Discrimination of infectious and noninfectious causes of early acute respiratory distress syndrome by procalcitonin

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Objective: To test the sepsis marker procalcitonin (PCT) for its applicability to discriminate between septic and nonseptic causes of acute respiratory distress syndrome (ARDS).

Design: Prospective study, assessing the course of PCT serum levels in early (within 72 hrs after onset) ARDS. The three other inflammation markers neopterin, interleukin-6 (IL-6), and C-reactive protein (CRP) were tested in parallel.

Setting: Twenty-four-bed medical intensive care unit of a 1,990-bed primary hospital, providing health care for an estimated 39,000 patients.

Patients: Twenty-seven patients, 18 male and nine female, aged 16-85 yrs, with early ARDS of known cause (17 with septic and ten with nonseptic ARDS) were enrolled in a prospective study between May 1994 and May 1995.

Interventions: Serum samples were drawn every 4-6 hrs for measurement of PCT, neopterin, IL-6, and CRP concentrations. Blood cultures, tracheal aspirates, and urine samples were obtained every 12-24 hrs. In 24 of 27 patients, bronchoscopic cultures were also obtained. Clinical sepsis criteria as defined by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference were checked daily.

Measurements and Main Results: Assessment of inflammation marker serum levels in septic vs. nonseptic ARDS. PCT serum levels were significantly higher ($p < .0005$) in the patients with septic ARDS than in patients with nonseptic ARDS within 72 hrs after onset of ARDS. There was no overlap between the two groups. Also, neopterin allowed a differentiation ($p < .005$), although a substantial overlap between serum levels of septic and nonseptic patients was observed. No discrimination could be achieved by determination of CRP and IL-6 levels.

Conclusion: PCT determination in early ARDS could help to discriminate between septic and nonseptic underlying disease.

Key Words: acute respiratory distress syndrome (ARDS); interleukin 6; neopterin; procalcitonin; C-reactive protein; sepsis; Acute Physiology and Chronic Health Evaluation II score; Murray score.
Acute respiratory distress syndrome (ARDS) is caused by severe pulmonary and systemic injuries of infectious and noninfectious origin. Sepsis is the injury most frequently encountered and has the worst prognosis (1, 2). Noninfectious causes of ARDS include trauma, toxic inhalation, aspiration, necrotizing pancreatitis, multiple transfusions, and autoimmune, malignant, and neurologic disorders. It may be advantageous to discriminate between infectious and noninfectious causes of ARDS, because there is evidence that in early endotoxin-induced ARDS, modulation of the local inflammation involving neutrophils may be possible (3, 4). In contrast, patients with late fibroproliferative ARDS seem to benefit from corticosteroid treatment (5, 6), and if the latter therapy is considered, ongoing infection should be excluded. The differential diagnosis of septic or nonseptic ARDS is difficult because patients with primarily noninfectious diseases treated in intensive care units frequently acquire bacterial superinfection and develop ARDS as a consequence of bacterial sepsis. A serum marker indicating severe bacterial infection would be useful in the decision about the need for antibiotic therapy and might become important for a future differential therapy of septic vs. nonseptic ARDS.

Serum levels of procalcitonin (PCT) have been reported to be elevated in sepsis (7). PCT, the prohormone of calcitonin, is a protein of 116 amino acids (molecular weight, 11,800) of known sequence (8). Molecular cloning and expression of the murine form was recently achieved (9). Although it is unclear at present which tissue is responsible for PCT liberation during inflammation, it does not seem to be the thyroid gland (7). Whereas invasive infections with bacteria, fungi, and parasites all lead to increased PCT (10-12), this has not been observed in cases of viral infection (7) or in inflammation caused by systemic autoimmune disease (13). It was the aim of this study to investigate whether determination of the new inflammation marker PCT could help to differentiate between infectious and noninfectious causes in early ARDS. The inflammation markers C-reactive protein (CRP), neopterin, and interleukin-6 (IL-6) were tested in parallel.

**MATERIALS AND METHODS**

**Patients.** Between May 1994 and May 1995, 27 patients with ARDS, 18 male and nine female, were prospectively included in our study and surveyed for 72 hrs after the onset of ARDS. All patients were mechanically ventilated because of severe hypoxemia. The diagnosis was established according to the definitions of acute lung injury and ARDS proposed by the American-European Consensus Conference on ARDS (2), and the following inclusion criteria were met: a) acute onset of lung failure; b) diffuse bilateral pulmonary infiltrates on the chest radiographs; and c) $\text{PaO}_2/\text{FiO}_2 \leq 200$ torr. Determination of the pulmonary artery occlusion pressure using a pulmonary artery balloon flotation catheter was performed in 21 patients and revealed values of $\leq 18$ mm Hg. Exclusion criteria for the study were: a) a patient history of restrictive lung disease; b) preexisting chronic heart failure; and c) left ventricular dysfunction with low cardiac output, assessed by echocardiography. No postoperative patients were included. The supportive therapy consisted of fluid restriction, administration of diuretics, positive end-expiratory pressure ventilation of 5-12 cm H$_2$O, and intermittent placement in a prone position (12 patients). Catecholamine treatment was adjusted to keep the mean arterial blood pressure $> 70$ mm Hg. Appropriate antibiotics were prescribed according to the sensitivity of the relevant bacteria isolated.

To differentiate between septic and nonseptic causes of ARDS, blood cultures, tracheal aspirates, and urine samples were obtained daily (every 12-24 hrs) from all patients and screened for infectious specimens. Twenty-four patients also underwent bronchoscopy with microbiological testing of
Bronchoalveolar lavage fluid at the onset of ARDS. Bronchoscopic cultures were obtained, using 80-100 mL of lavage fluid and discarding the first two 10-mL aliquots. The bronchoscopic cultures were assessed qualitatively. *Legionella pneumophila* was diagnosed if a positive direct fluorescent antibody test in bronchoscopic lavage fluid and a four-fold increase in the serum antibody titer were present.

At time of inclusion into the study, clinical state and severity of lung damage were recorded using the Acute Physiology and Chronic Health Evaluation II and Murray (14) scores. The PaO$_2$/FIO$_2$ was obtained repeatedly during the first 72 hrs after onset of ARDS, and this served as an index variable for the course of lung failure during the observation period. Clinical sepsis criteria as defined by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (15) were checked for all patients. Variables routinely obtained were body core temperature (measured by nasopharyngeal or urine catheter sensor), white blood cell count, and cardiac output (estimated by dilution of injected cold saline solution in the 21 patients monitored by pulmonary artery catheter).

Patients who a) fulfilled all criteria of sepsis (as defined by the American College of Chest Physicians/Society of Critical Care Medicine consensus conference) and b) had positive microbiological results from at least one blood culture or from bronchoscopic material, with detection of bacteria not likely to be contaminants, were diagnosed as having "septic ARDS." Patients with negative microbiological results, in whom a nonseptic disease known to be associated with ARDS could be ascertained in the clinical course, were diagnosed as having "nonseptic ARDS."

**Laboratory Analyses.** During the observation period, i.e., during 72 hrs after diagnosis of ARDS, serum samples were drawn every 4-6 hrs for measurement of PCT, neopterin, IL-6, and CRP concentrations. The samples were stored at -20°C (-4°F) until the time of analysis. Determination of PCT, neopterin, IL-6 and CRP serum values was performed from the stored samples only, when all samples had been collected and the patients had already been allocated to the infectious or noninfectious groups according to microbiological and (in the case of autopsy) histologic results. Procalcitonin was measured by PCT immunoluminometric assay (LUMItest, Brahms Diagnostica, Berlin), neopterin by neopterin-ELISA (ELItest, Brahms Diagnostica), IL-6 by an immunoenzymetric method (IL6-EASIA, Medgenix Diagnostics, Fleurus, Belgium), and CRP by nephelometry (N-Latex-CRP, Behringwerke, Marburg, Germany), with normal values of <0.5 ng/mL for PCT, ≤10 nmol/L for neopterin, ≤10 pg/mL for IL-6, and <6 mg/L for CRP.

**Statistics.** The two-tailed Mann-Whitney U test was performed to test for significant differences between patients with ARDS of infectious and noninfectious cause. The laboratory variables were log-transformed to allow for better graphic comparison between variables. The study protocol was approved by the local institutional review board, and the review board waived the need for informed consent.

**RESULTS**

In 17 of 27 patients, ARDS could be attributed to bacterial sepsis, with identification of the causative bacteria from material obtained during the study period in all cases. Sixteen of 17 patients with sepsis had bacterial pneumonia and septic shock, and one patient developed ARDS in the course of Gram-negative sepsis resulting from cholangitis. In contrast, there was no hint of an infectious cause of ARDS in 10 of the 27 patients under survey. The latter patients developed ARDS as a result of various direct or indirect injuries to the lung. If not known beforehand, the underlying disease of the nonseptic
ARDS patients was diagnosed by transbronchial biopsy or, in one case, by autopsy. Table 1 and Table 2 summarize the clinical characteristics at the onset of ARDS, the underlying diseases, the results of microbiological testing, and the outcome for the patients with ARDS of infectious and noninfectious causes, respectively. It is notable that whereas the severity of lung damage as assessed by the Murray score was similar in both groups (2.69 ± 0.44 vs. 2.80 ± 0.32), the nonseptic patients had significantly lower Acute Physiology and Chronic Health Evaluation II scores ($p = .02$), indicating multiple organ dysfunction already at the onset of ARDS in the septic group. All patients subsequently given the diagnosis of sepsis met the clinical sepsis criteria as defined by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (2).

### Table 1. Clinical characteristics of the 17 patients with acute respiratory distress syndrome of infectious origin

![Table 1](image1)

### Table 2. Clinical characteristics of the 10 patients with acute respiratory distress syndrome of noninfectious origin

![Table 2](image2)

The serum levels for PCT, CRP, neopterin, and IL-6 are shown in Figure 1 for the patients with ARDS of infectious vs. noninfectious origin. Whereas there is a clear overlap between the two groups for CRP and IL-6 serum levels, PCT and neopterin serum concentrations are significantly ($p < .0005$ for PCT, $p < .005$ for neopterin) higher in the patients who acquired ARDS in the course of sepsis compared with patients with ARDS of noninfectious origin. The elevations in PCT and neopterin serum concentrations were already present in the early phase of septic ARDS, before bacteria were isolated and the diagnosis of sepsis was confirmed. Body core temperature and white blood cell count did not differ significantly between the groups.
Figure 1. Serum levels for procalcitonin, neopterin, interleukin-6, and C-reactive protein for all 10 patients with nonseptic acute respiratory distress syndrome (ARDS) (left) and all 17 patients with septic ARDS (right) before and during the first 3 days after the onset of ARDS. Procalcitonin and neopterin levels are clearly higher in patients with septic ARDS.

In Figure 2, only the maximum serum levels of PCT, CRP, neopterin, and IL-6, obtained at three consecutive times (on days 1, 2, and 3 after diagnosis of ARDS), are shown for the two separate groups of patients with septic and nonseptic ARDS. PCT and neopterin values differed significantly between the groups on all 3 days, whereas IL-6 showed just significant differences only on days 1 and 2. CRP did not differ between the groups.

Figure 2. Maximum serum levels of procalcitonin (PCT), neopterin, interleukin-6 (IL-6), and C-reactive protein (CRP) obtained during days 1, 2, and 3 after onset of acute respiratory distress syndrome (ARDS) for patients with nonseptic (-) and septic (+) ARDS. *Significant difference (p < .05) between the septic and nonseptic groups determined by the Mann-Whitney U test. PCT and neopterin serum levels are significantly higher in septic ARDS on all 3 days.

DISCUSSION

We undertook this study to evaluate the new sepsis marker PCT with regard to its usefulness in discrimination between early septic and nonseptic ARDS. In all patients, the underlying disease could be ascertained. Impairment of lung function was comparable in both groups. As our results show, PCT was invariably elevated into the pathologic range in patients with septic ARDS, and there was no overlap between the groups of septic and nonseptic patients, the latter displaying no or only moderately elevated PCT levels. The difference was already present in the early phase of evolving ARDS, thereby allowing a discrimination between septic and nonseptic ARDS before the results of microbiological testing are generally available. Procalcitonin concentrations > 5 ng/mL in this study strongly suggested a septic disease. However, the critically ill patients with nonseptic ARDS also displayed serum PCT levels up to 2.9 ng/mL. This is substantially higher than the level described for healthy controls, in whom PCT levels are <0.5 ng/mL (14). Whereas, from our experience, evolving ARDS in a patient with serum PCT values < 3.0 ng/mL and negative microbiological results for bacterial, fungal, or viral infection suggests...
nonseptic ARDS, subsequent studies with larger numbers of patients may define the threshold level of PCT more precisely, above which septic disease should be assumed.

The acute-phase protein CRP was equally elevated in both patient groups. The T-cell and monocyte activation marker IL-6 was significantly more elevated during the initial 48 hrs of the observation period in the group with sepsis, but it showed a wide range of serum concentrations, with a substantial overlap between septic and nonseptic patients. Interestingly, IL-6 was clearly elevated above the normal range in nonseptic patients as well, suggesting that this cytokine is not involved in the mechanisms leading to a release of PCT. Neopterin, synthesized by \( \gamma \)-interferon-activated macrophages, and PCT were only moderately elevated in nonseptic ARDS and were substantially elevated in septic ARDS. Also for neopterin, the differences between the two groups were significant for all 3 days of the observation period; therefore, testing for neopterin would be of comparable diagnostic value. In some septic patients, the elevation in PCT levels was more pronounced than the elevation in neopterin serum concentrations. The source of PCT liberation is not clear; however, one might speculate that PCT is produced by peripheral mononuclear blood cells in response to an inflammatory signal in a manner similar to neopterin.

With regard to the therapeutic implications of PCT determination in patients with ARDS, until now there has been no difference in the treatment of early ARDS, whether of septic or nonseptic origin. Experimental evidence derived from rat models of endotoxin-induced ARDS, however, suggests possibilities for therapeutic interference. One strategy might be to modulate the mediator cascade leading to neutrophil inflammation in the lung tissue, e.g., by administration of antibodies to IL-8, a potent neutrophil chemotactic factor (3) or by administration of thrombomodulin (4). In patients with microbiological detection of Gram-negative infection and elevated serum PCT, Gram-negative sepsis with endotoxemia is likely. PCT thus could facilitate the decision for treatment if a therapy for early endotoxin-induced ARDS should become available. In late ARDS, the proposed methylprednisolone scheme (1-2 mg/kg/day [5]) can be used safely only if ongoing infection is excluded. Here also, PCT may add to diagnostic accuracy and help to select suitable patients for corticosteroid treatment. PCT may indicate the need for antibiotic treatment and perhaps also be useful in the monitoring of antibiotic therapy in ARDS patients, who are prone to severe infectious complications.

In summary, PCT and to some extent neopterin seem to be diagnostic tools for differentiating between septic and nonseptic underlying disease in early ARDS.

REFERENCES [Click here for reference links. (14 references linked.)]


