ELSEVIER

The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

ORIGINAL CLINICAL SCIENCE

# Post-operative kinetics of procalcitonin after lung transplantation

Mathieu Desmard, MD, PhD,[a] Abdel Benbara, MD,[a] Sandrine Boudinet, MD,[a] Herve Mal, MD, PhD,[b] Monique Dehoux, MD, PhD,[c] Gabriel Thabut, MD, PhD,[b] and Philippe Montravers, MD, PhD[a]

*From the [a]Département d'Anesthésie Réanimation; [b]Service de Pneumologie B; and the [c]Laboratoire de Biochimie, Université Paris Diderot, APHP, CHU Bichat-Claude Bernard, Paris, France.*

**KEYWORDS:**
biomarker;
lung transplantation;
procalcitonin;
pulmonary infection;
primary graft dysfunction;
kinetics

**BACKGROUND:** Post-operative infections are a major complication after lung transplantation (LT). Early bacterial pneumonia worsens the prognosis of LT. Procalcitonin (PCT) has been proposed as an early and rapid laboratory marker of infection and sepsis. PCT could be a useful biomarker of pulmonary infection after LT, but the early kinetics of PCT in this setting are unknown. We evaluated the kinetics of PCT and the impact of respiratory tract infection on PCT concentrations.

**METHODS:** Over a 12-month period, PCT concentrations were determined daily in each patient admitted to our ICU for LT. Epidemiologic, clinical, laboratory and outcome data were obtained. A diagnosis of respiratory tract infection was suspected on clinical examination and confirmed by microbiologic culture.

**RESULTS:** Twenty-six consecutive patients were included and 397 blood samples were obtained (13 [range 4 to 66] samples per patient). Plasma PCT reached a peak in the first 24 hours post-transplantation (5.72 [0.11 to 93.8] ng/ml), with a progressive decline over the first 7 post-operative days. Doubling of plasma PCT levels after an initial decrease was significantly associated with respiratory tract infection in transplanted patients (RR = 4.2 95% CI [1.95 to 9.03]).

**CONCLUSIONS:** A non-specific increase in PCT values was observed during the first week post-LT. In combination with microbiologic cultures, PCT assays may be useful after the first post-operative week as an aid in the diagnosis of bacterial pulmonary infection.

J Heart Lung Transplant 2015;34:189–194



Procalcitonin (PCT) has been proposed as an early and rapid laboratory marker of infection and sepsis.[1] The efficacy of PCT for detection of infection in non-immunocompromised patients has been assessed at various sites of infection and was found to be more sensitive than C-reactive protein for differentiating bacterial from viral infection or non-infectious causes of inflammation.[2] The use of PCT has been proposed in the decision-making process of antibiotic therapy and could lead to a decreased number of treatments with no negative impact on the clinical or laboratory outcome of patients suspected to have pulmonary infection.[3,4] Similarly, repeated assays with PCT have been used to monitor the duration of antibiotic therapy.[5,6]

In transplant recipients, PCT has been shown on several occasions to be a valuable parameter for detection of infection.[7,8] However, few data have been published on the kinetics of PCT after lung transplantation (LT).[9] Infectious complications after LT remain a common life-threatening

Reprint requests: Mathieu Desmard, MD, PhD, Département d'Anesthésie Réanimation, Université Paris Diderot, APHP, CHU Bichat-Claude Bernard, 46 rue Henrui Huchard, Paris 75018, France. Telephone: +33-16-1697-208. Fax: +33-16-1693-506.
E-mail address: desmardmathieu@yahoo.fr

1053-2498/$ - see front matter 
http://dx.doi.org/10.1016/j.healun.2014.09.025

complication with pneumonia as the main culprit. In the first month after LT, as in the general surgical population, nosocomial bacterial infections predominate. Although the incidence of nosocomial pneumonia has declined to about 15% of lung transplant recipients,[10] mortality has remained high,[11] reaching 58% as reported in one study.[12] In this setting, PCT may be of value for early detection of nosocomial pneumonia and for differentiating colonization from infection.

Based on this hypothesis, we assessed the kinetics of plasma PCT concentrations by daily assays in all patients undergoing LT over a period of 1 year, from the first post-operative day until discharge from the surgical intensive care unit (ICU).

## Methods

### Study population

Over a 12-month period, this prospective, single-center observational study included all patients undergoing LT and admitted to the ICU for post-operative care.

Peri-operative care, including anesthesia and monitoring techniques, was standardized for all patients. Donor assessment, recipient selection, donor/recipient matching, lung procurement and preservation and surgical technique have been described elsewhere and correspond to our standard protocol.[13,14]

### Post-operative management

Patients were extubated when the standard criteria were obtained (hemodynamically stable, no significant bleeding, percutaneous oxygen saturation $>95\%$, with inspired fraction of oxygen [$FIO_2$] $<0.4$). Bronchial aspirates with fiber-optic bronchoscopy were performed daily for the first 3 days post-operatively, then on demand based on the clinical judgment of the physician in charge.

Immunosuppression was based on triple therapy with cyclosporine, azathioprine and prednisolone. Prophylaxis for cytomegalovirus infection was achieved with intravenous ganciclovir. Diagnosis of graft rejection was assessed by transbronchial biopsy. Samples were collected on demand in cases of unexplained deterioration of pulmonary function (hypoxemia, new infiltrates, etc.).

### PCT measurements

After institutional review board approval and informed consent, plasma PCT concentrations were monitored daily from the first post-operative day (Day 1) until discharge from ICU or death. Blood samples collected after Day 28 post-operatively were not analyzed. Circulating plasma PCT levels were determined by a time-resolved, amplified cryptate emission technology assay (Kryptor PCT; Brahms AG, Hennigsdorf, Germany), with an assay sensitivity of 0.06 mg/liter (upper reference range 0.5 ng/ml in healthy subjects).

### Data collection

Demographic characteristics and underlying diseases were recorded during the first 24 post-operative hours, which included: age; gender; underlying disease; indication for lung transplantation; use of anti-microbial agents for $>24$ hours during the 3 months preceding lung transplantation; and pre-operative corticosteroid therapy. Intra-operative characteristics were recorded, including: type of surgical procedure (single lung or bilateral sequential lung transplantation); operating time; graft ischemia time; and number of units of packed red blood cells administered during surgery. Pre-transplant tracheal bacterial colonization and donor and recipient viral serology were recorded. Severity of illness at ICU admission was assessed using Simplified Acute Physiology (SAPS) II scores.[15] Grading of primary graft dysfunction (PGD) severity was determined using the $PaO_2/FIO_2$ ratio and the presence of infiltrates on chest X-ray in the immediate post-operative period (T0), and at 24 (T24), 48 (T48) and 72 (T72) hours post-surgery.[16]

### Diagnosis of pulmonary infection

Fiber-optic bronchoscopy was performed daily. Collection and processing of microbiologic samples were performed according to the usual techniques. Lower respiratory tract infection was suspected on the basis of a new or persistent lung infiltrate on chest X-ray, temperature $\geq 38.3$ºC or $<36$ºC, increased white blood cell count, decreased $PaO_2/FIO_2$ ratio and purulent endotracheal aspirate or sputum. Pneumonia was diagnosed on the basis of the results of microbiologic culture of bronchial samples yielding $\geq 10^6$ colony-forming units (CFU)/ml. Empiric anti-microbial therapy based on local guidelines was initiated in every case of suspected pneumonia, and definitive treatment was adapted after identification and susceptibility testing. The medical and paramedical team was blinded to the PCT assay results at the time of initiation of empiric antibiotic therapy or targeted therapy.

### Outcome

Patients were followed until discharge from the ICU. Time and cause of death were recorded. The total duration of post-operative mechanical ventilation, length of ICU stay and length of hospital stay data were obtained.

### Statistical analysis

Results are expressed as numbers and proportions or median and range. Continuous variables were compared by 2-tailed non-parametric Mann–Whitney *U*-test for comparisons between 2 groups, and the non-parametric Kruskal–Wallis test with Dunn's post-test was used for multiple comparisons. Proportions were compared using the chi-square test or Fisher's exact test as appropriate. Correlations were assessed using Spearman's test. $p < 0.05$ was considered significant.

## Results

### Demographic and clinical characteristics

Twenty-six consecutive patients (17 men, median age 53 [range 30 to 65] years) underwent single ($n = 14$, 54%) or bilateral ($n = 12$, 46%) LT for emphysema ($n = 13$, 50%), pulmonary fibrosis ($n = 7$, 27%) and miscellaneous ($n = 6$, 23%) causes, including 3 transplantations done with cardiopulmonary bypass. Demographic characteristics and peri-operative parameters are presented in Table 1.