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Dynamic bedside assessment of the physiologic effects of prone position in acute respiratory distress syndrome patients by electrical impedance tomography

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ABSTRACT

BACKGROUND: Prone position (PP) improves acute respiratory distress syndrome (ARDS) survival by reducing the risk of ventilation-induced lung injury. However, inter-individual variability is a hallmark of ARDS and lung protection by PP might not be optimal in all patients. In the present study, we dynamically assessed physiologic effects of PP by Electrical Impedance Tomography (EIT) and identified predictors of improved lung protection by PP in ARDS patients.

METHODS: Prospective physiologic study on 16 intubated, sedated and paralyzed patients with ARDS undergoing PP as per clinical decision. EIT data were recorded during two consecutive steps: 1) baseline supine position before and after a recruitment maneuver (RM); 2) prone position before and after a RM. “Improved lung protection” by PP was defined in the presence of simultaneous improvement of ventilation homogeneity (Hom), alveolar overdistension and collapse (ODCL) and amount of recruitable lung volume by RM in comparison to supine.

RESULTS: PP vs. supine increased the tidal volume distending the dependent regions (Vt_{dep}), resulting in improved Hom (1.1±0.9 vs 1.7±0.9, p=0.021). PP also reduced ODCL (19±9% vs 28±8%, p=0.005) and increased the recruitable lung volume (80[71–157]ml vs 59[1–110]ml, p=0.025). “Improved lung protection” by PP was predicted by lower Vt_{dep}, higher Vt_{ndep} and poorer Hom measured during baseline supine position ($p<0.05$).

CONCLUSIONS: EIT enables dynamic bedside assessment of the physiologic effects of PP and might support early recognition of ARDS patients more likely to benefit from PP.

Keywords:

Electrical Impedance; Prone Position; Acute Respiratory Distress Syndrome; Respiratory Failure; Ventilator-Induced Lung Injury.

Introduction

Despite extensive research efforts and significant improvements in patient management, mortality of patients with the acute respiratory distress syndrome (ARDS) remains high[1]. Prone position (PP) is an inexpensive, simple and effective intervention to improve outcome of patients with severe ARDS, with an absolute survival benefit around 15%[2,3], albeit its application in clinical practice remains sub-optimal [4]. Compared with supine position, PP significantly improves arterial oxygenation[2,5]. However, post-hoc analysis of a recent large randomized trial on PP in ARDS showed that the increase of PaO_2/FiO_2 was similar in survivors vs. non-survivors[6], suggesting that the mechanisms through which PP improves outcome might be more closely related to physiologic benefits increasing lung protection. Indeed, previous data suggest that PP may reduce the risk of ventilator-induced lung injury (VILI)[5,7-10] by decreasing ventilation heterogeneity and alveolar over-distension and through optimization of lung recruitment[11]. Monitoring such improvements at the bedside could allow more adequate understanding of the effectiveness of PP at the individual patient-level.

Inter-individual variability in the distribution of lung edema and regional mechanics is a hallmark of ARDS. Recent studies suggest that such variability could undermine efficacy of treatments such as higher positive end-expiratory pressure levels or restrictive fluid administration in ARDS patients[12,13]. On the contrary, early recognition of ARDS sub-phenotype might enhance appropriate allocation of specific therapies, ultimately increasing their efficacy[12].

In the present study, we hypothesized that a dynamic monitor of regional lung mechanics and recruitment such as electrical impedance tomography (EIT) might represent a useful tool for bedside monitoring of the physiologic effects of PP. Moreover, we explored whether EIT-based measures of lung heterogeneity could represent a more sensitive tool for prediction of improved lung protection by PP while the patient is still supine.

Methods

Study population

We conducted a prospective, bi-centric study on 16 ARDS patients admitted to the general Intensive Care Units (ICUs) of Maggiore Policlinico Hospital, Milan, and of San Gerardo Hospital, Monza, Italy. All patients were supine, deeply sedated, paralyzed and on volume-controlled mechanical ventilation as per clinical indication and had not been turned to prone position during their ICU stay before study inclusion. Inclusion criteria were: diagnosis of ARDS[1] according to the Berlin definition and clinical decision to apply prone position. Exclusion criteria were: age <18 years, pregnancy, severe hemodynamic instability, evidence of pneumothorax, history of severe chronic obstructive pulmonary disease, intracranial hypertension, contraindication to use of EIT (e.g., cardiac pacing). Institutional Ethical Committees of both centers approved the study and informed consent was obtained from each patient according to local regulations. The study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

After enrollment, demographic data, ARDS etiology, severity of illness at admission (expressed as simplified acute physiology score, SAPS II), baseline clinical ventilation settings and arterial blood gas analysis were recorded.

Study protocol

Tidal volume (Vt ≈ 6-8 ml/Kg predicted body weight [PBW]), respiratory rate (RR), PEEP and FiO_2 set by the attending physicians in supine position were left unchanged throughout the study.

The EIT belt was placed, while in supine position, at 5th-6th intercostal space and connected to the EIT monitor (PulmoVista 500, Dräger Medical GmbH, Lübeck, Germany). EIT applies small alternated electrical current around the patient's thorax and generates tomographic quantitative images of gas distribution within the chest at 20 Hz. EIT data were continuously recorded during all the study phases (see below), with interruption during turning to PP. All EIT data were stored and analyzed off-line[14,15].

The study consisted of two steps performed in sequence:

1. Supine position before (20 minutes) and after (20 minutes) a recruitment maneuver (RM);
2. Prone position before (20 minutes) and after (20 minutes) a recruitment maneuver (RM).

Patients were not disconnected from the ventilator during the pronation maneuver.

RM was performed by application of continuous airway pressure of 40 cmH_2O for 40 seconds. Between the two steps, EIT monitoring was interrupted, body position was changed to prone and 15-20 minutes were waited to verify clinical stability.

During the last minutes before each RM, arterial blood gas analysis was collected. Furthermore, end-expiratory and end-inspiratory occlusions were performed. Airway pressure and flow tracings were continuously recorded.

The study protocol timeline is reported in Figure 1.

Analysis of ventilation tracings and EIT data

From off-line analysis of the ventilation waveforms, we measured end-inspiratory plateau pressure (Pplat) (i.e. the airway pressure value at the end of an inspiratory hold), total positive end-expiratory pressure (PEEPtot) (i.e. the airway pressure value at the end of an expiratory hold) and tidal volume (Vt) and we calculated airway driving pressure (DP) as DP = Pplat – PEEPtot and respiratory system static compliance (Crs) as Crs = Vt/DP.

We divided the EIT chest-imaging field in two equal size sections by horizontal midline and we defined dependent (dep) and non-dependent (ndep) regions according to gravity. Thus, anatomical sections differed from functional sections in supine vs. prone position: as an example, the region between chest midline and sternum was analyzed as non-dependent in supine position and as dependent in PP. From off-line analysis of EIT tracings recorded right before the RM (analysis of ten breaths), we measured:

1. The regional Vt distribution (Vt_{ndep} and Vt_{dep});
2. The homogeneity of tidal ventilation distribution (Hom), as the Vt_{ndep}/Vt_{dep} ratio, with ratio of 1 corresponding to perfect ventilation homogeneity;
3. Regional respiratory system compliance, calculated as: $Crs_{ndep} = Vt_{ndep}/DP$; $Crs_{dep} = Vt_{ndep}/DP$;
4. Alveolar overdistension and collapse (ODCL): pixel-by-pixel compliance was calculated as Δimpedance-pixel/DP and the change between PP vs. supine was used to compute overdistension and collapse, as previously described[16,17];

From the EIT tracings obtained in the final minutes of recording after each RM (analysis of ten breaths), recruitable lung volume was measured as the increase in end-expiratory lung volume induced by the RM (ΔEELV). ΔEELV was calculated as the changes in end-expiratory lung impedance between the level measured right before each RM and the one reached 20 minutes after the RM, both in supine and PP, multiplied by the ratio between Vt in milliliters and Vt in impedance arbitrary units, as previously described[17,18]. For a more detailed explanation of EIT data analysis, please see the “Supplementary Digital Material: Supplementary Material and Methods an Supplementary Figure 1”.

Patients with “improved lung protection” were considered those with simultaneous improvement of Hom, ODCL and recruitable lung volume induced by PP, while patients with “partial lung protection” were considered those in whom at least one of the 3 mechanisms wasn’t improved by PP[14]. An improvement in Hom was defined as reaching a value of Vt_{ndep}/Vt_{dep} closer to 1 in PP as compared to supine position (SP); an improvement in ODCL was defined as a decrease in ODCL value in PP as compared to SP and an improvement in recruitable lung volume induced by prone position was defined as an increase in end-expiratory lung volume after a recruitment maneuver in PP as compared to SP.

Statistical analysis

Sample size calculation allowed to detect an absolute decrease in tidal ventilation inhomogeneity of 0.8 ± 1 unit (paired samples Student’s t-test), with power of 0.80 and α of 0.05 (two-tailed). Normal distribution of data was tested by the Shapiro-Wilk Normality Test. Normally distributed data are indicated as mean ± standard deviation, while median and inter-quartile range [IQR] are used to report non-normally distributed variables. Comparisons between variables measured during supine vs. PP were performed by paired samples Student’s t-test or Wilcoxon test, for data with normal or non-normal distribution, respectively. Comparisons between variables measured during the baseline supine step in patients showing “improved lung protection” vs. those with “partial lung protection” by PP were performed using Student’s t-test or Mann-Whitney U-test, as appropriate. Then, variables showing a $p\text{-value} < 0.1$ at univariate analysis (namely, Vt_{ndep}, Vt_{dep}, Crs_{dep}, Hom) were tested as predictors of “improved lung protection” by PP through receiver operator characteristic (ROC) curves. For each ROC curve, we calculated the sensitivity, specificity, positive and negative predictive value (PPV and NPV, respectively), accuracy, and optimal cut-off point using Youden’s index. Statistical analysis was performed by SigmaPlot 12.0 (Systat Softwere Inc., San Jose, CA).

RESULTS

Patient characteristics

Patients were 57 ± 18 years old and 8 (50 %) were women. Etiology of ARDS was primary in 12 (75%) patients and infectious in 10 (63%) patients. PaO_2/FiO_2 was 153 ± 63 mmHg, and in nine patients (56%) it was below 150 mmHg. Baseline clinical ventilation settings were: PEEP 13 ± 3 cmH_2O, Vt 6.5 ± 1.2 ml/kg PBW, Pplat 25 ± 3 cmH_2O. The study was performed after 2 [1 – 12] days from intubation. Hospital mortality was 31%.

Dynamic assessment of the physiologic effects of prone position by EIT

Ventilation parameters, gas exchange and EIT-based measures in the supine vs. PP are reported in Table 1. While global mechanics and gas exchange didn't change, PP induced a significant redistribution of tidal volume from non-dependent towards dependent lung regions (Table 1 and Figure 2). Compared to supine position, Vt_{dep} increased by 43 ± 53% (p = 0.009) and Vt_{ndep} decreased by 20 ± 32 % (p = 0.011) in the PP, yielding significantly increased homogeneity of tidal ventilation distribution during PP vs. supine (1.1 ± 0.9 vs 1.7 ± 0.9, p = 0.021). PP might have led to tidal ventilation redistribution through significant decrease of Crs_{ndep} (Table 1). Finally, turning the patients to the prone position significantly reduced alveolar overdistension and collapse (19 ± 9 % vs 28 ± 8 %, p = 0.005) and increased recruitable lung volume (80 [71 – 157] ml vs 59 [1 – 110] ml, p = 0.025). Individual data of the enrolled patients are reported in the "Supplementary Digital Material: Supplementary Results".

Predictors of "improved lung protection" by PP

PP simultaneously improved ventilation homogeneity, alveolar overdistension and collapse and recruitable lung volume in 6 (38%) patients (Table 2). The group with "improved lung protection" showed larger Vt_{ndep}, smaller Vt_{dep}, lower Crs_{dep} and worse ventilation homogeneity measured during the baseline supine position as compared to the "partial lung protection" group (Table 2). Online video 1 and 2 show ventilation distribution during baseline supine position in representative patients with partial (more homogenous, Supplementary Video 1) vs. improved (less homogenous, Supplementary Video 2) lung protection by PP. Vt_{ndep}, Vt_{dep} and Hom were predictors of "improved lung protection" at ROC curves analysis (Vt_{ndep}: AUC-ROC = 0.775, 95% CI = 0.503 to 0.941, p = 0.044; Vt_{dep}: AUC-ROC = 0.783, 95% CI = 0.512-0.945, p = 0.038; Hom: AUC-ROC = 0.783, 95% CI = 0.512-0.945, p = 0.038) while Crs_{dep} wasn't (p = 0.069). Cut-off values of 62% for Vt_{ndep}, 35%

for Vt_{dep} and 1.6 for Hom were all associated with 67% sensitivity, 90% specificity, 80% PPV and 82% NPV for positive response to prone position.

DISCUSSION

The main findings of our study can be summarized as follows: EIT was used to assess homogeneity of regional ventilation distribution, alveolar overdistention and collapse and shows their improvement as well as lung recruitability induced by PP; patients in whom PP induces simultaneous improvement of ventilation homogeneity, alveolar overdistension-collapse and recruitable lung volume (i.e., patients with "improved lung protection" by PP) are characterized by larger inhomogeneity of tidal ventilation distribution during baseline ventilation in the supine position.

Previous studies using static analysis of chest computed tomography images showed that PP induces a redistribution of gas within the ARDS lung, because of the reduced ventral-to-dorsal gravitational pleural pressure gradient[19] that might enhance lung recruitment and decrease hyperinflation[20,21]. Indeed, the use of EIT allowed us to dynamically observe a more homogeneous distribution of ventilation by PP: while a major portion of ventilation reaches the non-dependent regions in the supine position, tidal volume splits almost equally between dependent and non-dependent regions in the PP. This effect likely derived from an overall improvement of the distribution of regional compliances, as indicated by the decrease in alveolar overdistension and collapse measured by EIT. The two conditions (i.e., redistribution of lung inflation and changes in the dynamic regional lung mechanics) are likely interconnected: the reduced lung weight overwhelming dependent lung might improve regional mechanics and ventilation without changing mechanical ventilation settings[20,22,23]. To this end, a recent experimental study demonstrated that PP induced a more homogeneous regional distributions of gas volume and ventilation in the presence of asymmetric chest disease[24]. As we showed that PP promotes lung recruitability, this could further reduce collapse and minimize the risk of opening and closing phenomena in dependent lung regions, while decreasing dynamic overinflation of non-dependent regions[21,25]. Given our and previous results, we might speculate that the observed improvements could decrease the risk of VILI during PP and it seems reasonable to hypothesize that the survival benefit associated with PP may derive from enhanced lung protection[8,10]. Indeed, a recent study in an animal model of ARDS suggested that PP might limit progression of lung injury by minimizing regional ventilation imbalance during tidal insufflation[9]. As it has been demonstrated that improved survival by PP is not associated with increased oxygenation[6,26,27], our data confirm the potential independency between oxygenation response and homogeneity/recruitment response to PP. Indeed, previous studies showed that oxygenation response did not correlate with the static distribution of non-aerated lung tissue[28] nor with lung recruitability[29]. Moreover, lack of correlation was described also between oxygenation response and changes in regional lung aeration evaluated by ultrasound[30].

Given the recent surge in attention to personalized treatments in the ICU, early recognition of patients more likely to have a positive response to PP in terms of lung protection could maximize the clinical benefits[31]. Interestingly, classic indexes of ARDS severity could not differentiate between patients with improved vs. partial lung protection, the only difference being a significantly higher distribution of tidal volume to the non-dependent lung regions, a lower tidal volume distending the dependent lung and higher baseline ventilation inhomogeneity during baseline supine position. EIT could therefore help identifying a subpopulation of patients who may specifically benefit from PP to prevent lung damage.

Our study has several limitations. First, the sample size is relatively small but several physiologic parameters, including respiratory mechanics, gas exchanges and dynamic regional EIT measurements were recorded in each patient to investigate the specific effects of prone position. Second, study phases were relatively short and we explored only the early response to PP, while the effects on oxygenation, mechanics and ventilation distribution may evolve over time during a PP session. Third, EIT explores only a portion of the lungs, corresponding roughly to half of their size; however, several studies showed that it represents an accurate method to continuously monitor changes in ventilation homogeneity, end-expiratory lung inflation and recruitment at the bedside[16]. Fourth, we studied only the physiologic effects of turning the patient from supine to prone position and not vice-versa, since the two main study phases were not performed in random order. Fifth, this study was not powered to explore the correlation between response to PP and clinical outcome. Therefore, further research is needed to assess the correlation between regional lung protection by PP and the clinical outcome of ARDS patients.

CONCLUSIONS

Prone position is an easy, effective and inexpensive therapeutic option for ARDS patients that effectively reduces mortality. EIT is a dynamic bedside radiation-free lung imaging method that could enhance monitoring of the lung protective effects of PP, including ventilation homogeneity, over-distension and collapse, and recruitable lung volume. Moreover, the use of EIT might help early recognition of the patients more likely to obtain improved lung protection by turning prone before position change.

WHAT IS KNOWN

- Prone position improves outcome of patients with severe ARDS

WHAT IS NEW

- EIT is a bedside method to dynamically monitor prone position
- Proning improves lung homogeneity and reduces hyperdistension and collapse measured by EIT
- Patients with worse homogeneity while supine benefit from prone position the most

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NOTES

Conflicts of interest. Giacomo Grasselli received payment for lectures from Maquet, Draeger Medical and Fisher&Paykel and travel-accommodation-congress support from Biotest (all unrelated with the present work). No conflicts of interest related to this study have been declared by co-authors.

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Authors’ contributions. GG, TM, GB, AP and GF contributed to design the conception and design of the study. FDC, CT, ML, MA, CA, AL, AG, NE, AB and EM participated in acquisition and analysis of data for the study. FDC, TM, ES and GG drafted the work. All authors collaborated to interpret data, revise the work critically for important intellectual content, and approve the final version of the manuscript.

TABLES

Table 1. Comparison between variables in the supine vs. prone position

Variable	Supine position (n=16)	Prone position (n=16)	P-value
Plateau Pressure (cmH_2O)	25 ± 3	26 ± 3	0.143^*
Driving Pressure (cmH_2O)	11 [9 – 13]	12 [8 – 14]	$0.078^§$
Crs (ml/cmH_2O)	38 [25 – 47]	33 [25 – 52]	$0.151^§$
Minute ventilation (L/min)	10.6 [8.4 – 11.3]	10.5 [9.0 – 11.2]	$0.970^§$
PaO_2 (mmHg)	76 [67 – 84]	83 [67 – 101]	$0.252^§$
PaO_2/FiO_2 (mmHg)	130 [101 – 162]	146 [107 – 224]	$0.252^§$
$PaCO_2$ (mmHg)	49 ± 5	48 ± 8	0.848^*
pH	7.37 [7.35 – 7.42]	7.37 [7.34 – 7.44]	$0.470^§$
Vt_{ndep}, %	59 ± 14	45 ± 17	**0.007^***
Vt_{dep}, %	41 ± 13	55 ± 17	**0.008^***
Crs_{ndep} (ml/cmH_2O)	25 ± 13	18 ± 12	**0.006^***
Crs_{dep} (ml/cmH_2O)	16 ± 8	20 ± 11	0.083^*
Ventilation homogeneity	1.7 ± 0.9	1.1 ± 0.9	**0.021^***
ODCL (%)	28 ± 8	19 ± 9	**0.005^***
ΔEELV (ml)	59 [1 – 110]	80 [71 – 157]	**$0.025^§$**

Data are reported as mean ± standard deviation or median [interquartile range].

* ~~repeated measures~~ paired samples Student’s t-test was used; § Wilcoxon test was used

Crs = compliance of the respiratory system; PaO_2 = Arterial oxygen partial pressure; PaO_2/FiO_2 = oxygen partial arterial tension/inspired oxygen fraction; $PaCO_2$ = Arterial carbon dioxide partial pressure; Vt = tidal volume; dep = dependent; non-dep = non-dependent; ODCL = Alveolar overdistension and collapse; ΔEELV = recruitable lung volume.

Table 2. Comparison of baseline variable between improved lung protection indices (ventilation homogeneity, alveolar overdistension and collapse and recruitable volume) responders and partial responders.

Variable	**Improved lung protection by PP (n= 6)**	**Partial lung protection by PP (n = 10)**	**P-value**
PEEP (cmH_2O)	14 [11 – 17]	14 [13 – 15]	0.956§
Plateau Pressure (cmH_2O)	26 ± 3	25 ± 3	0.703*
Driving Pressure (cmH_2O)	11 ± 4	12 ± 5	0.901*
Crs (ml/cmH_2O)	38 ± 25	42 ± 16	0.691*
Minute ventilation	10.8 [8.8 – 11.3]	10.6 [7.2 – 11.3]	0.871§
PaO_2 (mmHg)	81 ± 14	75 ± 15	0.409*
PaO_2/FiO_2	156 ± 81	131 ± 36	0.403*
$PaCO_2$ (mmHg)	50 ± 5	48 ± 6	0.573*
pH	7.370 [7.360 – 7.408]	7.365 [7.340 – 7.435]	0.703§
Vt_{ndep}, %	66 ± 7	53 ± 13	**0.054***
Vt_{dep}, %	34 ± 7	47 ± 13	**0.039***
Crs_{ndep} (ml/cmH_2O)	20 [15 – 32]	24 [15 – 29]	0.786
Crs_{dep} (ml/cmH_2O)	9 [7 – 18]	18 [15 – 23]	**0.057§**
Ventilation homogeneity	2.1 ± 0.7	1.3 ± 0.5	**0.023***
ODCL (%)	27 ± 7	28 ± 8	0.840*
∆EELV (ml)	6 [-3 – 71]	81 [29 – 114]	0.255§

Data are reported as mean ± standard deviation or median [interquartile range].

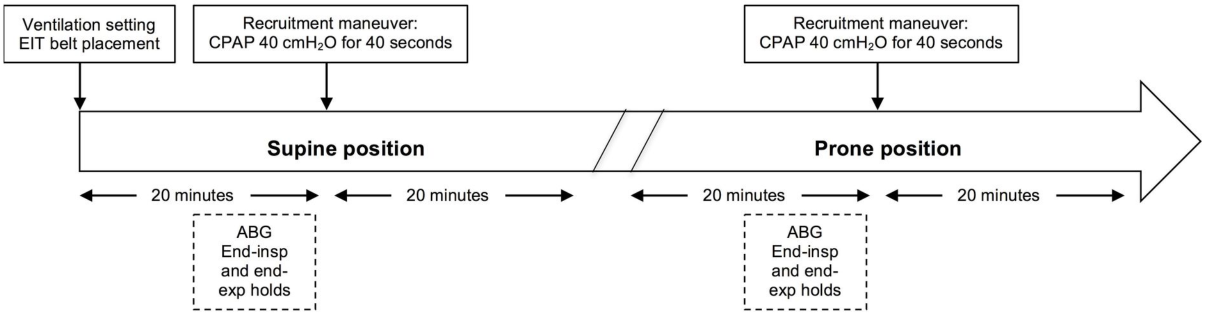
* Student’s t-test was used; §Mann-Whitney U-test was used

PP = prone position; PEEP = positive end-expiratory pressure; PaO_2 = Arterial oxygen partial pressure; PaO_2/FiO_2 = oxygen partial arterial tension/inspired oxygen fraction; $PaCO_2$ = Arterial carbon dioxide partial pressure; Vt = tidal volume; dep = dependent; non-dep = non-dependent; Crs = compliance of the respiratory system.

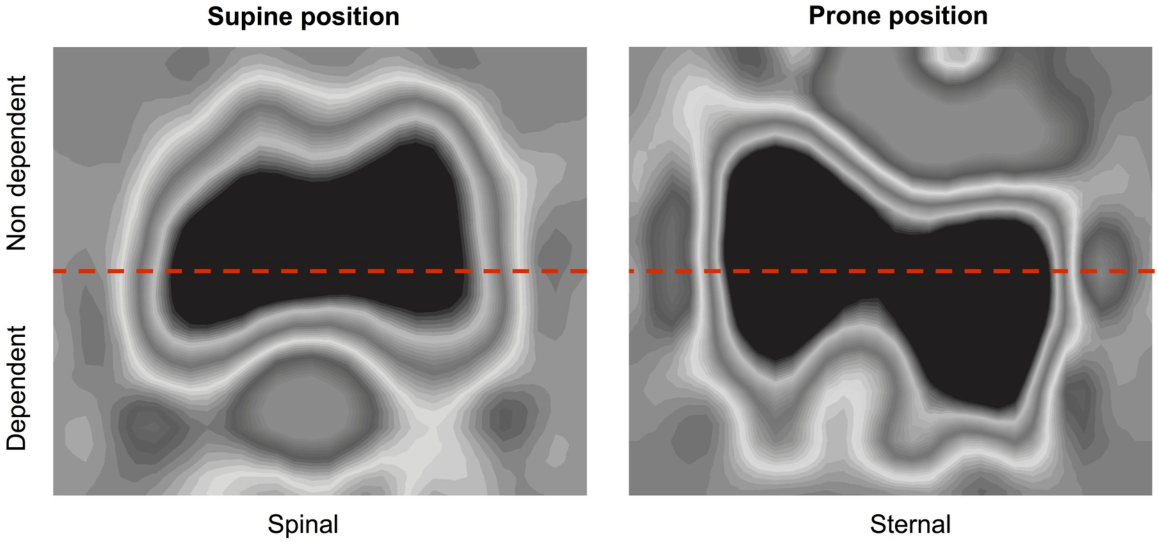
TITLE OF FIGURES

Figure 1. Timeline of the study protocol.

Figure 2. Redistribution of ventilation with prone position (PP). In a representative patient, PP (right) induced a significant increase in ventilation of dependent regions and a significant decrease in ventilation of non-dependent regions, ameliorating ventilation homogeneity (i.e. the ratio between the air distending the ventral and the dorsal part of the lung). The black areas represent the aerated lung tissue.



Ventilation setting
EIT belt placement
Recruitment maneuver:
CPAP 40 cmH2O for 40 seconds
Recruitment maneuver:
CPAP 40 cmH2O for 40 seconds
Supine position
Prone position
20 minutes
20 minutes
20 minutes
20 minutes
ABG
End-insp
and end-
exp holds
ABG
End-insp
and end-
exp holds


Supine position
Prone position
Non dependent
Dependent
Spinal
Sternal

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