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Alveolar and Serum Procalcitonin

Diagnostic and Prognostic Value in Ventilator-associated Pneumonia

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Background: **The potential role of serum and alveolar procalcitonin as early markers of ventilator-associated pneumonia (VAP) and its prognostic value were investigated.**

Methods: **Ninety-six patients with a strong suspicion of VAP were prospectively enrolled. VAP diagnosis was based on a positive quantitative culture obtained *via* a mini–bronchoalveolar lavage of 10^3 colony-forming units/ml or more. Blood and alveolar samples were collected for procalcitonin measurement and analyzed for diagnostic and prognostic evaluation on days 0, 3, and 6. Sensitivity, specificity, positive likelihood ratio, and receiver-operating characteristic curves were analyzed to define ideal cutoff values and approach the decision analysis.**

Results: **Serum procalcitonin was significantly increased in the VAP group (n = 44) compared with the non-VAP group (n = 52): 11.5 ng/ml (95% confidence interval, 5.9–17.0) *versus* 1.5 ng/ml (1.1–1.9). A serum procalcitonin concentration greater than 3.9 ng/ml (best cutoff value) was considered positive for the VAP diagnosis (sensitivity, 41%; specificity, 100%). Serum procalcitonin was significantly increased in the nonsurvivors compared with the survivors for the VAP group: 16.5 ng/ml (95% confidence interval, 8.1–24.9) *versus* 2.9 ng/ml (1.2–4.7). The best cutoff value for serum procalcitonin of the nonsurvivors in the VAP group was 2.6 ng/ml (sensitivity, 74%; specificity, 75%; positive likelihood ratio, 2.96). Regarding VAP diagnosis and prognosis, no significant differences were found for alveolar procalcitonin in all groups.**

Conclusions: **Serum but not alveolar procalcitonin seems to be a helpful parameter in the early VAP diagnosis and an appropriate marker for predicting mortality.**

VENTILATOR-ASSOCIATED pneumonia (VAP) remains the second leading type of nosocomial infection according to the National Nosocomial Infection Survey of the Centers for Disease Control and Prevention (Atlanta, GA).[1] VAP seems to be associated with high mortality.[2,3] Delays in the administration of adequate antimicrobial treatment increase the risk of hospital mortality.[2,4] The optimal technique for the diagnosis of VAP has not been determined, but there are some acceptable methods.[5] However, results of quantitative cultures are not available until 24–72 h after the procedure. Rapid identification of VAP in critically ill patients is required to improve survival and to reduce toxicity of expensive treatment.

Better markers of sepsis should ease the diagnosis, help to control therapy, and assess prognosis. Although cytokines, such as interleukin (IL)-6 and IL-8, correlate to some degree with the severity of sepsis and patient outcome, they are not established for the diagnosis and clinical decision making at the bedside.[6] Numerous clinical studies have proposed procalcitonin as a specific marker of bacterial infection or general inflammation status.[7–10] Procalcitonin has also been described as a good predictor of disease severity and antibiotherapy efficiency.[11] Procalcitonin also is released rapidly and has a long half-life, and the assay is highly reproducible. Thus, procalcitonin could be a useful tool in the early diagnosis of VAP. Therefore, the aim of our study was to assess the usefulness and reliability of serum and bronchoalveolar lavage (BAL) procalcitonin in the early diagnosis and prognosis of VAP.

Material and Methods

After local ethics committee approval (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale Lyon A, Lyon, France), 106 consecutive patients undergoing mechanical ventilation were included over a 2-yr period at the intensive care unit, Hotel-Dieu Hospital-Lyon (Lyon, France). Blood and BAL samples were collected from 10 routine postoperative patients and constituted the control group: all had elective gynecologic or intestinal surgical procedures and were not suspected to have VAP. Ninety-six patients were highly suspected to have VAP: all had a fever ($\leq$ 38.5°C), purulent tracheal aspirates, leukocytosis ($\geq 12 \times 10^9$/l), and new or persistent radiographic lung infiltrates unrelated to cardiogenic causes. Clinical and laboratory data were collected, including temperature, hemodynamics, respiratory rate, arterial blood gas data, white blood count, and serum and alveolar procalcitonin concentrations. BAL, blood culture, and urine tractus samples were screened for infectious specimen. Samples were only taken from patients who had not received systemic or topical antimicrobial therapy during the 3 days before the study.

Sampling Technique

We obtained 106 mini-BAL samples using the blinded PBAL catheter technique (Combicath; Plastimed, St. Leu La Foret, France). During the procedure, 100% oxygen was administered, and patients were sedated with intravenous narcotics and paralyzed with curare. Topical

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anesthesia was not used. Cardiovascular and oxygen saturation monitoring was performed during the entire procedure. Tracheal sputum was aspirated and collected before introducing the protected catheter. The PBAL catheter was inserted using the previously described technique.[12] After the blinded introduction in the bronchial system, the inner catheter was advanced until resistance was encountered, and 20 ml sterile saline was administered. The fluid was then withdrawn by hand suction into the infusion syringe. When at least 5 ml fluid had been sterilely retrieved, the entire catheter was removed. The entire sampling procedure lasted less than 2 min and was performed by the same physician. The PBAL was repeated on days 3 and 6 for procalcitonin measurements, except in the control group. Meanwhile, blood samples were collected. Some of the alveolar samples were sent to the laboratory for bacteriologic analysis (Gram staining and quantitative culture). Other alveolar samples were centrifuged (1,500 rpm, 10 min) and supernatants were immediately stored at −80°C until procalcitonin measurements.

Bacteriologic Analysis

The same technologist processed all bacterial analysis.

Microscopic Examination. Aliquots of 0.2 ml from the original suspension were centrifuged at 300*g* for 10 min. Slides were Gram stained and examined at high magnification (×100). The possible presence of microorganisms was assessed on 10–50 fields and classified according to Gram stain morphology.

Quantitative Cultures. The fluid was diluted to obtain concentrations of 10^{-1}, 10^{-3}, and 10^{-5}. Samples were then plated onto Petri dishes: Colombia agar, chocolate agar, trypticase soy, McConkey agar, and Sabouraud agar. Bacterial colonies were counted and identified using conventional techniques.

Immunologic Analysis

The same technologist performed all measurements. Procalcitonin was determined using an immunoluminometric assay (Lumitest; Brahms Diagnostica, Berlin, Germany). The procalcitonin assay had a lower limit of 0.10 ng/ml.

Diagnostic Categories

The final diagnosis of pneumonia (VAP group) was based on positive results of PBAL quantitative culture ($\geq 10^3$ colony-forming units/ml on any media). VAP was excluded if the one of the following criteria was fulfilled: negative or nonsignificant growth in culture of BAL and full recovery without antimicrobial therapy, or diagnosis of another disease of the chest accounting for the chest radiograph abnormality (non-VAP group).

Definition of the bacterial infection was based on the American College of Chest Physicians and the Society of Critical Care Medicine Consensus Conference Criteria to categorize patients into systemic inflammation response syndrome, sepsis, severe sepsis, and septic shock.[13] Antibiotherapy was started based on Gram staining results and adjusted based on quantitative culture and antibiogram results.

Statistical Analysis

Patients were divided into three groups. The VAP group contained patients suspected to have VAP with positive PBAL quantitative culture (VAP group); the non-VAP group contained patients suspected to have VAP with negative PBAL quantitative culture; the control group consisted of patients not suspected to have VAP.

Demographic and procalcitonin data are expressed as mean with 95% confidence interval. Sensitivity and specificity are expressed in percentage.

Statview 5.0 (SAS Institute Inc., Cary, NC) was used to analyze the experimental data. After confirming normally distributed data, demographic and clinical data were compared using the chi-square test or the Student *t* test when appropriate. The one-way analysis of variance with repeated measures was used to evaluate differences between the samples collected at different times (D0, D3, D6; significance, $P < 0.05$). The Bonferroni *post hoc* test was used to locate the significance. Sensitivity, specificity, and positive likelihood ratio were estimated using a standard formula.[14] Receiver-operating characteristic (ROC) curves were analyzed to define the optimal cutoff value using MEDCALC (Medcalc Software, Mariakerke, Belgium) as the biostatistics software.

Results

Table 1 shows demographic and clinical data of all patients divided into subgroups and shows the primary indications for ventilator support.

The diagnosis of VAP was established in 44 cases (VAP group): 17 patients had gram-negative bacilli, 13 patients had gram-positive cocci, and polymicrobial growth was seen in 14 patients. PBAL quantitative culture was negative in 52 patients (non-VAP group). During or after the sampling procedure, no major hemodynamic changes, pneumothorax, or hemorrhage were observed. The mini-BAL effluent had 1% squamous epithelial cells or less in all patients.

Serum procalcitonin was significantly increased in the VAP group compared with the non-VAP group until day 3: 11.5 ng/ml (95% confidence interval, 5.9–17.0) *versus* 1.5 ng/ml (1.1–1.9) on day 0 and 7.5 ng/ml (6.3–8.7) *versus* 1.25 ng/ml (1.03–1.47) on day 3 (fig. 1A). Regarding VAP diagnosis, no significant differences occurred in the VAP group compared with the non-VAP group for the alveolar procalcitonin (fig. 1B). The cutoff value of serum procalcitonin for the VAP diagnosis (from the ROC curve; area under the curve [AUC] = 0.787) was

Table 1. Demographic and Clinical Data of Patients Entering the Study

	VAP Group (n = 44)	Non-VAP Group (n = 52)	*P* Value*
Age (yr)	53 (48.4–56.4)	48 (44–52)	0.15
Gender (M/F)	18/26	21/31	0.88
SAPS II	36 (34–38)	34 (31–36)	0.13
Postoperative respiratory failure (%)	21 (48)	24 (46)	0.96
Exacerbation of COPD (%)	18 (41)	14 (27)	0.22
Community-acquired pneumonia (%)	2 (5)	4 (8)	0.83
Acute pancreatitis (%)	1 (3)	2 (4)	0.88
Cardiogenic shock (%)	0 (0)	2 (4)	0.52
Neurologic disease (%)	4 (9)	2 (4)	0.56
Miscellaneous (%)	2 (5)	0 (0)	0.34
Sepsis (%)	7 (16)	11 (21)	0.69
Severe sepsis (%)	12 (27)	16 (31)	0.89
Septic shock (%)	6 (14)	5 (10)	0.77
Days in ICU	14 (12.3–16.6)	12 (9.6–15.3)	0.25
Nonsurvivors (%)	64	48	0.19

Results are expressed as mean (95% confidence interval).

* *t* test and chi-square test (or *z* test), respectively for quantitative and categorical variables.

VAP = ventilator-associated pneumonia; SAPS II = simplified acute physiology score; COPD = chronic obstructive pulmonary disease; ICU = intensive care unit.

3.9 ng/ml (sensitivity, 41%; specificity, 100%; fig. 2). Serum procalcitonin was significantly increased in the nonsurvivors compared with the survivors for the VAP group: 16.5 ng/ml (95% confidence interval, 8.1–24.9) *versus* 2.9 ng/ml (1.2–4.7) (fig. 3A). The cutoff value for serum procalcitonin of the nonsurvivors in the VAP group (from the ROC curve; AUC = 0.607) was 2.6 ng/ml (sensitivity, 74%; specificity, 75%; positive likelihood ratio, 2.96). Regarding VAP prognosis, no significant differences were found for the alveolar procalcitonin in all groups (fig. 3B).

When comparing the evolution of the serum procalcitonin values of the nonsurvivors and the survivors in the VAP group, significant differences were seen on days 3 and 6 (fig. 3A). When comparing the evolution of the alveolar procalcitonin values of the nonsurvivors and the survivors in the VAP group, significant differences were seen on days 0 and 3 (fig. 3B).

Discussion

Our study shows that patients with confirmed VAP have significantly increased concentrations of procalcitonin in serum. Our data suggest that procalcitonin measurements in serum may be useful for the early diagnosis of VAP. We also demonstrated that the presence of an increased concentration of procalcitonin in serum could be an original approach to the prognostic of VAP. Last, our results support the idea that the concentrations of procalcitonin in bronchoalveolar fluid are not helpful regarding the diagnosis and the prognosis of VAP.

Limitations of the Study

First, PBAL was considered the reference method to diagnose VAP. This technique has been advocated as a potentially better alternative compared with bronchoscopic procedures because of its minimal invasiveness, wide availability, and relative cost,[12,15] although the open lung biopsy represents the ideal criterion. However, this gold standard technique for evaluating the diagnosis of VAP remains problematic, and the appropriateness of studying a diagnostic test only among dead patients is debated.[16] Second, the lower threshold value (0.1 ng/ml) of the Lumitest kit assay may be inappropriate for detecting low significant alveolar concentrations. Third, because we used a blinded BAL fluid sampling method, noninvolved lung fluids could have been analyzed and could have underestimated alveolar procalcitonin concentrations. Nevertheless, Monton *et al.*[17] did not confirm that cytokines production is compartmentalized; therefore, one would not expect to find increased alveolar concentration of procalcitonin. Last, antimicrobial therapy was started after the Gram staining results and thus before measurement of procalcitonin concentrations on days 3 and 6. Thus, procalcitonin concentrations could have been underestimated and therefore could not exhibit significant differences in the serial concentrations.

Limitations and inaccuracies in clinical decision making have motivated the development of techniques to establish the diagnosis of VAP.[18] Direct examination and cultures of tracheal aspirates have been commonly used to diagnose VAP but are nonspecific for establishing the presence of VAP partly because of tracheobronchial bacterial colonization.[18] Several methods have been developed in an attempt to improve their diagnostic specificity, including elastin fibers examination,[19] and identification of antibody-coated bacteria.[20] However, the sensitivity of these techniques varies from 55 to 75%, and they lack specificity in the presence of previous antibiotics administration or certain disease processes.[21,22] Bronchoscopic and nonbroncho-

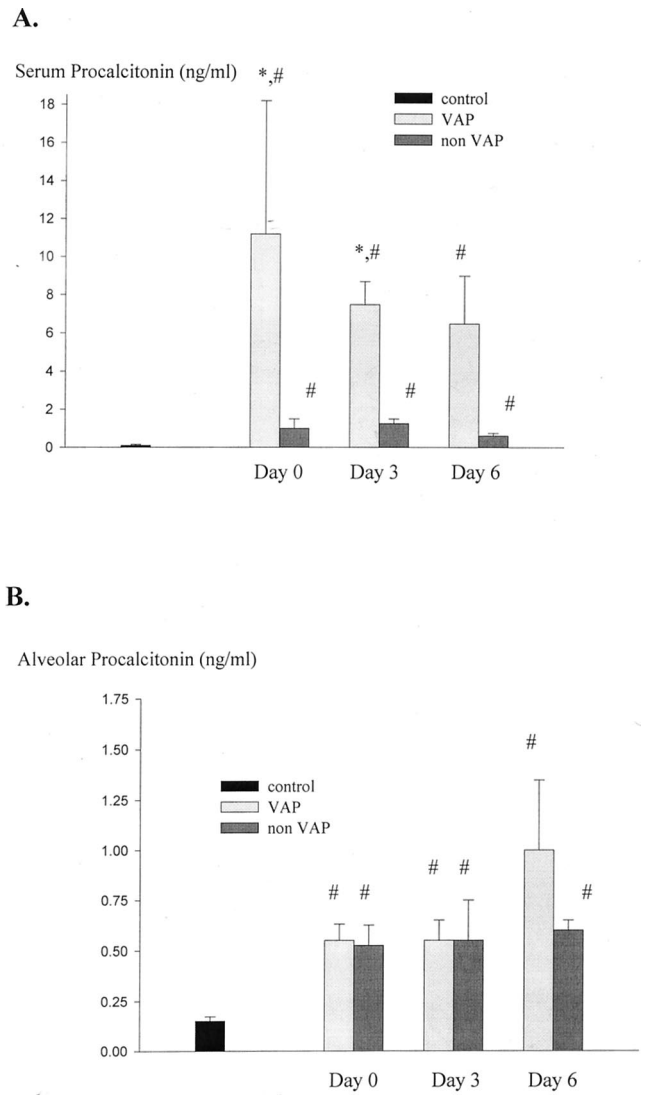

Fig. 1. (*A*) Comparison of serum concentrations of procalcitonin (mean with 95% confidence interval) between the control group, the ventilator-associated pneumonia (VAP) group, and the non-VAP group on days 0, 3, and 6. **P* < 0.02 *versus* the non-VAP group; #*P* < 0.02 *versus* the control group. (*B*) Comparison of alveolar concentrations of procalcitonin (mean with 95% confidence interval) between the control group, the VAP group, and the non-VAP group on days 0, 3, and 6. #*P* < 0.02 *versus* the control group.

scopic sampling of the lower airways seems to be accepted as the most accurate method of diagnosis of VAP, but bacterial results can be delayed.[19] Intracellular organisms examination,[23] endotoxin measurement,[24] and nuclear probes[25] have been applied to such samples to aid the VAP diagnosis. However, their cost or their unavailability did not lead to routine use.

According to our findings, the measurement of procalcitonin in serum represents a potential adjunct to the early diagnosis of VAP and possesses significant interest for the VAP prognosis. However, bronchoalveolar fluid procalcitonin concentrations remained at a low level, limiting their clinical utility.

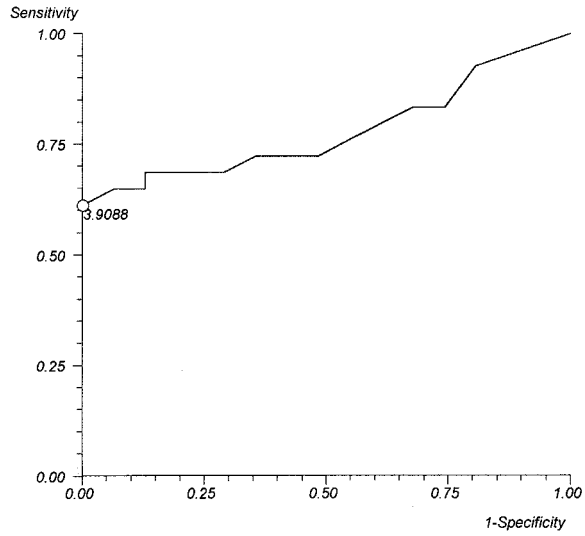

Fig. 2. Receiver-operating characteristic curve analysis: serum concentrations of procalcitonin and the diagnosis of ventilator-associated pneumonia.

Recently, Nijsten *et al.*[26] showed that both *in vivo* and *in vitro* IL-6 and tumor necrosis factor α (TNF-α) release procalcitonin. Various studies have shown an increased inflammatory lung response in pneumonia, and TNF-α seems to be the key mediator of the inflammatory response to miscellaneous pathogens.[27] Monton *et al.*[17] assessed the cytokine expression of 12 severe nosocomial pneumonia in the serum and in bronchoalveolar lavage and found that TNF-α and IL-6 concentrations were significantly higher systemically than in the lung. In alveolar fluid, IL-6 was the only cytokine to be significantly increased. Moreover, the intratracheal instillation of lipopolysaccharide in rats increased the concentration of alveolar TNF-α without increasing serum concentrations,[28] supporting the hypothesis that the alveolar membrane could be a strong filter to circulating cytokines. Dehoux *et al.*[29] explored patients with unilateral pneumonia and found higher concentrations of cytokines in the involved lungs compared with the noninvolved lungs and blood. Therefore, because of the blinded alveolar sampling method, noninvolved lung fluids could have been analyzed and could have underestimated alveolar cytokines concentrations. Therefore, in our study, systemic cytokine production can explain increased serum procalcitonin concentrations, whereas the low alveolar procalcitonin release could be explained by the absence of the local mediators.

When comparing the evolution of the serum procalcitonin values between the VAP group and the non-VAP group, serum procalcitonin was significantly higher in the VAP group until day 3. Antibiotics were started according to the bacterial examination 24 h after the first mini-BAL procedure. Thus, serum procalcitonin did not have much time to decrease in case of effective treatment.

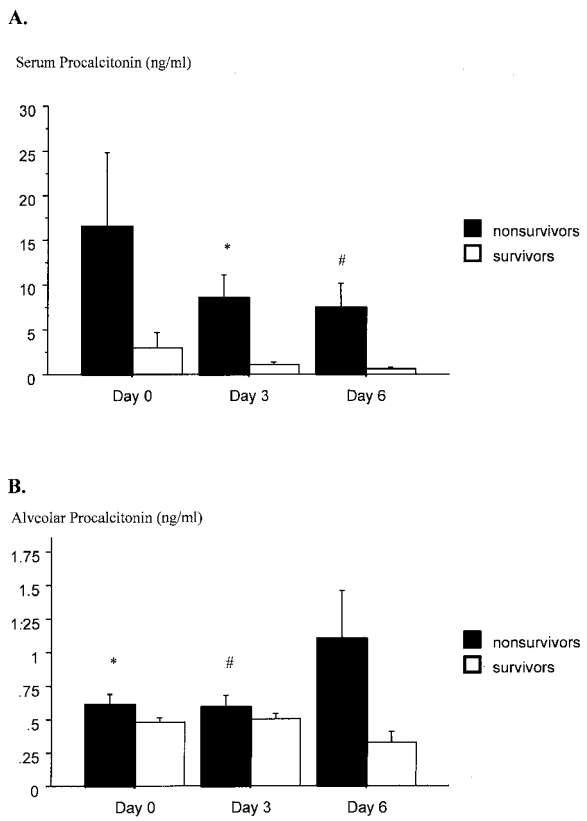

Fig. 3. (*A*) Comparison of serial concentrations of circulating procalcitonin (mean with 95% confidence interval) in the ventilator-associated pneumonia group between the survivors and the nonsurvivors patients. *$P < 0.02$ *versus* day 0; #$P < 0.02$ *versus* day 3. (*B*) Comparison of serial concentrations of alveolar procalcitonin (mean with 95% confidence interval) in the ventilator-associated pneumonia group between the survivors and the nonsurvivors patients. *$P < 0.02$ *versus* day 6; #$P < 0.02$ *versus* day 6.

The cutoff ROC curve value of serum procalcitonin to diagnose VAP (3.9 ng/ml) exhibits a low sensitivity (41%) and an excellent specificity (100%). This fulfills physicians needs: highly specific tests to diagnose VAP, to avoid expensive and ineffective antibiotics and to decrease potential emergence of multiresistant microorganisms.

We found a significant relation between serum procalcitonin values and mortality. In our study, area under the ROC curve (AUC) was 0.787. Bossink *et al.*[30] have demonstrated in 300 hospitalized medical patients with fever that AUC for mortality was 0.79 for respiratory rate, 0.69 for elastase-α1-antitrypsin concentration, 0.65 for heart rate, 0.61 for procalcitonin concentration, and 0.60 for leukocyte count. Thus, serum procalcitonin and elastase-α1-antitrypsin concentrations may predict microbial infection, bacteremia, and mortality more effectively than do clinical symptoms. The strong relation between serum procalcitonin and survival has been shown by Ugarte *et al.*[31] in a large cohort of critically ill patients. In this latter work, infected nonsurvivors have higher concentrations of serum procalcitonin compared with infected survivors. Interestingly, Shröder *et al.*[32] have recently studied 24 patients with septic shock and have shown that in nonsurvivors, serum procalcitonin remained increased, whereas the course of survivors was characterized by decreased values, which were significantly lower at every time point compared with those patients who died. In our study, the serum procalcitonin concentrations were more increased in nonsurvivors with VAP. This agrees in part with the significant correlation found by Monton *et al.*[17] between serum concentrations of cytokines and scores designed to assess severity of illness. Recently, Bonten *et al.*[33] investigated the correlation between the circulating IL-6 and IL-8 concentrations and the prognosis in patients with VAP. They found that high serum concentrations of cytokines were associated with higher mortality rates.

In summary, the current study supports new findings regarding procalcitonin. The bronchoalveolar concentrations of procalcitonin are not increased during VAP, whereas the values of circulating procalcitonin are associated with confirmed VAP. It is clear that high procalcitonin concentrations are found only in blood.[34] Serum concentrations of procalcitonin are also correlated with higher mortality rates in nonsurvivors with VAP. We found a positive likelihood ratio of 2.96. This means that a serum procalcitonin concentration greater than 2.6 ng/ml is almost three times more likely to occur in a nonsurvivor than in a survivor of VAP. Therefore, serum procalcitonin could be an interesting tool in the early diagnosis of VAP and a helpful marker of prognosis. These findings warrant further studies that will take into consideration the limitations of our work.

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