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How reliable is procalcitonin as an inflammatory marker?[1)]

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Abstract

The role of procalcitonin (PCT) plasma levels as a diagnostic tool for intensive care patients has been intensively investigated during the past years. In particular for recognition of bacterial infections, PCT levels have been shown to be superior to other clinical and biochemical markers. Furthermore, some very recent studies show that in patients with lower respiratory tract infections PCT guided antibiotic therapy reduces antibiotic use and thereby may also reduce duration of stay of patients in hospital and thus cut hospitalisation costs. However, various studies indicate that the value of PCT as a prognostic marker is limited because of false positive or negative values. Despite these limitations PCT plasma levels are currently measured in intensive care units. The present study summarises the possible clinical uses of this laboratory marker as a diagnostic tool for the assessment of critically ill patients.

Keywords: infection; inflammatory marker; interleukin 6 (IL-6); procalcitonin; sepsis.

Introduction

Procalcitonin (PCT) is formed physiologically in the thyroid C-cells as a prohormone of calcitonin. In contrast to calcitonin, PCT is not involved in the regulation of the calcium balance. In healthy people, PCT plasma levels are very low. Already in 1993, it was shown that acute inflammatory diseases, such as severe infections including sepsis, are associated with a strong increase in PCT levels [1]. Although PCT is not produced by circulating blood cells, its synthesis is associated with the release of proinflammatory cytokines. Experimentally, the PCT synthesis and release are both induced by bacterial toxins as well as by inflammatory mediators such as TNF and IL-6. The administration of endotoxin, an inflammation-inducing bacterial component, in healthy volunteers leads to cytokine release into the circulation within one or two hours. After about four hours, the PCT levels increase and reach a plateau within 8 to 24 h [2]. Thus, PCT release is a part of the non-specific inflammatory response of the organism which is induced and coordinated by the release of cytokines during infectious diseases. However, the pathophysiological significance of the PCT release is not clearly understood.

While the injection of cytokines such as TNF leads to a significant, dose-dependent inflammatory response in animal models or in healthy volunteers, the administration of PCT is not associated with any inflammatory immune response. However, in a hamster model it has been shown that an existing sepsis is enhanced and mortality is increased by the administration of the PCT. Conversely, neutralizing antibodies have a protective effect [3]. This suggests that PCT itself does not trigger a systemic inflammatory response, but as a secondary mediator of the inflammatory response, it may contribute to the amplification and prolongation of sepsis.

In recent years, the diagnostic value of PCT levels has been investigated in many inflammatory diseases. Thus, PCT was introduced as a marker for the detection and quantification of the severity of sepsis. Furthermore, PCT levels were presented as a differential diagnostic marker for distinguishing between bacterial and viral infections, as a prognostic marker for survival, to assess the success of treatment following surgery or antibiotic therapy, as well as a marker of disease severity after trauma or burns. As expected, the parameter could not satisfy all expectations. However, some clear indications for PCT determination have been worked out that allow the incorporation of PCT levels into diagnostic and therapeutic strategies. The current status of the clinical application of PCT plasma levels will be shown below.

Clinical application of PCT levels

Markers of infection

A major indication for measurement of PCT is a suspicion of an infection. As early as back in the 1990s, a connection between the release of PCT and the evidence of infection was observed. In particular in patients with severe bacterial

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infections and sepsis, as well as meningitis and malaria, the PCT levels were significantly increased [4]. For the diagnosis of a bacterial infection a high diagnostic specificity and sensitivity could be demonstrated [5]. In addition, a correlation between PCT levels and the severity of the inflammatory response was detected. To assess the severity of an inflammation, a 1992 consensus conference introduced definitions for systemic inflammatory reactions, infections and sepsis. At that consensus conference, the term SIRS (systemic inflammatory response syndrome) was defined for the first time for a systemic inflammatory response using the leukocyte count (>12,000 or <4000 cells/µL), heart rate (>90 beats/min), respiration (respiratory rate >20/min, $paCO_2$<32 mm Hg) and body temperature (>38 or <36°C). The term sepsis was reserved for the additional evidence of an infection [6]. A variety of studies have subsequently shown that patients with sepsis exhibited significantly higher PCT levels than patients with SIRS without infection [7–10]. In addition, patients with sepsis, severe sepsis and septic shock present with increasing PCT concentrations as an indicator of the severity of the disease [7, 11, 12]. These observations have led to a new edition of the ACCP/SCCC criteria to include PCT plasma levels as a criterion for the detection of an infection [13, 14].

However, the clinical significance of PCT to differentiate infectious from noninfectious causes of sepsis has been the subject of controversial discussions in the literature [15–18]. In particular, some large meta-analyses indicate no clear benefit of PCT levels as markers of infection [19, 20]. Nor has any clear threshold been defined for the detection of possible sepsis. The different results in the literature can be explained by different measurement methods and by differences in the inclusion criteria of patients [21, 22]. Moreover, it was shown that a whole range of non-infectious clinical events, such as drug-induced hyperthermia, autoimmune diseases, transfusion reactions, tumors and trauma as well as surgical trauma can lead to an increase in circulating PCT levels. This also explains why the sensitivity of PCT levels to detect a positive blood culture is indeed high, while the specificity is only about 60% [23]. Despite these limitations, many studies show that the specificity and sensitivity of PCT levels are higher for the diagnosis of bacterial infection than those of other parameters, such as the still most widely used CRP levels or the leukocyte count [24]. Furthermore, recent studies show that PCT levels are better markers to distinguishing between SIRS and sepsis than CRP, IL-6 and LBP plasma levels [10, 25]. Overall, the present data suggest that an increase in PCT levels in high-risk intensive care patients must be seen as a suspected underlying or incipient infection and in any case must be further clarified.

Therapy control

In addition to the high specificity and sensitivity for detecting bacterial infections, many studies also reveal a high negative predictive value, i.e., a high probability of absence of an infection with low PCT levels. As early as 2002 Chirouze et al. [26] hypothesized that in patients with acute fever and low PCT levels (<0.4 ng/mL), an infection was unlikely (negative predictive value: 98.8%) and that an unnecessary antibiotic treatment could be avoided. This aspect was examined by many other studies in the following years. Thus, in 2004 [27] a plot was presented to control antibiotic therapy by PCT levels in patients with deep respiratory infections. While for patients with PCT levels above 0.25 µg/L empirical antibiotic treatment was recommended, at low PCT levels (<0.25 µg/L or <0.1 µg/mL), antibiotic therapy should be largely avoided. The clinical evaluation of this study showed that this procedure had no negative effect on the clinical outcome, but produced a significant reduction in antibiotic consumption [27]. In a subsequent study on hospitalized patients with nosocomial pneumonia, it was possible to reduce significantly antibiotic therapy using the PCT-guided algorithm without negative effects on the duration of hospital stay or the incidence of complications [28]. Similar results have been reported in patients with chronic obstructive lung disease, ventilator-associated pneumonia and deep airway infections [29–31].

Furthermore, a similar approach of the PCT-guided antibiotic treatment was studied in outpatients with respiratory infections requiring treatment. In this study, one group of patients was treated with antibiotics only when they had a PCT value of over 0.25 ng/mL despite clinical evidence of infection. In the control group, all patients were treated with antibiotics according to evidence-based guidelines [32]. In this study the antibiotic therapy could also be significantly reduced without any negative influence on the outcome of treatment by PCT-guided antibiotic therapy. In a recent study involving patients with acute respiratory infections, PCT-guided antibiotic therapy in connection with a clinical suspicion of bacterial infection actually achieved a reduction in antibiotic consumption by over 40% [33].

In addition to these previously mentioned studies which were conducted exclusively on patients with respiratory infections, similar studies on the significance of PCT in the treatment of other infectious diseases are now available. Thus, it was also possible to reduce antibiotic consumption in several studies on ICU patients with sepsis using a PCT-guided algorithm, without worsening the complication rate, the mortality or the stay in ICU [34, 35]. Furthermore, the benefit of a PCT-guided antibiotic therapy was confirmed in a multicenter study of non-surgical intensive care patients with a suspected infection [36]. The Neonatal Procalcitonin Intervention Study (NeoPlnS) demonstrated successful PCT control of antibiotic therapy also for newborns. However, in this study a small risk for exacerbating neonatal infections by removal of antibiotic therapy could not be excluded. Another limitation of this study was the indication of antibiotic therapy solely based on the clinical assessment by the neonatologist and not according to defined sepsis criteria [37].

In a recent study of 110 surgical ICU patients with clinical suspicion of infection, serial measurements were used to assess whether in addition to a fixed PCT threshold, the drop in PCT levels would allow the termination of an ongoing antibiotic therapy. In this study, a reduction in the duration of antibiotic treatment by about 2 days was achieved, without worsening the clinical outcome [38]. The importance of PCT follow up

levels was also investigated in septic patients and existing empirical antibiotic therapy [39]. In this study a distinction was made between appropriate antibiotic treatment documented by a subsequent microbial investigation and antibiotic treatment not directed against the causal pathogen. While antibiotic therapy directed at the causal pathogen produces a decline of PCT levels within two days, antibiotic treatment not directed against the triggering pathogen was associated with a further increase in PCT levels. This suggests that PCT may be used in particular as a "therapy success marker" during an empirical antibiotic therapy. Whereas a decline of the PCT values following the initiation of antibiotic therapy may be associated with therapeutic success, the absence of such drop could be recognized as an alarm signal. For clinical applications, however, the relevant thresholds must yet be defined for the respective underlying diseases and stages of the disease in further studies. The identification of such specific thresholds, however, is often difficult due to the high variability of PCT levels in the course of the disease [40].

Furthermore, the relevance of a further increase in PCT levels for ICU patients is unclear. Recently a randomized study showed that the increase of an existing antibiotic therapy in connection with increasing PCT levels had no benefit for sepsis patients [41]. In this study, in fact, increased organ damage and a prolonged length of stay in intensive care were observed for the PCT-guided therapy group. This supports the hypothesis that low or decreasing PCT levels have a high negative predictive value for the presence of infections, whereas increasing PCT levels may have other causes than infections and are not suitable for therapy control. For the final assessment, however, further studies are needed.

Empirical antibiotic therapy is an established treatment for high-risk patients suspected with infectious diseases. A PCT-controlled reduction of antibiotic use might not only reduce the adverse effect of this treatment, but also prevent the development of resistance of nosocomial pathogens. In addition, there is an ongoing discussion about potential cost savings through reduction of antibiotic therapy. Whether serial measurements of PCT are cost saving is doubtful because PCT analysis itself is expensive [42]. In two studies of patients with acute respiratory infection, it was, indeed, shown that the control of antibiotic therapy could be accomplished with two PCT measurements per patient [31] or even only a single measurement [43]. In particular the more recent studies indicate, however, that serial PCT measurements were essential as part of treatment control [44].

Prognostic markers

The prognostic value of PCT levels has been investigated in several studies. Whereas in some studies elevated PCT levels were clearly associated with a poor prognosis, other studies could not show a clear correlation between PCT levels and mortality. Moreover other studies show a similar low prognostic value of PCT and CRP levels [45].

In our own studies we were able to show that the prognostic value of IL-6 levels is superior to PCT concentrations in intensive care patients during the very early phase of the first increase of fever [46]. This was especially due to the large variation of PCT levels in this early phase of the disease. Follow-up studies in ICU patients, showed a better prognostic value of PCT levels in comparison to leukocyte count or CRP levels [47]. Possibly, in these patients PCT is increased as a response to the release of endotoxin from the intestines induced by translocation and thus represents the severity of the inflammatory trauma. This hypothesis is supported by a study on cardiac patients in whom the PCT release is also correlated with the systemic inflammatory response [48]. However, in this patient cohort, the respective mean values for the different patient groups exhibit a large heterogeneity. Therefore no clear threshold can be defined [49].

In the early studies prognostic value of PCT levels in patients with fully established sepsis was not significant [12]. These studies indicate that the levels of proinflammatory cytokines, such as IL-6, are more suitable. The prognostic value of PCT levels, however, increase when measured in the course of the disease. But it should be pointed out that PCT levels drop significantly in the lethal phase [3]. To what extent this must be interpreted as a reduction of PCT synthesis or as a complete failure of the immune system is still unclear. Overall, PCT levels, despite a correlation with survival in certain patient groups, do not appear to be optimal prognostic markers.

Summary

PCT levels are important diagnostic tools in intensive care medicine. During clinical routine, however, in some cases unexplained low PCT levels in spite of severe systemic infections have been reported. Vice versa, excessively high levels with a relatively moderate clinical picture can be observed. Although these cases are rare, they may affect the diagnostic value of PCT levels and must be considered in the diagnostic use of this parameter.

Increased PCT levels are usually associated with the presence of an infection, particularly a bacterial infection. The specificity and positive predictive value for detecting an infection are in most studies higher than 80%, thus exceeding those of other biochemical markers [10, 11, 50, 51]. However, it should be noted that other clinical causes rather than infectious diseases can also lead to an increase in circulating PCT levels. Diseases with elevated PCT levels without detectable bacterial infection include calcitonin-producing tumors, pneumonitis, ARDS, severe burns, major surgery, severe trauma, burns or other severe inflammatory reactions without detectable bacterial involvement. Also after therapy with antithymocyte antibodies, and in apparently healthy newborns, an increase in PCT can be observed. It is not clear yet whether these PCT increases are actually false-positive or induced by a low, non-detectable bacteremia or endotoxemia.

So-called false low or negative values, i.e., infectious diseases without substantial PCT release can occur during localized infections (e.g., abscesses) and endocarditis. Furthermore, in the early phase of an infection, PCT levels are often not yet detectable. For the early detection of

inflammatory events, other parameters, such as IL-6 levels, seem to be better suited [45]. In the case of ventilator-associated pneumonia, false low PCT levels are also observed in spite of an underlying infection event. This may be due to the fact that ventilator-associated pneumonia is often caused by few virulent pathogens [21].

Despite false positive and false negative values, PCT levels currently appear to be the best biochemical markers to identify patients with bacterial infections. Low PCT levels indicate the absence of a bacterial infection or may be an indicator of successful antibiotic therapy. Future studies must show whether serial measurements of PCT, together with IL-6 plasma levels and other organ function markers, may contribute to improvement of mortality and morbidity.

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