Letter to the Editor

Determinants of procalcitonin concentration in acute heart failure

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Procalcitonin (PCT) is an up-regulated protein in infectious states and thus an indicator for severity of bacterial infections [1]. In patients with acute dyspnea, plasma PCT has been used to differentiate between acute heart failure (AHF) and superimposed pneumonia [2,3]. In this setting, it has shown to be a promissory marker to guide antibiotic treatment and prevent adverse outcomes. Nevertheless, minor elevations of PCT in unselected patients admitted for AHF. Thus, we studied a cohort of 261 patients consecutively admitted for AHF and in the absence of active infection we sought to determine clinical factors related to PCT in unselected patients admitted for AHF. This study was approved by an institutional review committee and all patients gave an informed consent. Plasma PCT, interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor alpha (TNF-α) and endotoxin were obtained in the first blood sample obtained at emergency room using commercially available assays [Electys BRAHMS PCT (sensitivity range: 0.02 ng/mL), HSCYTOMAG-60SK (High Sensitivity Human Cytokine Magnetic panel Milliplex) and PYROCHROME (sensitivity range: 0.005 EU/mL), for PCT, cytokines and endotoxin.

Table 1. Baseline characteristics.

Table 2. Cytokines and endotoxin.

Abbreviations: AHF: acute heart failure; ACEI/ARB: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; SBP: systolic blood pressure; DBP: diastolic blood pressure; NT-proBNP: amino-terminal pro-brain natriuretic peptide; TNThs: high-sensitivity troponin T; C-reactive protein; CRP: C-reactive protein; IL-1b: interleukin-1b; IL-6: interleukin-6; IL-10: interleukin-10; TNF-α: tumor necrosis factor alpha; LDL: low density protein; HDL: high density lipoprotein; LVEF: % left ventricular ejection fraction.

Values are expressed as mean ± standard deviation, unless otherwise specified; categorical variables are presented as percentages.

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Fig. 1. Functional form of the adjusted association among different plasmatic biomarkers and PCT concentration. Variables modeled with fractional polynomials. PCT: procalcitonin (ng/ml), logPCT: logarithm of PCT, GFR: glomerular filtration rate (ml/min/1.73 m²), HDL: high density lipoprotein (mg/dl), TNT hs: high-sensitivity troponin T (pg/ml), PCR: C-reactive protein (mg/l), GGT: gamma-glutamyl transpeptidase (U/l) and Na: sodium (mEq/l).
and endotoxin, respectively]. The logarithm of PCT (logPCT) was used as a dependent variable in a multivariable linear regression analysis. The linearity assumption for all continuous covariates was simultaneously tested and transformed, if appropriate, with fractional polynomials. A 2-sided p-value of <0.05 was considered to be statistically significant for all analyses. All analyses were performed using Stata 13.1.

The mean age of the sample was 73.2 ± 10.4 years; 50.4% were male, 55.3% exhibited left ventricular ejection fraction (LVEF) >50%. The median (IQR) for PCT was 0.06 ng/ml (0.04–0.10). Table 1 summarizes the clinical characteristics of the study sample. In a univariate context, estimated glomerular filtration rate (eGFR) showed the strongest correlation with logPCT (r = 0.34, p < 0.001). Of note, important risk factors such as systolic blood pressure (r = 0.05, p = 0.410), heart rate (r = −0.09, p = 0.162), age (r = 0.11, p = 0.075), LVEF (r = 0.03, p = 0.628) and NT-probrain natriuretic peptide (r = 0.23, p < 0.001) were not or modestly correlated with logPCT. Likewise, cytokines [IL-1b (r = −0.04, p = 0.521), IL-6 (r = 0.036, p = 0.561), IL-10 (r = 0.012, p = 0.849) and TNF-α (0.003, r = 0.967)] did not correlate with logPCT. In a multivariable setting and ranked in the order of importance (drop in R2), eGFR (31.1%), high density lipoprotein (HDL) (14%), leukocyte count (13.5%), high-sensitivity troponin T (9.8%), C-reactive protein (9.5%), relative lymphocyte count (5.9%), prior use of beta-blockers (5.7%), gamma-glutamyl transpeptidase (5.5%), sodium (2.8%) and endotoxin (2.2%) showed to influence the mean of logPCT. A negative relationship was found for eGFR, HDL, relative lymphocyte and prior use of beta-blockers. A “J”-shape curve was found for leukocyte count; and a positive relationship was found for the rest of covariates included in the final model. Plots depicting the direction and magnitude of these above relationships are presented in Fig. 1. The multivariate model accounted for 39% of the variability in logPCT.

Present findings suggest a complex and multifactorial role in the pathophysiology of PCT elevation in AHF. In fact, surrogate markers of inflammation (leukocytes, low lymphocytes count, C-reactive protein, low HDL and endotoxin) and venous congestion (sodium, gamma-glutamyl transpeptidase and even low eGFR) predicted logPCT. Based on the above results, and in the absence of signs of hypoperfusion (mean systolic blood pressure of our sample was 148 ± 34 mm Hg) together with renal dysfunction, we speculate that most of the PCT elevation occurs as a result of endotoxin translocation in patients with abdominal/gut congestion [5]. Despite the fact that endotoxin level was modestly associated to logPCT, it is well-known that endotoxin-stimulated immune response may also occur through the lymphatic system [6] and its assessment, with available assays, is difficult and subject to important limitations that ultimately affect the reliability of the measurement [7]. In our opinion, the fact that low HDL and low relative lymphocyte count also predicted LogPCT reinforces the notion that PCT up-regulation strongly depends on lipopolysaccharide-stimulated immune activation. Low HDL is associated with enhanced inflammatory and coagulation responses on endotoxin challenge [8] and it is known that the administration of Escherichia coli lipopolysaccharide to humans causes a biphasic response in neutrophils, but a more uniform response in lymphocytes, evidenced by a nadir of lymphopenia at 1.5 h and 4 h [9]. Therefore, we believe that PCT may be considered as a potential biomarker for the estimation of endotoxin-immune activation in patients with AHF and no-evidence of infection. This is of particular interest since the inability to detect endotoxia reliably in clinical setting has impeded its widespread use in daily clinical practice [7]. In conclusion, we found that renal function and surrogates of venous congestion and inflammation were the main clinical determinants of PCT concentration in unselected patients admitted with AHF and no-evidence of infection. Further studies are warranted to confirm these results and to explore the clinical utility of this biomarker for risk stratification and targeting new therapies.

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**Conflict of interest**

The authors report no relationships that could be construed as a conflict of interest.

**References**

[4] McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787–847.