammation, VILI, end-organ dysfunction, and, ultimately,

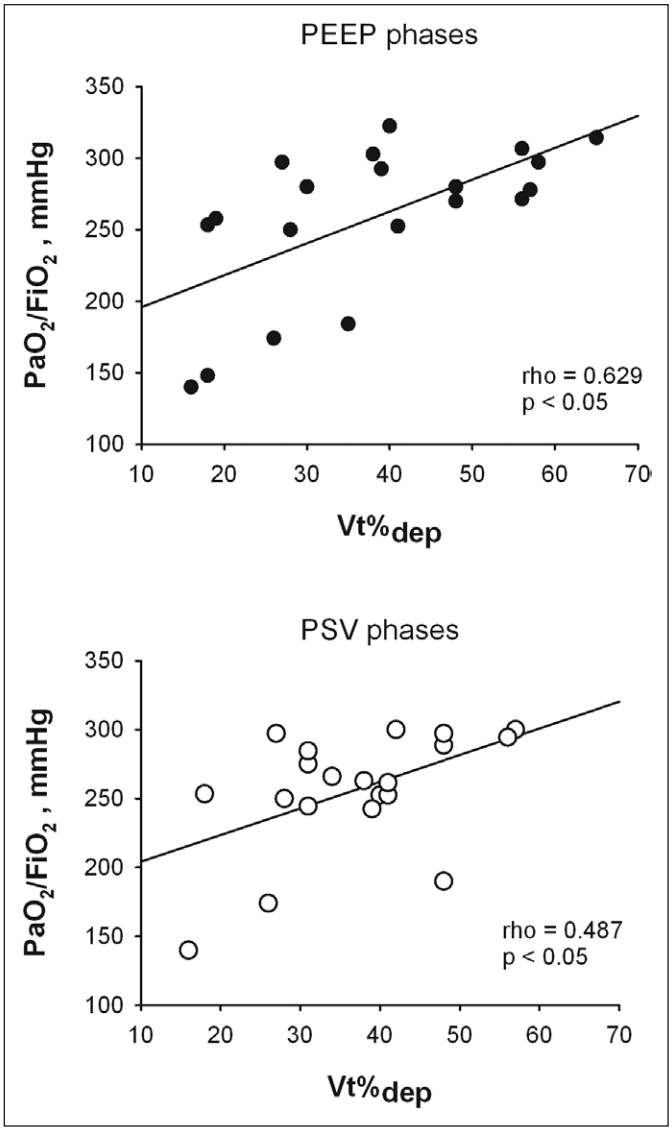

Figure 5. Pao_2/Fio_2 ratios were significantly correlated in acute respiratory distress syndrome patients with ventilation of dependent lung regions ($Vt\%_{dep}$) during all study phases, probably because of better ventilation-perfusion matching. PEEP = positive end-expiratory pressure; PSV = pressure support ventilation.

death (3, 9). In keeping with these results, in this study, we showed that nonsurvivors had lower proportions of tidal ventilation reaching collapsed dependent lung regions and lower antero-posterior ventilation homogeneity. Published studies and our results might suggest that MV strategies that increase ventilation of dependent lung regions may be beneficial in patients with ARDS (9).

EIT uses alternate electrical currents to measure the distribution of impedance within a body from measurements on its surface (14–17). It was developed in early 1910s and then adapted in late 1970s as a medical technique (18). Soon after, researchers observed that EIT was particularly suited to image the lungs, and since then, EIT has been validated in several preclinical lung imaging studies: Hinz et al (27), for example, induced ARDS in 12 pigs, intubated and mechanically ventilated, by oleic acid and measured tidal ventilation distribution by EIT and by ventilation scintigraphy using ^{99m}Tc-labeled carbon particles. In that study, Hinz et al (27) reported a highly significant linear correlation between regional ventilation measured by EIT and scintigraphy scanning with R^2 of 0.92 (range 0.86–0.97), during both controlled and assisted MV. Thus, EIT lung imaging is reliable, rapid, noninvasive, and relatively simple to use, and these characteristics enhanced EIT use as a monitoring technique for intensive care, surgical, and emergency patients (14, 16). As a matter of facts, the number of publications on EIT in international scientific journals is rapidly growing: researchers are particularly interested in EIT role in titration and personalization of lung protective MV (15). EIT also has many important limitations: it lacks standardization, spatial resolution is low, and it can only track changes of lung air content and not of lung tissue content. In conclusion, EIT is not a substitute for CT scan, but results from the present and previous studies (15) seem to indicate that EIT might represent an alternative to CT scans when they are not either appropriate (e.g., for daily assessment of regional lung mechanics) or feasible (e.g., for monitoring of regional ventilation in spontaneously breathing patients).

Our study has a few important limitations: 1) We studied patients with ARDS when switched from controlled MV to PSV as per clinical decision (i.e., 4 ± 5 days after diagnosis) and studied a population with mild-to-moderate lung injury severity. As a consequence, our results may not apply to patients with more severe ARDS and with larger and thicker collapse of dependent regions, who deserve to be formally studied in future. 2) EIT offers data only from a single biconvex slice of the lungs, 10–15 cm thick (15–17). Therefore, the behavior of all other lung areas can only be inferred, and the assumption that EIT data represent the entire lung may be clinically misleading. Studies adopting two or more EIT monitoring devices simultaneously applied at different chest levels may yield more accurate and global results. 3) Our study design did not allow us to test the interaction between PEEP and pressure support on regional distribution of tidal ventilation. To do so, we should have added one extra study phase (PSV level tested during study phase 3 and $PEEP_{high}$). However, with this study design, the time spent by each patient with the EIT electrodes belt was already close to that suggested by manufacturer to avoid skin lesions (1–1.5 hrs). 4) We did not measure directly the mechanisms at the basis of the observed redistribution phenomena (i.e., recruitment at higher PEEP levels and increased diaphragm activity at lower PSV), but we used reasonable surrogates (i.e., $\Delta EELI_{gl}$ and p0.1). 5) Although interesting, the abovementioned correlation between ventilation distribution and mortality needs further validation because of the small sample size.

CONCLUSIONS

In patients with ARDS, after switching to assisted MV, lower pressure support and higher PEEP levels induce redistribution of tidal ventilation fractions from nondependent to dependent lung regions and increase antero-posterior ventilation

homogeneity by different mechanisms (i.e., higher force generated by diaphragm vs. regional alveolar recruitment). The association between ARDS patients' outcome and ventilator settings that induce dependent redistribution of tidal ventilation remains to be established.

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