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Diagnostic bronchoalveolar lavage in patients with pneumonia produces sepsis-like systemic effects*

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Abstract. Fever following fiberoptic bronchoscopy occurs in 10–25% of the patients and its origin is not well understood. We prospectively examined changes in body temperature (T°), mean systemic arterial pressure (MAP) and oxygenation after 2 bronchoalveolar lavages (BAL, bronchoscopic and non-bronchoscopic) for 34 procedures in 25 intubated patients. In patients with pneumonia (11 investigations) we observed a rise in T° 3 h after bronchoscopic and non-bronchoscopic BAL, $p < 0.0001$, a decrease in MAP, $p = 0.008$ and arterial oxygenation, $p = 0.002$. Of patients with pneumonia 73% had a rise in T° of more than 1 °C compared with only 17% of those without pneumonia ($p = 0.005$). Patients without pneumonia (23 procedures) had no significant changes in T°, MAP and arterial oxygenation following the 2 BAL procedures. Changes in T° correlated significantly with those in MAP, and with the level of endotoxin in bronchoscopic BAL fluid. These findings suggest that BAL in patients with pneumonia may cause intravascular translocation of toxins or mediators producing pyrogenic and hypotensive effects.

Key words: Bronchoscopy – Nosocomial pneumonia – Sepsis – Endotoxin – Fever – Intensive care unit

Life-threatening complications of flexible fiberoptic bronchoscopy such as serious arrhythmia, bleeding, pneumonia or pneumothorax are rare (0.01–0.3%) [1–4], but seem more frequent in critically ill patients (4%) [5]. Fever, considered as a minor reaction occurs in 10–25% [6–9] of these patients. The mechanism responsible for the fever is thought to be related to an infectious process but no bacteremia has been documented [6, 10, 11]. Systemic hypoxemia during and after bronchoscopy is frequent, especially in critically ill patients with compromized pulmonary gas exchange [5] and can lead to arrhythmia [12, 13]. This can be prevented by increasing the inspired fraction of oxygen [14, 15]. The mechanism of hypoxemia after bronchoscopy is not entirely clear. No serious adverse effects have been reported with bronchoalveolar lavage procedures in ventilated patients [16–18] except for a median decrease in arterial oxygen tension of 8 mmHg [19].

The purpose of the present study was to analyze the physiologic changes of cardiocirculatory and respiratory functions after bronchoscopic and non-bronchoscopic bronchoalveolar lavages in patients with and without pneumonia requiring mechanical ventilation.

Patients and methods

The investigations were performed in 25 critically ill intubated patients hospitalized in our surgical intensive care unit between January and April 1989. A total of 34 bronchoscopic bronchoalveolar lavages (BAL) followed by non-bronchoscopic BAL were performed for the diagnosis of ventilator-associated pneumonia [20]. Comparison of the diagnostic yield of bronchoscopic and non-bronchoscopic BAL was the purpose of another study [20]. The study was approved by the Committee for Ethics in Human Research of our institution and informed consent was obtained by the patient or the next of kin.

Bronchoalveolar lavage procedure

Ten minutes before the procedure the ventilator was set in an assist-controlled mode at an inspired fraction of oxygen (FiO_2) of 1.0 and the patient was sedated with i.v. morphine 0.05–0.1 mg/kg and/or i.v. midazolam 0.1–0.2 mg/kg. Fiberoptic bronchoscopy was then performed through a swivel adaptor (Bodai suction-safe™ Swivel Y, Sontek Medical, Hingham, MA) and the endotracheal tube, and advanced into the tracheobronchial tree with instillation of 10–15 ml of 2% Lidocaine. BAL was performed through the bronchoscope after having obtained a wedged position in the pulmonary lobe corresponding to a localized infiltrate on the chest radiograph. A total of 100 ml sterile isotonic saline was instilled by aliquots of 50 ml. When no or diffuse infiltrates were visible on chest radiograph, BAL was done in the right inferior or middle lobe. A second BAL was then done with a catheter introduced blindly into the tracheobronchial tree until a wedged position was achieved and lavage with 2 aliquots of 50 ml of saline was done. Mean yield for bronchoscopic and non-bronchoscopic BAL was 30%. Patients with the adult respiratory distress syndrome (ARDS) received only a total of 75–100 ml of saline for BAL. Blood gas measure-

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ments were subsequently done every 30–60 min and FiO_2 reduced when PaO_2 allowed it.

Bacteriology and determination of endotoxin

BAL fluids were then immediately sent to our microbiology laboratory, plated out on 4 different media (McConckey, Colistin-nalidixic acid, chocolate and sheep blood agar) using a "Spiral Plater® Volume Deposition" (Spiral system™ Instruments, Inc., Bethesda, MD), allowing quantitative bacterial cultures, and incubated in a 5% CO_2-enriched atmosphere for 48–72 h. Determination of bacterial species were done using standard techniques. Part of the native BAL fluid was rapidly preserved at −70 °C in pyrogen-free tubes for subsequent batched determination of endotoxin using a chromogenic limulus lysate assay (Coatest™, KabiVitrum AG, Küssnacht, Switzerland) as previously described for the other body fluids [21].

Definition of pneumonia

Pneumonia was diagnosed using a clinical pulmonary infection score (CPIS) [20]. This score takes into account 6 "clinical" variables: 1) body temperature; 2) blood leucocytes and band forms; 3) purulence and volume of tracheal secretions; 4) arterial oxygenation; 5) chest radiograph and 6) Gram stain and semiquantitative culture of tracheobronchial aspirates. Each of the variables is given a value of 0–2. When added together, the CPIS is obtained, varying between 0 (no signs of pneumonia) and 12 (marked signs of pneumonia). Patients were considered as having a ventilator-associated pneumonia when the CPIS was greater or equal to 7 points [20]. This scoring system and the threshold value of 7 has been previously observed to be 100% specific and 93% sensitive to detect pneumonia in ventilated patients, i.e. with significant amounts of bacteria in BAL fluid. Significant amounts of bacteria was defined as a bacterial index (sum of the $\log_{10}$ of quantity of the different bacteria cultured in 1 ml of BAL fluid) equal or above 5 [19, 20, 22]. Absence of pneumonia was defined as a CPIS <7 points together with a careful clinical follow-up indicating no subsequent appearance of clinical or bacteriologic signs of pneumonia. In a previous study [20], a current antibiotic treatment slightly lowered the sensitivity to detect pneumonia with quantitative culture of BAL fluid expressed with the bacterial index, from 93 to 87.5%. Histologic pneumonia was confirmed in 3 patients from the pneumonia group who had a necropsy, and excluded in 3 patients without clinical signs of pneumonia who had a post-mortem examination [20].

Clinical variables

Variables such as rectal temperature (T°), arterial oxygenation (expressed as arterial partial pressure of oxygen/inspired fraction of oxygen, PaO_2/FiO_2 ratio) and mean systemic arterial pressure (MAP) were recorded during the 3 h preceeding bronchoscopic and non-bronchoscopic BAL, as well as 1, 3, 5, 7, 10 and 15 h after these 2 procedures.

Statistical analysis

Variation of T°, PaO_2/FiO_2 and MAP were subjected to a one-way analysis of variance for repeated measurements. Correlations and linear regressions were done using the method of the least squares. Comparison of categorical variables were performed with the χ^2-test with the Yates' correction and comparison of unpaired values from two groups using a Mann Whitney U-test. A $p<0.05$ was considered significant. Values are expressed as means±SEM.

Results

General data

In the 25 patients studied, 34 bronchoscopic and non-bronchoscopic BAL were performed. Eleven episodes of pneumonia were diagnosed in 9 patients. Pulmonary infection was excluded 23 times in 16 patients. Characteristics of the patients studied are summarized in Table 1. Bacteriology and endotoxin levels in BAL fluids recovered by bronchoscopy from patients with pneumonia are indicated in Table 2. The bacterial index (BI) of bronchoscopic BAL fluids from patients with pneumonia was 8.3±0.9 (range: from 4.3 to 13.6) and in patients without pneumonia 1.8±0.3 (range: from 0 to 4.7).

Baseline values were obtained by calculating the mean values for the 3 h preceeding the 2 procedures.

Temperature

Baseline values of T° were not significantly different between the two groups of patients with and without pneumonia (38.1±0.2 vs 37.6±0.2 °C, $p = 0.054$). After bronchoscopic and non-bronchoscopic BAL, rectal temperature increased significantly in patients with pneumonia ($p<0.0001$) but not in those without pneumonia (Fig. 1). A rise of more than 1 °C from the baseline value occurred in 73% of the patients with pneumonia compared with 17% of patients without pulmonary infection ($p = 0.005$). Peak T° occurred 3 h after the procedures in patients with pneumonia.

Mean arterial pressure (MAP)

Baseline values of MAP in patients with pneumonia were higher than in those without pneumonia (98±5 vs 79±3 mmHg, $p = 0.005$). ARDS patients had a lower MAP, probably due to the therapeutically induced hypovolemia [23], when compared to other patients of the group without pneumonia (69±4 vs 90±3 mmHg, $p = 0.0037$). Excluding ARDS patients resulted in a non-significant difference of baseline MAP between patients with and without pneumonia (98±5 vs 90±3 mmHg, $p = 0.08$). Including or excluding patients with ARDS did however not affect the significance of changes of MAP and PaO_2/FiO_2 after the 2 BAL procedures. MAP decreased significantly after bronchoscopic and non-bronchoscopic BAL in patients with pneumonia ($p = 0.016$) but not in those without pneumonia (Fig. 2). In patients with pneumonia, the lowest MAP was observed 5 h after the 2 procedures (−10±2.7% compared to baseline).

Table 1. General patient data

Number of patients	25
Number of bronchoscopic and non-bronchoscopic BAL[a] performed	34
Age, years, median (range)	53 (18–75)
APACHE II[b], points, median (range)	12 (4–21)
Duration of intubation in days, median (range)	10 (3–60)
Diagnosis	
Multiple trauma	10
Head trauma	5
Complicated cardiovascular surgery	4
Oesophagectomy	2
Pancreatitis	2
Peritonitis	2
Episodes of pneumonia (%)	11/34 (32%)
Mortality, patients (%)	5/25 (20%)

[a] BAL, bronchoalveolar lavage

[b] APACHE II, Acute physiology and Chronic Health Evaluation II score [34]

Table 2. Quantitative culture, bacterial index, endotoxin level in bronchoscopic BAL fluid and maximum elevation of body temperature ($\Delta T°$) in 9 intubated patients with pneumonia (11 episodes)

Patient and episode no.	Quantitative culture of bacteria in BAL fluid	Bacterial index [22]	Endotoxin level (endotoxin unit/ml)	Maximum $\Delta T°$ (°C)
1.	400 *S. pneumoniae* 240 *Streptococcus* sp. 260 *S. aureus* 160 *C. albicans*	9.6	0.5	1.75
2.	10^6 *H. influenzae* 4×10^3 *S. aureus*	9.6	85.7	1.1
3.	5×10^3 *M. morganii* 600 *Streptococcus* sp.	6.5	22.5	1.65
4.	10^5 *P. aeruginosa* 60 *S. aureus*	6.8	8.3	1.4
5. 1st episode	10^6 *H. influenzae*	6	18.3	1.2
2nd episode	10^4 *Streptococcus* sp. 760 *H. influenzae* 40 *Acinetobacter* sp.	9.5	11.3	1.15
6. 1st episode	10^4 *H. influenzae* 120 *P. vulgaris* 40 *C. albicans*	7.7	15	0.55
2nd episode	160 *H. influenzae* 120 *P. aeruginosa*	4.3	1.9	1.05
7.	10^6 *H. influenzae* 4×10^4 *S. pneumoniae* 10^3 *N. meningitidis*	13.6	12.8	1.25
8.	10^5 *C. albicans*	5	0.3	0.75
9.	5×10^4 *H. influenzae* 5.6×10^3 *S. pneumoniae* 180 *S. aureus*	12.5	7.5	0.4

Arterial oxygenation

Baseline values of PaO_2/FiO_2 in patients with and without pneumonia were not significantly different (30.6 ± 3.2 vs 27.6 ± 3.9 kPa, $p = 0.25$). ARDS patients had significantly lower PaO_2/FiO_2 compared to the other patients without pneumonia (17.5 ± 1.3 vs 42.9 ± 4.2 kPa, $p<0.0001$). Excluding ARDS patients resulted in a significant difference of baseline PaO_2/FiO_2 between patients with and without pneumonia (30.6 ± 2.8 vs 42.9 ± 4.2 kPa, $p = 0.043$), with lower oxygenation in patients with pneumonia. PaO_2/FiO_2 decreased significantly after bronchoscopic and non-bronchoscopic BAL in patients with pneumonia ($p<0.0001$) but not in those without pneumonia (Fig. 2) and lowest PaO_2/FiO_2 was observed 1 h after the 2 procedures ($-25.5\pm5.5\%$ compared to baseline).

Physiological changes and endotoxin levels in BAL fluid

A discrete correlation between the rise of temperature ($\Delta T° = T° -$ baseline T°) and the decrease in mean arterial pressure ($\Delta MAP = MAP -$ baseline MAP) after bronchoscopic and non-bronchoscopic BAL was observed at times 1, 3 and 5 h ($r = 0.4$, $p = 0.03$, $r = 0.37$, $p = 0.048$ and $r = 0.38$, $p = 0.04$ respectively). The best correlation was seen between $\Delta T°$ at time 3 h and ΔMAP at time 5 h after the 2 BAL procedures ($r = 0.55$, $p = 0.002$). Endotoxin levels measured in bronchoscopic BAL fluids from patients with ventilator-associated pneumonia were significantly higher than those from non-infected patients (median: 11.3 Endotoxin Unit/ml (EU/ml), range: 0.3 to 85.7 EU/ml versus 0.1 EU/ml, ≤0.06 to 1.6 EU/ml, $p<0.0001$). A loose correlation was observed between the endotoxin level measured in BAL fluid and $\Delta T°$ at 3 h ($r = 0.37$, $p = 0.031$). No correlation was found between the change in arterial oxygenation and the level of endotoxin in BAL fluid.

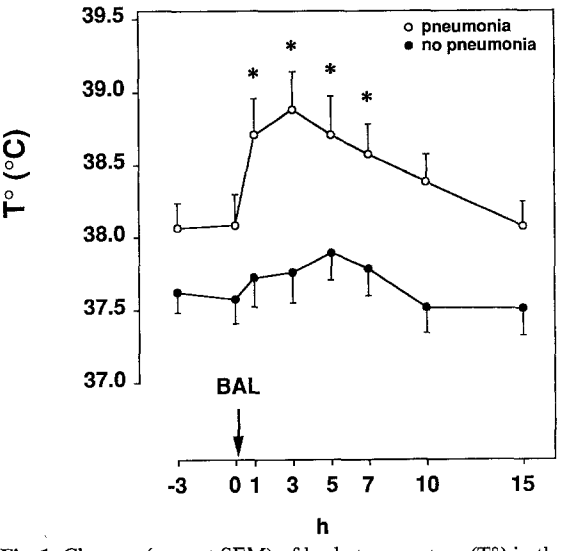

Fig. 1. Changes (mean±SEM) of body temperature (T°) in the 15 h following bronchoscopic and non-bronchoscopic bronchoalveolar lavage (BAL) obtained from patients with pneumonia ($n = 11$) and without pneumonia ($n = 23$). T° increase was significant only in patients with pneumonia ($p<0.0001$). *Asterisks* indicate significant changes compared to baseline

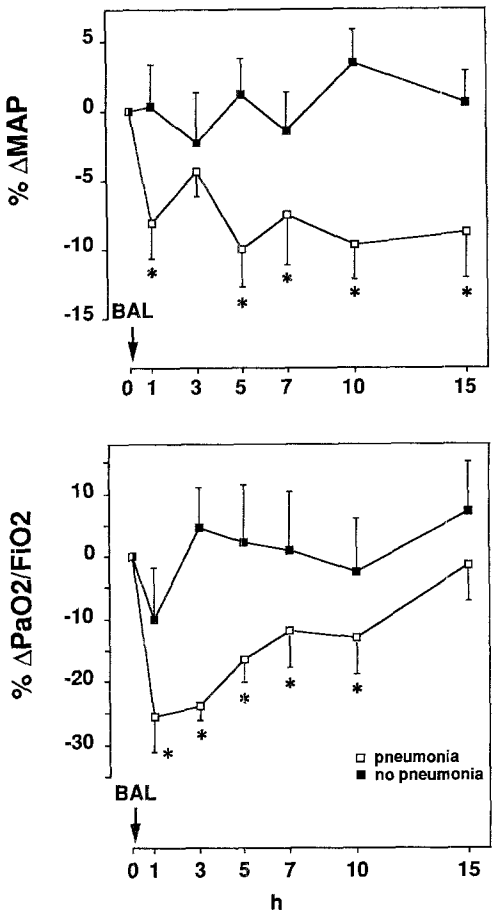

Fig. 2. Percent changes (mean ± SEM) of mean systemic arterial pressure (% ΔMAP) [top] and percent changes of PaO_2/FiO_2 ratio (% $\Delta PaO_2/FiO_2$) [bottom] in the 15 hours following bronchoscopic and non-bronchoscopic BAL obtained from patients with pneumonia ($n = 11$) and without pneumonia ($n = 23$). Changes were significant only in patients with pneumonia (ΔMAP, $p = 0.016$ and $\Delta PaO_2/FiO_2$, $p < 0.0001$). *Asterisks* indicate significant changes compared to baseline

Discussion

The present investigation reveals significant changes in cardiorespiratory function and body temperature following bronchoscopic and non-bronchoscopic bronchoalveolar lavage (BAL) in patients with pneumonia but not in those without pulmonary infection undergoing these procedures. Fever post-fiberoptic bronchoscopy, with or without ancillary maneuvers such as brushing, lavage or transbronchial needle aspiration occurs in 10–25% of non-intubated patients [6–9]. The reason for thermic elevation remains unclear. After rigid bronchoscopy, hyperthermia has occasionally been associated with bacteremia [24]. With the flexible bronchoscope, no bacteremia could be documented to explain fever occurring after the procedure [6, 7, 9, 10]. An infectious mechanism is thought to be the source of this phenomenon, but this has never been confirmed. Few studies were done on fiberoptic bronchoscopy in critically ill patients and data on frequency and origin of post-bronchoscopy fever are lacking [5, 25].

In our series, fever after bronchoscopic and non-bronchoscopic BAL (rise of more than 1 °C) occurred in 73% of the intubated patients with pneumonia and in 17% of patients without pneumonia. Similarly a significant decrease in systemic arterial pressure occurred only in patients with pulmonary infections. Experimental endotoxinemia in humans is associated with hyperthermia and hypotension [26]. Our patients with pneumonia had body temperature and systemic arterial pressure changes after the BAL procedures comparable to those observed in healthy volunteers receiving intravenous endotoxin injection [26]. The delay for peak temperature (3 h) and lowest mean arterial pressure (5 h) was similar in both studies. In addition, a significant correlation was observed between changes in temperature and those of mean arterial pressure after bronchoscopic and non-bronchoscopic BAL. These findings suggest that a sepsis-like mechanism, possibly endotoxin-mediated may be responsible for fever and decrease in systemic arterial pressure after these procedures. Trouillet et al. [27] observed increased mean heart rate and cardiac output after fiberoptic bronchoscopy, similar to findings in patients with endotoxinemia or septic shock [26]. Endotoxin tests were found to be of limited value for detection of endotoxinemia. Endotoxin blood levels, able to produce systemic effects, are very low (as low as 0.1 ng), below or very close to the limit of detection of tests such as the limulus lysate assay [21]. However, in more heavily infected body fluids like BAL, endotoxin can be valuable for the diagnosis of Gram-negative infections [28, 29].

Significant amounts of endotoxin were present in BAL fluid in our patients with Gram-negative pneumonia. Of the patients without pneumonia 17% also had fever after the BAL procedures. This could be due to the presence of Gram-negative bacteria colonizing the lower airways, a frequent observation in intubated patients. Studies on BAL in ventilated patients do not describe serious adverse effects of this procedure [16–18]. Only Guerra et al. reported a small decrease (median 8 mmHg) in arterial oxygenation after BAL [19]. However, mild physiologic changes like those observed in our study in a subgroup of patients could have been missed in other investigations.

We postulate that bronchoscopic and non-bronchoscopic BAL could be responsible for a translocation of endotoxin from colonized or infected lower airways into the blood stream or lymph channels through an impaired alveolar-capillary barrier due to infection. The passage of endotoxin or other bacterial products into the circulation can lead to mediator release such as tumor necrosis factor and interleukins [30] and to systemic responses like fever, hypotension and hyperdynamic state, similar to sepsis. Further studies with dosage of these mediators are needed to confirm this hypothesis. Moreover, we observed these physiologic changes after 2 BAL procedures. The type and severity of such changes after a single BAL in ventilated patients remain to be defined.

Hypoxemia during fiberoptic bronchoscopy can occur, leading to arrhythmia, but is preventable by increasing FiO_2 [12–15]. Several mechanisms could be implicated in the fall of PaO_2: decreased tidal volume due to high airway resistance caused by the bronchoscope, i.e. an obstruction of 50% when used through a 8-mm endotracheal tube [31]; suction through the bronchoscope and

changes in functional residual capacity [32, 33]. Persisting hypoxemia or a fall of the PaO_2/FiO_2 ratio after bronchoscopic and non-bronchoscopic BAL are probably due to other mechanisms. In our study, patients with pneumonia had a more pronounced and prolonged decrease in arterial oxygenation than patients without pneumonia, but no correlation was found with the level of endotoxin in BAL. An increased shunt effect secondary to filling of alveoli with BAL could be due to a reduced reserve of infected lungs and possibly cause prolonged impaired oxygenation. Return to baseline occurred within 15 h in our study, corresponding possibly to the time necessary to reabsorb the 200 ml of saline used for the 2 BAL procedures.

In conclusion, the data of the present study show that fever and decrease in systemic arterial pressure are frequent after BAL procedures in patients with pneumonia. These changes have a time course very similar to effects of experimental endotoxinemia in human volunteers [26]. This suggests that endotoxin, other bacterial products or cytokines may be translocated from the lower airways to the systemic circulation by these procedures. Arterial hypoxemia is more pronounced and of longer duration in patients with pneumonia than in those without pulmonary infection, possibly due to the effect of BAL and/or endotoxin mobilization on alveolar-capillary gas exchange.

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