

# Assessment of the Accuracy of Procalcitonin to Diagnose Postoperative Infection after Cardiac Surgery

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**Background:** Cardiopulmonary bypass induces a nonspecific inflammatory response. Procalcitonin has been advocated as a specific biomarker for infection. The authors studied the accuracy of procalcitonin to diagnose postoperative infection after cardiac surgery and compared it with those of C-reactive protein, white blood cell count, and interleukins 6 and 8.

**Methods:** The authors prospectively included 100 patients scheduled to undergo elective cardiac procedures with cardiopulmonary bypass. Blood samples were taken before surgery and each day over the 7-day postoperative period, and measurement of procalcitonin, C-reactive protein, white blood cell count, and interleukins 6 and 8 were performed. Diagnosis of infection was performed by a blinded expert panel. Data are expressed as value [95% confidence interval].

**Results:** Infection was diagnosed in 16 patients. Procalcitonin was significantly higher in infected patients, with a peak reached on the third postoperative day. Only the areas under the receiver operating curve of procalcitonin (0.88 [0.71–0.95]) and C-reactive protein (0.72 [0.58–0.82]) were significantly different from the no-discrimination curve, and that of procalcitonin was significantly different from those of C-reactive protein, white blood cell count, and interleukins 6 and 8. A procalcitonin value greater than 1.5 ng/ml beyond the second day diagnosed postoperative infection with a sensitivity of 0.93 [0.70–0.99] and a specificity of 0.80 [0.70–0.87]. Procalcitonin was significantly higher in patients who died (27.5 [1.65–40.5] vs. 1.2 [0.7–1.5] ng/ml;  $P < 0.001$ ).

**Conclusion:** Procalcitonin is a valuable marker of bacterial infections after cardiac surgery.

CARDIAC surgery with cardiopulmonary bypass (CPB) induces an acute inflammatory response that may lead to a systemic inflammatory response syndrome.<sup>1</sup> Because of this inflammatory response, conventional clinical and biologic signs may be misleading in the diagnosis of postoperative complications, particularly infection.<sup>2</sup> Despite the use of new treatment modalities, mortality in sepsis remains high, and the existence of an early biologic marker to diagnose the occurrence of infection in

the postoperative period after cardiac surgery would be of considerable contribution to start an adequate therapeutic strategy. Moreover, it has been recently demonstrated that an earlier therapeutic intervention may improve the prognosis in sepsis and septic shock.<sup>3</sup>

For a few years, attention has been focused on procalcitonin as a potential biologic marker of bacterial infection.<sup>4</sup> Procalcitonin is a propeptide of calcitonin produced by the thyroid gland and is usually undetectable in the blood of healthy humans. Procalcitonin has been considered as one of the most effective markers of bacterial sepsis, providing a new tool for early diagnosis and prognostic assessment of infection in various clinical conditions.<sup>5,6</sup> Nevertheless, the interest of procalcitonin in the diagnosis of bacterial infection in critically ill patients remains less defined.<sup>7,8</sup> Moreover, in the surgical setting such as cardiac surgery, the value of procalcitonin remains a matter of debate. Indeed, either minor or moderate elevation of procalcitonin has been observed postoperatively depending on surgical stress in the absence of any evidence of infection.<sup>9,10</sup>

Therefore, the aim of our study was to determine the accuracy of procalcitonin to diagnose postoperative infection after conventional CPB surgery, and to compare it with those of C-reactive protein (CRP), white blood cell count (WBC), interleukin 6 (IL-6), and interleukin 8 (IL-8).

## Materials and Methods

This was a single-center prospective study performed between January 2003 and June 2003. The study was conducted according to Good Clinical Practice standards and the Declaration of Helsinki, and was approved by the Tunis University Ethical Committee (Tunis, Tunisia). Waived informed consent was authorized because routine care of the patient was not modified. Our study followed the Standards for Reporting of Diagnostic Accuracy recommendations regarding the report of studies of diagnostic accuracy.<sup>11</sup> Patients scheduled to undergo elective open heart surgery with CPB were included. Exclusion criteria were age less than 16 yr, clinically detectable preoperative infection, systemic disease, and corticoids within the last 7 days before surgery.

### Perioperative Management

Patients were premedicated with 1 mg/kg oral hydroxyzine the night before surgery and 1 h before surgery. After preoxygenation, intravenous anesthesia was induced with propofol (3 mg/kg) and remifentanyl (0.5

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$\mu\text{g}/\text{kg}$ ). Tracheal intubation was performed after adequate muscular relaxation had been obtained with cisatracurium (0.15 mg/kg). Anesthesia was maintained with continuous administration of propofol and remifentanyl, whose doses were adapted by the anesthesiologists. Monitoring included electrocardiography, pulse oximetry, end-tidal carbon dioxide, and invasive arterial blood pressure using a radial artery catheter. Right heart catheterization was used only when preoperative left ventricular ejection fraction was less than 0.40. Antibiotic prophylaxis consisted of 2 g cefazolin after induction and 1 g every 4 h during surgery and maintained during 24 h postoperatively. No antibiotic therapy was administered routinely in the absence of any bacteriologic positive sample.

After heparin administration (300 U/kg), myocardial preservation during CPB was performed with intermittent infusion of cold crystalloid cardioplegia and moderate hypothermia (32°C). No antifibrinolytic therapy was administered. Tracheal extubation was performed when patients met all the following criteria: hemodynamic stability, adequate muscle strength, full consciousness, stable body temperature (36°–37°C), and adequate ventilation.

#### *Biologic Measurement*

Blood samples for biologic measurements were drawn after induction of anesthesia (baseline), at the end of CPB, and daily until the seventh postoperative day.

Procalcitonin was measured by an immunoluminometric assay (LUMitest Procalcitonin; Brahms Diagnostica, Berlin, Germany) whose detection limit was 0.08 ng/ml. Normal values were less than 0.5 ng/ml, and the coefficient of variation of the measurement was less than 5%.

C-reactive protein was measured by automatic laser nephelometry (BN 100 analyzer; Boehringer Dade, Marburg, Germany), normal values were less than 6 mg/l, and the coefficient of variation of the measurement was less than 5%. WBC counts were determined by using an automatic counter (Gene-s; Coulter, Paris, France). Normal values were between 4,000 and 12,000 cells/mm<sup>3</sup>.

In a subgroup of patients, IL-6 (n = 52) and IL-8 (n = 54) were measured only twice, before surgery and on the third postoperative day, and using semiautomated, chemiluminescent immunoassays (ImmulateOne; DPC-Biermann, Bad Nauheim, Germany). Normal values of plasma IL-6 and IL-8 levels were 1–11.3 and 4–27 pg/ml, respectively. The coefficients of variation of the measurement were 6% and 6.5% respectively.

#### *Diagnosis of Infection*

After surgery, clinical investigations, including body temperature and microbiologic and radiologic examinations, were performed daily until intensive care unit discharge. The American College of Chest Physicians/Society of Critical Care Medicine consensus classification

was used for diagnosis of systemic inflammatory response syndrome, sepsis, and septic shock.<sup>12</sup> Pneumonia was defined as follows: (1) body temperature greater than 38°C; (2) infiltrate on chest radiograph; (3) leukocytosis (> 12,000 cells/mm<sup>3</sup>); and (4) microorganism isolated in bronchial secretions. Mediastinitis was defined as described by El Oakley *et al.*<sup>13</sup> as follows: (1) body temperature greater than 38°C; (2) leukocytosis (> 12,000 cells/mm<sup>3</sup>); and (3) presence of pus, bacterial growth, or both, identified in mediastinal tissue samples obtained during surgical reexploration.

The final diagnosis of infection was determined by two independent experts in regard to the complete medical chart. In cases of disagreement among the two experts, a consensus was reached by a third expert. Each final diagnosis was classified as certain (high probability), possible, low probability (unlikely), or absent. The final diagnosis was reached when it was classified as certain or possible by the experts and ruled out when it was classified as absent or unlikely by the experts. Experts were blinded for procalcitonin, IL-6, and IL-8, but not for WBC and CRP, which are routinely used. Patients were divided into two groups: the control group, who did not develop any postoperative infection, and the infection group, who developed postoperative infection.

We also recorded the diagnosis of infection suspected by the medical team in charge of the patient postoperatively, the administration of any new antibiotics during at least 24 h in the postoperative period being considered as a diagnosis of infection. The diagnostic accuracy of the medical team was estimated taking the diagnosis of the expert panel as the reference and compared to that of procalcitonin. However, because this diagnosis by the medical team could occur at any time postoperatively and because the medical team was aware of the complete evolution of some of the biologic markers (WBC, CRP), we expected that its accuracy would be greater than that of any biologic marker alone. Therefore, we also recorded the delay of performing this diagnosis (*i.e.*, the delay to administer antibiotics) and compared it with the delay for procalcitonin to reach a value greater than 1.5 ng/ml.

#### *Diagnosis of Other Complications*

Because postoperative infection could also be associated with other complications and/or poor preoperative conditions (potential severity bias), we also assessed postoperative cardiac complications. As previously described,<sup>14</sup> the following postoperative cardiac events were considered: myocardial infarction postoperative (new Q waves of more than 0.04 s and 1 mm deep or a reduction in R waves of more than 25% in at least two continuous leads of the same territory); requirement of an inotropic agent; use of an intraaortic balloon pump in the intensive care unit; ventricular arrhythmia (sustained and requiring treatment); and atrial fibrillation or flutter.

**Table 1. Characteristics of Patients in the Control and Infection Groups**

	Infection Group (n = 16)	Control Group (n = 84)	P Value
Age, yr	60 ± 13	57 ± 12	NS
Body mass index	26 ± 6	26 ± 4	NS
Sex			NS
Men	9 (56)	56 (67)	
Women	7 (44)	28 (33)	
SAPS II score	26 [24–35]	19 [19–24]	0.006
APACHE II score	10 [7–11]	7 [7–8]	0.01
EuroSCORE	2 [1–4]	1 [1–2]	0.01
CPB duration, min	114 ± 43	117 ± 51	NS
Aortic cross clamping, min	78 ± 35	80 ± 38	NS
LVEF < 40%	8 (50)	20 (24)	NS
Surgical procedure			NS
Coronary artery bypass graft	8 (50)	50 (59)	
Valvular surgery	9 (44)	31 (37)	
Combined surgery	0 (0)	3 (4)	

Data are expressed as mean ± SD, median [95% confidence interval], or number (percentage).

APACHE = Acute Physiology and Chronic Health Evaluation; CPB = cardiopulmonary bypass; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LVEF = left ventricular ejection fraction; NS = not significant; SAPS = Simplified Acute Physiology Score.

Then, we assessed the association between elevated procalcitonin and the occurrence of any cardiac event.

#### Statistical Analysis

Data are expressed as mean ± SD or median [95% confidence interval] in nonnormally distributed variables (Kolmogorov-Smirnov test). Comparisons between the two groups were performed using the Student *t* test, the Mann-Whitney test, and the Fisher exact method, when appropriate. The Bonferroni correction was applied for multiple comparisons. Comparison of two medians in the same sample was performed using the Wilcoxon test.

Assessment of the diagnostic accuracy was performed by calculating the sensitivity, specificity, positive and negative predictive values, and accuracy (defined as the sum of concordant cells divided by the sum of all cells in the two-by-two table) and their 95% confidence intervals. We used the maximum value of each biologic marker on the third postoperative day or later because we observed in a preliminary study that procalcitonin and CRP were at their maximum on the third postoperative day. We determined the receiver operating curve (ROC) and calculated the area under the ROC curve and its 95% confidence interval. Comparison of areas under the ROC curve was performed using a nonparametric technique.<sup>15</sup> The ROC curve was used to determine the best threshold for each biomarker to diagnose infection. The best threshold was the one that minimized the distance to the ideal point (sensitivity = specificity = 1) on the ROC curve, as previously described.<sup>16</sup>

Assuming an  $\alpha$  risk of 0.05, a  $\beta$  risk of 0.20, and that the accuracy of CRP should be 0.70, we calculated that 98 patients should be included to be able to detect an increase in accuracy of procalcitonin to 0.85, using the McNemar test (Nquery 3.0 Advisor; Statistical Solutions Ltd., Cork, Ireland). Therefore, we decided to include 100 patients.

All *P* values were two-tailed, and a *P* value of less than

0.05 was considered significant. Statistical analyses were performed using the NCSS 2004 software (Statistical Solutions Ltd.).

#### Results

One hundred patients were included in the study, 65 (65%) men and 35 (35%) women, with a mean age of 58 ± 12 yr. Sixteen patients (16%) were categorized into the infection group, and there was an excellent agreement between experts for the diagnosis of infection (94%). As shown in table 1, no significant difference was found regarding duration of CPB and aortic cross clamp among the two groups. Baseline procalcitonin (0.21 [0.14–0.27] vs. 0.16 [0.12–0.31] ng/ml; not significant [NS]), CRP (8 [7–9] vs. 8 [5–9] mg/l; NS), WBC (8,800 [7,800–9,600] vs. 7,850 [6,400–10,500] mm<sup>-3</sup>; NS), IL-6 (8.0 [3.9–11.0] vs. 4.6 [2–22.9] pg/ml; NS), and IL-8 (11.5 [8.0–18.0] vs. 21.4 [8–49] pg/ml, NS) were not significantly different between the control and infection groups. All preoperative procalcitonin measurements were less than 0.5 ng/ml.

In the control group, 20 patients (24%) developed a postoperative systemic inflammatory response syndrome, and 38 patients (45%) developed cardiac events. In the infection group, patients had pneumonia (n = 9, 56%), mediastinitis (n = 3, 19%) and bacteremia (n = 3, 19%). In the remaining patient (n = 1, 6%), the infection site was not precisely identified. Duration of stay in the intensive care unit and duration of postoperative tracheal intubation were significantly longer in the infection group (table 2).

After CPB, procalcitonin was not significantly different between the control and infection groups (0.25 [0.17–0.40] vs. 0.25 [0.10–1.00] ng/ml; NS). In the control group, procalcitonin increased progressively from the

**Table 2. Postoperative Characteristics of Patients in the Control and Infection Groups**

	Infection Group (n = 16)	Control Group (n = 84)	P Value
Postoperative mechanical ventilation duration, h	87 [9–432]	17 [3–168]	0.02
Delayed extubation > 24 h	9 (56)	13 (15)	0.001
Postoperative cardiac complication			
Myocardial infarction	3 (19)	12 (14)	NS
Use of inotropic agents	12 (62)	38 (40)	NS
Use of intraaortic balloon pump	0	3 (4)	NS
Ventricular arrhythmia	2 (12)	4 (5)	NS
Atrial fibrillation	3 (19)	5 (6)	NS
All cardiac events	13 (81)	38 (45)	0.013
SIRS	9 (56)	20 (24)	0.015
ICU stay, d	5 [2–18]	3 [1–4]	0.01
Death	7 (44)	8 (10)	0.002

Data are expressed as median [95% confidence interval] or number (percentage).

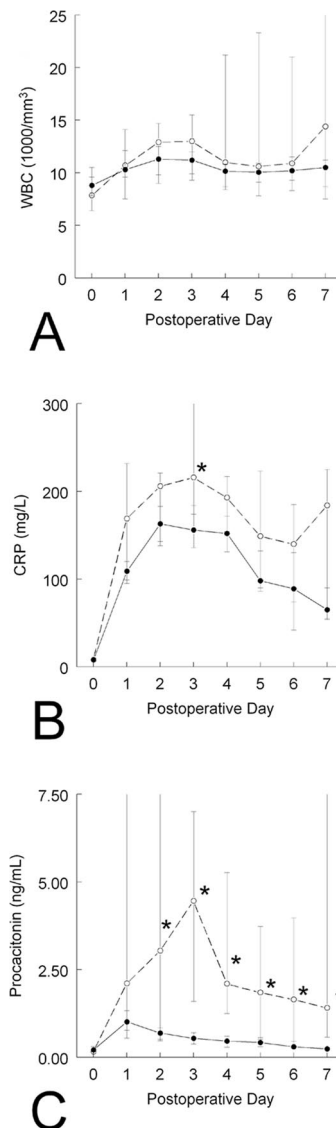
ICU = intensive care unit; NS = not significant; SIRS = systemic inflammatory response syndrome.

end of CPB, peaked on the first postoperative day (1.01 [0.54–1.33] ng/ml), and began to decrease from the second postoperative day (fig. 1), whereas in the infection group, procalcitonin peaked on the third postoperative day (4.46 [1.65–7.00] ng/ml) and remained elevated thereafter (fig. 1). In the control group, the maximum value of procalcitonin was significantly higher in patients with cardiogenic shock (13.8 [0.4–15.4] vs. 1.01 [0.7–1.4] ng/ml;  $P = 0.035$ ).

White blood cell count peaked on the third postoperative day, but there were no significant differences between the two groups (fig. 1). CRP peaked also on the third postoperative day and remained elevated in the two groups (fig. 1). At day 3, IL-6 (25.0 [19.6–36.9] vs. 28.0 [9.9–286] pg/ml; NS) and IL-8 (24.2 [17.3–45.3] vs. 31.0 [5–72.7] pg/ml; NS) were not significantly different between the two groups.

Only the areas under the ROC curve of procalcitonin and CRP were significantly different from the nondiscrimination curve (table 3 and fig. 2). When comparing the ROC curves, procalcitonin was more accurate than CRP, WBC, or IL-6 and IL-8 for the diagnosis of postoperative infection (fig. 2). The diagnostic variables of each biologic marker are depicted in table 4: Procalcitonin was better than CRP, WBC, IL-6, and IL-8. In contrast, when considering the occurrence of cardiac complication, the area under the ROC curve of procalcitonin was significantly lower (0.72 [0.62–0.82]), indicating a poorer prediction of cardiac complications than infection ( $P < 0.001$ ).

All infected patients and four noninfected patients received antibiotics. The diagnostic accuracy of the medical team was better than that of procalcitonin (table 4). The delay of the diagnosis in the infected patients was not significantly different between procalcitonin and the medical team (3.0 [3–3] vs. 3.5 [3–5] days; NS). Nevertheless, when considering any values of procalcitonin greater than 1.5 ng/ml and ascending as compared with its maximum at day 1, the diagnosis of infection could have been provided earlier by procalcitonin than by the



**Fig. 1. Comparison of white blood cell count (WBC; A), C-reactive protein (CRP; B), and procalcitonin (C) in the control (filled circles and unbroken line; n = 84) and infection (open circles and dotted line; n = 16) groups. Data are expressed as median [95% confidence interval]. \*  $P < 0.05$  (between-group comparisons, Mann–Whitney test with Bonferroni correction).**



**Table 3. Comparison of Areas under the Receiver Operating Characteristic Curve of Procalcitonin, CRP, WBC, IL-6, and IL-8 in the Diagnosis of Postoperative Infection**

Variable	Procalcitonin (n = 96)	CRP (n = 99)	WBC (n = 97)	IL-6 (n = 52)	IL-8 (n = 54)
Threshold	1.5 ng/ml	190 mg/l	12,000 cells/mm <sup>3</sup>	40 pg/ml	40 pg/ml
AUC <sub>ROC</sub>	0.88 [0.71–0.95]†	0.72 [0.58–0.82]*†	0.60 [0.39–0.75]*	0.53 [0.28–0.79]*	0.46 [0.17–0.75]*

Data are expressed as value [95% confidence interval].

\*  $P < 0.05$  vs. procalcitonin group. †  $P < 0.05$  vs. 0.5 (i.e., no discrimination).

AUC<sub>ROC</sub> = area under the receiver operating characteristic curve; CRP = C-reactive protein; IL = interleukin; WBC = white blood cell count.

medical team (2.0 [2–2] vs. 3.5 [3–5] days;  $P = 0.015$ ), a condition encountered in only one noninfected patient.

In the whole population, 15 patients (15%) died, 7 with infection. Maximum values of procalcitonin and WBC were significantly higher in patients who died than in the survivor group, whereas CRP, IL-6, and IL-8 were not significantly higher (table 5).

## Discussion

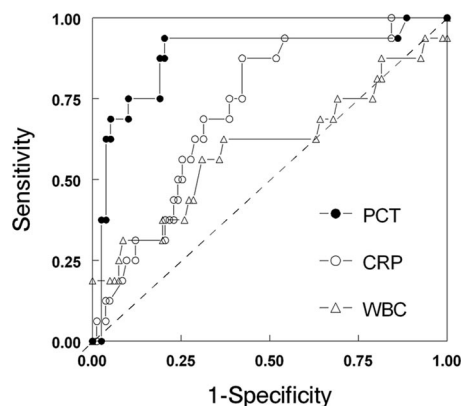
We observed that procalcitonin was significantly increased in patients with postoperative infection after cardiac surgery and that procalcitonin was more accurate than CRP, WBC, IL-6, and IL-8 to predict postoperative infection. Moreover, procalcitonin permitted an early diagnosis.

After CPB, activation of inflammatory cascades may occur, and this reaction shows strong similarities to those observed in sepsis.<sup>17</sup> In this context, the diagnosis of infection remains difficult, because conventional clinical and biologic signs may be misleading.<sup>18</sup> In the current study, we described the postoperative procalcitonin kinetics after cardiac surgery (fig. 1) and observed that procalcitonin was significantly higher in the infection group. The postoperative rise in procalcitonin observed in the control group is in agreement with previous studies.<sup>10,19</sup> Indeed, an increase in procalcitonin after CPB in the absence of postoperative

infection has already been noted by Meisner *et al.*,<sup>20</sup> and an elevated procalcitonin greater than 2 ng/ml can be observed after CPB in case of systemic inflammatory response syndrome, without any postoperative complication.<sup>21,22</sup> This increase may interfere with the diagnosis of infection during the immediate postoperative period. However, in contrast to other biologic markers that usually remain elevated for up to 2 weeks after surgery even in the absence of sepsis, procalcitonin has a transient rise that rarely exceeds 5 ng/ml in the absence of infection.<sup>5</sup> Beghetti *et al.*<sup>23</sup> showed that levels of IL-6 and CRP also increased significantly after cardiac surgery and remained elevated for up to 5 days postoperatively. Procalcitonin has been reported to rise earlier than CRP after the onset of sepsis and to decrease earlier during the course of controlled sepsis.<sup>6,24</sup>

In our study, procalcitonin was more accurate than other biologic markers to predict postoperative infection. Procalcitonin has already been postulated to be superior to commonly used laboratory tests, such as CRP or WBC, and to even correlate with the severity of microbial infection.<sup>25</sup> Balci *et al.*<sup>26</sup> showed that procalcitonin had the highest sensitivity and specificity for differentiating systemic inflammatory response syndrome from sepsis, followed by IL-2 and IL-8. In patients undergoing colorectal and aortic surgery, Reith *et al.*<sup>27</sup> observed that a value of procalcitonin greater than 1.0 ng/ml at day 1 after surgery was closely related to postoperative complications, such as pneumonia or anastomosis leak. The superiority of procalcitonin may be explained by its more specific increase in case of bacterial infection but also by its perioperative kinetics after CPB. Indeed, procalcitonin was only slightly and transiently increased after CPB, whereas the increase in CRP was more prolonged (fig. 1). Therefore, procalcitonin might be useful in the early recognition of an infection after CPB. Nevertheless, it should be pointed out that the diagnostic properties of procalcitonin could not be observed during the first 2 postoperative days (fig. 1).

After CPB, the cutoff value of procalcitonin as a marker of infection remains a matter of debate. Aouifi *et al.*<sup>28</sup> showed that, in the presence of fever, procalcitonin was reliable for diagnosis of infection after cardiac surgery, with sensitivity and specificity, respectively, at 0.85 and 0.95, and with a cutoff value of 1 ng/ml. Using a cutoff value of 0.5 ng/ml, Al Nawas *et al.*<sup>29</sup> found sensitivity



**Fig. 2. Comparison of the receiver operating characteristic curves showing the relation between sensitivity (true positive) and 1-specificity (true negative) in determining the predictive value of procalcitonin (PCT), C-reactive protein (CRP), and white blood cell count (WBC) for the diagnosis of postoperative infection.**

**Table 4. Comparison of the Efficiency of Procalcitonin, CRP, WBC, IL-6, and IL-8 in the Diagnosis of Postoperative Infection**

Variable	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
Procalcitonin (n = 96)	0.93 [0.70–0.99]	0.80 [0.70–0.87]	0.48 [0.32–0.65]	0.98 [0.92–1.00]	0.82 [0.74–0.89]
CRP (n = 99)	0.62 [0.39–0.81]*	0.69 [0.58–0.78]	0.28 [0.16–0.44]	0.90 [0.81–0.96]	0.68 [0.58–0.76]*
WBC (n = 97)	0.62 [0.39–0.81]*	0.60 [0.50–0.70]*	0.24 [0.13–0.38]	0.32 [0.19–0.49]	0.61 [0.51–0.70]*
IL-6 (n = 52)	0.33 [0.39–0.80]	0.77 [0.61–0.80]	0.32 [0.19–0.49]	0.89 [0.80–0.95]	0.70 [0.60–0.78]*
IL-8 (n = 54)	0.33 [0.49–0.87]	0.77 [0.59–0.78]	0.34 [0.21–0.50]	0.89 [0.78–0.95]*	0.70 [0.60–0.78]*
Medical team (n = 100)	1.00 [0.95–1.00]	0.80 [0.58–0.92]	0.95 [0.88–0.98]*	1.00 [0.81–1.00]	0.96 [0.90–0.98]*

Data are expressed as value [95% confidence interval].

\*  $P < 0.05$  vs. procalcitonin group.

CRP = C-reactive protein; IL = interleukin; WBC = white blood cell count.

and specificity of 60% and 79%, respectively. In another investigation, procalcitonin showed a divergent course with a second increase between the fourth and sixth postoperative days. At this time, no clinical sign of an infection was evident.<sup>30</sup> In our study, the method used to determine the threshold was determined *a priori* and did not favor either sensitivity or specificity. However, it should be pointed out that this threshold could be modified by the clinical conditions of the patient. Indeed, we observed high procalcitonin values in patients with cardiogenic shock. Lecharny *et al.*<sup>9</sup> also observed high procalcitonin during the first 24 postoperative hours in a subset of patients who had postoperative myocardial infarction without any evidence of infection. Nevertheless, the increase in procalcitonin during postoperative cardiogenic shock seems to be limited, and a major increase (> 10 ng/ml) has been reported to be highly indicative of a septic origin of the shock.<sup>5</sup> De Werra *et al.*<sup>31</sup> also demonstrated that procalcitonin was the best biologic marker to differentiate septic shock from cardiogenic shock. However, further studies with larger sample sizes are required to confirm our results and precisely determine the ideal threshold in the subgroup of patients with cardiogenic shock.

Postoperative infection could also be associated with other complications and/or poorer preoperative conditions (higher severity scores, lower left ventricular ejection fraction, as shown in tables 1 and 2), and therefore, the hypothesis of a severity bias could not be excluded. Clec'h *et al.*<sup>32</sup> demonstrated that procalcitonin is higher

in patients with septic shock who died than in those who survived. In contrast, they observed that procalcitonin was not significantly different between patients with cardiogenic shock who died or survived. However, we observed that procalcitonin was a poorer predictor of postoperative cardiac complications than of postoperative infection.

Our study provides some interesting information regarding the kinetics of procalcitonin that is important for conducting future research. First, it is obvious that, because of the inflammatory process related to CPB, all biomarkers increased during the first two postoperative days, thus precluding any diagnostic usefulness (fig. 1). At least in cardiac surgery, only the maintenance of a high level and/or a delayed increase in the biomarker beyond the early period could be used as an indicator of postoperative infection. This has several important consequences: (1) timing of the dosage is an important issues; (2) the early postoperative period, during which the diagnostic value of the biomarker is expected to be null because of the inflammatory process, should be precisely defined; and (3) beyond that early period, any maintenance of a high level or further increase in the biomarker should be considered for the diagnosis of postoperative infection. Because patients with postoperative infection had poorer preoperative clinical conditions (table 1), procalcitonin might be of particular interest in a subgroup of patients with higher risk of postoperative infection. In this population, the diagnostic accuracy of procalcitonin would be sufficient to help decide which patients should be treated with antibiotics, as already shown in patients with lower respiratory tract infections.<sup>33</sup> Considering the current overuse of antimicrobial agents, this policy might result in a decrease in their side effects, lower costs, and reduced emergence of drug resistance. Conversely, we noted that the diagnosis in the infected patients could occur earlier with procalcitonin, allowing an earlier administration of antibiotics in infected patients, and it should be emphasized that an earlier therapeutic intervention may improve the prognosis in sepsis and severe sepsis.<sup>3</sup> Nevertheless, this hypothesis must be further validated by larger studies because this analysis was clearly an *a posteriori* exploratory analysis performed in a small sample. Last, other promising biomarkers of bacterial

**Table 5. Comparison of the Maximum Value of Procalcitonin, CRP, WBC, IL-6, and IL-8 between the Surviving Patients and Those Who Died**

	Patients Who Died (n = 15)	Patients Who Survived (n = 85)	P Value
Procalcitonin, ng/ml	27.5 [1.65–40.5]	1.2 [0.7–1.5]	< 0.001
CRP, mg/l	232 [140–289]	202 [187–221]	NS
WBC, 10 <sup>3</sup> /mm <sup>3</sup>	19.3 [14.3–22.8]	13.5 [12.6–14.3]	< 0.001
IL-6, pg/ml	24 [24–24]	28 [20–37]	NS
IL-8, pg/ml	12 [12–12]	26 [20–45]	NS

Data are expressed as median [95% confidence interval].

CRP = C-reactive protein; IL = interleukin; NS = not significant; WBC = white blood cell count.

infection have been recently proposed, such as sTREM-1,<sup>34,35</sup> and further studies comparing them to procalcitonin are also mandatory.

Procalcitonin seems to correlate with the severity of sepsis and may be also useful in predicting the prognosis. In our study, higher procalcitonin values were observed in nonsurviving patients. As previously suggested,<sup>36,37</sup> we observed that constantly elevated procalcitonin in infected patients was associated with a poor prognosis. This result is in accord with previous studies in the emergency setting<sup>38</sup> and in critically ill patients.<sup>6,32</sup>

In conclusion, procalcitonin is an early and specific biologic marker of infection in patients undergoing cardiac surgery, a value greater than 1.5 ng/ml beyond the second postoperative day being strongly predictive of an infectious complication. Routine determination of procalcitonin may improve the treatment of these patients, enabling a more rapid diagnosis and preventing the use of unnecessary antibiotics that are known to select resistant strains. Further studies are needed to confirm this hypothesis.

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