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Jérôme Aboab
Bjorn Jonson
Achille Kouatchet
Solenne Taille
Lisbet Niklason
Laurent Brochard

Effect of inspired oxygen fraction on alveolar derecruitment in acute respiratory distress syndrome

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J. Aboab · A. Kouatchet · S. Taille · L. Brochard (✉)
Service de Réanimation Médicale de l'hôpital Henri Mondor,
AP-HP, 51, av. du Maréchal de Lattre de Tassigny, 94010 Créteil, France
e-mail: laurent.brochard@hmn.aphp.fr
Tel.: +33-1-49812389
Fax: +33-1-42079943

B. Jonson · L. Niklason
University Hospital, Department of Clinical Physiology,
Lund, Sweden

L. Brochard
Faculté de Médecine Paris 12, INSERM Unit 651,
Créteil, France

Abstract *Objective:* High fractions of inspired oxygen (FIO_2) used in acute lung injury (ALI) may promote resorption atelectasis. The impact of derecruitment related to high FIO_2 in ALI is debated. We evaluated derecruitment with 100% vs. 60% FIO_2 at two levels of positive end-expiratory pressure (PEEP). *Patients:* Fourteen consecutive patients with ALI were studied. *Interventions:* Recruited volume at two PEEP levels was computed from two pressure-volume curves, recorded from PEEP and from zero end-expiratory pressure, using the sinusoidal flow modulation method. PEEP-induced recruitment was measured during prolonged expiration as the difference between the two curves at a given pressure. PaO_2/FIO_2 was also measured. PEEP was 5 ± 1 or 14 ± 3 cmH_2O and FIO_2 was 60% or 100%, yielding four combinations. We looked for differences between the beginning and end of a 30-min period with each combination. *Measurement and results:* With low PEEP and 100% FIO_2, recruited volume decreased significantly from 68 ± 53 to 39 ± 43 ml and PaO_2/FIO_2 from 196 ± 104 to 153 ± 83 mmHg. With the three other combinations (low PEEP and 60% FIO_2 or high PEEP and 60% or 100% FIO_2) none of the parameters decreased significantly. *Conclusion:* In mechanically ventilated patients with ALI the breathing of pure oxygen leads to derecruitment, which is prevented by high PEEP.

Keywords Acute respiratory distress syndrome · Acute lung injury · Atelectasis · Oxygen inhalation · Oxygen toxicity

Introduction

In 1975 Dantzker [1] described a mathematical model for the increased occurrence of resorption atelectasis at high fractions of inspired oxygen (FIO_2) in lung areas characterized by a low ventilation-perfusion (V_A/Q) ratio. The model accurately predicted the effects of low vs. high FIO_2 during mechanical ventilation for surgery in patients who were free of pulmonary disease [2]. In acute respiratory distress syndrome (ARDS) alveolar collapse or flooding leads to arterial hypoxemia [3], probably with areas of low V_A/Q ratio. At high FIO_2 such areas are at high risk for resorption atelectasis. The impact of this phenomenon in ARDS remains debated. Some studies have found increased shunting when patients breathe 100% O_2 [4, 5] while others have shown stable or decreased

shunting with increasing FIO_2 [6]. Factors that may explain these discrepancies include heterogeneity among patients and differences in measurement techniques, study design, and ventilator settings.

The alveolar volume recruited by a specific level of positive end-expiratory pressure (PEEP) can be determined from elastic pressure-volume (P-V) curves recorded from PEEP and from zero end-expiratory pressure (ZEEP) [7, 8]. In ARDS alveolar recruitment improves oxygenation [9] and may decrease lung inflammation [10], the duration of mechanical ventilation, and mortality [11]. FIO_2 levels higher than those required to maintain adequate saturation are often used to prevent episodes of desaturation. However, high FIO_2 may promote atelectasis.

This study examined whether ventilation with 100% oxygen induces derecruitment in patients with ARDS and, if so, to determine whether high PEEP prevents derecruitment. This study as been presented previously in abstract form [12].

Methods

The Ethics Committee of the Henri Mondor University Hospital approved the study. Informed consent was obtained from each patient's next of kin. We included 14 consecutive patients who met criteria for acute lung injury (ALI) and ARDS [13] and who were receiving mechanical ventilation. Table 1 reports the main patient characteristics. Exclusion criteria were age under 18 years, chest tube, contraindication to sedation or paralysis, hemodynamic instability (mean arterial pressure below 60 mmHg), intracranial disease, and PaO_2/FIO_2 ratio less than 75 mmHg. All patients received volume-controlled mechanical ventilation (ServoVentilator 900C; Siemens-Elema, Solna, Sweden), in the supine position. Sedatives and neuromuscular blockers were given as a continuous infusion. If they did not have neuromuscular blockage for their current treatment, continuous infusion was introduced for making the measurements. Endotracheal suctioning was performed before the measurements if needed but was not repeated during the measurements. All patients had an arterial line for blood gas sampling and blood pressure monitoring. Blood gases were measured using a GEM Premier 3000 analyzer (Instrumentation Laboratory, Lexington, Mass., USA). In 3 of the 14 patients pulmonary compliance was too low and plateau pressure too high to allow use of the high PEEP level, and in one patient high PEEP was associated with endotracheal tube leakage. This left ten patients for whom data were obtained at the high PEEP level.

Measurement procedure

The patients were ventilated in volume-controlled mode with a tidal volume of about 6 ml/kg body weight. PEEP was either about 5 cmH_2O or about 15 cmH_2O, as detailed in Table 2. In each patient the low PEEP level was titrated based on saturation and the high level based on the plateau pressure. When transcutaneous oxygen saturation fell below 88% at 5 cmH_2O PEEP and 60% FIO_2, PEEP was increased to raise saturation. When the plateau pressure was greater than 35 cmH_2O with 15 cmH_2O PEEP, PEEP was decreased slightly. Four combinations were tested in random order: low PEEP (about 5 cmH_2O) with 100% FIO_2, high PEEP (about 15 cmH_2O) with 100% FIO_2, low PEEP with 60% FIO_2, and high PEEP with 100% FIO_2. To ensure standardization each period started with a recruitment maneuver consisting in two insufflations at 40 cmH_2O over 15 s separated by expiration at 15 cmH_2O. P-V curves and arterial blood gas levels were studied at the beginning and at the end of each 30-min period (Fig. 1).

Table 1 Characteristics of the 14 study patients with acute lung injury/acute respiratory distress syndrome (*ALI* acute lung injury, *ARDS* acute respiratory disease syndrome)

No.	Age (years)	SAPS II	Cause of ALI/ARDS	Underlying disease	Disease duration (days)
1	46	92	Sepsis	Lymphoma	6
2	56	27	Pneumonia	Epilepsy	1
3	44	28	Pneumonia	Meningitis	5
4	57	58	Sepsis	Pemphigus	3
5	68	73	Pneumonia	Thrombotic microangiopathy	2
6	58	64	Heat stroke	Alcoholism	0
7	57	58	Pneumonia	Lymphoma	2
8	54	43	Pneumonia	Alcoholism	1
9	48	42	Pneumonia	Acute lymphoid leukemia	7
10	66	81	Sepsis	Aortic valve replacement	5
11	78	69	Pneumonia	Chronic respiratory insufficiency	0
12	78	95	Sepsis	Prostate adenoma	3
13	75	73	Pneumonia	Obliterating arterial disease	2
14	37	70	Sepsis	Acute lymphoid leukemia	3
Mean ± SD	59 ± 13	62 ± 21	–	–	3 ± 2

Elastic pressure-volume curves

Elastic P-V curves were recorded and analyzed using the sinusoidal low-flow inflation technique [8, 14]. Curves starting at PEEP and at ZEEP were obtained as previously described [8] and recently improved by Bitzén et al. [15]. To avoid alveolar recruitment during recording of the first curve, i.e., the curve from PEEP, recording was limited to the current tidal volume and to the plateau pressure of ordinary breaths. The second curve was recorded from ZEEP to 45 cmH_2O. Total PEEP (PEEPtot) was recorded during an end-expiratory occlusion, while recording the first P-V curve for each test period (Fig. 1). Intrinsic positive end-expiratory pressure (PEEPi) was computed as the difference between PEEPtot and the set PEEP.

During the 6 s prolonged expiration at ZEEP an additional volume was expired in comparison to the ordinary expired volume. This additional volume (ΔV_{EXP}) represents PEEP-induced increase in end-expiratory lung volume [16] and was used to place the PEEP and ZEEP curves on the same volume axis (Fig. 2). The zero on the common volume axis was the volume reached during the prolonged expiration at ZEEP. P-V curves were analyzed as previously described [8, 9, 15, 17, 18, 19]. The volume recruited by PEEP (V_{rec}) was defined as the difference between the volume measured on the curve starting from PEEP and the volume measured at the same pressure on the curve starting from ZEEP (Fig. 2). The alveolo-arterial gradient of oxygen partial pressure ($AaPO_2$) was calculated in mmHg using

Table 2 Ventilatory conditions (*Vt* tidal volume, *RR* respiratory rate, *set PEEP-L* low set positive end-expiratory pressure, *PEEPtot-L* measured total positive end-expiratory pressure at low set PEEP level, *Pplat-L* plateau pressure at low set PEEP, *set PEEP-H* high set positive end-expiratory pressure, *PEEPtot-H* measured total positive end-expiratory pressure at high set PEEP, *Pplat-H* plateau pressure at high set PEEP, *na* not available)

No.	Vt (ml/kg)	RR (b/min)	Set PEEP-L (cmH_2O)	PEEPtot-L (cmH_2O)	Pplat-L (cmH_2O)	Set PEEP-H (cmH_2O)	PEEPtot-H (cmH_2O)	Pplat-H (cmH_2O)
1	6.4	33	5	9	34	na	na	na
2	5.4	30	6	9	19	15	17	26
3	5.4	25	5	7	18	na	na	na
4	5.7	20	5	14	27	16	18	30
5	5.0	21	4	7	17	16	17	28
6	6.3	22	5	10	20	16	17	27
7	6.1	25	3	5	34	na	na	na
8	6.0	24	5	5	15	10	11	22
9	6.9	29	9	10	35	13	16	38
10	5.7	20	4	5	28	10	11	34
11	5.3	25	5	8	21	15	17	28
12	6.3	32	5	7	28	10	12	35
13	5.7	25	5	6	16	15	16	29
14	5.8	23	5	11	31	na	na	na
Mean ± SD	6 ± 1	25 ± 4	5 ± 1	8 ± 3	24 ± 7	14 ± 3	15 ± 3	31 ± 6

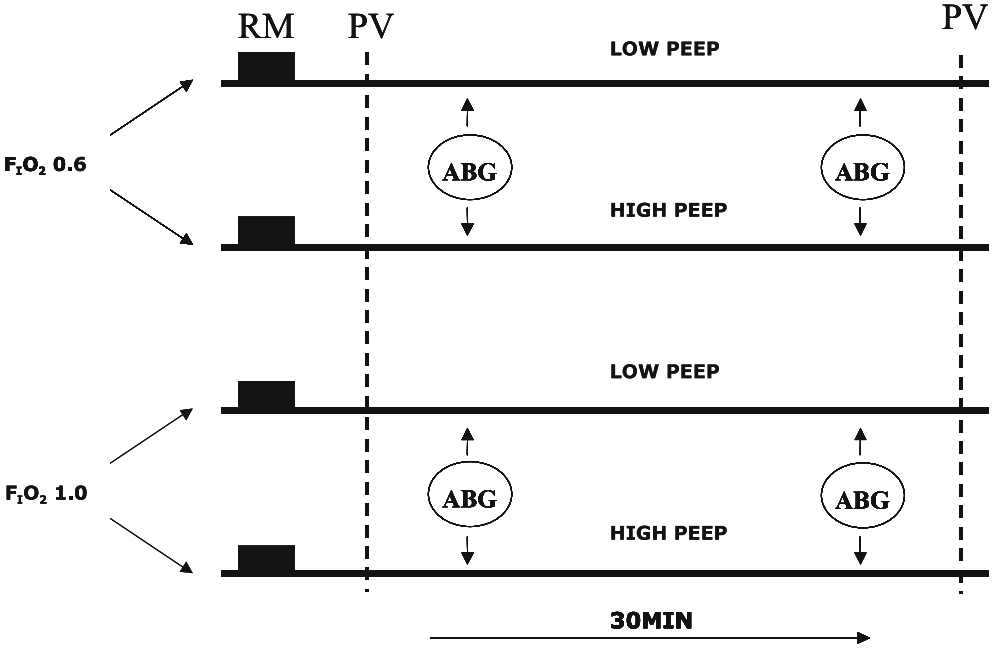

Fig. 1 Diagram of the study design. Patients were studied under four conditions (two PEEP levels, 5 and 15 cmH_2O, and two FIO_2 values, 60% and 100%, in random order. Pressure-volume (*P-V*) curves were obtained and arterial blood gases (*ABG*) measured. Recruitment maneuvers (*RM*) were used to standardize the volume before each sequence

the formula: $FIO_2 \times 100 \times$ (Pb-47)-$PaCO_2$/R-PaO_2, with $R = 0.8$.

Statistical analysis

Results are expressed as means ± SD and median when indicated. Comparisons of the four FIO_2/PEEP combinations were performed using Friedman analysis of variance for repeated measurements of nonparametric data. When the Friedman test was significant ($p < 0.05$), variables at the beginning and end of each period were compared using the Wilcoxon test for paired samples. Because this comparison indicated whether derecruitment or decreased oxygenation occurred during the period, it was the most relevant to our study objectives. Differences with p values smaller than 0.05 were considered statistically significant. Correlations were evaluated using Spearman's ρ correlation test.

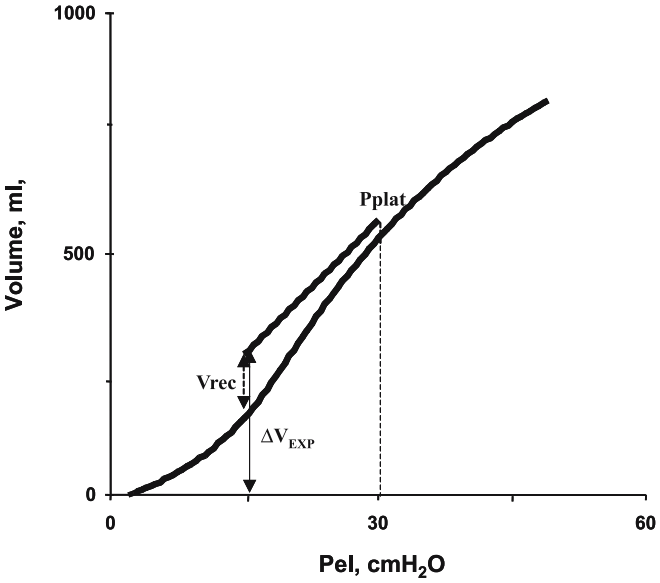

Fig. 2 Measurement of recruited volume (V_{rec}) and change in end-expiratory lung volume (ΔV_{EXP}) using the pressure-volume curve (P-V) technique. P-V curve from PEEP 15 cmH_2O, recorded over the range of the previous tidal volume and curve from ZEEP to about 45 cmH_2O, and passive spirometry from PEEP to ZEEP to measure the PEEP-induced ΔV_{EXP}. Recruited volume (V_{rec}) is the volume difference between the two curves at a given pressure

Results

Tables 3 and 4 show the main results. From the start to the end of 100% FIO_2/low PEEP, V_{rec}, ΔV_{EXP}, and PaO_2/FIO_2 decreased significantly and $AaPO_2$ increased significantly. None of the other three combinations induced similar changes. With 60% FIO_2/high PEEP, PaO_2 increased slightly but significantly. $PaCO_2$ and pH were similar at the start and end of the four study periods (eight measurements). Figure 3 reports V_{rec} variations at low PEEP and Fig. 4 PaO_2/FIO_2 variations at low PEEP. Detailed gas exchange data are reported in Table 3. The lower inflexion point of the P-V curve from ZEEP tended to decrease with 100% FIO_2/low PEEP, from 11.5 cmH_2O at the beginning to 8.2 cmH_2O at the end of the period. No differences in linear compliance were noted with any of the FIO_2/PEEP combinations (Table 3). In the four patients with no measurements at high PEEP, a high FIO_2 had little effect on oxygenation. Therefore excluding them from the analysis did not change the results, except that derecruitment at 100% FIO_2/low PEEP was only a trend ($p = 0.06$).

Correlations

We found a trend toward a correlation linking the V_{rec} difference between the start and end of the 100% FIO_2/low PEEP period to PEEPi at low PEEP, which reflects lung heterogeneity ($\rho = 0.52$, $p = 0.06$) and a significant cor-

Table 3 Pulmonary mechanics with different combinations of PEEP and FIO_2; mean ±SD (median), p values refer to comparisons between the start and end of each period (V_{rec} recruited volume, ΔV_{EXP} variation in expiratory volume after prolonged expiration, *Plip* lower inflexion point on the pressure-volume curve recorded from ZEEP, *Clin* compliance over the linear segment of this pressure-volume curve, *PEEP* positive end-expiratory pressure)

	V_{rec} (ml)	ΔV_{EXP} (ml)	Plip (cmH_2O)	Clin (ml/cmH_2O)
Low PEEP				
$FIO_2 = 1.0$	$p = 0.02$	$p = 0.03$		
Start	68 ± 53 (57)	246 ± 144 (267)	11 ± 4 (12)	44 ± 20 (47)
End	39 ± 43 (26)	206 ± 111 (235)	8 ± 4 (7)	42 ± 19 (40)
$FIO_2 = 0.6$	$p = 0.6$	$p = 0.2$		
Start	54 ± 37 (47)	208 ± 121 (267)	11 ± 5 (11)	46 ± 25 (42)
End	57 ± 71 (39)	193 ± 104 (225)	10 ± 5 (10)	44 ± 26 (37)
High PEEP				
$FIO_2 = 1.0$	$p = 0.9$	$p = 0.16$		
Start	297 ± 148 (311)	687 ± 311 (623)	13 ± 5 (13)	56 ± 25 (55)
End	299 ± 197 (234)	769 ± 389 (648)	12 ± 6 (12)	57 ± 22 (55)
$FIO_2 = 0.6$	$p = 0.6$	$p = 0.11$		
Start	299 ± 182 (277)	674 ± 296 (626)	10 ± 5 (12)	53 ± 24 (47)
End	292 ± 195 (247)	754 ± 374 (632)	10 ± 4 (11)	56 ± 25 (51)

Table 4 Gas exchange with four combinations of PEEP and FIO_2; mean ±SD (median), *p* values refer to comparisons between the start and end of each period (Wilcoxon test) (*AaPO*$_2$ alveolo-arterial difference in PO_2, *PEEP* positive end-expiratory pressure

	PaO_2/FIO_2 (mmHg)	$AaPO_2$ (mmHg)
Low PEEP		
$FIO_2 = 1.0$	$p = 0.03$	$p = 0.001$
Start	196 ± 104 (171)	455 ± 104 (482)
End	153 ± 83 (110)	558 ± 83 (602)
$FIO_2 = 0.6$	$p = 0.2$	$p = 0.006$
Start	144 ± 78 (115)	280 ± 45 (292)
End	138 ± 70 (107)	287 ± 40 (295)
High PEEP		
$FIO_2 = 1.0$	$p = 0.8$	$p = 0.5$
Start	233 ± 101 (223)	418 ± 96 (431)
End	238 ± 95 (223)	411 ± 87 (434)
$FIO_2 = 0.6$	$p = 0.05$	$p = 0.06$
Start	166 ± 59 (158)	266 ± 34 (276)
End	188 ± 73 (205)	255 ± 41 (257)

relation with total PEEP ($\rho = 0.63$, $p = 0.02$). None of the other correlations between the start and end of the 100% FIO_2/low PEEP period was significant (ΔV_{rec} vs. $\Delta PaO_2/FIO_2$, $p = 0.83$; $\Delta PaO_2/FIO_2$ vs. ΔV_{EXP}, $p = 0.2$; and ΔV_{rec} vs. ΔV_{EXP}, $p = 0.78$).

Discussion

During 30 min at 100% FIO_2/low PEEP, V_{rec} and PaO_2/FIO_2 decreased significantly, indicating derecruitment. Neither variable decreased at 60% FIO_2/low PEEP or at 100% FIO_2 with high or low PEEP, showing that derecruitment related to high FIO_2 was prevented by high PEEP in patients with ARDS.

Gas resorption atelectasis was documented during anesthesia in patients who had no lung disease [2, 20]. PEEP limited the occurrence of atelectasis [21, 22]. Shunting calculated from arterial and central venous blood gases increased at 100% FIO_2 in patients with ALI [5], possibly as a result of alveolar collapse or decreased hypoxic vasoconstriction in lung compartments having a low V_A/Q ratio. Functional residual capacity fell at high FIO_2, indicating that resorption atelectasis occurred in lung zones with a low V_A/Q ratio [5]. Of two studies using the multiple inert gas elimination technique [23] one [4] but not the other [6] showed that intrapulmonary shunting increased at 100% FIO_2, the mechanism being collapse of alveolar units characterized by low V_A/Q ratios. The discrepancy between these two studies is not easily explained, as the data on tidal volume and postinspiratory plateau pressures are incomplete. Tidal volume was 12 ml/kg body weight in one study [6] and

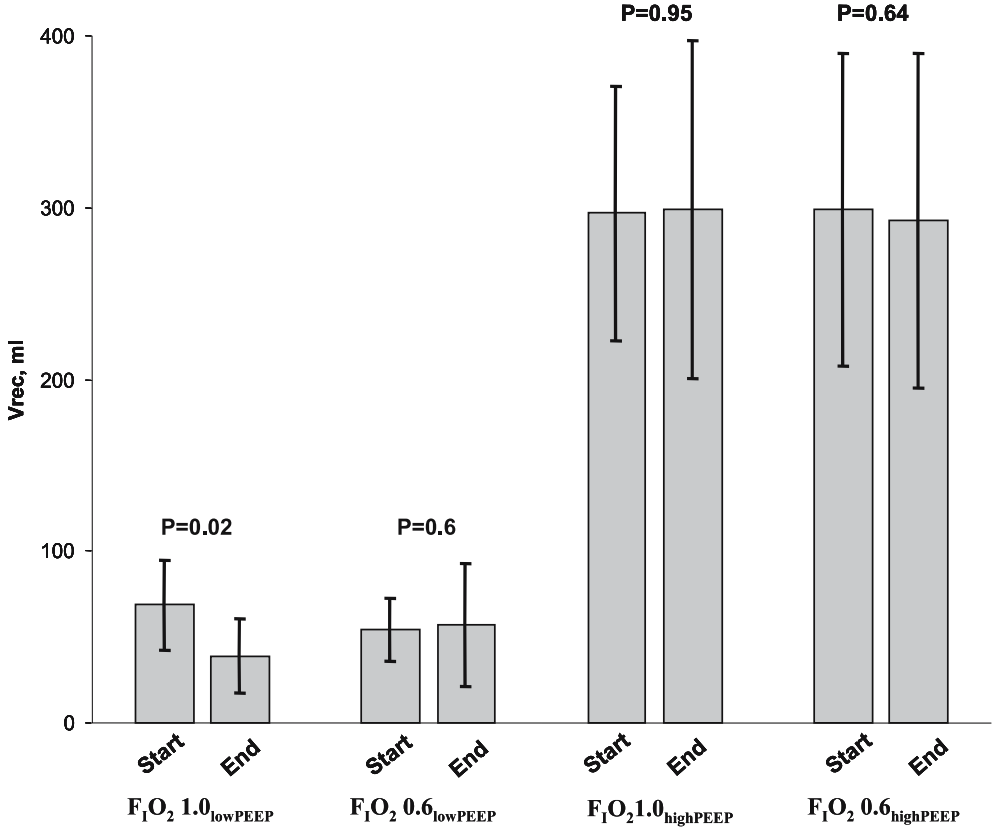

Fig. 3 Mean (±SD) values of V_{rec} as a function of PEEP and FIO_2. V_{rec} decreased significantly with low PEEP and 100% FIO_2

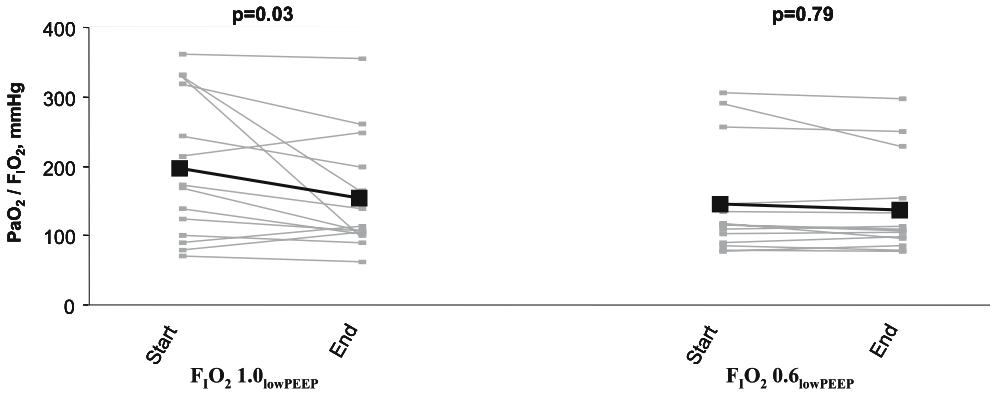

Fig. 4 Individual and mean (*bold*) values of PaO_2/FIO_2 as a function of FIO_2 level at low PEEP. The PaO_2/FIO_2 ratio decreased significantly at 100% FIO_2. No differences occurred at 60% FIO_2

was apparently smaller in the other [4]. This may partly explain the difference in the results, as a higher tidal volume enhances lung recruitment [17]. Neither study used a tidal volume of about 6 ml/kg, which was the value selected for our study, in line with the results of recent trials in patients with ARDS [24]. Discrepancies among earlier results, and the need to investigate a lower tidal volume, warranted our study. Our results indicate that lung collapse caused by a high FIO_2 can be prevented by a sufficiently high PEEP level, even when tidal volume is low. To allow PaO_2 equilibration, we waited at least 10 min after each FIO_2 change, in keeping with earlier data [25]. Equilibration of some of the PEEP effects requires about 20 min [19, 26, 27]. Therefore we considered that 30 min was sufficient for each test period.

Some of our patients had a high level of PEEPi related to high airway resistance and/or a high plateau pressure related to low respiratory system compliance. Both a high total PEEP and a high plateau pressure contribute to maintain recruitment [9, 17, 19]. These factors may have attenuated the effects of low PEEP with 100% FIO_2. On the other hand, the low tidal volume may have facilitated derecruitment [9, 17]. V_{rec} and PaO_2/FIO_2 were significantly higher at high PEEP (approx. 15 cmH_2O) than at low PEEP (approx. 5 cmH_2O), indicating a significant potential for recruitment in the study patients, and therefore a potential for derecruitment caused by denitrogenation and gas resorption atelectasis. With 100% FIO_2/low PEEP, a derecruitment was correlated almost significantly with measured PEEPi and significantly with PEEPtot. High PEEPi may indicate greater lung heterogeneity and therefore a greater number of areas with a low V_A/Q ratio. Also, PaO_2/FIO_2 values differed at the start of the 60% and 100% FIO_2 periods, as expected. This difference is ascribable to several factors including the shape of the oxyhemoglobin dissociation curve and the size of the hypoventilated areas [4, 6].

The PaO_2/FIO_2 decrease at 100% FIO_2 may be due to vasodilation within areas characterized by a low V_A/Q ratio. Therefore a more direct exploration of alveolar collapse based on V_{rec} measurement was essential. Previous studies used V_{rec} to evaluate recruitment using the P-V technique [8, 17, 18, 28]. In modificating this technique for our study, the first P-V curve recorded from the set PEEP level is limited to the tidal volume range. This was important to keep recruitment unchanged until recording of the second P-V curve, from ZEEP. V_{rec} and ΔV_{exp} decreased at 100% FIO_2, confirming that resorption atelectasis occurred at low tidal volume ventilation and low PEEP and explaining the PaO_2/FIO_2 decrease during the 100% FIO_2/low PEEP period. In line with our results, Villagra et al. [29] found that recruitment maneuvers in patients with ARDS were more effective at high FIO_2 values, suggesting that gas composition influences the effect of recruitment maneuvers on oxygenation.

At high PEEP high FIO_2 did not cause derecruitment as assessed by V_{rec} or PaO_2/FIO_2. Recommendations for ventilator settings in patients with ARDS are aimed at keeping the lung open without causing overdistension. In practice PEEP combined with tidal volume excursions is used to reopen collapsed lung areas, and a low tidal volume is used to avoid overdistension [9, 16]. The optimal PEEP level is debated [30]. When the highest possible PEEP is combined with low tidal volume, the FIO_2 level may have little impact on the occurrence of gas resorption atelectasis in patients with ALI/ARDS. In contrast, when a low PEEP level is preferred, careful FIO_2 setting is important to maintain adequate oxygenation without unduly increasing the risk for gas resorption atelectasis. Accordingly, high FIO_2 cannot be viewed as a safety measure.

This is the first study to investigate resorption atelectasis in ALI/ARDS using the P-V curve technique and gas exchange measurement. Derecruitment occurred at high FIO_2 and low PEEP. Our findings suggest explanations to discrepancies in the results of earlier studies. The effect of high FIO_2 was modest, dependent on the extent of hypoventilated areas, and dependent on ventilatory settings, notably the PEEP level.

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