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ORIGINAL

Effects of bronchoalveolar lavage volume on arterial oxygenation in mechanically ventilated patients with pneumonia

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Abstract *Objective:* To assess the effect of bronchoalveolar lavage (BAL) volume on arterial oxygenation in critically ill patients with pneumonia.
Design: Randomized clinical comparison.
Setting: Six-bed respiratory intensive care unit of a 850-bed tertiary care university hospital.
Patients: Thirty-seven intubated and mechanically ventilated patients with clinical suspicion of pneumonia.
Interventions: Bronchoscopically guided protected specimen brush (PSB) followed by either a "high volume" BAL ($n = 16$, protected catheter, mean volume: 131 ± 14 ml) or a "low volume" BAL ($n = 21$, protected double-plugged catheter, 40 ml volume for all patients).
Measurements: Arterial oxygen tension/fractional inspired oxygen (PaO_2/FIO_2) and mean arterial pressure (MAP) before and up to 24 h after the intervention. Bacterial growth in quantitative cultures. Analysis of variance for repeated measurements with inter-subject factors.
Results: All patients showed a lower PaO_2/FIO_2 ratio and higher MAP after the diagnostic procedure, without differences between the study arms ($p = 0.608$ and $p = 0.967$, respectively). Patients with significant bacterial growth ($p = 0.014$) and patients without preemptive antibiotic ($p = 0.042$) therapy showed a more profound and longer decrease in arterial oxygenation after the diagnostic procedure.
Conclusions: A decrease in the PaO_2/FIO_2 ratio was observed in all patients after a combined diagnostic procedure, independent of the BAL volume used. A significant bacterial burden recovered from the alveoli and no preemptive antibiotic therapy were associated with a larger and longer-lasting decrease in arterial oxygenation.

Key words Critically ill patients · Intensive care unit · Pneumonia · Diagnostic methods · Bronchoalveolar lavage · Oxygenation · Follow-up

Introduction

Fiberoptic procedures are useful in diagnosing nosocomial pneumonia and the tolerance of a bronchoalveolar lavage (BAL) is usually good, even in ventilated patients. Serious complications such as arrhythmia, bleeding or pneumothorax are rare [1, 2, 3] and acute hemodynamic effects are small [4, 5]. The effects of BAL on

gas exchange vary according to the patient group investigated and the duration of the follow-up period. A deterioration in arterial oxygenation is commonly described after BAL in the general population [6, 7] and in intubated critically ill patients [1, 8, 9]. Papazian and coworkers described a sustained decrease in PaO_2 after 1 h in critically ill patients, but did not follow them up thereafter [4]. Likewise, PaO_2 values were 20 % lower 2 h after BAL in another study in intubated patients, but the systematic follow-up was then discontinued [10]. In a study with a longer follow-up in critically ill, intubated patients, arterial oxygenation returned to baseline values only after 15 h [11].

The reasons for a decrease in arterial oxygenation after bronchoscopic BAL have not been clearly determined, but the volume of the lavage fluid and pneumonia could be contributing factors [11]. In this study, we therefore compared arterial oxygenation after the diagnostic bronchoscopic procedure including either a low-volume or a high-volume BAL in a randomized clinical comparison. In addition, we analyzed the effects of the bacterial burden recovered from the lungs and a preemptive antibiotic therapy on arterial oxygenation after the diagnostic procedure.

Material and methods

Population and design of the study

This randomized prospective study was conducted in the Hospital Clinic, a 850-bed university tertiary care hospital with six intensive care units (ICUs). All intubated and mechanically ventilated patients with clinical suspicion of pneumonia and without exclusion criteria were eligible for this study. Only the first episode of pneumonia during one hospitalization was studied.

- Clinical suspicion of pneumonia was given in the presence of new and persistent infiltrates (≤48 h) on the chest radiograph and at least two of the following three criteria on the day of the first appearance of the chest infiltrates: fever (≤38.3 °C), leukopenia or leukocytosis (≤4,000 or ≥12,000 mm^3), and purulent tracheal secretions [12].
- Exclusion criteria were: (1) clinically unstable condition (e.g. cardiac arrhythmia, acute ischemic heart disease), (2) known increased intracranial pressure, (3) small diameter endotracheal tube (≤7 mm) and (4) acute respiratory distress syndrome (ARDS) [13].

Patients were randomized when informed consent had been obtained from the next-of-kin. The patients included were randomly allocated to either low-volume or high-volume BAL by a computer-generated list. The allocation table was generated and disclosed by an independent person not an author of this paper. The study was approved by the ethics committee and conducted in accordance with its guidelines.

Data collection and clinical variables

Anthropometric characteristics were recorded and clinical data (mean arterial blood pressure (systolic pressure + 2 x diastolic pressure /3), fluid balance, red blood cell count, white blood cell count and other laboratory parameters were used for calculating severity of illness scores (SAPS II) [14]. Preemptive therapy with antimicrobial drugs was noted (any intravenous application for at least 24 h within 7 days prior to sampling of lower respiratory tract specimens). Blood samples were anaerobically collected through a polyethylene catheter (Seldicath, Plastimed, Saint-Leu-La-Fôret, France) inserted into the radial artery. Samples were immersed in ice and processed within 5 min in a blood gas analyzer (Radiometer, Copenhagen, Denmark). Arterial oxygen tension/fractional inspired oxygen (PaO_2/FIO_2) was then calculated for the following time points: before [T0] and immediately after the procedure [T+] and one [T1], three [T3], five [T5], ten [T10] and 24 [T24] h thereafter. Mean arterial pressure (MAP) was measured at T0, T1, T3, T5, T10 and T24. The duration of the entire diagnostic procedure from introduction until final removal of the bronchoscope was noted.

Sampling procedure

All investigations were performed consecutively during one session. The fiberoptic bronchoscopic examination was performed (Pentax FB18, Asahi Optical, Japan) after patients had been premedicated either with propofol or midazolam intravenously according to the applied sedation. No local anesthetics were administered, central airways were cleared prior to bronchoscopy with an endotracheal catheter to ensure bronchoscopic vision and to avoid suction with the bronchoscope. A special endotracheal adapter was used in order to continue mechanical ventilation. Patients were ventilated with volume control during bronchoscopy and ventilator settings were readjusted to pre-BAL values within 1 h. During bronchoscopy FIO_2 was set to 100 % and reduced according to the clinical condition after the procedure within 1 h. No bagging or other recruitment maneuvers were employed after the procedure. Bronchodilators were not given on a routine basis before or after the procedure, however, patients with chronic obstructive pulmonary disease (COPD) received a standardized protocol of nebulized β-2-agonists 4 times daily.

All microbiological sampling was performed in the pulmonary lobe corresponding to a localized infiltrate on the chest radiograph. First, a protected specimen brush (PSB; Microbiology Brush, Mill-Rose Laboratory, Ohio, USA) was used as described by Wimberley and coworkers [15]. After advancing the protected lavage catheter via the bronchoscope (Protected Bronchoalveolar Lavage Balloon Catheter, Mill-Rose Laboratory, Ohio, USA) BAL was performed according to Meduri and coworkers [16]. Up to five aliquots of 30 ml physiologic saline were instilled (range 90–150 ml) for BAL ("high volume"). In patients assigned to "low volume", a plugged lavage catheter (Combicath, Plastimed, Saint-Leu-La-Fôret, France) was guided bronchoscopically and two aliquots of 20 ml saline were used for BAL ("low volume").

Ventilatory parameters were recorded before and 1, 3, 5, 10 and 24 h after BAL and an attempt was made to maintain mechanical ventilation parameters constant throughout the follow-up. No positive end-expiratory pressure (PEEP) was applied during the diagnostic procedures and all patients received empirical antibiotic therapy after the diagnostic procedure [17].

Table 1 Comparison of general data for patients assigned to low-volume and high-volume bronchoalveolar lavage (*BAL* bronchoalveolar lavage, *COPD* chronic obstructive pulmonary disease, FIO_2 fractional inspired oxygen concentration, PaO_2 arterial oxygen tension, $PaCO_2$ arterial carbon dioxide tension, *SAPS II* Simplified Acute Physiology Score)

Parameters	Low-volume BAL ($n = 21$)	High-volume BAL ($n = 16$)	p value (95 % CI)
Age (years ± SD)	62 ± 17	61 ± 20	0.854 (–13.4 to 11.2)
Male, *n* (%)	13 (62)	13 (81)	0.285 (–9.3 to 47.3)
Smokers, *n* (%)	16 (76)	12 (75)	1.0 (–27.0 to 29.0)
Presence of comorbid illnesses, *n* (%)	14 (67)	12 (75)	0.876 (–21.2 to 37.2)
Causes of acute respiratory failure			
Exacerbated COPD, *n* (%)	9 (43)	7 (44)	0.957 (–31.2 to 33.2)
Aspiration, *n* (%)	2 (10)		0.315 (–2.8 to 22.8)
Post-surgical, *n* (%)	6 (29)	7 (44)	0.338 (–16.1 to 46.1)
Cardio-vascular	1	4	
Abdominal	4	2	
Neurosurgical	1	1	
Polytrauma, *n* (%)	2 (10)	2 (13)	1.0 (–17.9 to 23.9)
Others, *n* (%)	2 (10)	1 (6)	1.0 (–13.3 to 21.3)
SAPS II	8.8 ± 3.0	10.0 ± 2.3	0.189 (–0.61 to 3.0)
PaO_2/FIO_2 ratio ± SD	260 ± 106	277 ± 119	0.641 (–58 to 94)
$PaCO_2$, mmHg ± SD	36.1 ± 6.9	40.5 ± 10.5	0.639 (–7.7 to 4.8)
Mechanical ventilation, h ± SD (prior to BAL)	146 ± 165	120 ± 150	0.619 (–134 to 81)
Preemptive antibiotic therapy, *n* (%)	9 (43)	10 (63)	0.236 (–11.7 to 51.7)

Microbiological investigations

All samples were processed within 30 min. Samples were quantitatively plated on blood, chocolate, Wilkins-Chalgren and Sabouraud agar media in serial dilutions of 1:10, 1:100 and 1:1,000. If negative, the plates were abandoned after 3 days of testing for aerobic bacteria and after 4 weeks of testing for fungi. If positive, results were expressed as colony-forming units (cfu) per milliliter. Identification as well as susceptibility testing was performed using standard methods [18]. For purposes of analysis, only potentially pathogenic microorganisms (PPM) were taken into account. The following microorganisms were excluded as non-PPMs: *Streptococci spp.* except *Streptococcus pneumoniae, coagulase-negative Staphylococci, Neisseriae spp., Corynebacteriae spp.* and *Candida spp.*. Thresholds for significant growth of PPMs were: $\geq 10^3$ cfu/ml in PSB, and $\geq 10^4$ cfu/ml in BAL cultures.

Statistical analysis

The primary objective of this study was to compare arterial oxygenation after BAL with a low and a high lavage volume in a population of patients with clinical suspicion of pneumonia. A secondary objective was to investigate the possible role of viable bacteria within the lavage fluid in a concentration that has been accepted as microbiological confirmation of pneumonia [19]. Absolute and relative changes of arterial oxygenation over time were analyzed with a one-way analysis of variance for repeated measurements (ANOVA). The effect of the diagnostic procedure was assessed by comparing all consecutive values to the pre-BAL value (T0) as reference value (intra-individual comparison). Results of this analysis are reported for each follow-up time point (T+, T1, T3, T5, T10 and T24). The effect of the BAL volume was compared by introducing "low or high volume" as an inter-subject factor into the ANOVA model. Using this method it is possible to analyze whether the changes that are observed over time depend on the volume of the BAL. The results are reported as the interaction term between time and BAL volume (inter-individual comparison). This analysis was repeated for absolute values of MAP.

The secondary objective of this study was to assess the confounding role of the bacterial burden of the lung and the effect of antibiotic treatment on arterial oxygenation after the diagnostic procedure. To assess these effects accurately we included the results of quantitative cultures ("no significant growth" versus "significant growth") and antibiotic pre-treatment ("yes" versus "no" according to the definition given above) as additional inter-subject factors in the statistical model. The results are also reported as the interaction terms between time and pneumonia and time and preemptive antibiotic therapy, respectively.

Moreover, frequencies were compared with χ^2-test or Fisher's exact test, where appropriate. Differences in means were analyzed by Student's *t*-test. All data were processed with SPSS on a Windows 98 operating system. The level of significance was set at 5 % (all two-tailed). Data are reported as counts or mean ± standard deviation (SD).

Results

Study population

A total of 289 patients were admitted to our respiratory ICU during the study period and 64/289 (22 %) fulfilled the criteria for clinical suspicion of pneumonia. Among those, 14/64 (22 %) patients had at least one exclusion criterion and informed consent was denied or not available in 10/65 (16 %) patients. The remaining 40 patients were randomly assigned to a diagnostic procedure in-

Table 2 Ventilator settings and supplemental oxygen before the diagnostic procedure and during the follow-up period. No significant changes were observed for the comparison of the two groups during follow-up (p = n.s.) (*BAL* bronchoalveolar lavage, *FIO_2* fractional inspired oxygen concentration, *PEEP* positive end-expiratory pressure)

Mechanical ventilation	Low-volume BAL (n = 21)	High-volume BAL (n = 16)	p value (95 % CI)
FIO_2 (%)			
Before BAL	44.6 ± 11.8	46.7 ± 19.2	0.745 (–10.7 to 14.7)
1 h	50.7 ± 16.9	44.2 ± 14.4	0.302 (–19.4 to 6.3)
3 h	51.4 ± 17.9	49.2 ± 18.8	0.756 (–17.1 to 12.6)
5 h	49.3 ± 13.8	47.5 ± 14.2	0.749 (–13.2 to 9.5)
10 h	52.9 ± 20.2	46.0 ± 17.8	0.398 (–23.4 to 9.6)
24 h	49.2 ± 15.5	46.0 ± 17.8	0.647 (–17.7 to 11.2)
PEEP≥5 cmH_2O (n (%))			
Before BAL	4 (31)	4 (16)	0.704 (–11.7 to 41.7)
1 h	5 (24)	4 (25)	0.615 (–27.1 to 29.0)
3 h	5 (24)	5 (31)	0.444 (–22.1 to 36.1)
5 h	4 (19)	4 (25)	0.482 (–21.1 to 33.1)
10 h	4 (19)	1 (6)	0.266 (–7.4 to 33.4)
24 h	4 (19)	1 (6)	0.266 (–7.4 to 33.4)
Plateau pressure (cmH_2O)			
Before BAL	20.5 ± 5.4	21.8 ± 8.1	0.640 (–4.4 to 6.9)
1 h	20.7 ± 6.2	23.7 ± 8.6	0.319 (–3.0 to 8.9)
3 h	19.2 ± 6.0	22.7 ± 8.1	0.244 (–2.6 to 9.6)
5 h	19.7 ± 4.6	23.3 ± 7.0	0.145 (–1.4 to 8.7)
10 h	19.8 ± 5.1	22.5 ± 3.2	0.156 (–1.1 to 6.6)
24 h	19.1 ± 4.3	23.0 ± 4.2	0.051 (–0.2 to 7.8)
Peak pressure (cmH_2O)			
Before BAL	31.4 ± 7.8	30.4 ± 7.6	0.756 (–7.3 to 5.4)
1 h	29.6 ± 7.4	31.8 ± 8.3	0.494 (–4.2 to 8.5)
3 h	28.3 ± 6.4	29.9 ± 7.4	0.580 (–4.2 to 7.4)
5 h	28.3 ± 5.0	30.8 ± 7.1	0.314 (–2.6 to 7.8)
10 h	27.3 ± 5.2	30.9 ± 3.8	0.087 (–0.6 to 7.7)
24 h	28.4 ± 5.5	31.7 ± 5.5	0.182 (–1.7 to 8.4)
Tidal volume (ml)			
Before BAL	635.7 ± 116.9	727.9 ± 86.3	0.056 (–2 to 186)
1 h	622.5 ± 143.8	700.3 ± 81.4	0.149 (–30 to 180)
3 h	657.3 ± 120.6	690.1 ± 85.3	0.507 (–69 to 135)
5 h	648.4 ± 127.0	716.6 ± 71.5	0.180 (–35 to 171)
10 h	652.4 ± 119.0	711.3 ± 89.8	0.315 (–62 to 180)
24 h	689.6 ± 160.8	718.2 ± 79.0	0.693 (–123 to 180)
Minute ventilation (l/min)			
Before BAL	8.2 ± 2.4	9.9 ± 2.1	0.088 (–0.3 to 3.5)
1 h	8.7 ± 2.3	9.9 ± 2.1	0.190 (–0.6 to 3.0)
3 h	8.8 ± 2.5	10.0 ± 2.2	0.238 (–0.8 to 3.1)
5 h	8.8 ± 2.5	10.0 ± 2.2	0.238 (–0.8 to 3.1)
10 h	8.8 ± 2.5	9.7 ± 1.7	0.365 (–1.0 to 2.8)
24 h	8.3 ± 2.0	9.7 ± 1.7	0.105 (–0.3 to 3.1)

cluding either a low-volume (21/40, 53 %) or high-volume BAL (19/40, 47 %). Two patients had to be excluded from analyses because specimens were not available for quantitative cultures and one patient because the pulmonary infiltrate was due to atelectasis and resolved immediately after bronchoscopy (all three were allocated to high-volume BAL).

The clinical characteristics of the 37 patients analyzed (low-volume, n = 21, 57 %, high-volume, n = 16, 43 %) are compared in Table 1. No significant differences were observed for all comparisons made. The mean total amount of saline instilled was 131 ± 14 ml for the high-volume BAL and 40 ml for all patients with low-volume BAL (95 % CI 85–97 ml, $p < 0.001$). The mean duration of the diagnostic procedures tended to be longer with the high-volume BAL, but the difference was not significant (high-volume: 4.8 ± 1.4 min, low-volume: 4.0 ± 1.0 min, 95 % CI –0.8 to 1.6, $p = 0.077$). The clinical suspicion of pneumonia could be confirmed by quantitative bacterial cultures (growth above the defined thresholds) in 20/37 patients (54 %). The pathogens recovered were: *S. pneumonia* (6), *P. aeruginosa* (5), methicillin-sensitive *S. aureus* (4), *Citrobacter spp.* (4), *H. influenzae* (3), methicillin-resis-

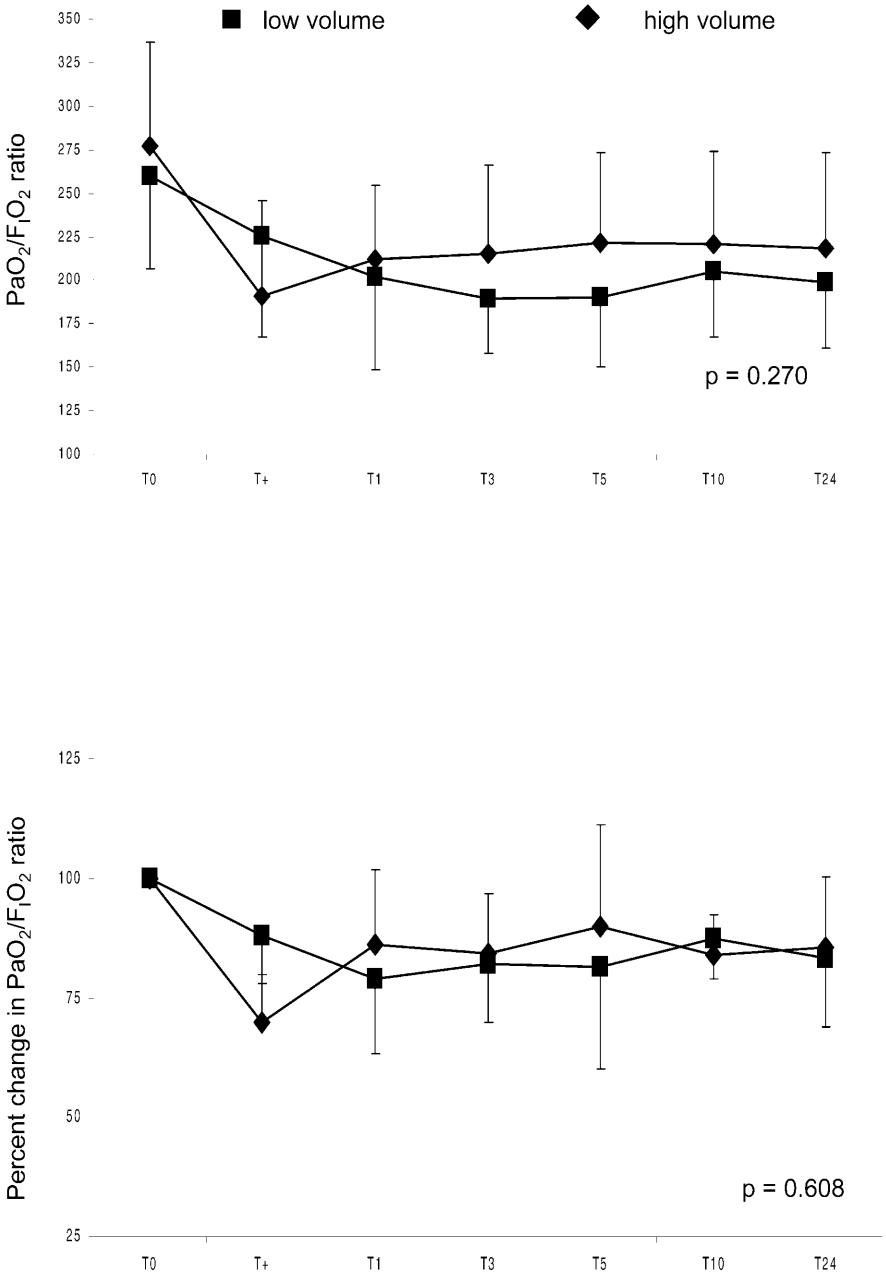

Fig. 1 Time course of the PaO_2/FIO_2 ratio after a bronchoscopically guided procedure involving either a low-volume (*filled squares*, $n = 21$) or high-volume bronchoalveolar lavage (*filled rhombi*, $n = 16$): before [T0], immediately after BAL [T+] and one [T1], three [T3], five [T5], ten [T10] and 24 h follow-up [T24]. Probability values represent the interaction term between the time course and lavage volume. No differences between study arms were found between absolute values of the PaO_2/FIO_2 ratio (**upper panel**) and the PaO_2/FIO_2 ratio expressed as percent change from baseline (**lower panel**)

tant *S. aureus* (3), *E. coli* (2), *Stenotrophomonas maltophilia* (2), *Serratia spp.* (1).

The proportion of patients with microbiologically confirmed pneumonia was significantly higher among patients who had received a diagnostic procedure including a low-volume BAL (15/21, 71 %) compared to patients who were investigated with high-volume BAL (5/16, 31 %, 95 % CI 10.2–69.8, $p = 0.015$). The percentage of patients who had received preemptive antibiotic therapy was comparable between the study groups. However, pneumonia could be microbiologically confirmed in fewer patients with a preemptive antibiotic therapy (5/19, 26 %) compared to those without (15/18, 83 %, 95 % CI 30.7–83.3, $p = 0.001$).

Mechanical ventilation

All patients were ventilated with volume control during BAL without extrinsic PEEP. The ventilator settings after the diagnostic procedure are summarized in Table 2. There was a trend towards higher airway pres-

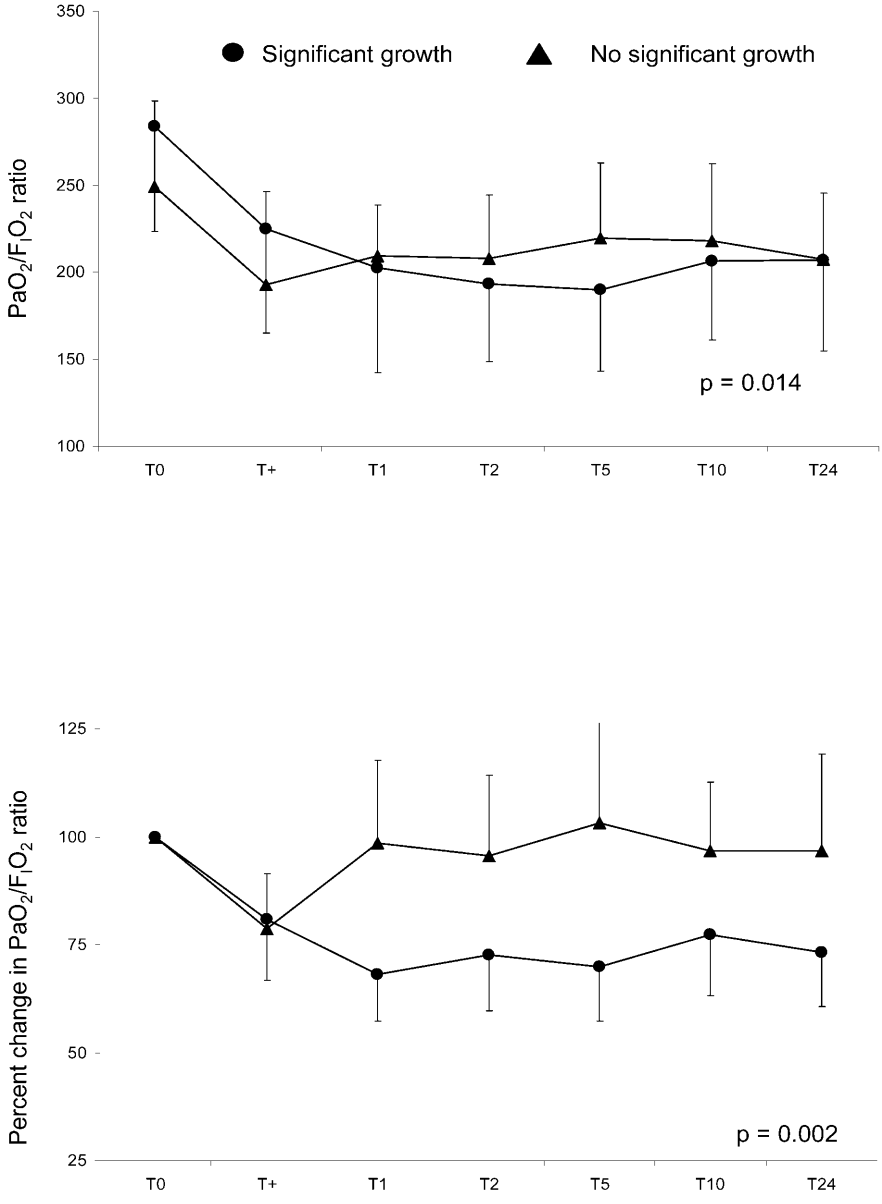

Fig. 2 Time course of the PaO_2/FIO_2 (absolute values, **upper panel**, values expressed as percent change from baseline, **lower panel**) ratio after a bronchoscopically guided diagnostic procedure. Patients with significant bacterial growth (*filled circles*, $n = 20$) experienced a more profound decrease in arterial oxygenation that lasted for a longer time as compared to patients with sterile cultures or without significant bacterial growth (*filled triangles*, $n = 17$). Probability values represent the interaction term between the time course and the results of quantitative bacterial cultures

sures and ventilation volumes in the group of patients who had been investigated with a high-volume BAL. The ventilator settings were not modified significantly compared with pre-BAL values during the follow-up (Table 2).

Arterial oxygenation and arterial carbon dioxide tension

The baseline PaO_2/FIO_2 ratio was 268 ± 110 for all patients and was not significantly different between the study groups (Table 1). The PaO_2/FIO_2 ratio, however, decreased significantly after the diagnostic procedure and was different from baseline during the entire follow-up period (T+: 210 ± 113, T1: 206 ± 97, T3: 200 ± 82, T5: 203 ± 90, T10: 212 ± 89, T24: 207 ± 90, $p < 0.001$ for all comparisons to baseline). However, these changes did not depend on the BAL volume utilized in the diagnostic procedure ($p = 0.270$, Fig. 1, upper panel).

When the changes in PaO_2/FIO_2 ratio were expressed as changes in percent from baseline, all follow-up values, except the measurement at 5 h, were significantly lower than baseline (T+: 80 ± 27 %, $p < 0.001$, T1: 82 ± 34 %, $p = 0.008$, T3: 83 ± 33 %, $p = 0.008$, T5: 85 ± 43 %, $p = 0.075$, T10: 86 ± 31 %, $p = 0.023$, T24: 84 ± 37 mmHg, $p = 0.022$). However, again these chan-

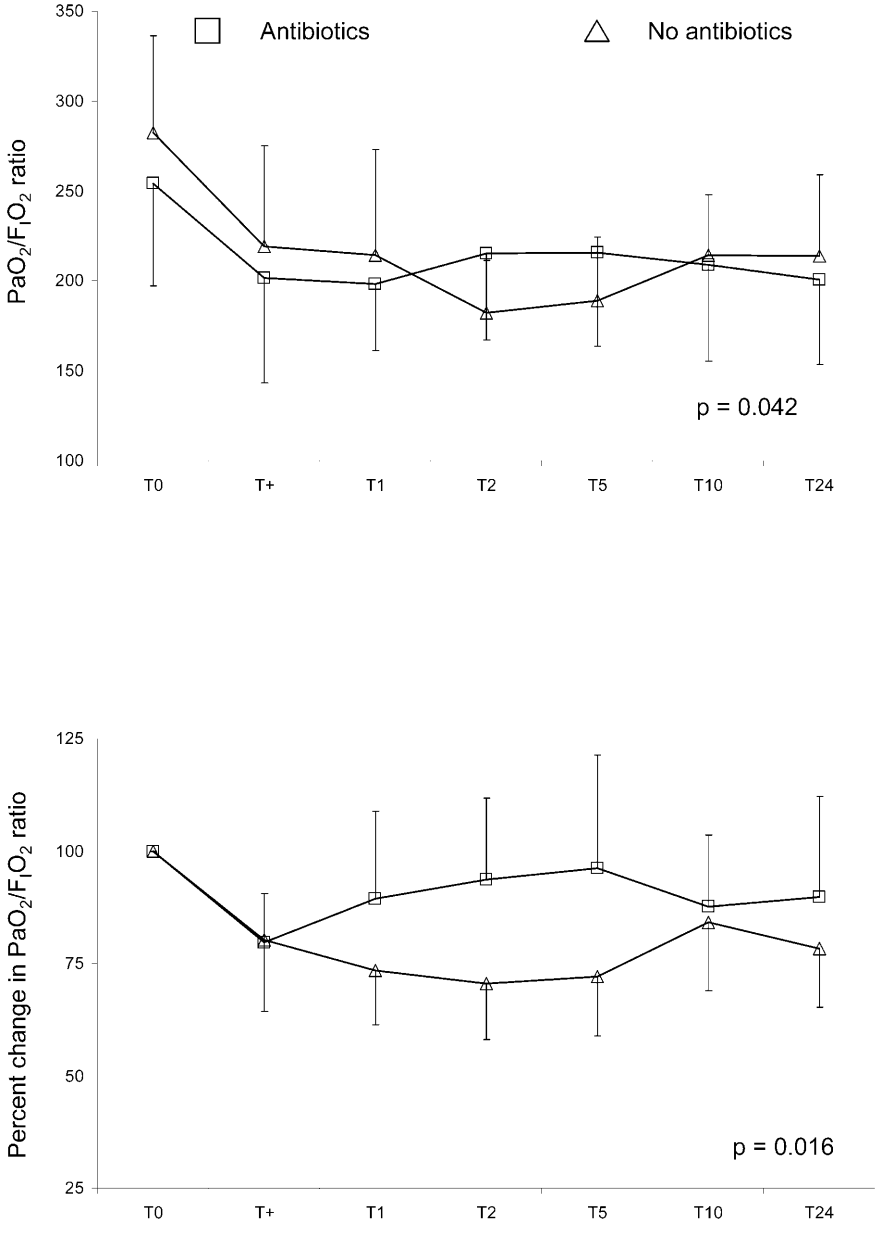

Fig. 3 Time course of the PaO_2/FIO_2 ratio (absolute values, **upper panel**, values expressed as percent change from baseline, **lower panel**) after a bronchoscopically guided diagnostic procedure. Patients without preemptive antibiotic therapy (*open triangles*, $n = 18$) experienced a more profound decrease in arterial oxygenation that lasted for a longer time as compared to pre-treated patients (*open squares*, $n = 19$). Probability values represent the interaction term between the time course and preemptive antibiotic therapy

ges did not depend on the BAL volume used in the diagnostic procedure ($p = 0.608$, Fig. 1, lower panel).

When the results of the quantitative bacterial cultures were introduced as an inter-subject factor into the analysis, we found that the decrease in the PaO_2/FIO_2 ratio was significantly more pronounced in the group of patients with significant bacterial growth (Fig. 2). Patients with significant growth in quantitative bacterial cultures experienced a longer and more significant decrease in the absolute value of the PaO_2/FIO_2 ratio compared to patients without significant growth or sterile cultures ($p = 0.014$, Fig. 2, upper panel). This difference was even more clear when the PaO_2/FIO_2 ratio was expressed as percent change from baseline ($p = 0.002$, Fig. 2, lower panel).

A similar pattern was observed when preemptive antibiotic therapy was analyzed as an inter-subject factor. Preemptive antibiotic therapy seemed to be a protective factor for a decrease in the absolute PaO_2/FIO_2 ratio ($p = 0.042$, Fig. 3, upper panel) and the PaO_2/FIO_2 ratio expressed as percent change from baseline ($p = 0.016$, Fig. 3, lower panel) alike.

Arterial partial pressure of carbon dioxide was 38.6 ± 9.0 mmHg before the diagnostic procedure and rose to 45.9 ± 11.5 mmHg thereafter for all patients ($p < 0.001$). However, the changes did not depend on

the BAL volume ($p = 0.169$), the results of quantitative cultures ($p = 0.630$) or a preemptive antibiotic therapy ($p = 0.402$).

Mean arterial pressure

Mean arterial pressure was 82 ± 18 mmHg in all patients before the diagnostic procedure and increased significantly thereafter (T1: 99 ± 14 mmHg, $p = 0.002$, T3: 103 ± 16 mmHg, $p < 0.001$, T5: 101 ± 17 mmHg, $p = 0.001$, T10: 100 ± 18 mmHg, $p = 0.003$, T24: 102 ± 19 mmHg, $p = 0.002$). The time course of the MAP was not significantly different in the two study arms ($p = 0.967$) between patients with and without significant growth in quantitative bacterial cultures ($p = 0.906$) or between patients with and without preemptive antibiotic treatment ($p = 0.365$).

Discussion

The main findings of this study were: (1) The arterial oxygenation was significantly lower up to 24 h after a combined diagnostic procedure with bronchoscopically guided PSB and BAL in critically ill patients with pneumonia. (2) Arterial oxygenation after the diagnostic procedure did not depend on the lavage volume. (3) The decrease in arterial oxygenation after the diagnostic procedure was significantly smaller in patients with negative quantitative bacterial cultures (or with growth below the threshold) or in those with preemptive antibiotic therapy.

Bronchoalveolar lavage is regarded as a safe and valid tool for the evaluation of ventilator-associated pneumonia, even in critically ill patients [4, 5, 8, 9, 20]. Most authors observed a fall in oxygenation after BAL and we could corroborate this finding. However, we were the first to include a 24-h follow-up period and we observed lower arterial oxygenation after the diagnostic procedure during the entire period. The mechanisms leading to the decrease in oxygenation after BAL are not fully understood. Further worsening of ventilation-perfusion mismatch through alveolar derecruitment, increased pulmonary shunting or both have been suggested as possible explanations [10]. Pugin and Suter observed that oxygenation after BAL did not return to baseline before 15 h [11]. They argued that this period probably corresponds to the time necessary to reabsorb the lavage fluid. If this were the case, the amount of lavage fluid instilled should play a role for the time course of arterial oxygenation after BAL. In our randomized clinical trial we compared a low-volume (40 ml for all patients) and a high-volume (mean volume 131 ± 14 ml) BAL and found no differences in the decrease of arterial oxygenation between these two groups. This has been described before in non-intubated, non-critically ill patients [6], where a larger lavage volume (200 ml versus 100 ml) was associated with a greater maximum decrease of arterial saturation of oxygen (SaO_2), but no differences in SaO_2 were found after 5 min of follow-up. This indicates that the lavage volume may not be a crucial factor for the decrease in oxygenation after the procedure.

All the patients in our study had at least a clinical suspicion of pneumonia and the diagnostic procedure was indicated to assess the bacterial burden of the lungs. We were therefore also able to relate the time course of arterial oxygenation after the diagnostic procedure to the results of quantitative bacterial cultures. We found pneumonia to be significantly more often microbiologically confirmed in patients receiving low-volume BAL. One might argue that – since we used concentrations – the low volume may have resulted in a higher concentration and thus more positive diagnoses. Papazian and coworkers compared BAL and mini-BAL with histology, which can be regarded as the gold standard for the diagnosis of pneumonia. They found the bacterial index to be similar with BAL and mini-BAL [21], a bias is therefore unlikely. Our data indicate that the group of patients with significant bacterial growth experienced – on average – a more profound decrease in oxygenation that lasted for a longer time as compared to patients without significant bacterial growth or sterile cultures.

One possible explanation for this observation may be that the degree of decrease in arterial oxygenation after a diagnostic procedure is related to the extent of pulmonary inflammation, the presence of bacterial pathogens or both [22]. In an animal model, Nahum and coworkers could show that the bacterial translocation from alveoli to bloodstream was associated with lung injury [23]. Our view can be supported by the fact that we also found preemptive antibiotic treatment to be a protective factor for arterial deoxygenation after the bronchoscopically guided diagnostic procedure. Regarding this issue, it has to be kept in mind that the diagnostic yield and preemptive antibiotic therapy have important interactions, because pre-treated patients are less likely to have significant growth in quantitative bacterial cultures [24]. However, we can not decide whether the bacterial load or the preemptive antibiotic were independent factors, because our study was too small to yield a valid interaction analysis.

Three limitations of this study deserve consideration. First, although we did not find differences in arterial oxygenation after the diagnostic procedure in relation to the volume of the lavage, we observed a clinically significant decrease in oxygenation in the entire population. One must therefore consider that the diagnostic procedure itself induced the observed changes in arterial oxygenation. We used a combined diagnostic procedure

consisting of a bronchoscopically guided PSB and BAL as recommended for the diagnosis of ventilator-associated pneumonia [25]. One might argue that the PSB prolonged the diagnostic procedure, however PSB is a fast method and the average time of our diagnostic procedure was less than 5 min, even in the group of patients who received a high-volume BAL. Second, the introduction of the bronchoscope leads to a reduced tidal volume and marked increase in airway resistance. This may result in transient hypoventilation and derecruitment of alveolar space, especially when the peak ventilation pressure is exceeded and the respiratory cycle has to be aborted. In addition, Klein and coworkers described a deterioration in pulmonary compliance after fiberoptic BAL that may further impair gas exchange [26]. It is therefore necessary to repeat our study with blind methods to find out whether differences in arterial oxygenation between high and low BAL volumes have been obscured by the effects of a bronchoscopic procedure in our study. Third, pneumonia may itself be associated with a deterioration of oxygenation during the course of illness. We did not include a control group with pneumonia which was microbiologically confirmed by a non-BAL method (e.g. PSB). The comparison between the group of patients with microbiologically confirmed pneumonia and clinical suspicion of pneumonia was only the secondary objective of our study and should be confirmed.

In conclusion, we found a decrease in arterial oxygenation up to 24 h after a combined diagnostic procedure including a bronchoscopically guided PSB and BAL. The time course of arterial oxygenation was not influenced by the lavage volume but depended on the bacterial burden recovered from alveolar space and/or the preemptive antibiotic therapy. Further studies are needed to corroborate these findings and to investigate the contributing role of the bronchoscope for the decrease in arterial oxygenation after a diagnostic procedure in critically ill patients.

References

1. Credle WFJ, Smiddy JF, Elliot RC (1974) Complications of fiberoptic bronchoscopy. Am Rev Respir Dis 109: 67–72
2. Pereira PM, Smiddy JF, Gruber B (1976) Deaths and complications associated with fiberoptic bronchoscopy. Chest 69: 747–751
3. Hertz MI, Woodward ME, Gross CR, Swart M, Marcy TW, Bitterman PB (1991) Safety of bronchoalveolar lavage in the critically ill, mechanically ventilated patient. Crit Care Med 19: 1526–1532
4. Papazian L, Colt HG, Scemama F, Martin C, Gouin F (1993) Effects of consecutive protected specimen brushing and bronchoalveolar lavage on gas exchange and hemodynamics in ventilated patients. Chest 104: 1548–1552
5. Chastre J, Trouillet JL, Vuagnat A, Joly-Guillou ML, Clavier H, Dombret MC, Gibert C (1998) Nosocomial pneumonia in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 157: 1165–1172
6. Pirozynski M, Sliwinski P, Zielinski J (1988) Effect of lavage volumes of BAL fluid on the arterial saturation. Eur Respir J 10: 943–947
7. Lin CC, Wu JL, Huang WC (1988) Pulmonary function in normal subjects after bronchoalveolar lavage. Chest 93: 1049–1053
8. Steinberg KP, Mitchell DR, Maunder RJ, Milberg JA, Whitcomb ME, Hudson LD (1993) Safety of bronchoalveolar lavage in patients with adult respiratory distress syndrome. Am Rev Respir Dis 148: 556–561
9. Kollef MH, Bock KR, Richards RD, Hearns ML (1995) The safety and diagnosis accuracy of minibronchoalveolar lavage in patients with suspected ventilator associated pneumonia. Ann Intern Med 122: 743–748
10. Montravers P, Gauzit R, Dombret MC, Blanchet F, Desmonts JM (1993) Cardiopulmonary effects of bronchoalveolar lavage in critically ill patients. Chest 104: 1541–1547
11. Pugin J, Suter PM (1992) Diagnostic bronchoalveolar lavage in patients with pneumonia produces sepsis-like systemic effects. Intensive Care Med 18: 6–10
12. Pingleton SK, Fagon JY, Leeper KV (1992) Patient selection for clinical investigation of ventilator-associated pneumonia: criteria for evaluating diagnostic techniques. Chest 105: 553S-556S
13. Bernard MS, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, LeGall JR, Morris A, Spragg R (1994) Report on the American-European Consensus Conference on acute respiratory distress syndrome: definitions, mechanisms, relevant outcomes and clinical trial coordination. Am J Respir Crit Care Med 149: 818–824
14. Le Gall JR, Lemeshow S, Saulnier F (1993) A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. JAMA 270: 2957–2963
15. Wimberley L, Falling LJ, Bartlett JG (1979) A fiberoptic bronchoscopy technique to obtain uncontaminated lower airway secretions for bacterial culture. Am Rev Respir Dis 119: 337–343
16. Meduri GU, Beals DH, Maijub AG, Baselski V (1991) Protected bronchoalveolar lavage: a new bronchoscopic technique to retrieve uncontaminated distal airway secretions. Am Rev Respir Dis 143: 855–864
17. American Thoracic Society (1996) Hospital-acquired pneumonia in adults: diagnosis, assessment, initial therapy and prevention: a consensus statement. Am J Respir Crit Care Med 153: 1711–1725
18. Lennette EH, Bullows A, Hausler WJ, Sadhomy HJ (1985) Manual of clinical microbiology, 4th edn. American Society for Microbiology, Washington
19. Chastre J, Fagon JY, Bornet-Lesco M, Calvat S, Dombret MC, Al Khani R, Basset F, Gibert C (1995) Evaluation of bronchoscopic techniques for the diagnosis of nosocomial pneumonia. Am J Respir Crit Care Med 152: 231–240
20. Torres A, El-Ebiary M, González J, Gene A, Rodriguez-Roisin R (1993) Specificity of endotracheal aspiration, protected specimen brush and bronchoalveolar lavage in mechanically ventilated patients. Am J Respir Crit Care Med 147: 952–957

21. Papazian L, Thomas P, Garbe L, Guignon I, Thirion X, Charrel J, Bollet C, Funetes P, Gouin F (1995) Bronchoscopic or blind bronchial sampling techniques for the diagnosis of ventilator-associated pneumonia. Am J Respir Crit Care Med 152: 1982–1991
22. Montón C, Torres A, El-Ebiary M, Filella X, Xaubet A, Puig de la Bellacasa J (1999) Cytokine expression in severe pneumonia: a bronchoalveolar lavage study. Crit Care Med 27: 1745–1753
23. Nahum A, Hoyt J, Schmitz L, Moody J, Shapiro R, Marini JJ (1997) Effect of mechanical ventilation strategy on dissemination of intratracheally instilled Escherichia coli in dogs. Crit Care Med 25: 1733–1743
24. Montravers P, Fagon JY, Chastre J, Lecso M, Dombret MC, Trouillet JL, Gibert C (1993) Follow-up protected specimen brushes to assess treatment in nosocomial pneumonia. Am Rev Respir Dis 147: 38–44
25. Chastre J, Fagon JY (1994) Invasive diagnostic testing should be routinely used to manage ventilated patients with suspected pneumonia. Am J Respir Crit Care Med 150: 570–574
26. Klein U, Zimmermann P, Karzai W, Hannemann U, Koschel U, Brunner JX, Remde H (1998) Changes in pulmonary mechanics after fiberoptic bronchoalveolar lavage in mechanically ventilated patients. Intensive Care Med 24: 1289–1293