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BRIEF REPORT

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Effects of a single-lung recruitment maneuver on the systemic release of inflammatory mediators

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Abstract *Objective:* To study the hypothesis, that systemic levels of pro-inflammatory and anti-inflammatory cytokines may be affected by a single recruitment maneuver in mechanically ventilated patients. *Design:* Prospective, interventional clinical trial. *Setting:* Intensive care unit of a university hospital. *Patients:* Sixteen mechanically ventilated patients with clinical and radiological signs of atelectasis. *Interventions:* A single recruitment maneuver (RM) was performed by elevating the airway pressure to 40 cmH_2O for 7 s. *Measurements and main results:* Plasmatic concentrations of interleukin (IL)-1β, IL-6, IL-8, IL-10, IL-12p70 and tumor necrosis factor (TNF-α), arterial blood gases and hemodynamic parameters were measured immediately before and 5–360 min after the RM. The RM caused a minor, nevertheless significant improvement of oxygenation ($p = 0.02$) and carbon dioxide elimination ($p = 0.006$) as well as a moderate drop of the mean arterial pressure ($p = 0.025$). In contrast, plasma concentrations remained unaffected by the RM in all six mediators measured. *Conclusion:* A single inflation with an airway pressure of 40 cmH_2O for 7 s improved gas exchange only slightly and did not modify systemic levels of inflammatory mediators in mechanically ventilated patients with radiological evidence of atelectasis.

Keywords Atelectasis · Cytokines · Mechanical ventilation · Recruitment maneuver · Ventilator-induced lung injury

Introduction

In acute respiratory failure, improved survival was demonstrated with low tidal volume (V_T) ventilation [1]. Consequently, the use of small V_T has been recommended during mechanical ventilation [2], but this strategy may facilitate alveolar de-recruitment and deterioration of gas exchange [3, 4]. Recruitment maneuver (RM) may improve gas exchange [3, 4, 5], but inflating the lungs to nearly vital capacity might be harmful due to stretch stress imposed on the pulmonary parenchyma. Alveolar macrophages liberate inflammatory cytokines in response to stretch [6], and injurious mechanical ventilation is associated with higher levels of inflammatory cytokines than protective ventilation [1, 7, 8]. Thus, inflammatory mediators released from the lung are proposed to contribute to ventilator-associated lung injury [9, 10]. The increase and decrease of systemic mediator levels occur rapidly if ventilation is changed [8], but the time period of stretch stress necessary to induce the production or liberation of mediators is unclear. In small animals hyperinflating the lungs for brief periods can alter microvascular permeability [11]. Thus, we hypothesized that one RM may potentially affect the balance of pro- and anti-inflammatory mediators and tested this hypothesis by studying systemic mediator levels in patients with radiological and clinical signs of atelectasis before and af-

ter a single RM. Inflating the lungs for 7–8 s only with an airway pressure (Paw) of 40 cmH_2O has been shown to effectively recruit atelectasis [12]. This short inflation period may decrease hemodynamic side effects and the risk for barotrauma compared to RMs with an extended inflation period and was therefore chosen in the present study.

Material and methods

With approval of the local ethics committee (application 4/7/02), 16 mechanically ventilated patients were enrolled into the study. Informed consent to participate in the study was obtained from their nearest relatives.

Inclusion criteria were:

- Age > 18 years
- Mechanical ventilation
- Arterial catheter inserted
- PaO_2/FiO_2 < 300 mmHg or decrease in PaO_2 > 50 mmHg within the last hour
- Radiological evidence of atelectasis in the chest X-ray
- Informed consent

Exclusion criteria were:

- Age < 18 years
- Elevated intracranial pressure > 25 mmHg
- Hemodynamic instability
- Bronchopulmonary fistula
- Emphysema

Patients were treated according to standard ICU care. Ventilatory settings before inclusion into the study were pressure-limited ventilation (pressure-controlled or pressure-regulated volume-guaranteed ventilation) with V_T between 5 ml/kg and 8 ml/kg (ideal body weight), an I:E ratio between 1:1 and 1:2, PEEP and FiO_2 adjusted to obtain an SaO_2 of 90–95%. V_T above 8 ml/kg ideal body weight were only permitted in patients with intracerebral lesions if hypercapnia could not be controlled otherwise. Blood pressure and SO_2 were displayed on a bedside monitor (Datex AS/3, Datex Division Instrumentarium, Helsinki, Finland). Arterial blood samples were analyzed with the ABL 725 (Radiometer Copenhagen, Denmark).

Protocol

During the study, patients were positioned supine; ventilatory settings remained unchanged and all manipulations were avoided. Hemodynamic data were continuously recorded. At baseline arterial blood was sampled for blood gas- and cytokine analysis. Then, Paw of 40 cmH_2O was applied for 7 s [12]. Thereafter, mechanical ventilation was continued, and arterial blood was sampled 5 min, 30 min, 60 min, 180 min and 360 min after the RM.

Ventilatory measurements

Gas flow and Paw were measured with the integrated monitoring of our ventilators (EVITA IV, Dräger, Lübeck, Germany or Servo-i Maquet, Solna, Sweden).

Cytokine measurements

Arterial blood samples were centrifuged at 3,000 cycles/s for 3 min; serum was aspirated and stored at –80°C. Simultaneous quantification of interleukin (IL)-1β, IL-6, IL-8, IL-10, IL-12p70 and tumor necrosis factor (TNF)-α levels was performed by a Cytometric Bead Array (Human Inflammation Kit, BD Biosciences, Heidelberg, Germany).

Statistical analysis

Results are expressed as mean ± SD. Statistical analysis was performed using the software package STATISTICA (StatSoft, Tulsa, OK, USA). An immediate effect of the RM on hemodynamics, gas exchange or respiratory compliance was assessed with a Wilcoxon matched-pairs test, by comparing baseline values with data obtained during the RM or 5 min thereafter. After the RM, the time course of these parameters was analyzed with a Friedman analysis of variance (ANOVA), which was also used to analyze the plasma cytokine concentrations throughout the study period. To compare single data points, Scheffé post-hoc analysis was performed. If cytokine levels were below the detection threshold, calculations were performed using the detection threshold as numerical values. $p < 0.05$ was chosen as the significance level.

Results

Patients

Patient characteristics are shown in Table 1. Ten of 16 patients met the ARDS (adult respiratory distress syndrome) or ALI (acute lung injury) criteria [13]. Fifteen patients had elevated levels of C-reactive protein and nine patients had elevated leucocytes, indicating an ongoing inflammatory response prior to the RM. One patient (No. 11) developed bronchospasm during the RM, which required antiobstructive therapy and a change of the respiratory settings. He was therefore excluded from the analysis. Thus, 15 patients completed the study protocol without adverse events.

Gas exchange, respiratory mechanics and hemodynamics

At baseline, oxygenation and respiratory compliance were markedly impaired (Table 2). Oxygenation improved slightly, immediately after the RM, ($p = 0.02$) and increased even further thereafter ($p = 0.019$; Fig. 1). $PaCO_2$ decreased after the RM ($p = 0.006$) and was subsequently stable (Table 2). Compliance was unchanged throughout the study period. Heart rate did not change over time, whereas the RM caused a moderate drop of the mean arterial pressure (MAP) (6 mmHg, $p = 0.025$).

Systemic levels of pro- and anti-inflammatory mediator

Before the RM, mediator concentrations above the lower detection limit were found in all patients for IL-6 and IL-8, in ten of 15 patients for IL-10 and IL-12p70, in seven of 15 patients for IL-1β and five of 15 patients for TNF-α levels. No change of the plasma mediator levels was observed during the study period (Fig. 2), regardless of whether all patients were analyzed, or a subgroup of five patients with the highest respective cytokine concentrations before the RM (Table 3).

Discussion

Serum-concentrations of pro- and anti-inflammatory mediators were not influenced by elevating Paw once to 40 cmH_2O for 7 s, regardless of whether all patients were analyzed or only a subgroup of five patients with the highest respective cytokine levels prior to the RM.

Mediator levels

The influence of mechanical ventilation on pro- and anti-inflammatory mediators is rather complex [14]. Injurious mechanical ventilation may increase systemic cytokine

Table 1 Patients' characteristics ($P_{Plateau}$ inspiratory plateau pressure, V_T tidal volume, *CRP* C-reactive protein, *WBC* white blood count)

Patient	Sex	Age	Diagnosis	Hours on ventilation	Pulmonary infiltrates	PaO_2/FiO_2 [mmHg]	PEEP [mbar]	$P_{Plateau}$ [mbar]	V_T [ml]	CRP [mg/l]	WBC [μl^{-1}]
01	M	64	Traumatic brain injury	230	Bilateral	180	8	28	800	108	10,800
02	M	66	Rectal cancer	319	Bilateral	117	12	34	390	213	21,400
03	M	53	Multiple trauma	6	Left	168	8	24	560	74	6,000
04	M	32	Multiple trauma	136	Bilateral	134	10	25	550	184	20,900
05	M	73	Subarachnoid hemorrhage	90	Bilateral	217	10	25	520	157	17,300
06	M	41	Traumatic brain injury	361	Bilateral	263	10	26	570	89	8,900
07	M	39	Traumatic brain injury	8	Right	310	8	18	625	17	14,200
08	M	42	Subarachnoid hemorrhage	120	Bilateral	195	10	23	330	208	13,900
09	M	35	Intracerebral bleeding	100	Bilateral	155	13	24	500	108	10,800
10	W	42	ARDS following aspiration	7	Bilateral	258	10	22	330	113	18,200
11	M	29	Multiple trauma	28	Bilateral	175	18	25	450	123	8,100
12	W	51	Peritonitis	85	No	229	8	20	530	302	7,600
13	W	43	Subarachnoid hemorrhage	85	Left	164	14	24	480	106	14,700
14	W	48	Subarachnoid hemorrhage	144	No	154	13	20	440	70	11,300
15	W	70	Femur fracture	9	No	227	10	24	500	5	10,600
16	W	54	Spinal cord injury C6/7	2	No	178	10	22	440	14	12,600

Reference values: *CRP* ≤ 8 mg/l; leucocytes: 4000–11,000 μl^{-1}

Table 2 Hemodynamic and ventilatory variables. Data are presented as mean ± SD. (*Crs* compliance of the respiratory system, *HR* heart rate, *MAP* mean arterial pressure, *n.m.* not measured, *RM* recruitment maneuver)

	Baseline	p value[1]	RM	5 min post RM	30 min post RM	60 min post RM	180 min post RM	360 min post RM	p value[2]
MAP [mmHg]	86 ± 11	0.025	80 ± 12	82 ± 10	85 ± 13	86 ± 13	90 ± 13	90 ± 12	0.027
HR [beats/min]	78 ± 13	0.66	77 ± 18	78 ± 13	78 ± 4	78 ± 13	78 ± 14	78 ± 14	0.94
Crs [ml/mbar]	37 ± 10	0.20	n.m.	39 ± 11	38 ± 11	38 ± 10	39 ± 11	37 ± 11	0.34
PaO_2/FiO_2	195 ± 52	0.02	n.m.	202 ± 57	207 ± 58	209 ± 63	223 ± 69[$]	226 ± 67[$]	0.019
$PaCO_2$	41.7 ± 7.4	0.006	n.m.	40.0 ± 5.9	39.9 ± 5.7	39.2 ± 4.0	39.8 ± 5.7	39.2 ± 4.1	0.70

[1] Level of significance for comparison of baseline vs. RM (MAP and HR) or 5 min post RM (Crs, PaO_2/FiO_2, $PaCO_2$) using the Wilcoxon matched-pairs test [2] Level of significance for a parameters change between 5 min and 360 min after the RM using a Friedman ANOVA
[$] Significant difference compared to baseline according to Scheffé post-hoc analysis

Table 3 Systemic mediator concentrations (*IL* interleukin, *RM* recruitment maneuver, *TNF* tumor necrosis factor, *Upper 33%* subgroup of five patients with the highest respective plasma mediator level)

	Baseline	5 min post RM	30 min post RM	60 min post RM	180 min post RM	360 min post RM	*p* value
IL-1b [pg/ml]	57.9 ± 44.8	33.7 ± 11.6	29.8 ± 13.1	48.1 ± 17.9	46.7 ± 22.2	35.7 ± 20.9	0.33
Upper 33%	74.1 ± 42.9	32.3 ± 15.5	24.9 ± 14.9	30.3 ± 20.2	26.8 ± 18.6	35.0 ± 25.1	0.42
IL-6 [pg/ml]	64.7 ± 76.8	61.9 ± 69.5	61.0 ± 70.0	65.6 ± 80.4	65.3 ± 76.2	61.5 ± 68.9	0.88
Upper 33%	145.7 ± 42.9	139.1 ± 70.4	138.2 ± 72.6	150.6 ± 90.5	149.9 ± 75.9	133.4 ± 72.3	0.66
IL-8 [pg/ml	22.4 ± 21.2	19.7 ± 20.4	17.8 ± 15.2	17.7 ± 14.3	19.4 ± 15.8	19.3 ± 20.6	0.10
Upper 33%]	44.3 ± 25.4	38.9 ± 27.3	34.8 ± 15.8	33.9 ± 13.6	37.6 ± 14.8	38.8 ± 27.4	0.20
IL-10 [pg/ml]	2.5 ± 1.1	2.1 ± 0.6	2.2 ± 0.8	2.6 ± 0.8	2.0 ± 0.6	2.6 ± 0.9	0.79
Upper 33%	3.3 ± 0.8	2.5 ± 0.4	2.8 ± 0.7	2.8 ± 1.0	2.2 ± 0.6	2.5 ± 1.1	0.30
IL-12p70 [pg/ml]	3.9 ± 1.9	3.6 ± 1.1	3.7 ± 0.9	3.9 ± 1.4	3.4 ± 2.1	3.6 ± 1.4	0.62
Upper 33%	5.2 ± 1.8	2.6 ± 1.9	3.5 ± 0.9	3.5 ± 2.1	3.3 ± 2.7	2.1 ± 1.4	0.34
TNF-α [pg/ml]	2.8 ± 5.1	3.0 ± 5.3	2.7 ± 5.2	2.9 ± 6.3	2.4 ± 4.8	2.7 ± 5.9	0.08
Upper 33%	6.8 ± 8.3	5.7 ± 9.2	5.4 ± 9.0	6.1 ± 10.9	5.0 ± 8.2	5.8 ± 10.1	0.11

levels in ARDS patients, but pro- and anti-inflammatory cytokines are affected at the same time [8]. In lung-healthy patients, a potentially injurious ventilation had no effects on systemic cytokine levels, even though the performed operating procedures induced some kind of immune response [15]. The majority of our patients had been treated in the ICU for more than 48 h, showed signs of an ongoing immune response and fulfilled ARDS or ALI criteria [13]. Surprisingly, the plasmatic mediator levels in our study were lower than those previously reported in ARDS patients [7, 8]. Thus, it is possible that our patients were not vulnerable to ventilator-associated lung injury, similarly to lung-healthy patients [15]. However, according to the results of a recent study, all of our patients were at risk for ventilator-associated lung injury [16], so that this explanation seems rather unlikely.

Recruitment maneuver

Different RMs have been described in an attempt to reopen atelectasis with minimal side effects [17]. In lung-healthy patients, a minimum Paw of 40 cmH_2O is necessary to effectively recruit atelectasis [18], and approximately the same Paw has been applied in ARDS patients for sustained inflation RMs [17]. However, the optimal duration of such a sustained inflation has never been investigated in ARDS patients. In experimental lung injury [19] and patients during general anaesthesia [12], recruitment follows an exponential time course characterized by a maximum recruitment effect during the beginning of inflation, followed by a progressive decline of additionally recruited atelectasis over time. The time constants for recruitment averaged 1–4 s [12, 19]. Consequently, the RM performed in the present study should reopen 80–90% of the recruitable lung tissue, so that a longer inflation period would have been most likely with only little further effect.

Effect of the recruitment maneuver on pulmonary gas exchange and hemodynamics

Oxygenation and carbon dioxide elimination improved after the RM, indicating recruitment. However, a marked inter-individual variability was observed for the oxygenation effect, which in addition was clinically unimportant in the majority of patients (Fig. 1). This finding is in line with previous results, since the effect of a RM on

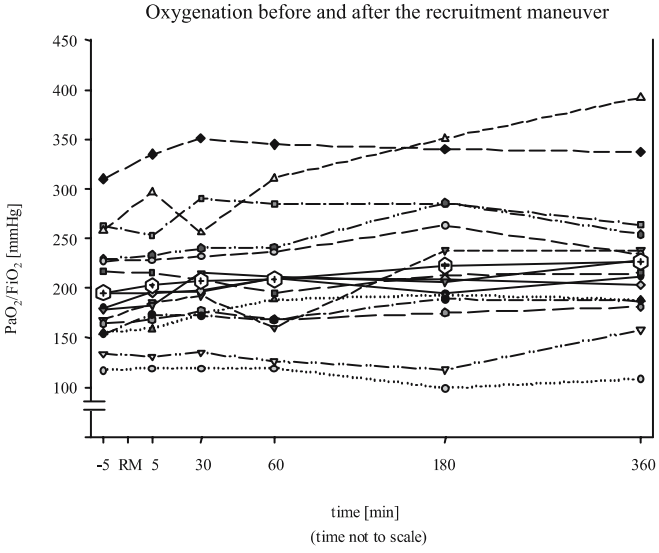

Fig. 1 Oxygenation before and after the recruitment maneuver. The time course of oxygenation expressed as PaO_2/FiO_2 on the *y*-axis is shown before and after the recruitment maneuver (*RM*) for individual patients. The mean value ⌖ is marked by a *bold line*. Note that oxygenation improved only slightly immediately after the RM, but continued to improve throughout the study period, although ventilatory settings were not changed compared to baseline (−5 min)

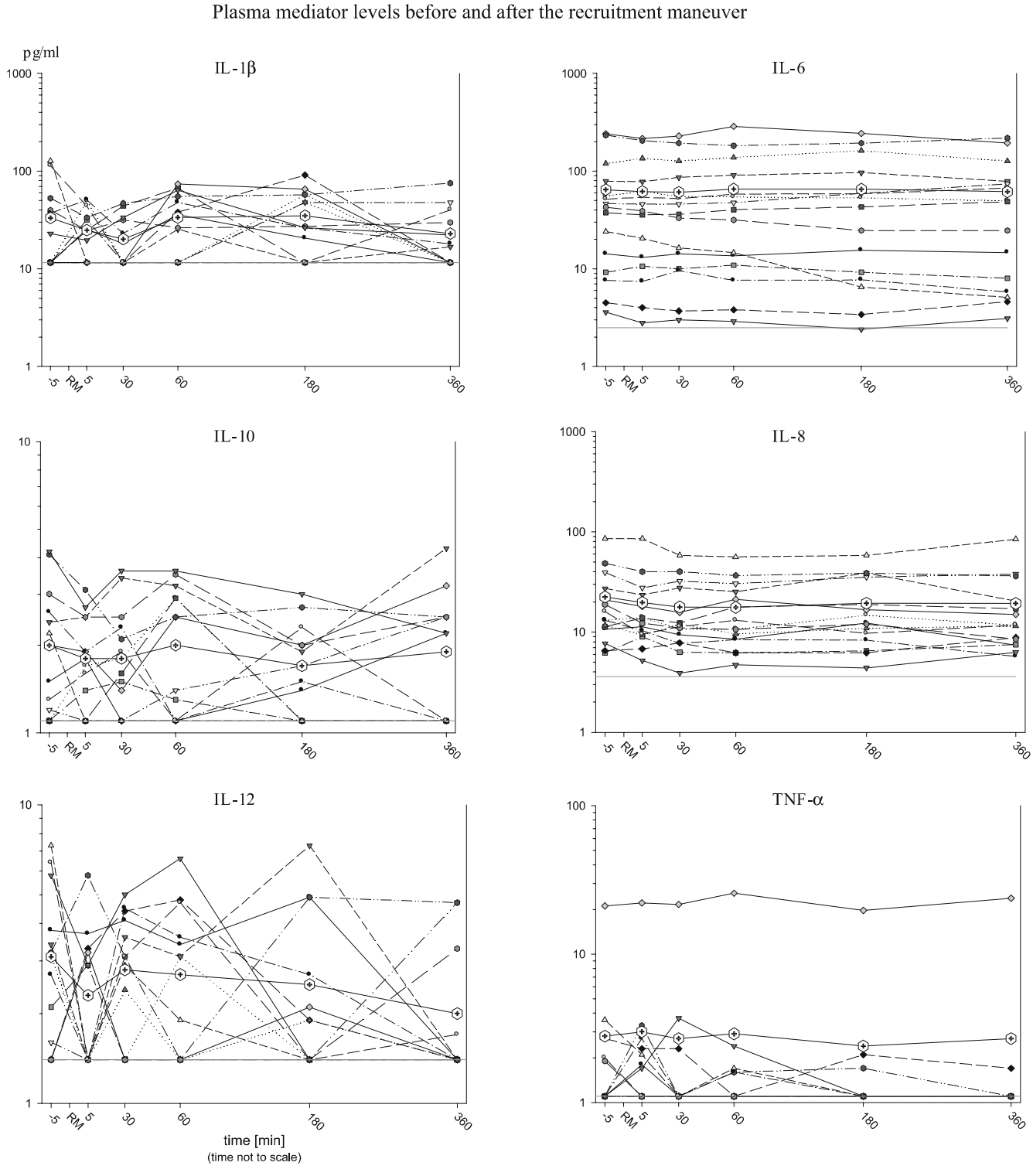

Fig. 2 Plasma mediator levels before and after the recruitment maneuver. The different *panels* show the time course of the plasmatic mediator concentrations before and after the recruitment maneuver (*RM*) for individual patients. In each *panel*, the mean value ⊕ is marked by a *bold line* and the lower detection limit is given by a *horizontal line*. The plasmatic mediator concentrations were not affected by the RM

gas exchange may depend on the etiology of respiratory failure, the duration of mechanical ventilation and the lung volume history [17]. The blood pressure drop during the RM is a well known phenomenon [17]. Since we limited the inflation period to 7 s, the decrease of MAP was moderate and clinically unimportant in most patients.

Conclusion

A single RM, performed by inflating the lungs with an airway pressure of 40 cmH_2O for 7 s has no measurable effect on the systemic concentration of pro- and anti-inflammatory mediators in ventilated patients with clinical and radiological evidence of atelectasis.

References

1. The Acute Respiratory Distress Syndrome Network (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342:1301–1308
2. Brower RG, Rubenfeld GD (2003) Lung-protective ventilation strategies in acute lung injury. Crit Care Med 31:S312–S316
3. Bendixen HH, Hedley-Whyte J, Laver MB (1963) Impaired oxygenation in surgical patients during general anesthesia with controlled ventilation: A concept of atelectasis. N Engl J Med 269:991–996.
4. Richard JC, Maggiore SM, Jonson B, Mancebo J, Lemaire F, Brochard L (2001) Influence of tidal volume on alveolar recruitment. Respective role of PEEP and a recruitment maneuver. Am J Respir Crit Care Med 163:1609–1613
5. Patroniti N, Foti G, Cortinovis B, Maggioni E, Bigatello LM, Cereda M, Pesenti A (2002) Sigh improves gas exchange and lung volume in patients with acute respiratory distress syndrome undergoing pressure support ventilation. Anesthesiology 96:788–794
6. Pugin J, Dunn I, Jolliet P, Tassaux D, Magnenat JL, Nicod LP, Chevrolet JC (1998) Activation of human macrophages by mechanical ventilation in vitro. Am J Physiol 275:L1040–L1050
7. Ranieri VM, Suter PM, Tortorella C, De Tullio R, Dayer JM, Brienza A, Bruno F, Slutsky AS (1999) Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. JAMA 282:54–61
8. Stuber F, Wrigge H, Schroeder S, Wetegrove S, Zinserling J, Hoeft A, Putensen C (2002) Kinetic and reversibility of mechanical ventilation-associated pulmonary and systemic inflammatory response in patients with acute lung injury. Intensive Care Med 28:834–841
9. Pinhu L, Whitehead T, Evans T, Griffiths M (2003) Ventilator-associated lung injury. Lancet 361:332–340
10. Marini JJ, Gattinoni L (2004) Ventilatory management of acute respiratory distress syndrome: a consensus of two. Crit Care Med 32:250–255
11. Dreyfuss D, Soler P, Saumon G (1992) Spontaneous resolution of pulmonary edema caused by short periods of cyclic overinflation. J Appl Physiol 72:2081–2089
12. Rothen HU, Neumann P, Berglund JE, Valtysson J, Magnusson A, Hedenstierna G (1999) Dynamics of re-expansion of atelectasis during general anaesthesia. Br J Anaesth 82:551–556
13. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, LeGall JR, Morris A, Sprgg R, The Consensus Committee (1994) Report of the American-European consensus conference on ARDS: definitions, mechanisms, relevant outcomes and clinical trial coordination. Intensive Care Med 20:225–232
14. Dreyfuss D, Ricard JD, Saumon G (2003) On the physiologic and clinical relevance of lung-borne cytokines during ventilator-induced lung injury. Am J Respir Crit Care Med 167:1467–1471
15. Wrigge H, Uhlig U, Zinserling J, Behrends-Callsen E, Ottersbach G, Fischer M, Uhlig S, Putensen C (2004) The effects of different ventilatory settings on pulmonary and systemic inflammatory responses during major surgery. Anesth Analg 98:775–781
16. Gajic O, Frutos-Vivar F, Esteban A, Hubmayr RD, Anzueto A (2005) Ventilator settings as a risk factor for acute respiratory distress syndrome in mechanically ventilated patients. Intensive Care Med 31:922–926
17. Richard JC, Maggiore S, Mercat A (2003) Where are we with recruitment maneuvers in patients with acute lung injury and acute respiratory distress syndrome? Curr Opin Crit Care 9:22–27
18. Rothen HU, Sporre B, Engberg G, Wegenius G, Hedenstierna G (1993) Re-expansion of atelectasis during general anaesthesia: a computed tomography study. Br J Anaesth 71:788–795
19. Neumann P, Berglund JE, Mondejar EF, Magnusson A, Hedenstierna G (1998): Dynamics of lung collapse and recruitment during prolonged breathing in porcine lung injury. J Appl Physiol 85:1533–1543