Detection of acute phase response and infection. The role of procalcitonin and C-reactive protein

M. ROTHENBURGER[1], A. MARKEWITZ[1], T.LENZ[1], H. G. KAULBACH[1], K. MAROHL[2], W. D. KUHLMANN[3], C. WEINHOLD[1]

[1]Department of Cardiovascular Surgery, [2]Department of Anesthesiology, Central Military Hospital, Koblenz, Germany
[3]Central-Laboratory-Institute, Koblenz, Germany

Clin. Chem. Lab. Med. 37, 275-279, 1999

Objective

Established parameters, e.g. C-reactive protein (CRP), do not differentiate specifically enough between patients developing an infection and those exhibiting an acute phase response following cardiac surgery. The objective of this prospective study was to investigate if procalcitonin (PCT) is more helpful than CRP.

Methods

During a 1-year period, seven out of 563 patients (1.2%) developed systemic infections (group A) after cardiac operations with cardiopulmonary bypass (CPB), and additional eight patients (1.4%) had local wound infections requiring surgical therapy (group B). Blood samples for PCT and CRP measurements were taken preoperatively, at the onset of infection (d1), as well as on the third day (d3), fifth day (d5), and seventh day (d7) following diagnosis of infection. Forty-four randomly selected patients undergoing cardiac surgery with CPB without clinical signs of infection, additional intensive care unit (ICU) management or additional antibiotic treatment served as control (group C) to assess the PCT and CRP contribution to acute phase response. PCT and CRP levels were measured preoperatively, on the first (d1), third (d3) and fifth day (d5) after operation.

Results

At the onset of infection, PCT levels (median interquartile range 25%-75%) increased significantly in group A as compared to baseline values (10.86 [3.28-15.13] ng/ml vs. 0.12 [0.08-0.21] ng/ml), and decreased during treatment to still significantly elevated values on d5 (0.56 [0.51-0.85] ng/ml). CRP levels were significantly elevated on all days investigated with no trend towards normalisation (d1: 164.5 [137-223] mg/l vs. 1.95 [1.1-2.8] mg/l preoperatively, d5: 181.1 [134-189.6] mg/l). In group B, no increase in PCT levels, but a significant increase of CRP from d1 (165.9 [96.6-181.6] mg/l vs. 3.7 [2-4.3] mg/l preoperatively) until d5 (98 [92.8-226.2] mg/l) was detected. In group C, postoperative PCT levels increased slightly but significantly in the absence of infection on d1 (0.46 [0.26-0.77] ng/ml vs. 0.13 [0.08-0.19]

ng/ml preoperatively), and d3 (0.37 [0.2-0.65] ng/ml) and reached baseline on d5 (0.24 [0.11-0.51] ng/ml). CRP levels were significantly elevated as compared to baseline on all postoperative days investigated (baseline: 1.75 [0.6-2.9] mg/l, d1: 97.5 [74.5-120] mg/l, d3: 114 [83.05-168.5] mg/l, d5: 51.4 [27.4-99.8] mg/l). PCT showed a significant correlation to CRP in group A ($r=0.48$, $p<0.001$), a weak correlation in group C ($r=0.27$, $p=0.002$) and no correlation in group B. Intergroup comparison revealed a significant difference for PCT between all groups (A>C>B) and significantly higher CRP levels in group A vs. C and in group B vs. C. Thus, the pattern high PCT/high CRP appears to indicate a systemic infection, while low PCT/high CRP indicates either acute phase response or local wound problems, but no systemic infection. The cost for PCT measurements was 5.6-fold higher as compared to CRP.

Conclusion

Due to the significant differences in the degree of increase, PCT appears to be useful in discriminating between acute phase response following cardiac surgery with CPB or local problems and systemic infections, with additional CRP-measurement increasing the specificity.

References

1. Le Moullec JM, Julliennec A, Chesnais J. The complete sequence of human procalcitonin. FEBS Lett 1984; 167:93-7.
2. Gendrei D, Raymond J, Assicot M, Moulin F, Iniguez JL, Lebon P, Bohuon C. Measurement of procalcitonin levels in children with bacterial or viral meningitis. Clin Infect Dis 1997; 24 (6):1240-2.
3. Assicot M, Gendrei D, Carsin H, Raymond J. Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet 1993; 341 (8844):515-8.
4. Gendrei D, Assicot M, Raymond J, Moulin F, Francual C, Badoual J, Bohuon C. Procalcitonin as a marker for the early diagnosis of neonatal bacterial infection. J Pediatr 1996; 128(4):570-3.
5. AI Nawas B, Shah PM. Procalcitonin with and without immunosuppression and sepsis. Infection 1996; 24 (6):434-6.
6. Boeken U, Feindt P, Petzold T, Klein M, Micek M, Mohan E, *et al.* Procalcitonin (PCT): Diagnostischer Stellenwert und Einfluß von EKZ, SIRS, Sepsis und Gabe von Aprotinin. Thoracic Cardiovascular Surgeon, 1998; Suppl 94:99.
7. Dandona P, Nix D, Wilson MF, Aljada A, Love J, Assicot M, et *al.* Procalcitonin increase after endotoxin injection in normal subjects. J Clin Endocrinol Metab 1994; 79 (6): 1605-8.
8. Petitjean S, Assicot M, Bohuon C. Etude de l'immunoreactivité calcitonin-like au cours de processus infectieux. Immunoanal Biol Spec 1994; 9:54-8.
9. Carsin H, Assicot M, Feger F, Roy , Pennacino I, Le-Bever H, et *al.* Evolution and significance of circulating procalcitonin levels compared with IL-6, TNF alpha and endotoxin levels early after thermal injury. Burns 1997; (3):218-34.
10. Agrawal A, Kilpatrick JM, Volanakis JE. Structure and function of human C-reactive protein. In: Markewitz A, Kushner I, Baumann H, editors. Acute phase proteins. Boca Raton: CRCPess 1993:79-92.
11. Nylen ES, Al-Arifi A, Becker KL, Snider RH, Alzeer A. Effect of classic heatstroke on serum procalcitonin. Crit Care Med 1997; 25 (81:1362-5.

12. Staehler M, Hammer C, Meiser B, Reichart B. Procalcitonin: a new marker for differential diagnosis of acute rejection and bacterial infection in heart transplantation. Transplant Proc 1997; 29 (1-2):584-5.
13. Berger D, Bölke E, Huegel H, Seidelmann M, Hannekum A, Beger HG. New aspects concerning the regulation of the postoperative acute phase reaction during cardiac surgery. Clin Chim Acta 1995; 239:121-130.
14. Colley CM, Fleck A, Goode AW, Muller BR, Myers MA. Early time course of the acute phase response in man. J Clin Pathol 1983; 36:203-7.
15. Crockson RA, Payne CJ, Ratcliff AP, Soothill JF. Time sequence of acute phase reactive proteins following surgical trauma. Clin Chim Acta 1966; 14:435-41.
16. Aronsen KF, Ekelund G, Kindmark CO, Laurell CB. Sequential chances of plasma proteins after surgical trauma. Scand J Clin Lab Invest 1972; 29 (Suppl 1241:127-36.
17. Fischer, CL, Gill C, Forrester MG, Nakamura R. Quantification of acute phase proteins postoperatively. Am J Clin Pathol 1976; 66:840-6.
18. Myers MA, Fleck A, Sampson B, Colley CM, Bent J, Hall G. Early plasma protein and mineral changes after surgery: a two stage process. J Clin Pathol 1984; 34:862-6.
19. Dominioni L, Dionigi R, Cividini F. Determination of C-reactive protein and alpha-1-antitrypsin for quantitative assessment of surgical trauma. Eur J Surg Res 1980; Suppl 1:133.
20. Brewster N, Guthrie C, McBirnie J. CRP levels as a measure of surgical trauma: a comparison of different general surgical procedures. J R Coll Surg Edinb 1994; 39:86-8.
21. AI Nawas B. Procalcitonin in diagnosis of severe infection. Eur J Med Res 1996; 1:331-3.
22. Davis TME, Assicot M, Bohuon C. Serum procalcitonin concentrations in acute malaria. Trans R Soc Trop Med Hyg 1994; 88:670-3.
23. Richard-Lenoble D, Duong TH, Ferrer A, Lacombe C, Assicot M, Gendrei D, *et al.* Changes in procalcitonin and interleukin 6 levels among treated African patients with different clinical forms of malaria. Trans R Soc Trop Med Hyg 1997; 91 (3):305-6.
24. Gendrei D, Bohuon C. Procalcitonin, a marker of bacterial infection [editorial]. Infection 1997; 25 (3):133-4.
25. Zeni F, Viallon A, Assicot M. Serum procalcitonin in sepsis: relation to severity and cytokines (TNF, IL-6, IL-8). [abstract]. Clin Intensive Care 1994; 5:suppl 2.
26. Monneret G, Labaune JM, Isaac C, Bienvenu F, Putet G, Bienvenu J. Procalcitonin and C-reactive protein levels in neonatal infections. Acta Paediatr 1997; 86 (2):209-12.
27. De Werra I, Jaccard C, Corradin SB, Chiolero R, Yerson B, Gallati H, et *al.* Cytokines, nitrite/nitrate, soluble tumor necrosis factor receptors, and procalcitonin concentrations: comparisons in patients with septic shock, cardiogenic shock, and bacterial pneumonia. Crit Care Med 1997; 25 (4):607-13.
28. Eberhard OK, Haubitz M, Brunkhorst FM, Kliem V, Koch KM, Brunhorst R. Usefullness of procalcitonin for differentiation between activity of systemic autoimmune disease (systemic lupus erythematosus/systemic antineutrophil cytoplasmic antibody-associated vasculitis) and invasive bacterial infection. Arthritis-Rheum 1997; 40 (7):1250-6.
29. Nylen ES, O'Neill W, Jordan MH, Snider RH, Moore CF, Lewis M, *et al.* Serum procalcitonin as an index of inhalation injury in burns. Horm Metab Res 1992; 24(9):439-43.
30. Smith M, Suputtamongkol Y, Chaowagull W. Serum procalcitonin in melioidosis. Clin Infect Dis 1995; 20:641-5.

31. Whicher JT, Evans SW. Acute phase proteins. Hosp Update 1990; 15:899-905.
32. Staeler M, Hammer C, Meiser B, Fürst H, Reichart B, Schildberg FW. Differential acute graft rejection and infection diagnosis with procalcitonin and cytokines. Langenbecks Arch Chir Suppl Kongressbd 1997; 114:205-9.