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REVIEW

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Procalcitonin as a marker of the systemic inflammatory response to infection

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Introduction

Severe infections and sepsis are common causes of morbidity and mortality in intensive care units. Such conditions are accompanied by clinical and laboratory signs including changes in body temperature, leukocytosis, and tachycardia. However, these manifestations of systemic inflammation may be noninfectious in origin and are neither specific nor sensitive for sepsis. A similar inflammatory response occurs in patients suffering from pancreatitis [1], major trauma [2], and burns [3] without infectious complications. It is therefore frequently difficult to distinguish between patients in organ dysfunction or shock who have systemic infection and those who do not [4]. Bacteriological evidence of infection may not develop concurrently with clinical signs of sepsis. Positive bacteriological results may be due to contamination, and negative results do not exclude the presence of infection or sepsis. Since these standard clinical and laboratory parameters lack sensitivity and specificity, other markers are needed to provide an early indication of an infectious cause of a generalized inflammatory response, and thus allow early diagnosis and more specific therapeutic interventions. One such parameter, procalcitonin, has recently gained interest as a possible marker of the systemic inflammatory response to infection.

Biology of procalcitonin

Procalcitonin, a propeptide of calcitonin, is normally produced in the C-cells of the thyroid gland [5, 6]. A specific protease cleaves procalcitonin to calcitonin, katacalcin, and an N-terminal residue [5]. Normally all the procalcitonin is cleaved, and none released into the bloodstream. Procalcitonin levels are therefore very low (< 0.1 ng/ml) in healthy humans. However, during severe infections with systemic manifestations procalcitonin levels increase to over 100 ng/ml. Remarkably, the large amounts of procalcitonin produced during infections do not lead to an increase in plasma calcitonin levels or activity [7]. In contrast to the short half-life of calcitonin (10 min), procalcitonin has a long half-life of approximately 22–35 h in serum [8, 9].

During severe systemic infections procalcitonin is probably produced by extrathyroid tissues. Patients who have previously undergone total thyroidectomy can still produce high levels of procalcitonin during a severe infectious episode [7]. The exact site of procalcitonin production during sepsis is uncertain. In a hamster model of sepsis procalcitonin mRNA was found in numerous tissues [10]. Studies in our laboratory have implicated mononuclear leukocytes [11]; endotoxin and sepsis-related proinflammatory cytokines had pronounced stimulatory effects on procalcitonin mRNA expression in human mononuclear leukocytes when measured by the reverse-transcriptase polymerase chain reaction. Endotoxin was the strongest stimulus while

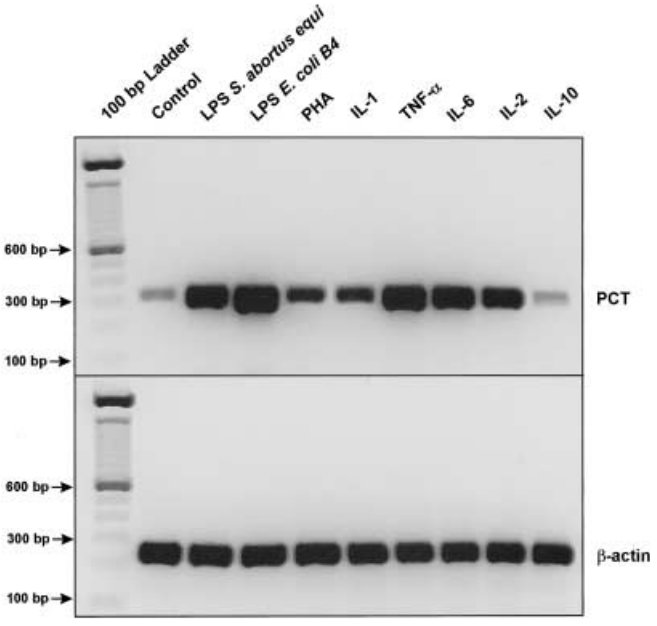

Fig. 1 Induction of mRNA of procalcitonin *(PCT)* in peripheral blood monocytes by various mediators of the inflammatory response. Peripheral blood monocytes were stimulated ex vivo with endotoxin [*lane 3 Salmonella abortus equi (LPS S. abortus equi)*; *lane 4 Escherichia coli* B4 (*E. coli B4*, *lane 4*)], phytohemagglutinin *(lane 5, PHA)* and the cytokines IL-1, TNFα, IL-6, IL-2, IL-10 *(lanes 6–10)*. mRNA of PCT and of β-actin was amplified semiquantitative by reverse-transcriptase polymerase chain reaction, and amplification products were separated on a 2% agarose gel *(above)*. The sizes of the amplification products matched that which was predicted from the position of the primer pairs, and the known cDNA sequences were validated by restriction digestion (data not shown). (From [11])

the anti-inflammatory cytokine interleukin (IL) 10 had no effect (Fig. 1). To evaluate whether mRNA is associated with expression into an intracellular protein we collected mononuclear cells of patients with high procalcitonin plasma levels and treated them with stained antibodies directed against katacalcin and calcitonin. We then observed intracellular staining of katacalcin and calcitonin using flow cytometric analysis [12]. These studies suggest that mononuclear cells are a possible source of procalcitonin during sepsis.

The (patho)physiological role of procalcitonin during sepsis is unclear. In an experimental study Nylen et al. [13] found that procalcitonin administration decreases survival, and that neutralization of procalcitonin increases it. This suggests that procalcitonin is an integral part of the inflammatory process to infection. In healthy volunteers [14] injected with *Escherichia coli* endotoxin, procalcitonin levels, undetectable at baseline, started to rise 4 h after endotoxin injection and reached a plateau of 4 ng/ml at 8–24 h. Tumor necrosis factor (TNF) α and IL-6 levels peaked 2–3 h after endotoxin and were undetectable at 24 h (Fig. 2). A rare and interesting case suggests that the same kinetics can be expected to occur in human septic shock [15]. Hemodialysate of calf blood contaminated with *Acinetobacter baumanii* was injected into a 76-year-old patient, leading to septic shock within hours. TNFα was detectable in serum at 1.5 h, peaked at 3 h, and declined thereafter. Procalcitonin was first detectable at 3 h, peaked at 300 ng/ml 14 h after the injection, and remained elevated for more then 24 h. Thus, in response to endotoxin or live bacteria, increases in circulating procalcitonin levels occur shortly after cytokine levels have peaked. Differences in the half-lives of procalcitonin (22–35 h) and the cytokines measured may explain why procalcitonin is detectable for longer. Alternatively, cytokines released after endotoxin administration may induce procalcitonin production. One study has shown that TNFα infusion into animals induces procalcitonin production although the levels measured were much lower then those encountered during infection [16]. Our in vitro studies also suggest that endotoxin is a more potent stimulator of procalcitonin mRNA than TNFα or other proinflammatory cytokines [17] (Fig. 1).

Fig. 2 Kinetic and half-life of procalcitonin after a hemodialysate of calf blood contaminated with *Acinetobacter baumanii* was injected into a 76-year-old patient leading, within hours, to septic shock. (From [15])

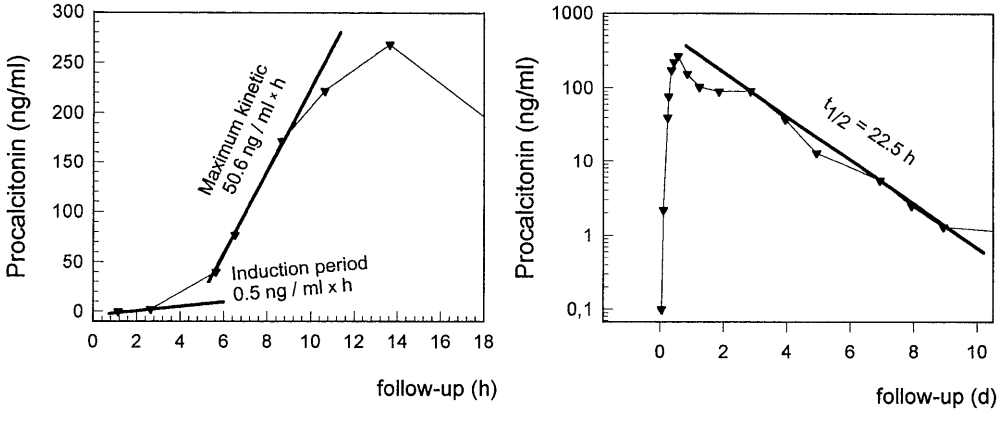

Table 1 Plasma levels of procalcitonin and C-reactive protein in infectious and noninfectious diseases (*CA* community acquired, *SIRS* systemic inflammatory response syndrome, *NR* not reported)

Category	*n*	Procalcitonin (ng/ml)	C-reactive protein (mg/l)	Reference
Infectious				
Sepsis	53	6.6 ± 22.5	NR	[57]
Septic shock	20	34.7 ± 68.4	NR	[57]
Severe sepsis and septic shock	85	31.8 (0.5–5420)	NR	[20]
Peritonitis	14	(1.1–35.3)3	NR	[20]
Pneumonia	7	2.4 ± 3.7	NR	[21]
Severe bacterial infection	19	6 –53	NR	[7]
Bacterial meningitis	–	54.5 ± 69.1	144.1 ± 69.1	[58]
Pneumonia CA	149	0.2 (0.1–6.7)	NR	[20]
Local infection	11	0.3–1.5	30.3 ± 7.6	[59]
Urinary tract infection	–	0.38 ± 0.19	120 ± 8.9	[60]
Pyelonephritis	–	5.37 ± 1.9	–	
Viral meningitis		0.32 ± 0.35	14.8 ± 14.1	[40]
Viral infection	18	0–1.4	NR	[59]
Noninfectious				
SIRS	215	0.6 ± 2.2	NR	[57]
ICU patients	79	0.5 (median)	56 (median)	[49]
Pancreatitis	–	0.39 ± 0.38	96.6 ± 97.5	[33]
Cardiogenic shock	7	1.4 ± 1.9	NR	[21]
Cardiogenic shock	29	48 ± 16	154 ± 22	[26]
Heatstroke	25	3.4 ± 1	NR	[29]

Procalcitonin can be measured with a commercial immunoluminometric assay (B.R.A.H.M.S. Diagnostica GmbH, Berlin, Germany). The assay uses two antibodies that bind to two sites (calcitonin and katacalcin) of the procalcitonin molecule, thus ruling out cross-reactivity. The detection limit of the assay is 0.1 ng/ml. Procalcitonin levels of healthy subjects are usually lower than 0.1 ng/ml [7]. Experimentally, detection of even lower levels of procalcitonin than 0.1 ng/ml is possible. Detecting levels lower than 0.1 ng/ml may elucidate the biology of procalcitonin, or perhaps help to identify localized infections.

Introduction of procalcitonin as a marker of infection

Procalcitonin serum levels increase during severe generalized bacterial, parasitic, or fungal infections with systemic manifestations. Procalcitonin levels do not rise, or do so only to a moderate degree, during severe viral infections or inflammatory reactions of noninfectious origin. An initial, well-documented study [7] conducted in 79 children with suspected infections found that procalcitonin levels were very low (<0.1 ng/ml) in those with no infection and very high (6–53 ng/ml) in those with severe infections. Resolution of infection with antibiotic therapy led to decreases in procalcitonin levels. Both localized bacterial infections (without systemic manifestations) and viral infections produced only small to modest increases (0.3–1.5 ng/ml). Calcitonin was undetectable in these patients, regardless of procalcitonin levels. A study in neonates evaluated the reliability of procalcitonin concentrations for the diagnosis of early-onset (0–48 h) and late-onset (3–15 days) sepsis. Procalcitonin was a good indicator of both early-onset (sensitivity 93 %, specificity 96 %) and late-onset (sensitivity and specificity 100 %) sepsis [18].

In view of the above findings, procalcitonin has been proposed as an indicator of severe generalized infections and sepsis. It is not a marker of infection as such since localized infections or infections without systemic manifestation may cause no or only small increases in procalcitonin levels [19]. One study found procalcitonin levels to be very low or undetectable in patients with community-acquired pneumonia (median 0.2, range 0.1–6.7 ng/ml, $n = 149$) whereas patients with pneumonia and sepsis had very high levels (median 31, range 0.5–5420 ng/ml) [20]. Another study reported mean procalcitonin values of 2.4 ng/ml in patients with pneumonia without sepsis and values of 31 ng/ml in those with sepsis [21]. Therapeutic measures such as antibiotics may therefore be necessary in patients with pneumonia despite normal procalcitonin levels. Likewise, the fact that elevated procalcitonin values during severe infections may decrease to very low levels with appropriate therapy does not always indicate complete eradication of the infection but merely that generalization of the infection or the systemic response is under control. Continuation of antibiotic therapy or surgical measures may still be necessary. Table 1 summarizes the findings of some procalcitonin studies during infection.

Table 2 Sensitivity and specificity of various cutoff values of procalcitonin for differentiating infectious and noninfectious causes of a systemic inflammatory response syndrome

Diagnosis	*n*	Procalcitonin (ng/ml)	Sensitivity (%)	Specificity (%)	Cutoff value (ng/ml)	Reference
Pancreatitis			94	91	>1.8	[33]
Infected	18	–				
Noninfected	32	–				
Autoimmune disease			100	84	>0.5	[56]
No infection	42	<0.5				
Bacterial infection	16	1.9 ± 1.19				
Acute meningitis			94	100	–	[40]
Viral	41	0.32 (0–1.7)				
Bacterial	18	54.5 (4.8–110)				
Renal transplantation			87	70	>0.5	[36]
Acute rejection	13	–				
Infection	17	–				
ICU patients			67.6	61.3	>0.6	[49]
No infection	79	0.5 (median)				
Infection	111	2.5 (median)				

Procalcitonin in patients with noninfectious systemic inflammatory response syndrome

Systemic inflammatory syndromes of noninfectious causes also lead to increases in procalcitonin levels. Patients with major trauma or surgery [22, 23], and patients undergoing cardiopulmonary bypass [24] may present with increased procalcitonin levels without any evidence of severe infection. However, the median values under these conditions are usually below those found in severe sepsis and septic shock. One study in patients with noninfectious systemic inflammation after cardiopulmonary bypass reports a rise in procalcitonin, especially in those with acute lung injury [25]. However, at least one-third of the patients developing acute lung injury had increased levels of procalcitonin even before the operation. Increases in procalcitonin have also been reported in patients with cardiogenic shock [21, 26]. Depending on the severity and duration of cardiogenic shock, the levels of procalcitonin may be moderate (around 1.4 ng/ml) or very high (>40 ng/ml). It may be hypothesized that increases in procalcitonin levels after trauma, hemorrhagic shock, cardiopulmonary bypass, and during cardiogenic shock stem from translocation of bacteria or of bacterial products due to hypoperfusion of the gut mucosa. A recent study found patients with chronic heart failure to suffer from endotoxemia and immune activation, findings which also suggest mesenteric venous congestion, gut hypoperfusion, and translocation of bacteria or bacterial products [27, 28]. Procalcitonin has also been reported in patients suffering from heat stroke [29] and in patients receiving TNFα [30], OKT3, or antilymphocyte serum.

Procalcitonin levels may increase during the first day of life without infections. Once taken into account, however, this does not decrease the utility of procalcitonin in detecting infections in the neonatal period [18]. Lastly, patients with C-cell carcinoma of the thyroid gland [31] and small-cell carcinoma of the lung [32] without underlying infection may also have increases in procalcitonin levels.

Procalcitonin in the differential diagnosis of the systemic inflammatory response syndrome

Systemic inflammatory states of various causes are common among critically ill patients. Procalcitonin can help to identify an infectious cause or infectious complications in patients with a systemic inflammatory response syndrome (SIRS).

In patients with pancreatitis, infection of necrotic tissue indicates the need for operative intervention. Since pancreatitis induces systemic inflammation even in the absence of infection, common clinical and laboratory signs of inflammation do not differentiate between patients with or without infected necrosis. One study found that procalcitonin levels higher than 1.8 ng/ml predicted infection of the necrosis with 80 % sensitivity and 93 % specificity, values comparable to those of fine-needle aspiration, with 80 % sensitivity and 90 % specificity. The diagnostic accuracy improved if increases in procalcitonin levels (>1.8 ng/ml) occurred at least twice during the observation period [33]. Procalcitonin has also been used to distinguish infectious from noninfectious causes of the acute respiratory distress syndrome (ARDS) in adults [34]. During the first 72 h of hospitalization procalcitonin levels were significantly higher ($p<0.0005$) in 17 patients with septic ARDS than in 10 with nonseptic ARDS, with no overlap between the two groups. Differentiation was not possible using plasma C-reactive protein or IL-6. Likewise, procalcitonin may help to differ-

entiate systemic fungal and bacterial infections from episodes of graft rejection in patients after liver [35], kidney [36], and heart [37, 38] transplantation.

Increases in procalcitonin levels are specific only for bacterial and parasitic infections. Regarding fungal infections the data based on case reports are controversial [35, 39]. Procalcitonin levels remain normal or increase only moderately during viral infections. Procalcitonin has therefore been used to differentiate between viral and bacterial infections. Neonates and children with bacterial meningitis are reported to have significantly higher levels of procalcitonin (mean: 57.9 ng/ml) than those with viral meningitis (mean: 0.3 ng/ml) [40]. In patients infected with human immunodeficiency virus (HIV) procalcitonin levels are increased only in those with bacterial sepsis, whereas HIV infection alone, even in the later stages of the disease, does not lead to increases in procalcitonin levels [41]. Immune deficiency other than HIV infection also does not appear to affect procalcitonin release during infections. During sepsis procalcitonin levels increase comparably in immune-deficient and immune-competent patients, and in patients with low neutrophil counts and those with high counts [42, 43]. Table 2 summarizes the sensitivity and specificity of various cutoff values of procalcitonin for differentiating infectious versus noninfectious causes of a SIRS.

Procalcitonin for predicting severity of infection and outcome

Procalcitonin levels rise with increasing severity of the inflammatory response to infection. When patients were categorized into SIRS, sepsis, severe sepsis, and septic shock using criteria published by the Consensus Conference [44], procalcitonin levels were particularly elevated in patients with severe sepsis and septic shock [45]. A recent study [46] measured TNFα, IL-6, C-reactive protein, and procalcitonin levels for 14 days after the diagnosis of sepsis. Procalcitonin levels in survivors were consistently lower than in nonsurvivors during the 14-day period. C-reactive protein, IL-6, and TNFα were not significantly or consistently increased in nonsurvivors, probably because of a high day-to-day variability. C-reactive protein was increased in survivors and nonsurvivors to an almost identical extent. Since procalcitonin levels relate to the severity of the inflammatory response to infection, efficient therapeutic measures may lead to corresponding decreases in procalcitonin levels. On the other hand, increasing or high procalcitonin levels may indicate a poor prognosis. In pediatric patients, successful antibiotic treatment is reflected by falling procalcitonin levels [7]. In a study performed at our institution [47] procalcitonin values obtained on the day on which sepsis was diagnosed were significantly higher in nonsurvivors than survivors. Furthermore, procalcitonin levels increased during the course of disease in nonsurvivors whereas they decreased in surviving patients. In patients with melioidosis (infection with *Burgholderia pseudomallei*) a fatal outcome was associated with levels of procalcitonin significantly higher than those seen in survivors [48]. A recent study by Ugarte et al. [49] found procalcitonin to be significantly higher in survivors of sepsis than in nonsurvivors. Procalcitonin may thus serve as an important indicator of the severity and prognosis of infection and allow assessment of the efficacy of therapeutic measures.

In a recent prospective study in septic patients we showed that elevated procalcitonin levels are correlated with elevated levels of TNF-α and IL-6 [61]. Based on the area under the curve of the receiver-operating characteristic curves, the predictive capability was highest for procalcitonin, moderate for C-reactive protein, and low for leukocyte counts and body temperature. Thus procalcitonin may be an early and better marker of elevated cytokines than the more classic criteria of systemic inflammation.

Procalcitonin and other markers of infection

C-reactive protein is a frequently used marker for assessing the severity of the inflammatory response to infections. Many studies underline the value of this marker in clinical practice. C-reactive protein has been used to differentiate between true pneumonia and endotracheal infections in patients with chronic obstructive lung disease [50], to increase diagnostic accuracy in patients with appendicitis [51], to detect postoperative sepsis in infants [52], as an indicator of the resolution of sepsis [53], and to differentiate between bacterial and viral infections [54]. However, procalcitonin may be superior to C-reactive protein in identifying and assessing the severity of an infection. Numerous studies underline the different features of plasma levels of procalcitonin and the other inflammatory parameters in patients with sepsis and infection. In patients with pancreatitis procalcitonin (>1.8 ng/ml) has been shown more accurately to identify an infected necrosis than C-reactive protein [33]. In patients after renal transplantation procalcitonin is more specific than C-reactive protein in differentiating infection from graft rejection [36]. In critically ill children with infectious disease [55] procalcitonin increases earlier and returns to the normal range more quickly than C-reactive protein. A 14-day follow-up study in septic patients observed C-reactive protein levels, although increased, to be almost identical in survivors and nonsurvivors; procalcitonin levels, however, were consistently lower in survivors [62]. These studies, as well as clinical experience, suggest that procalcitonin and C-reactive protein are equally accurate in diagnosing infectious complications in patients with localized

infection [49], but that procalcitonin is superior in identifying and assessing the severity of the infection.

Potential clinical use

Early diagnosis of sepsis in critically ill patients is important in preventing further complications. In many cases patient history, presentation setting, and physical examination with or without routine laboratory parameters suffice to establish the diagnosis of sepsis. This careful evaluation of the patient is of the utmost importance in interpreting any laboratory result. Procalcitonin proves clinically helpful if used within this context. However, in some cases it may be difficult to identify the presence of sepsis, or to follow its severity, on clinical evidence alone. In these cases a marker of sepsis such as procalcitonin may provide crucial information.

Procalcitonin measurements may be helpful in differentiating between infectious and noninfectious causes in patients presenting with a SIRS, for example, pancreatitis, after major operations and trauma, and in ARDS. After transplantation it may differentiate between graft rejection and infection. High procalcitonin values or abrupt increases in these patients should initiate a search for the source of infection. Procalcitonin may also be helpful in assessing the severity of infection, the prognosis of disease, and the response to therapeutic measures. Furthermore, procalcitonin measurements may be helpful in differentiating between viral and bacterial infections (with systemic manifestations).

Immunomodulatory studies of sepsis have been unsuccessful. One possible reason is that the severity of the inflammatory response cannot be adequately monitored or measured. Using markers which assess the severity of the inflammatory and cytokine response, such as procalcitonin, may enhance the benefits of immunomodulatory therapy [61]. However, further investigations are needed to verify this hypothesis.

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