

Response to Recruitment Maneuver Influences Net Alveolar Fluid Clearance in Acute Respiratory Distress Syndrome

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Background: Alveolar fluid clearance is impaired in the majority of patients with acute respiratory distress syndrome (ARDS). Experimental studies have shown that a reduction of tidal volume increases alveolar fluid clearance. This study was aimed at assessing the impact of the response to a recruitment maneuver (RM) on net alveolar fluid clearance.

Methods: In 15 patients with ARDS, pulmonary edema fluid and plasma protein concentrations were measured before and after an RM, consisting of a positive end-expiratory pressure maintained 10 cm H₂O above the lower inflection point of the pressure–volume curve during 15 min. Cardiorespiratory parameters were measured at baseline (before RM) and 1 and 4 h later. RM-induced lung recruitment was measured using the pressure–volume curve method. Net alveolar fluid clearance was measured by measuring changes in bronchoalveolar protein concentrations before and after RM.

Results: In responders, defined as patients showing an RM-induced increase in arterial oxygen tension of 20% of baseline value or greater, net alveolar fluid clearance ($19 \pm 13\%/h$) and significant alveolar recruitment (113 ± 101 ml) were observed. In nonresponders, neither net alveolar fluid clearance ($-24 \pm 11\%/h$) nor alveolar recruitment was measured. Responders and nonresponders differed only in terms of lung morphology: Responders had a diffuse loss of aeration, whereas nonresponders had a focal loss of aeration, predominating in the lower lobes.

Conclusion: In the absence of alveolar recruitment and improvement in arterial oxygenation, RM decreases the rate of alveolar fluid clearance, suggesting that lung overinflation may be associated with epithelial dysfunction.

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RECENT studies have reported improved outcome for patients with acute respiratory distress syndrome (ARDS) ventilated with tidal volumes of 6 ml/kg.^{1,2} A low tidal volume, by reducing ventilator-induced lung overinflation, may decrease the lung and systemic inflammatory reaction.³ ARDS is characterized by a protein-rich alveolar edema,⁴ the amount of which depends in part on the alveolar fluid clearance resulting from Na/K adenosine triphosphatase-dependent pumps.⁵ Classically, alveolar fluid clearance is considered as maintained in cardiogenic pulmonary edema, impaired in ARDS,⁶ and not affected by mechanical ventilation.⁷ A recent animal study, however, has demonstrated that a reduction of tidal volume improves alveolar fluid clearance.⁸ The authors hypothesized that the reduced injury of the alveolar epithelium resulting from the low tidal volume decreased lung inflammatory reaction, thereby improving alveolar fluid clearance. Protective ventilation may add to the reduction of tidal volume a recruitment maneuver (RM). An RM improves arterial oxygenation and respiratory mechanics by increasing the amount of gas in nonaerated lung areas.⁹ By providing alveolar recruitment, RM may reduce lung stretch and the inflammatory reaction caused by mechanical ventilation¹⁰ and therefore increase alveolar fluid clearance. As recently demonstrated,¹¹⁻¹³ it may also induce overinflation, which, in turn, could damage the alveolar epithelium and impair net alveolar fluid clearance.

The purpose of this study was to assess whether the response to an RM performed in ARDS patients on protective mechanical ventilation had an impact on net alveolar fluid clearance.

Materials and Methods

The study was approved by the institutional review board of Clermont-Ferrand, France, and informed consent was obtained from the patients' next of kin.

Study Population

We studied 15 consecutive, unselected patients who met the ARDS criteria of the American European Consensus Conference.¹⁴ Exclusion criteria were refusal of consent, age younger than 18 yr, chronic respiratory insufficiency (chronic obstructive pulmonary disease, asthma, restrictive respiratory insufficiency), intracranial hypertension, bronchopleural fistula, and the persistence of unstable hemodynamics despite appropriate

support therapy. Patients were orally intubated, sedated with sufentanil (25 $\mu\text{g}/\text{h}$) and midazolam (5 mg/h), paralyzed with cisatracurium (15 mg/h), and ventilated with an Evita 2 Dura ventilator (Dräger, Lubeck, Germany). All patients were equipped with a radial or femoral arterial catheter (Arrow Inc., Erding, Germany). pH, arterial oxygen tension (Pao_2), and arterial carbon dioxide tension (Paco_2) were measured using an IL BGE blood gas analyzer (Instrumentation Laboratory, Paris, France). The patients were on volume-controlled mechanical ventilation with a tidal volume of 6 ml/kg and the highest respiratory rate allowing maintenance of Paco_2 of 46 mmHg or less without intrinsic positive end-expiratory pressure (PEEP).¹⁵ The fraction of inspired oxygen (Fio_2) was set at 1, inspiratory-to-expiratory ratio was set at 1:2, and PEEP was set at 3 $\text{cm H}_2\text{O}$ above the lower inflection point of the pressure-volume (P-V) curve¹⁶ or at 10 $\text{cm H}_2\text{O}$ in the absence of a lower inflection point.

Measurement of Alveolar Fluid Clearance

A 14-French, 51-cm catheter (PharmaPlast, Maersk Medical, Denmark) was passed through the endotracheal tube and wedged into the distal airway. Then, a continuous negative pressure of $-400 \text{ cm H}_2\text{O}$ was applied during 5–30 s to obtain edema fluid (at least 0.5 ml).⁶ Bronchoalveolar fluid was collected in a sterile container (Novatech SA, Plan de Grasse, France) and subsequently transferred into an Eppendorf tube (Eppendorf SA, Hamburg, Germany) for immediate analysis. After centrifugation for 5 min at 10,000 rpm (Biofuge; Heraeus Instruments, Hanau, Germany), the supernatant was recovered for quantifying proteins, according to the biuret method, and albumin, according to the bromocresol green method, in a Modular analyzer (Roche/HITACHI, Mannheim, Germany). Percent alveolar fluid clearance was calculated as

$$\text{Percent alveolar fluid clearance} = 100 \times [1 - (\text{edema protein}_{\text{pre-RM}} / \text{edema protein}_{\text{post-RM}})]$$

and expressed in $\%/h$ by dividing the number by the time separating the two bronchoalveolar samples (expressed in hours).

Measurement of Alveolar Recruitment by P-V Curve Method

Positive end-expiratory pressure-induced changes in end-expiratory lung volume (ΔEELV) were measured using a heated pneumotachograph (Hans Rudolph, Inc, Kansas City, KA) positioned between the Y piece and the connecting piece. The pneumotachograph was previously calibrated by a supersyringe filled with 1,000 ml of air. The precision of the calibration was 3%. The respiratory tubing connecting the endotracheal tube to the Y piece of the ventilatory circuit was occluded by a clamp at end-expiration while the ventilator was disconnected from the patient. The clamp was then released,

and the exhaled volume measured by the pneumotachograph was recorded on a Macintosh Performa 6400 computer using the Acqknowledge 3.7 software (Biopac Inc., Goleta, CA).

Pressure-volume curves of the respiratory system were measured on an Evita 2 Dura ventilator using the low constant flow method as described by Lu *et al.*¹⁶ During the maneuver, the peak airway pressure was limited to 50 $\text{cm H}_2\text{O}$. P-V curves were measured in zero end-expiratory pressure (ZEEP) and PEEP conditions. For each patient, alveolar recruitment was measured using the P-V curve method as follows: The P-V curves in ZEEP and PEEP conditions were constructed. ΔEELV was then added on each volume that served for constructing the P-V curve in PEEP. The two curves were then placed on the same pressure and volume axes. Recruited volume was defined as the difference in lung volume between PEEP and ZEEP at an airway pressure of 15 $\text{cm H}_2\text{O}$.¹⁷ A single measurement of alveolar recruitment was performed per patient, 1 and 4 h after RM. A significant lung recruitment after RM was defined, *a posteriori*, as a lung recruitment of 50 ml or greater 1 h after RM.

Study Design

First, hemodynamic and respiratory parameters (blood gas, recruited volume, and ventilator settings) were measured and recorded on a Macintosh Performa 6400 computer using the Acqknowledge 3.7 software, and a sample of bronchoalveolar fluid was collected for measuring protein concentration. The RM was then immediately performed by increasing PEEP 10 $\text{cm H}_2\text{O}$ above the lower inflection point for 15 min, the patient being on volume-controlled ventilation. If necessary, tidal volume was decreased to maintain plateau pressure below the upper inflection point or below 35 $\text{cm H}_2\text{O}$ if the upper inflection point could not be identified on the ZEEP P-V curve. During the RM, the maximum peak airway pressure was limited to 50 $\text{cm H}_2\text{O}$. In the case of severe arterial hypotension (systolic arterial pressure $< 60 \text{ mmHg}$) or severe hypoxemia (oxygen saturation measured by pulse oximetry $< 80\%$), the RM was immediately stopped. A positive response to RM was defined, *a priori*, as a 20% increase in Pao_2 1 h after RM. After the RM, the patient was ventilated with the initial ventilator settings. One and four hours later, bronchoalveolar fluid was collected for measuring protein concentration, and cardiorespiratory measurements were recorded.

Statistical Analysis

The statistical analysis was performed using the Statview 5.0 software (SA Institute Inc., Cary, NC). All data are expressed as mean \pm SD. Baseline clinical characteristics were compared between responders and nonresponders using the Student *t* test for parametric data and the Mann-Whitney *U* test for nonparametric data. After verifying the normal distribution of quantitative data

Table 1. Clinical Characteristics of the Patients

Patient	Age, yr/Sex	Cause of ICU Admission	Cause of ARDS	SAPS II	Delay, h	LIP, cm H ₂ O	UIP, cm H ₂ O	Loss of Lung Aeration	Outcome
Nonresponders									
1	59/M	Liver trp	Sepsis	48	12	12	35	Focal	D
2	63/M	Bleeding	Aspiration pneumonia	62	12	13	44	Focal	S
3	78/M	Pneumonia	Pneumonia	51	24	12	—	Focal	S
4	74/M	Sepsis	Aspiration pneumonia	78	24	13	—	Focal	D
12	41/F	Pancreatitis	Sepsis	45	36	10	39	Focal	D
13	55/F	Multiple trauma	SIRS	53	24	14	42	Focal	S
14	36/M	Pancreatitis	Sepsis	32	48	12	43	Focal	D
Mean ± SD	58 ± 15			52 ± 14	25 ± 12	12 ± 1.2	40 ± 3		
Responders									
5	38/M	Pneumonia	Pneumonia	24	12	9	45	Diffuse	S
6	68/M	Pneumonia	Pneumonia	80	24	12	42	Diffuse	D
7	38/M	Aspiration pneumonia	Aspiration pneumonia	60	12	12	—	Diffuse	D
8	49/M	Pneumonia	Pneumonia	33	24	12	48	Patchy	S
9	28/M	Multiple trauma	SIRS	40	24	12	49	Diffuse	S
10	63/M	Eso surg	Aspiration pneumonia	78	12	9	46	Diffuse	S
11	57/M	Eso surg	Aspiration pneumonia	22	12	13	—	Diffuse	S
15	75/F	Peritonitis	Sepsis	76	48	15	40	Diffuse	D
Mean ± SD	51 ± 17			51 ± 24	21 ± 12	11 ± 2	45 ± 3		

ARDS = acute respiratory distress syndrome; D = deceased; Delay = delay between the diagnosis of acute respiratory distress syndrome and inclusion in the study; Diffuse = diffuse loss of aeration; Eso surg = esophageal surgery; Focal = focal loss of aeration; ICU = intensive care unit; LIP = lower inflection point of the pressure–volume curve; Liver trp = liver transplantation; Patchy = patchy loss of aeration; S = survived; SAPS = Simplified Acute Physiologic Score, evaluated at the beginning of the study; SIRS = systemic inflammatory response syndrome; UIP = upper inflection point of the pressure–volume curve.

using the Kolmogorov-Smirnov test, changes in cardiorespiratory parameters were analyzed by a two-way analysis of variance for repeated measures (baseline, 1 h and 4 h after RM) and one grouping factor (responders and nonresponders or recruiters and nonrecruiters), followed by a Student-Newman-Keuls *post hoc* comparison test. The statistical significance level was fixed at 0.05.

Results

Twelve men and three women, with an average age of 56 ± 16 yr, were included in the study. The reasons for admission to the intensive care unit and the clinical

characteristics of the patients are shown in table 1. All patients had severe hypoxemia with a $\text{PaO}_2/\text{FiO}_2$ ratio of 163 ± 64 mmHg, a mean chord compliance of 31 ± 5 ml/cm H₂O, and a mean alveolus/plasma protein ratio of 1.16 ± 0.46 . Eight patients were considered as responders, and seven were considered as nonresponders. Changes in cardiorespiratory parameters after RM are shown in table 2. The only significant hemodynamic change was a decrease in arterial pressure during the RM in nonresponders.

As shown in figure 1, PaO_2 increased in responders by 181% and 185% ($P < 0.0001$) 1 and 4 h after baseline. As shown in figure 2, the improvement in arterial oxygenen-

Table 2. Recruitment Maneuver–induced Changes in Cardiorespiratory Parameters

	Before RM		During RM		1 h after RM		4 h after RM	
	Resp	Nonresp	Resp	Nonresp	Resp	Nonresp	Resp	Nonresp
HR, beats/min	104 ± 18	105 ± 18	109 ± 21	112 ± 41	105 ± 20	112 ± 21	102 ± 17	111 ± 19
SAP, mmHg	121 ± 15	118 ± 15	102 ± 25	71 ± 29*†	107 ± 23	120 ± 9	112 ± 19	122 ± 23
MAP, mmHg	81 ± 17	81 ± 8	70 ± 11	55 ± 6*†	77 ± 13	84 ± 6	77 ± 16	82 ± 15
DAP, mmHg	63 ± 10	63 ± 8	59 ± 22	44 ± 5*†	67 ± 9	63 ± 5	63 ± 7	63 ± 8
PEEP, cm H ₂ O	13 ± 2	14 ± 1	21 ± 2	22 ± 1	13 ± 2	14 ± 1	13 ± 2	14 ± 1
VT, ml	469 ± 78	472 ± 89	460 ± 72	401 ± 66*†	469 ± 78	472 ± 89	469 ± 78	472 ± 89
RR, cycles/min	23 ± 2	23 ± 6	23 ± 2	23 ± 6	23 ± 2	23 ± 6	23 ± 2	23 ± 6
Pplat, cm H ₂ O	29.8 ± 3	29.2 ± 5	37 ± 3	38 ± 2	29.2 ± 2	29.5 ± 3	28.4 ± 4	29.3 ± 2
C _{chord} , ml/cm H ₂ O	31 ± 6	32 ± 8	32 ± 7	28 ± 5	31 ± 3	31 ± 5	32 ± 9	31 ± 7

All data are expressed as mean ± SD.

* $P < 0.05$ vs. baseline. † $P < 0.05$ vs. responders.

C_{chord} = chord compliance; DAP = diastolic arterial blood pressure; HR = heart rate; MAP = mean arterial blood pressure; Nonresp = nonresponders; PEEP = positive end-expiratory pressure; Pplat = plateau pressure; Resp = responders; RM = recruitment maneuver; RR = respiratory rate; SAP = systolic arterial blood pressure; V_T = tidal volume.

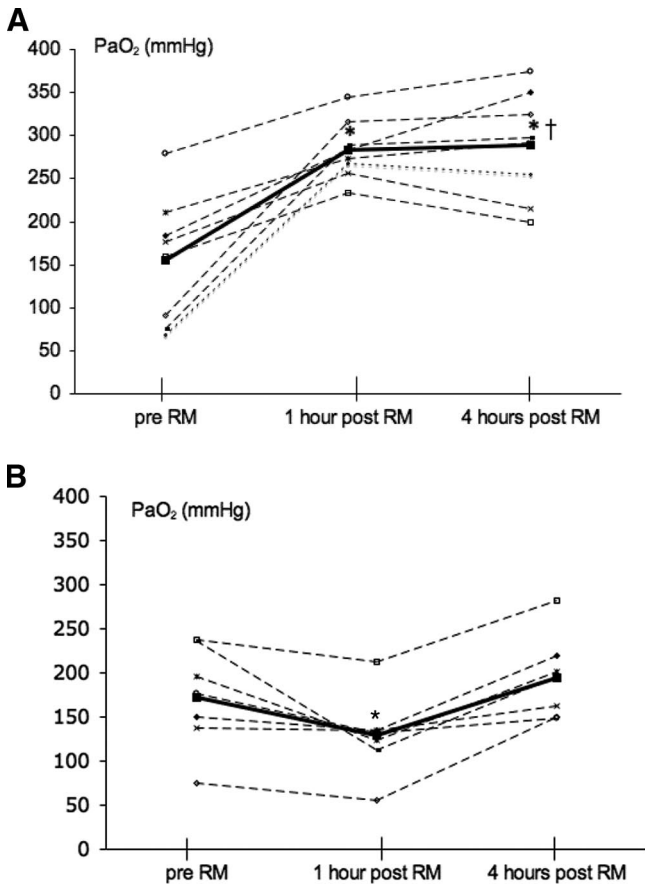


Fig. 1. Individual (dashed lines) and mean (solid lines) values of arterial oxygen tension (Pao₂)/fraction of inspired oxygen (Fio₂) before and 1 and 4 h after the recruitment maneuver (RM) in responders (A) and nonresponders (B). * *P* > 0.05 versus baseline. † *P* < 0.05 versus 1 h. Responders are patients in whom an increase in Pao₂ of 20% of baseline values or greater was observed 1 h after RM.

ation was associated with a significant and sustained alveolar recruitment (103 ± 154 ml at 1 h and 113 ± 101 ml at 4 h). In nonresponders, there was a 9% significant decrease in Pao₂ 1 h after baseline, whereas Pao₂ returned to baseline values 4 h later. Among nonresponders, the RM-induced alveolar recruitment was observed in two patients only and, as a mean, the recruited volume was not statistically significant (31 ± 114 ml at 1 h and 98 ± 168 ml at 4 h). As shown in figure 3, a significant correlation was found between RM-induced changes in arterial oxygenation and RM-induced alveolar recruitment.

As shown in figure 4, in responders, alveolar concentration of proteins increased by 26% at 1 h (*P* = 0.17) and by 40% at 4 h (*P* = 0.018). In nonresponders, alveolar concentration of proteins decreased by 18% at 1 h (*P* = 0.042) and by 14% at 4 h (*P* = 0.043). The serum protein level remained unchanged at the different times of the study (table 3). Individual values of net alveolar fluid clearance are shown in figure 5. One hour after baseline, a positive net alveolar fluid clearance was

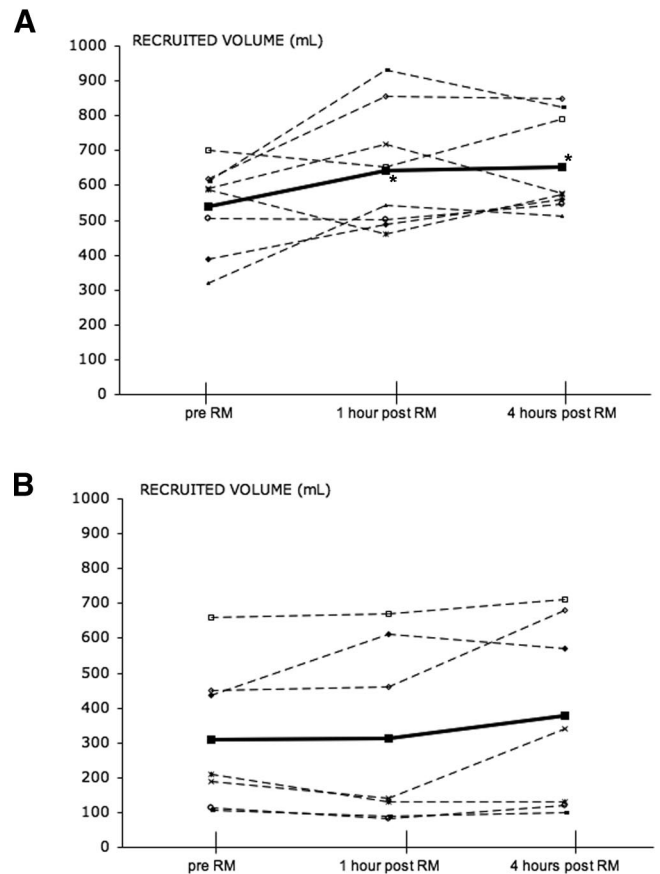


Fig. 2. Individual (dashed lines) and mean (solid lines) values of recruited volume before and 1 and 4 h after the recruitment maneuver (RM) in responders (A) and nonresponders (B). * *P* < 0.05 versus baseline. Responders are patients in whom an increase in arterial oxygen tension of 20% of baseline values or greater was observed 1 h after RM.

measured in responders (19 ± 13%/h; *P* = 0.018), whereas no net fluid clearance occurred in nonresponders (-24 ± 11%/h; *P* = 0.017). As shown in figure

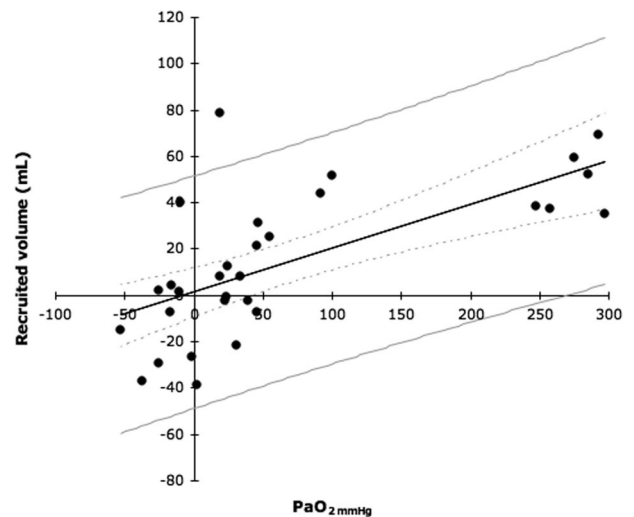


Fig. 3. Correlations between recruitment maneuver-induced recruited volume and changes in arterial oxygenation. Pao₂ = arterial oxygen tension.

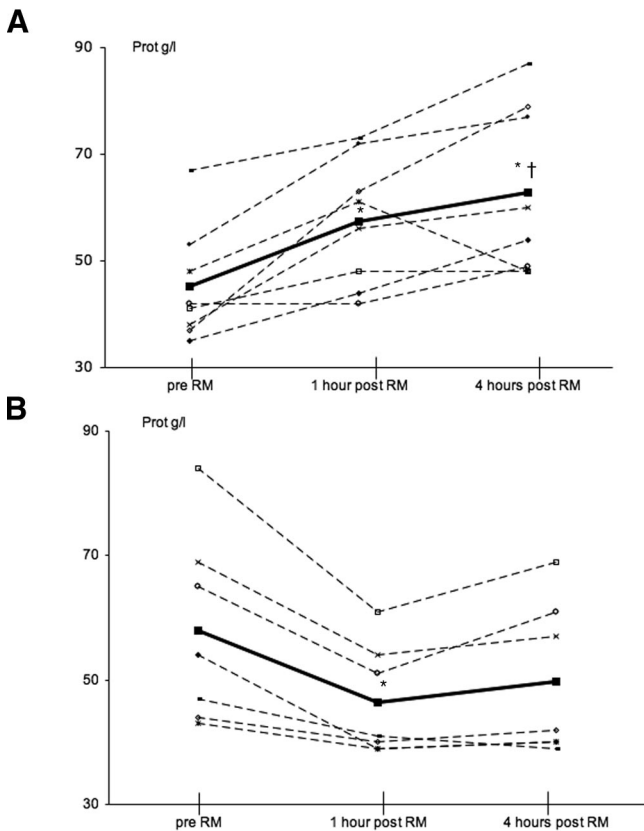


Fig. 4. Individual (dashed lines) and mean (solid lines) values of alveolar fluid protein concentrations (Prot) before and 1 and 4 h after the recruitment maneuver (RM) in responders (A) and nonresponders (B). * $P < 0.05$ versus baseline. † $P < 0.05$ versus 1 h. Responders are patients in whom an increase in arterial oxygen tension of 20% of baseline values or greater was observed 1 h after RM.

6, in patients in whom a significant alveolar recruitment (150 ± 109 ml) was measured by the P-V curve method 1 h after RM (“recruiters”), alveolar concentration of proteins increased by 8% at 1 h ($P < 0.05$) and by 11% at 4 h ($P < 0.05$). In “nonrecruiters,” alveolar concentration of proteins decreased by 6% at 1 h (not significant) and by 2% at 4 h (not significant).

Discussion

In patients with ARDS, a “negative” response to an RM in terms of arterial oxygenation and alveolar recruitment is accompanied by the lack of net alveolar fluid clearance. When the RM induces alveolar recruitment and improves arterial oxygenation, a net alveolar fluid clearance is observed, likely resulting in resorption of alveolar edema.

Methodologic Considerations

Several bronchoalveolar fluid samples were collected to assess changes in protein concentration over time and calculate the net alveolar fluid clearance. As described in the reference study,⁶ bronchoalveolar samples were collected by inserting blindly a suction catheter into the

Table 3. Recruitment Maneuver–induced Individual Changes in Alveolar/Plasmatic Protein Ratio

Patient	Before RM			1 h after RM			4 h after RM		
	Alv	Plas	Ratio	Alv	Plas	Ratio	Alv	Plas	Ratio
1	44	43	1.02	39	43	0.91	42	45	0.93
2	69	55	1.25	54	55	0.98	57	54	1.06
3	54	49	1.10	39	49	0.80	40	48	0.83
4	84	35	2.40	61	35	1.74	69	36	1.92
5	65	58	1.12	51	58	0.88	61	58	1.05
6	43	40	1.08	39	40	0.98	40	40	1.00
7	47	39	1.21	41	39	1.05	39	39	1.00
8	37	49	0.76	63	51	1.24	79	48	1.65
9	38	42	0.90	56	42	1.33	60	44	1.36
10	37	49	0.76	44	49	0.90	54	52	1.04
11	51	54	0.94	58	54	1.07	48	55	0.87
12	42	43	0.98	42	43	0.98	49	44	1.11
13	48	35	1.37	61	35	1.74	48	40	1.20
14	67	53	1.26	73	53	1.38	87	51	1.71
15	53	41	1.29	72	41	1.76	77	40	1.93
Mean	52	46	1.16	53	46	1.18	57	46	1.24
SD			0.39			0.34			0.37

Alv = alveolar protein concentration; Plas = plasmatic protein concentration; RM = recruitment maneuver.

upper airways through the endotracheal tube. Previous studies have demonstrated that a catheter blindly inserted in the respiratory tract goes in 90% of cases into the inferior bronchus of the right lower lobe,¹⁸ a lung area predominantly involved in ventilator-associated pneumonia¹⁹ and ARDS.²⁰ The reproducibility of the method was high, as attested by identical protein concentrations measured in consecutive samples taken at a few-minute interval. Examination of two consecutive samples by electrophoresis confirmed that increases in protein concentrations were related solely to the absorption of fluid and not to any protein neosynthesis.^{5-7,21-23} Contrary to the recommendations of Matthay *et al.*⁶ in their reference study, no heparin was added to the samples. In all patients, it was possible to recover alveolar fluid. In some patients, however, the quantity of bronchoalveolar fluid was very small, on the order of 1 ml. The addition of heparin, even in a tiny quantity, would have diluted the sample by a substantial factor, thereby exposing to the risk of underestimating the true protein concentration. Cardiogenic pulmonary edema, well-known to be hemorrhagic, was absent in the current study as attested by a high alveolar/plasma protein ratio,

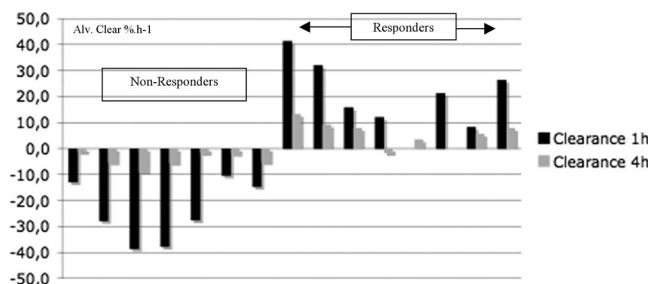


Fig. 5. Individual changes of alveolar clearance (Alv Clear) 1 and 4 h after recruitment maneuver in responders and nonresponders.

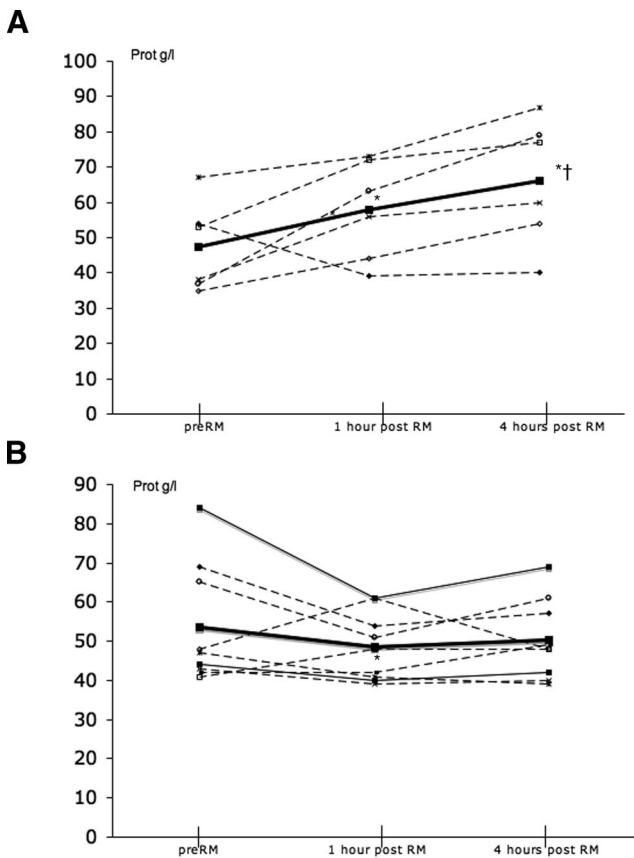


Fig. 6. Individual (dashed lines) and mean (solid lines) values of alveolar fluid protein concentrations (Prot) before and 1 and 4 h after the recruitment maneuver (RM) in recruiters (A) and nonrecruiters (B). * $P < 0.05$ versus baseline. † $P < 0.05$ versus 1 h. Recruiters are patients in whom recruited volume was 50 ml or greater 1 h after RM.

and coagulation of bronchoalveolar samples was never observed.

It must be pointed out that the technique of bronchoalveolar sampling may have grossly interfered with the effect of RM on arterial oxygenation. In experimental animals and patients with severe bronchopneumonia, alveolar edema is scarce.^{19,24} Obtaining distal bronchoalveolar samples, a procedure equivalent to endotracheal suctioning, may require prolonged suctioning and contribute to lung derecruitment and deterioration of arterial oxygenation.^{25,26} In the current study, recovery of bronchoalveolar fluid was obtained within 5 s in nine patients and within 30 s in six, exposing the latter to the risk of derecruitment at each sampling procedure. This is why measurements and recordings of cardiorespiratory parameters always preceded the distal bronchoalveolar sampling procedure.

The RM used in the current study consisted of the application of a high PEEP for 15 min while limiting plateau airway pressure to upper distending pressure of the P-V curve or to 35 cm H₂O. Such an RM is derived from a technique of "extended sigh" applied for 2 min, recently proposed by Lim *et al.*²⁷ The authors underscored the advantages of an RM prolonged in time by

showing substantial alveolar recruitment in experimental animals¹² and marked increase in arterial oxygenation in a series of 20 patients with ARDS.²⁷ In the current study, the RM duration was extended to 15 min and aimed at optimizing alveolar recruitment.

RM-induced Changes in Net Alveolar Fluid Clearance

The current study shows that an RM may not provide net alveolar fluid clearance when not associated with alveolar recruitment and improvement in arterial oxygenation. It confirms a recent experimental study performed in rats with acute lung injury caused by acid instillation.²⁸ In his study, it was found that an RM made of two consecutive 30-s lung inflations at 30 cm H₂O was protective against endothelial injury but not against alveolar epithelium injury. In fact, in four animals, alveolar fluid clearance was impaired first by acid instillation and further by RM.²⁸ Our study shows that the effect of RM on alveolar fluid clearance is not univocal and depends on the resulting physiologic changes. If RM induces significant alveolar recruitment and improvement in arterial oxygenation, alveolar fluid clearance can be maintained at a high value. If RM induces preferentially (over) inflation of previously aerated lung regions rather than recruitment, it does not provide net alveolar fluid clearance. In nonresponders, the lack of improvement of arterial oxygenation, as well as the deterioration of arterial pressure after RM, indirectly suggests the presence of lung overinflation/overdistension,^{13,29-32} a morphologic effect directly evidenced in a recent experimental study.¹² In previous studies, several conditions have been considered as limiting RM-induced alveolar recruitment, although each of them remains controversial: pulmonary ARDS,³³ late stage of ARDS,³⁴ and previous recruitment with PEEP.^{35,36} In responders, the recruited volume and the resulting increase in Pao₂ were comparable to those reported in previous studies.^{27,34,37,38} The RM response was not influenced by the etiology of lung injury (pulmonary *vs.* nonpulmonary ARDS) but seemed dependent on lung morphology. Patients with diffuse loss of aeration had a positive response to RM in terms of arterial oxygenation and alveolar recruitment, whereas patients with focal loss of aeration had a negative response. This result confirms our previous findings that the presence of a large proportion of the lung remaining fully aerated tends to limit the alveolar recruitment resulting from a given increase in intrathoracic pressure.³⁹ The study does not provide direct evidence that an RM, successful in terms of oxygenation, increases alveolar fluid clearance in comparison with baseline ventilator settings applied during protective mechanical ventilation. One hour after RM, however, the net alveolar fluid clearance was 19%/h, a value much higher than generally observed in ARDS patients on protective mechanical ventilation: Among 79 patients with ARDS, only 9 had an

alveolar fluid clearance of 15%/h or greater.⁴⁰ Therefore, one can reasonably assume that an RM producing alveolar recruitment provides significant alveolar fluid clearance and contributes to fluid removal from the alveolar space. A further study comparing alveolar fluid clearance before and after RM is required to confirm this hypothesis.

At the bedside, RM is performed for improving arterial oxygenation, and, therefore, responders and nonresponders were defined *a priori* according to changes in arterial oxygenation. Analyzing the effect of RM on the basis of RM-induced recruited volume measured by the P-V curve method strongly suggests that alveolar recruitment is a key factor of the beneficial effect of RM on net alveolar fluid clearance (fig. 6). As previously demonstrated for PEEP,⁴¹ a weak but statistically significant correlation was found between RM-induced alveolar recruitment and RM-induced improvement in arterial oxygenation (fig. 3). In fact, alveolar recruitment is an anatomical phenomenon depending exclusively on the penetration of gas into poorly or nonaerated lung regions, whereas arterial oxygenation is a complex physiologic parameter depending on multiple factors such as lung aeration, regional pulmonary flow, and cardiac index. Therefore, it may be tempting to classify the response to RM (beneficial or nonbeneficial) according to the recruited volume and not to changes in arterial oxygenation. Some methodologic limitations of the P-V curve method, however, should be pointed out and preclude characterizing the response to RM exclusively on RM-induced alveolar recruitment. As recently demonstrated,⁴² the P-V curve method markedly underestimates alveolar recruitment in ARDS patients with diffuse loss of lung aeration. Consequently, it is highly likely that RM-induced lung recruitment was underestimated to some degree in the eight patients with diffuse loss of lung aeration. Classifying the patients according to recruited volume only, would have inevitably led to misclassification of some patients and confusion in the interpretation of the effects of RM on net alveolar fluid clearance. A further study, based on computed tomography measurement of lung recruitment, is required to definitively confirm that RM-induced lung recruitment is the key factor influencing net alveolar fluid clearance.

Hypothesis on RM-induced Net Alveolar Fluid Clearance

Different hypothesis may be proposed to explain how RM influences net alveolar fluid clearance. In hydrostatic pulmonary edema, the alveolar-capillary barrier is not injured, and the mechanisms of alveolar fluid clearance are preserved.^{43,44} The increase in intrathoracic pressure decreases the alveolar capillary pressure gradient and promotes rapid removal of pulmonary edema from the alveolar space. In high permeability-type pulmonary edema, the alveolar-capillary barrier is injured and Na/K

adenosine triphosphatase-dependent pumps are impaired,⁷ both factors that promote alveolar flooding from the vascular compartment.

The mechanisms by which RM can restore a net alveolar fluid clearance remain speculative. Alveolar recruitment could induce either an up-regulation of the Na/K pumps or a "recruitment" of aquaporins.⁴⁵ Another hypothesis, purely "mechanical," must be considered. As in hydrostatic pulmonary edema, the increase in alveolar pressure accompanying lung recruitment may reduce the amount of fluid penetrating in the alveolar space through the injured alveolar-capillary barrier by opposing the alveolar capillary pressure gradient. Last, it is highly likely that the finding of a net alveolar fluid clearance in "recruiters" only could reflect an increased surface area for fluid resorption resulting from the recruited alveolar spaces. In nonresponders, whose loss of aeration is predominantly focally distributed, the overinflation/overdistension of normally aerated lung regions^{46,47} may extend injury of the alveolar capillary barrier,⁴⁸ reduce the efficiency of aquaporins,^{35,49} and increase the amount of alveolar edema. The lack of alveolar recruitment does not engage the different mechanisms that increase alveolar fluid clearance, and as a consequence, the final result is the lack of net alveolar fluid clearance. Further experimental studies are required to understand how lung aeration and positive alveolar pressure influence net alveolar fluid clearance.

In conclusion, RM applied during lung-protective mechanical ventilation may provide net alveolar fluid clearance, depending on the degree of lung recruitment. From a clinical point of view, the lack of improvement in arterial oxygenation and hemodynamic impairment during the RM, two issues frequently observed in patients with a focal loss of aeration, are associated with no net alveolar fluid clearance that may impair resorption of pulmonary edema. If RM markedly improves arterial oxygenation, as frequently observed in patients with a diffuse loss of lung aeration, a net positive alveolar fluid clearance might be expected with a reduction of the amount of pulmonary edema. Further studies are required to assess whether the beneficial effect of RM in terms of net alveolar fluid clearance influences lung fluid balance over several hours or days.

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