Alveolar recruitment during prone position: time matters

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ABSTRACT

Alveolar recruitment is one of the beneficial effects of prone positioning in patients with ARDS (acute respiratory distress syndrome). However, responses vary among patients and, therefore, we hypothesized that alveolar recruitment is an individual time-dependent process and its measurement might be helpful to ‘dose’ prone positioning individually. In 13 patients diagnosed with ARDS, EELV (end-expiratory lung volume) was measured in the supine position, immediately after turning to the prone position, at 1, 2, 4 and 8 h in the prone position and after returning to the supine position. Responders were defined based on a 30% increase in oxygenation. EELV increased in responders, whereas it remained constant in non-responders. The time course was different in individual patients. In some responders, a plateau was reached as early as 2–4 h, whereas, in others, 8 h of prone positioning was not sufficient to allow complete recruitment. The increase in lung volume was associated with both an increase in arterial oxygenation and a decrease in venous admixture. Furthermore, responders had significantly lower baseline EELVs than non-responders. In conclusion, alveolar recruitment during prone positioning has been characterized as an individual time-dependent process. Its measurement might be useful to apply prone positioning more individually and might also help to identify responders.

INTRODUCTION

ARDS (acute respiratory distress syndrome) is characterized by non-cardiogenic pulmonary oedema, ventilation/perfusion mismatch, intrapulmonary shunting and severely impaired oxygenation. In addition to ventilation with high $F_{i}O_{2}$ (fraction of inhaled oxygen) concentrations and PEEP (positive end-expiratory pressure), prone positioning has been shown to improve arterial oxygenation in approx. 60–80% of the patients [1,2].

Several mechanisms of improved gas exchange have been described during prone positioning [3–7], including a decrease in ventilation/perfusion mismatch, change in regional diaphragm motion and improved removal of secretions. The increase in EELV (end-expiratory lung volume) as one important mechanism to improve gas exchange during prone positioning was originally proposed by Douglas et al. [8]. Since then, few studies have described lung volume recruitment during prone positioning over extended periods of time [9,10].

In routine clinical practice, prone positioning is usually initiated based on different criteria, including morphological alterations of the lung [as determined by CT (computer tomography)] and disturbance of gas exchange

Key words: acute lung injury, acute respiratory distress syndrome (ARDS), alveolar recruitment, end-expiratory lung volume, prone position.

Abbreviations: ARDS, acute respiratory distress syndrome; CO, cardiac output; CT, computer tomography; EELV, end-expiratory lung volume; $F_{i}O_{2}$, fraction of inhaled oxygen; FRC, functional residual capacity; FRCpred, predicted FRC; FRCrel, relative FRC; $P_{a}CO_{2}$, arterial partial pressure of carbon dioxide; $P_{a}O_{2}$, arterial partial pressure of oxygen; $P_{a}O_{2}/F_{i}O_{2}$ ratio, oxygenation quotient; PBW, predicted body weight; PEEP, positive end-expiratory pressure; $P_{et}CO_{2}$, end-tidal partial pressure of carbon dioxide; $Q_{v}/Q_{t}$, venous admixture; $V_{e,exp}$, expired tidal volume.

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(as assessed by blood gas analysis). Patients remain in the prone position for 8–12 h, although both shorter and longer periods have been reported. Improvement in gas exchange is often used to indicate successful prone positioning. Measuring alveolar recruitment, however, has not yet become a standard in monitoring patients during prone positioning, most probably because of technical limitations. Therefore it is not surprising that data on time courses of lung recruitment during prone positioning are rare.

In the present study, we hypothesize that the measurements of EELV might be valuable in assessing the individual response to prone positioning over time, thus allowing 'dose' prone positioning individually and decreasing the potential risk and side effects caused by overlong positioning. Furthermore, we hypothesize that the initial EELV might be indicative of recruitable airspace and, therefore, serve as a predictive factor in the response to prone position. In the present study, EELV was measured at different time points during an 8-h period of prone positioning by using a simplified rebreathing technique. Individual time courses of lung volume recruitment were recorded and compared with changes in arterial oxygenation and shunt perfusion.

MATERIALS AND METHODS

Patients

The study was approved by the local Ethics Committee, and informed consent was obtained from the patients’ closest relatives. Patients were enrolled when they met ARDS criteria, and prone positioning was indicated by meeting the following criteria: (i) mechanical ventilation with $F_{\text{O}_2} > 0.5$ at PEEP $> 10 \text{ cm H}_2\text{O}$ for at least 24 h, or (ii) radiographic evidence of pulmonary densities (CT scan and/or chest X-ray) being constant or increasing within 24 h [11]. Onset of respiratory failure was less than 72 h before the time of inclusion [12]. All patients were intubated orotracheally and sedated.

Exclusion criteria were a case history of previous prone positioning and treatment with nitric oxide. Patients with obstructive airway disease, who consequently might have an altered baseline EELV, were also excluded from this study. Patients receiving a lateral decubitus position were not enrolled in the study.

Measurements were stopped when oxygen saturation decreased to 89% or less, or when haemodynamic instability occurred during the study period (decrease of mean arterial pressure by more than 25 mmHg compared with baseline).

Experimental protocol

Patients were mechanically ventilated in the volume-controlled mode (Servo 900C Ventilator; Siemens Elema). Tidal volumes were applied based on the patient’s PBW (predicted body weight; 6–8 ml/kg of PBW). $F_{\text{O}_2}$ and PEEP levels, initially set by a clinician aiming for optimization of arterial oxygenation, were kept unchanged. Ventilatory settings remained unchanged throughout the measurement period. Respiratory muscle relaxation was ensured during the respiratory mechanics measurements with vecuronium bromide (0.1 mg/kg of PBW). Balanced fluid management was maintained during the study period ($\pm 200 \text{ ml/24 h}$).

Patients were kept in a prone position for 8 h. The upper thorax and pelvis were supported by foam rubber pads, permitting the abdomen to protrude. The head was turned laterally and also supported by pads, and the arms were placed parallel to the body. Following a period of stable ventilation for at least 1 h, measurements were performed in the following order: $Q_{\text{i}}/Q_{\text{o}}$ (venous admixture) was calculated from arterial and mixed venous blood gas analyses (ABL555; Radiometer Medical); oxygenation quotient was calculated as the $P_{\text{aO}_2}$ (arterial partial pressure of oxygen)/$F_{\text{O}_2}$ ratio; the difference between the $P_{\text{aCO}_2}$ (arterial partial pressure of carbon dioxide) and $P_{\text{ETCO}_2}$ (end-tidal partial pressure of carbon dioxide) was calculated as an indicator of dead space ventilation. Haemodynamic parameters and ventilatory settings were also determined. CO (cardiac output) was then measured by the bolus thermodilution technique (REF 831F75; Baxter) and was calculated as a mean of three consecutive measurements. EELV was determined as described below.

Baseline values were obtained in supine position ($S_0$). Further measurements were performed immediately after turning to the prone position ($P_2$; less than 30 min after $S_0$), after 1, 2, 4 and 8 h periods in prone position ($P_1$, $P_2$, $P_3$ and $P_4$), and within 1 h following return to the supine position ($S_1$).

EELV

EELV was determined using a simplified rebreathing method [10]. Patients were ventilated manually from a rebreathing bag filled with 1% (v/v) sulphur hexafluoride in oxygen. Sulphur hexafluoride can be regarded as inert when applied in low concentrations at atmospheric pressures [13]. The rebreathing system was set up parallel to the patients’ breathing circuit. Mechanical ventilation was interrupted at the end of expiration, and the rebreathing bag was connected to the airways of the patient (AMIS 2001 Intensive Care Monitoring System; INNOVISION) [14]. A significant loss of PEEP was avoided by occluding the endotracheal tube with a clamp before disconnecting from the ventilator [15]. Patients were then ventilated manually from the rebreathing bag for 40 s with a rate of 20 breaths/min. Using a side port at the proximal end of the endotracheal tube, the gas concentration of insoluble sulphur hexafluoride was measured continuously during the rebreathing manoeuvre with a photo- and magneto-acoustic gas analyser.
The volume of the bag was 1.2 litres, and no significant shrinkage was observed during the rebreathing period. The estimate of EELV is based on the knowledge of the initial rebreathing bag volume and determination of the total distribution volume for the insoluble gas (sulphur hexafluoride), which, in turn, is determined by the dilution of this gas [17]. The rebreathing manoeuvre itself might have biased EELV in that either additional lung recruitment (increased tidal volume) or derecruitment (unobserved PEEP loss) was being induced. To rule out a significant influence on EELV, duplicate measurements were performed within 15 min. This was also done to verify the reproducibility of the EELV measurements.

FRC_{rel} [relative FRC (functional residual capacity)]

FRC_{pred} (predicted FRC) was calculated using the equations as described by Roca et al. [18] (body mass index was considered; with equation 1 for men and equation 2 for women).

\[
FRC (\text{ml}) = 50.244 \times H - 137.195 \times BSA + 17.649 \times A - 2318
\]  
(1)

\[
FRC (\text{ml}) = 30.780 \times H - 56.134 \times BSA - 2318
\]  
(2)

where H is height (in cm), BSA is body surface area (body weight/height^2; in kg/cm^2), and A is age (in years).

FRC_{rel} was calculated by dividing the actual EELV by FRC_{pred}. FRC_{rel} was used to determine the predictive value of EELV.

Lung volume recruitment

The difference between EELV prior to (S₀) and at the end of (Pₑ) prone positioning was defined as total lung volume recruitment. A negative value indicated a derecruitment. The absolute change in EELV was used to calculate regression between lung recruitment and changes in the Pao₂/F,O₂ ratio and Q_/Q_.

Definition of responders

Patients were defined as responders to prone positioning when their Pao₂/F,O₂ ratio had increased by at least 30 % at the end of the prone period compared with baseline values (Pₑ − S₀) [9,19,20].

Statistical analysis

Data are expressed as means ± S.D., unless stated otherwise. Initial differences between responders and non-responders were evaluated using the non-parametric Mann–Whitney test [9]. Baseline EELV was compared using analysis of covariance, adjusting for baseline covariates of V_{t,exp} (expired tidal volume) and PEEP, as these parameters might have influenced baseline EELV but were not standardized. One-way ANOVA for repeated measurements was used to determine changes over time. Linear regression was calculated by the least squares method. Predictive value of FRC_{rel} was calculated by logistic regression. The reproducibility of the EELV measurements was determined according to the suggestions by Bland and Altman [21]. In all statistical analyses, P ≤ 0.05 was considered significant.

RESULTS

A total of 13 patients were included in the study. One patient did not tolerate prone positioning as indicated by oxygen saturation decreasing immediately to 87 %. This patient was excluded from the study, leaving 12 patients to enter study analysis. Biometric and baseline respiratory characteristics are shown in Table 1.

Response to prone positioning

The mean baseline Pao₂/F,O₂ ratio was 150 ± 47 mmHg. Changes in the Pao₂/F,O₂ ratio at the end of prone positioning (Pₑ) varied from − 8 to + 254 mmHg (mean, 93 ± 81 mmHg). Eight patients had an increase in Pao₂/F,O₂ ratio by more than 30 % at Pₑ and were defined as responders (Figure 1). Baseline values of ventilatory settings, parameters of gas exchange and haemodynamics were not different among responders and non-responders (Table 2). However, EELV was significantly lower in responders (see below).

EELV

Initial EELV varied from 1100–3900 ml (mean, 2200 ± 800 ml) in the supine position. Baseline EELV might have been affected by ventilatory settings, including V_{t,exp} and PEEP, which had not been standardized. Therefore analysis of covariance, adjusting for these parameters, was used to compare baseline EELV between responders and non-responders. EELV was 1800 ± 500 ml in responders and 3000 ± 800 ml in non-responders (P = 0.02). Responders had a continuous increase in EELV, whereas EELV in non-responders remained unaffected (Figure 2). Analysis of the individual time courses revealed that, in three responders, lung recruitment occurred early and no significant increase was observed after 2 h (one responder) or 4 h (two responders) in the prone position. By contrast, in five responders, lung recruitment was prolonged, as the peak in EELV might not have been reached within the study period of 8 h. Mean EELV did not change within 1 h after being returned to the supine position, suggesting that prone positioning, in fact, induced (sustained) alveolar recruitment, rather than lung overdistension (S₀, 1800 ± 500 ml; Pₑ, 2460 ± 720 ml; and S₁ = 2380 ± 670 ml; P < 0.05 when S₁ compared with Pₑ and S₀).
Table 1  Biometric and baseline respiratory characteristics
Onset of ARDS, time (in h) between ARDS onset and beginning of measurements. "Responders/non-responders to prone positioning; $P_{\text{plat}}$, plateau pressure; EELV$_{S0}$, baseline EELV as measured in supine position; FRC$_{\text{pred}}$ calculated as described by Roca et al. [18].

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Type of ARDS</th>
<th>Onset of ARDS (h)</th>
<th>Responder/non-responder*</th>
<th>Outcome</th>
<th>$F_{\text{i}}O_{2}$ (mMhg)</th>
<th>$P_{\text{aw}}/F_{\text{i}}O_{2}$ (cm H$_2$O)</th>
<th>$P_{\text{plat}}$ (cm H$_2$O)</th>
<th>PEEP</th>
<th>$V_{e\text{-exp}}$ (ml/kg of PBW)</th>
<th>EELV$_{S0}$ (ml)</th>
<th>FRC$_{\text{pred}}$ (ml)</th>
<th>EELV$<em>{S0}$/FRC$</em>{\text{pred}}$</th>
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<td>75</td>
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<td>Survived</td>
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<td>23</td>
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<td>2000</td>
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<td>Died</td>
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<td>Non-responder</td>
<td>Survived</td>
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<td>18</td>
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<td>80</td>
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<td>Non-responder</td>
<td>Survived</td>
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<td>79</td>
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<td>Survived</td>
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<td>10</td>
<td>7.8</td>
<td>2000</td>
<td>4800</td>
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<td>Mean ± S.D.</td>
<td></td>
<td>58 ± 16</td>
<td>179 ± 6</td>
<td>82 ± 8</td>
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<td>37 ± 22</td>
<td></td>
<td>0.7 ± 0.2</td>
<td>150 ± 47</td>
<td>26 ± 4</td>
<td>14 ± 4</td>
<td>7.9 ± 0.5</td>
<td>2200 ± 800</td>
<td>4000 ± 800</td>
<td>0.58 ± 0.25</td>
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Figure 1  $P_{aO_2}/F_{iO_2}$ ratio of responders (a) and non-responders (b) at the various measurement points
$S_0$, initial supine position; $P_0$, immediately following prone positioning; $P_1$, $P_2$, $P_4$ and $P_8$, after 1, 2, 4 and 8 h in the prone position; $S_1$, following return to supine. Improvement of $P_{aO_2}/F_{iO_2}$ ratio at $P_8$ compared with the baseline value was used to define responders and non-responders.

Table 2  Baseline parameters in responders and non-responders
Values are means ± S.D. PIP, peak inspiratory pressure; PAP$_{mean}$, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; $S_vO_2$, mixed venous oxygen saturation. *Difference in EELV was determined by analysis of covariance, adjusting for baseline covariates of $V_{t,exp}$ and PEEP.

<table>
<thead>
<tr>
<th></th>
<th>Responders</th>
<th>Non-responders</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>8</td>
<td>4</td>
<td></td>
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<tr>
<td>$V_{t,exp}$ (ml/kg of PBW)</td>
<td>8.0 ± 0.4</td>
<td>7.8 ± 0.7</td>
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<td>PEEP (cm H$_2$O)</td>
<td>14 ± 4</td>
<td>14 ± 3</td>
<td>0.83</td>
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<td>PIP (cm H$_2$O)</td>
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<tr>
<td>PAP$_{mean}$ (mmHg)</td>
<td>29 ± 4</td>
<td>32 ± 7</td>
<td>0.34</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>14 ± 4</td>
<td>15 ± 3</td>
<td>0.43</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>8.3 ± 2.0</td>
<td>8.9 ± 3.3</td>
<td>0.69</td>
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<tr>
<td>$P_{aO_2}/F_{iO_2}$ ratio (mmHg)</td>
<td>153 ± 42</td>
<td>144 ± 62</td>
<td>0.78</td>
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<tr>
<td>$P_{aCO}_2$ (mmHg)</td>
<td>44 ± 3</td>
<td>47 ± 8</td>
<td>0.26</td>
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<tr>
<td>$S_vO_2$ (%)</td>
<td>71 ± 4</td>
<td>73 ± 6</td>
<td>0.50</td>
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<td>$Q_{L}/Q_{T}$ (%)</td>
<td>34.4 ± 5.1</td>
<td>38.0 ± 6.0</td>
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<tr>
<td>EELV (ml)</td>
<td>1800 ± 500</td>
<td>3000 ± 800</td>
<td>0.02*</td>
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</table>

EELV was measured by a rebreathing manoeuvre, which might have affected EELV itself. To rule out a major bias, duplicate EELV measurements were performed. The mean difference between two consecutive measurements was $-16 ± 145$ ml. A Bland and Altman plot showed that the biggest difference between the measurements occurred within the limits of agreement (bias ± two S.D.; Figure 3), indicating that (i) the rebreathing manoeuvre itself did not induce recruitment or de-recruitment, and (ii) EELV was measured with a good reproducibility.

FRC$_{rel}$
Individual FRC$_{pred}$ was determined using the equations described by Roca et al. [18], and FRC$_{rel}$ was calculated ($EELV_{S0}/FRC_{pred}$) (Table 1). FRC$_{rel}$ was significantly lower in responders compared with non-responders ($0.46 ± 0.13$ vs. $0.82 ± 0.27; P = 0.02$; Figure 4). Furthermore, a low FRC$_{rel}$ was predictive of response to prone positioning ($P = 0.05$).
Figure 3 Reproducibility of EELV measurements
Since the rebreathing procedure might have induced lung recruitment or derecruitment, EELV measurements were repeated after 15 min. A Bland and Altman plot showed a good agreement between first and second measurement, indicating that the EELV measurement did not induce major changes in lung volume and was measured with a good reproducibility. Bias (solid line) was $-16 \pm 145$ ml with a lower and upper limit of agreement (dashed lines) of $-306$ and $274$ ml respectively ($n = 56$).

Figure 4 Relative baseline EELV in responders and non-responders
Baseline EELV in responders and non-responders were referred to the FRC$_{\text{pred}}$ as described in the Materials and methods section (FRC$_{\text{rel}}$). FRC$_{\text{rel}}$ was significantly lower in responders than in non-responders ($P = 0.02$). Furthermore, a low FRC$_{\text{rel}}$ was predictive of response to prone positioning (see the Results section).

Gas exchange
Initial $Q_s/Q_t$ was $34.4 \pm 5.1\%$ in responders and $38.0 \pm 6.0\%$ in non-responders ($P = 0.30$). In responders, shunt fraction decreased significantly ($P < 0.0001$) to $23.0 \pm 3.5\%$ at $P_8$. In contrast, mean $Q_s/Q_t$ did not change in non-responders. After returning to the supine position ($S_0$), $Q_s/Q_t$ in responders remained low, consistent with sustained alveolar recruitment. Regression analysis revealed a linear correlation between the absolute increase in EELV and both the decrease in $Q_s/Q_t$ ($R^2 = 0.55$, $P = 0.01$; Figure 5a) and increase in the $P_{\text{ao}}/F_{\text{i}}O_2$ ratio ($R^2 = 0.65$, $P = 0.02$; Figure 5b).

At baseline, $P_{\text{aco}} - P_{\text{etaco}}$ amounted to $9.8 \pm 5.1$ mmHg in responders and $5.4 \pm 3.3$ mmHg in non-responders ($P = 0.15$). $P_{\text{aco}} - P_{\text{etaco}}$ decreased significantly in responders ($P = 0.0006$), whereas it remained unchanged in non-responders ($P = 0.42$). $P_{\text{etaco}}$ might be influenced by changes in CO and minute ventilation; however, both parameters did not change in our study (results not shown). The decrease in $P_{\text{aco}} - P_{\text{etaco}}$ correlated with lung recruitment (results not shown).

DISCUSSION
The present study demonstrates that the time course of lung recruitment in ARDS patients subjected to prone positioning is dependent on the individual. Although in some patients recruitment peaked as early as 2–4 h, it was not completed until 8 h or more in others. This might indicate that alveolar recruitment should be acknowledged as an independent guide in the adjustment of the duration of prone positioning for an individual. Finally, a low FRC$_{\text{rel}}$ might be indicative of the response to prone positioning.

Douglas and co-workers [8] were the first to propose that the improvement in gas exchange during prone positioning might be caused by an increase in FRC. They concluded that prone positioning might have similar effects as the application of PEEP, but not bearing
the risks of barotrauma or compromised CO. Prone positioning was shown to increase FRC in healthy anaesthetized adults [18,22]; however, data on the effect of prone positioning on FRC in injured lungs are controversial. In some animal models, FRC did not change during prone positioning [23], whereas Martynowicz and co-workers [24] found an increase in FRC when oleic-acid-injured lungs from dogs were placed in the prone position. Pelosi et al. [10,25] evaluated the change of EELV in patients with ARDS during prone ventilation. Without separating responders from non-responders, these workers observed a significant increase in EELV [25]. Reasons for these obvious discrepancies among studies include variability in the experimental design (e.g. use of muscle relaxation, abdominal support etc.) and selection of patients (ARDS compared with non-ARDS patients; adults compared with children; inclusion of patients with chronic obstructive pulmonary disease etc.). Most importantly, the observed time period differs significantly among the different studies. As demonstrated in the present study, increases in EELV might be delayed and the time course is specific for each individual. Measuring EELV as early as 1 or 2 h in the prone position might fail to detect late EELV changes [10,26]. Separating responders from non-responders might also reveal differences in EELV changes which otherwise might go unrecognized. In the present study, only responders exhibited a significant increase in EELV, whereas lung volume did not change in non-responders. The time course of recruitment in responders was dependent on each individual as, in some patients, almost complete recruitment was observed as early as 2–4 h after turning to the prone position. In contrast, other responders did not complete recruitment within the 8-h period of prone positioning. It remains speculation as to whether the increase in arterial oxygenation in early responders continued when these patients had been returned to the supine position earlier than after 8 h. However, it appears reasonable to acknowledge alveolar recruitment as an additional parameter to estimate success and ‘dose’ of prone positioning.

Non-responders in the present study had rather high EELV levels at baseline and during prone ventilation, particularly when compared with the findings of Pelosi et al. [25]. Therefore we speculate that, in the present study, higher PEEP levels or tidal volumes may have induced lung overdistension in these patients. However, the difference between Paco₂ and Petco₂ was not increased in non-responders, making dead space ventilation and lung overdistension rather unlikely. The significantly lower body weight of the patients in the study by Pelosi et al. [25] (83 ± 8 compared with 68 ± 13 kg; P = 0.002) might be one possible explanation for the differences in baseline EELV.

The increase in EELV in responding patients may reflect re-opening of previously collapsed alveoli [25–28], re-aeration of oedema-filled alveoli [24,29,30] and distension (or overdistension) of already ventilated lung regions. In the present study, we have shown that the rise in EELV was accompanied by a decrease in both Qs/Ql and the difference between Paco₂ and Petco₂, suggesting that re-opening of previously collapsed alveoli or re-aeration of oedema-filled lung spaces were major contributors to the rise in EELV. Furthermore, we have demonstrated that EELV did not decrease within the first hour after returning to the supine position, indicating that the improvement in gas exchange was caused by a sustained recruitment, rather than by changes only in the ventilation–perfusion distribution.

Different mechanisms are hypothesized to facilitate alveolar recruitment during prone positioning. In the prone position, the pleural pressure gradient is smaller than in the supine position and the heart is resting mostly on the sternum, thus exerting less pressure on pleura and lung [31]. In addition, the cephalad pressure of the diaphragm is reduced in the prone position. Hence prone positioning reduces the compression of the lung and enforces re-opening of collapsed areas.

Prone positioning is known to improve oxygenation even without affecting EELV [10]. Therefore changes in EELV might not be a prerequisite for the beneficial effects observed during prone positioning, and the causality between both parameters was not tested in the present study. In addition to alveolar recruitment, changes in ventilation/perfusion ratio might be an independent key factor for the improvement of gas exchange during prone positioning. Pulmonary perfusion has been demonstrated to predominate in dorsal and basal lung regions [32,33]. More importantly, the effect of gravity on the distribution seems limited [34], thus positioning might not alter pulmonary perfusion. In contrast, distribution of ventilation changes significantly with position. In the supine position, ventilation is decreased in dependent regions. This vertical gradient seems to be abolished in the prone position [35], resulting in a more uniform ventilation. Taken together, ventilation–perfusion distribution is more homogeneous in the prone position and regional perfusion matches ventilation better than in supine [36]. Thus prone positioning reduces shunt perfusion in the setting of lung injury. Positive-pressure ventilation amplifies this effect during prone position by directing the pulmonary blood flow to the more ventilated (non-dependent) regions [37]. Rearrangement of the chest wall compliance, allowing the dorsal rib cage to move, might also contribute to the redistribution of ventilation [10].

Since there are risks involved in prone positioning, e.g. pressure sores, accidental displacement of tracheal tube or increased need for sedation and muscle relaxation, identifying responders early would be useful. Morphological characteristics from CT scans have failed to predict the response to prone positioning [38]. The
origin of ARDS (pulmonary or extrapulmonary) might influence at least the time course of improvements in oxygenation [39]. Lee et al. [20] found a higher initial intrapulmonary shunt in responders (39.8 ± 1.5 compared with 35.3 ± 1.1 %). In the present study, the difference in the shunt had a similar trend, but failed to be statistically significant (38.0 ± 6.0 compared with 34.4 ± 5.1 %).

Ranieri et al. [40] found that the recruited volume correlated negatively with plateau pressure on ZEEP (zero end-expiratory pressure). In the present study, plateau pressure did not differ between responders and non-responders. The only significant difference between responders and non-responders to prone therapy was a lower baseline EELV in responders. Furthermore, a low FRC_{rel} in our patients was predictive of their response to prone positioning.

Methodological considerations and limitations

Patients in the present study were heterogeneous with respect to their ventilatory settings. Although tidal volumes were standardized, \( F_O_2 \) and PEEP levels were set by a clinician. This might have led to higher \( P_a_O_2 \) levels than originally suggested by the ARDS Network. However, ventilatory settings were not changed during the study period, hence measuring and comparing changes in lung recruitment and gas exchange over time appear justified.

Patients in the present study were kept in the prone position for 8 h according to our study protocol. However, lung recruitment in some responders might not have been completed at this time. These patients might have benefited from a longer period in the prone position.

EELV was determined by an inert gas rebreathing method which measured the dilution of insoluble sulphur hexafluoride. General problems and limitations of this method have been discussed in detail previously [41] and might also apply to the system used in the present study. Patients were manually ventilated with a high tidal volume. This might have led to an additional recruitment, due to the rebreathing manoeuvres. In contrast, bag shrinkage due to the gas withdrawal by the analysing system might have counteracted this. An initial loss of PEEP was avoided by clamping the endotracheal tube before disconnecting it from the ventilator at end-expiration, but the PEEP level might not have been maintained during the rebreathing manoeuvre. However, duplicate EELV measurements showed no difference between first and second measurement, indicating that the rebreathing procedure did not induce major changes in EELV. Most patients received a higher \( F_O_2 \) during the rebreathing period. Absorption atelectasis might have led to an underestimation of EELV; however, this phenomenon might be negligible given the rather short observation period.

In conclusion, our data demonstrate the individuality of the time course of alveolar recruitment in responders to prone positioning. In some patients, complete recruitment can be observed between 2 and 4 h, whereas, in others, it might take more than 8 h to complete. The bedside measurement of EELV might be useful to individually adjust the duration of prone positioning. Finally, a low baseline EELV was shown to be predictive of the response to prone positioning.

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