D. Gendrel, C. Bohuon

Procalcitonin, a Marker of Bacterial Infection

Calcitonin and its propeptide, procalcitonin (PCT), and other peptide products of the calcitonin gene are known to be elevated in medullary thyroid carcinoma and in several other systemic diseases. But the demonstration of high procalcitonin concentrations without increase of calcitonin in patients with severe bacterial infection is a recent clinical finding in humans [1]. PCT is a 116 amino acid peptide which undergoes post-translational proteolysis into the mature hormone, calcitonin, composed of 32 aminoacids. PCT, which is low or undetectable in serum of healthy subjects, infants or adults, reaches high concentrations in patients with severe bacterial infection, septicemia or meningitis and decreases rapidly after appropriate antibiotic therapy. Moreover, in patients with acute viral infection or with inflammatory diseases, PCT is low.

The transformation of procalcitonin into calcitonin occurs in thyroid C cells. Calcitonin and PCT are both elevated in sera of patients with thyroid carcinoma originating in these cells. The type of cells producing PCT during sepsis is not known, but in infected patients with high circulating PCT levels, calcitonin is undetectable. Thyroid is not the sole tissue involved in the secretion, since an infection-associated rise of PCT has been shown in a thyroidectomised patient with septicemia [1].

The mechanism of PCT production is unclear. Rapid and substantial release of PCT has been observed in patients with final-stage cancer after intravenous administration of interleukin-2 or TNF [1]. After endotoxin injection, PCT increases at 3–4 h in blood of healthy volunteers and then rises rapidly to a plateau at 6 h and remains elevated until at least 24 h. In the same patients, TNFα and IL6 peak at 90 min and 3 h and reach baseline concentrations at 6 and 8 h, respectively [2]. Differences in the magnitude of the PCT peaks are observed between the patients, but a marked rise is present in all subjects. However, preliminary studies performed *in vitro* with endothelial cells, lymphocytes or macrophages do not reveal PCT secretion after addition of endotoxin to medium.

Procalcitonin measurement is actually performed with a immunoluminometric assay (BRAHMS Diagnostica, Berlin). Two monoclonal antibodies bind PCT at two different sites (the calcitonin and the katacalcin segments). This assay, which is specific for the proCT molecule, requires 20 µl of plasma and can be done within 2 h. Its detection limit is 0.1 µg/l. Inter- and intra-assay variations at both low and high concentrations are less than 8% and 7%, respectively. Using this assay, plasma proCT levels in healthy adult subjects are < 0.1 µg/l.

Up to now, in the absence of an animal model, only clinical data collected in humans are available. Serum calcitonin-like reactivities have already been reported in various extrathyroid disorders, including bacterial infections, but the methods employed were unable to discriminate calcitonin and procalcitonin [3, 4]. In these assays, high procalcitonin levels were probably measured as a slight increase of calcitonin, due to a cross-reactivity of the antibodies. Since the publication of our first study, numerous data from other groups have confirmed the evidence that PCT blood concentrations are closely related to severe invasive bacterial infections. When the infection is locoregional or confined to a single organ, without systemic response of the inflammatory reaction, the PCT is low or moderately increased. Melioidosis, a potentially severe infection caused by the gram-negative bacillus *Pseudomonas pseudomallei* is a good example. PCT has been found to be an excellent marker of disease activity (low in patients with abscess and high at septicemic phase) and a good prognostic indicator [5].

One of the most interesting indications of PCT in clinical practice is the monitoring of critically ill patients with a possibility of sepsis [6–10]. Very high levels of procalcitonin are a characteristic of septic shock and contrast with the reduced levels observed in cardiogenic shock, while proinflammatory cytokines are elevated in both groups [6]. Procalcitonin allows the differential diagnosis between bacterial and nonbacterial aetiologies of acute situations. In adult respiratory distress syndrome the discrimination in both groups, with or without bacterial etiology, is not possible by C-reactive protein and interleukin 6, since both parameters are increased by non-specific inflammation. In contrast, PCT is elevated only in patients with bacterial etiology, without overlapping with the group of ARDS of toxic origin [7]. A very similar situation is found in acute pancreatitis for biliary versus toxic aetiology: only PCT allows a discrimination but not CRP and IL6 [7–8]. After major digestive surgery, the rise of procalcitonin during the daily follow-up of patients is an early indicator of septic complication with a marked increase in non-survivors versus survivors. After transplantation surgery, patients with acute rejection had normal or slightly increased PCT concentrations, while PCT was high in those with bacterial or fungal infections. In all these situations with important inflammatory reaction and increase of proinflammatory cytokines and CRP, a procalcitonin rise is a marker of sepsis [8–10]. Moreover, in chronic inflammatory diseases, such as Crohn's disease, ulcerative colitis, nephrotic syndrome or juvenile arthritis, procalcitonin is low. But, in acute *Plasmodium falciparum* malaria attacks, a disease in which TNF-alpha is produced, PCT reaches high levels [11].

Prof. *D. Gendrel*, Hôpital Saint-Vincent de Paul, 82 avenue Denfert-Rochereau, F-75014 Paris; Prof. *C. Bohuon*, Institut Gustave Roussy, Villejuif, France.

Procalcitonin is useful in young patients to differentiate between viral and bacterial infection. In 18 children with bacterial meningitis, PCT at hospital admission ranged from 4.8 to > 200 μg/l and < 1.2 μg/l in 45 cases of viral meningitis [12]. Comparing the diagnostic value of different parameters, we have found that sometimes CRP and more often IL 6 values had an important overlapping zone in 22 septicemic children and 51 others infected by viruses, while PCT values were always < 1 μg/l in the viral group and only in 1/22 in the bacterial group [13].

The delayed diagnosis and treatment of bacterial infection continue to be a major cause of morbidity and mortality in neonates and reliable laboratory tests are needed. Elevated procalcitonin levels are mainly associated with neonatal bacterial sepsis, and decrease rapidly after appropriate antibiotherapy. PCT remains low in viral infections and in bacterial colonization of neonates without invasive infection, and the false-negative results are rare [14]. The main problem for interpretation of high PCT levels in neonatology concerns the cases of some neonates with severe and prolonged hypoxemia or multiorgan failure syndrome and without evidence of infection. The rise of PCT is possibly related to the translocation of enterotoxin from the digestive tract. But high PCT levels were also found in patients with an extended tissue injury, such as burns or severe trauma, and an unknown cellular factor could be involved in PCT production.

Further studies are needed to confirm the first results and to determine the cut-off values. We need an animal model to explore the mechanisms of PCT production. But PCT appears to be an early and discriminant marker of severe bacterial infections.

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