

REVIEW

Procalcitonin in Acute Heart Failure; Summarizing the Evidence After the IMPACT-BIC-18 Trial

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ABSTRACT

Acute heart failure is a time critical disease and it is of outmost importance to identify the underlying precipitating factors as soon as possible as this can improve patient outcomes. Infection is such a significant factor. Procalcitonin, as a biomarker of bacterial infection, can be used in acute heart failure patients to establish the diagnosis of concomitant bacterial infection. Procalcitonin can guide the early initiation of antibiotic therapy and provide prognostic information regarding acute heart failure patients. This short narrative review summarizes the current evidence on procalcitonin use in acute heart failure including the preliminary results of the IMPACT-BIC-18 trial.

KEY WORDS: *Acute heart failure,
procalcitonin, biomarker, infection*

LIST OF ABBREVIATIONS:

AHF: Acute heart failure
CRP: C-reactive protein
ESC: European Society of Cardiology
HF: Heart failure
MR-proANP: Mid-regional pro-atrial
natriuretic peptide
PCT: Procalcitonin
WBC: White Blood Cell

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INTRODUCTION

Acute heart failure (AHF) is defined as a rapid onset of new or worsening signs and symptoms of HF.¹ It includes patients presenting for the first time with typical symptoms and signs of HF (*de novo* AHF) and also those with decompensation of their preexisting cardiomyopathy (acute decompensated HF). The European Society of Cardiology (ESC) guidelines recognize AHF as a time critical disease (like acute coronary syndromes) and stress the importance of identifying the underlying precipitating factors as soon as possible.² This is actually the real challenge in AHF; to identify the underlying cause or precipitant that requires immediate attention and intervention. One of the most important and common precipitants is infection. It is thus essential to have a way to diagnose the concomitant presence of infection. Procalcitonin (PCT) is a 116 amino acid precursor of the hormone calcitonin, which is normally produced by the C-cells of the thyroid.³ During a bacterial infection PCT levels increase within 2 to 4 hours of infection and peak around 24 to 48 hours and one can observe up to a 10⁵-fold increase (C-reactive protein -CRP- in comparison shows only a 10- to 10²-fold increase).⁴ On the other hand, viral infections result in down-regulation of PCT. According to a recent Cochrane meta-analysis the use of PCT to guide initiation and duration of antibiotic treatment in acute respiratory tract infections results in lower risks of mortality, lower antibiotic consumption, and lower risk for antibiotic-related

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side effects.⁵ Therefore, PCT is a marker of bacterial infection, and recent studies also propose its use in decision-making of antibiotic therapy in patients with AHF by identifying the patients with concomitant or triggering bacterial infection.⁴ On the other hand, inflammation may be an important precipitating and/or causal factor in AHF, which may influence patient prognosis.⁴ The purpose of this short review is to present the current knowledge on the use of PCT as a biomarker of inflammation and prognosis in AHF patients as well as a guiding biomarker for initiation of antibiotic therapy.

PCT AS A BIOMARKER OF INFLAMMATION IN AHF

Mesenteric venous congestion might cause inflammation in HF, by causing bacterial translocation from the intestinal lumen into the blood circulation, thus causing endotoxemia and immune activation.⁶ In this context, PCT levels are higher in patients with edematous HF as compared with patients with compensated HF and to controls without HF.⁷ PCT could be therefore an indicator of endotoxin-immune activation, as PCT levels correlate both with markers of inflammation and of venous congestion.⁸ In a Chinese study, that included 4698 cases, it was shown that patients with simple HF had significantly higher PCT levels than normal controls, whereas patients with bacterial infection complicated by congestive HF had significantly higher PCT levels than those with simple infection.⁹ These findings further support a role of PCT as an inflammatory marker in AHF even in the absence of bacterial infection. Recently, a French group also concluded that AHF is associated with systemic inflammation and that PCT can be used as a biomarker to show this association.¹⁰

PCT AS A PROGNOSTIC BIOMARKER IN AHF

In a sub-study of the BACH trial, a significant association was observed between high PCT levels (>0.21 ng/mL) and reduced survival rate of AHF patients assessed at 90 days, compared to those with low PCT levels (<0.05 ng/mL), but this trial also included patients with concomitant pneumonia.¹¹ In the VERYfing DYspnea trial in the group of AHF patients the combined use of PCT plus mid-regional pro-atrial natriuretic peptide (MR-proANP) was able to predict both rehospitalization and death at 90 days.¹² This was also shown in a smaller trial where baseline and serial in-hospital measurements of PCT had a significant but modest prognostic value for 3-month all-cause mortality/hospitalization in patients with AHF without clinical signs of infection at admission.¹³ In another trial of 261 AHF patients and no evidence of infection, PCT was independently and positively

associated with the risk of long-term (median follow-up of 2 years) death and recurrent hospitalizations.¹⁴ In 1781 patients of the PROTECT trial, which included AHF patients without clinical signs of infection, patients with AHF and significantly elevated PCT levels, indicating probable undiagnosed and/or untreated bacterial infection, had poorer in-hospital and post-discharge outcomes, despite similar severity of HF.¹⁵ A recent meta-analysis of seven studies that measured PCT in HF patients, with or without infection showed that the mortality of HF patients whose serum PCT levels were elevated was significantly higher than that of HF patients whose PCT levels were normal at 30, 90, and 180 days.¹⁶ This meta-analysis adds further support on the prognostic information that PCT levels can have in AHF patients.

PCT AS A BIOMARKER TO GUIDE ANTIBIOTIC TREATMENT IN AHF

The idea of using PCT as a biomarker to guide antibiotic therapy in AHF patients comes from studies that used PCT in patients with lower respiratory tract infections.⁵ Two studies exploring this concept were published in the last few years in the field of AHF. In the BACH trial, AHF patients with an elevated PCT concentration (>0.21 ng/mL) had a worse outcome if not treated with antibiotics, while patients with low PCT values (<0.05 ng/mL) had a better outcome if they did not receive any antibiotics.¹¹ A sub-analysis from the ProHOSP trial, including only the 233 HF patients showed that congestive HF patients presenting to the emergency department with respiratory symptoms and suspicion of respiratory infection had decreased antibiotic exposure and improved outcomes when PCT measurement was used to exclude bacterial infection and guide antibiotic treatment.¹⁷

NEW EVIDENCE

The results of the ACE 2 study regarding PCT were published only a few months ago.¹⁸ PCT levels were measured <24 h of admission in 310 patients with acute dyspnea and compared to CRP and white blood cell (WBC) count in the total population and the subset of AHF patients. In AHF patients, PCT levels were superior to CRP and WBC in the diagnosis of concurrent pneumonia. Furthermore, during a median follow-up of 823 days PCT levels were associated with all-cause mortality. This association, however, did not remain statistically significant after multivariate analysis.¹⁸

The IMPACT-BIC-18 study (www.clinicaltrials.gov; NCT02392689) was a large, multicenter, randomized controlled trial comparing PCT-guided patient management with standard management in the emergency department.⁴ The trial was initiated in 2014 and it was announced as a late-breaking

abstract presentation at the latest Heart Failure Association congress (May 2018, Vienna). Patients were enrolled if they presented to the emergency department with dyspnea and suspected AHF as indicated by increased levels of natriuretic peptides.⁴ A cut-off level of 0.2 ng/mL was used to decide the initiation of antibiotic therapy in the PCT-guided group, whereas antibiotic treatment was solely based on clinical judgement in the control group. Patients were followed-up 30 and 90 days after randomization to evaluate the survival status, hospitalizations, and antibiotic therapy variables.⁴ The study was prematurely terminated after randomizing 75% of the patients because there was no significant difference between the arms in either the primary endpoint of 90-day mortality or a secondary endpoint of 30-day mortality. As suggested by the leading investigator, the lack of benefit of a PCT-guided antibiotic initiation strategy might be due to two reasons; the relatively low risk of death (the total mortality rate was only 9.2% compared with 18% reported on previous studies) and the very low infectious burden of the studied patient population (the mean PCT level was 0.07 ng/mL and only 16.4% of patients had a level above 0.2 ng/mL).¹⁹

LIMITATIONS

The purpose of this short manuscript was to present the latest evidence on the use of PCT in AHF and not to produce a systematic review on the topic. Given the narrative nature of this review, specific guidelines for conducting and reporting systematic reviews were not applied.

CONCLUSION

PCT can potentially be a valuable tool for the cardiologist working at the emergency department and has also been included in the latest ESC guidelines as a lab test to be considered. In patients with AHF it can provide us with useful information regarding their management and prognosis. Furthermore, in countries, such as Greece, where there is increasing antibiotic overprescription and antibiotic resistance, this is an extremely valuable addition to our armamentarium. We are advocating its use in the emergency department as a tool to help us in the decision to administer antibiotics to AHF patients in whom there is clinical uncertainty regarding a superimposed bacterial infection and to alarm us so that we can quickly involve an infectious disease expert in the management of our patient.

REFERENCES

1. Gheorghiade M, Zannad F, Sopko G, et al. Acute heart failure

- syndromes: current state and framework for future research. *Circulation* 2005;112:3958-3968. doi:10.1161/CIRCULATIONAHA.105.590091. PubMed PMID:16365214.
2. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; 37:2129-2200. doi: 10.1093/eurheartj/ehw128. PubMed PMID: 27206819.
3. Christ-Crain M, Jaccard-Stolz D, Bingisser R, et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet* 2004; 363:600-607. doi: 10.1016/S0140-6736(04)15591-8. PubMed PMID: 14987884.
4. Mockel M, Searle J, Maisel A. The role of procalcitonin in acute heart failure patients. *ESC Heart Fail* 2017; 4:203-208. doi: 10.1002/ehf2.12189. PubMed PMID: 28772049; PubMed Central PMCID: PMC5542739.
5. Schuetz P, Wirz Y, Sager R, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. *Cochrane Database Syst Rev* 2017;10:CD007498. doi: 10.1002/14651858.CD007498.pub3. PubMed PMID: 29025194.
6. Anker SD, Egerer KR, Volk HD, et al. Elevated soluble CD14 receptors and altered cytokines in chronic heart failure. *Am J Cardiol* 1997;79:1426-1430. PubMed PMID: 9165177.
7. Niebauer J, Volk HD, Kemp M, et al. Endotoxin and immune activation in chronic heart failure: a prospective cohort study. *Lancet* 1999; 353:1838-1842. doi: 10.1016/S0140-6736(98)09286-1. PubMed PMID: 10359409.
8. Mollar A, Villanueva MP, Carratala A, Nunez E, Sanchis J, Nunez J. Determinants of procalcitonin concentration in acute heart failure. *Int J Cardiol* 2014; 177:532-534. doi: 10.1016/j.ijcard.2014.08.106. PubMed PMID: 25194863.
9. Wang W, Zhang X, Ge N, et al. Procalcitonin testing for diagnosis and short-term prognosis in bacterial infection complicated by congestive heart failure: a multicenter analysis of 4,698 cases. *Crit Care* 2014; 18:R4. doi: 10.1186/cc13181. PubMed PMID: 24393388; PubMed Central PMCID: PMC4056105.
10. Boulogne M, Sadoune M, Launay JM, et al. Inflammation versus mechanical stretch biomarkers over time in acutely decompensated heart failure with reduced ejection fraction. *Int J Cardiol* 2017;226:53-59. doi: 10.1016/j.ijcard.2016.10.038. PubMed PMID: 27788390.
11. Maisel A, Neath SX, Landsberg J, et al. Use of procalcitonin for the diagnosis of pneumonia in patients presenting with a chief complaint of dyspnoea: results from the BACH (Biomarkers in Acute Heart Failure) trial. *Eur J Heart Fail* 2012; 14:278-286. doi: 10.1093/eurjhf/hfr177. PubMed PMID: 22302662; PubMed Central PMCID: PMC3284113.
12. Travaglino F, Russo V, De Berardinis B, et al. Thirty and ninety days mortality predictive value of admission and in-hospital procalcitonin and mid-regional pro-adrenomedullin testing in

- patients with dyspnea. Results from the VErYfing DYspnea trial. *Am J Emerg Med* 2014; 32:334-341. doi: 10.1016/j.ajem.2013.12.045. PubMed PMID: 24559907.
13. Loncar G, Tscholl V, Tahirovic E, et al. Should procalcitonin be measured routinely in acute decompensated heart failure? *Biomark Med* 2015; 9:651-659. doi: 10.2217/bmm.15.29. PubMed PMID: 26174839.
 14. Villanueva MP, Mollar A, Palau P, et al. Procalcitonin and long-term prognosis after an admission for acute heart failure. *Eur J Intern Med* 2015; 26:42-48. doi: 10.1016/j.ejim.2014.12.009. PubMed PMID: 25592074.
 15. Demissei BG, Cleland JG, O'Connor CM, et al. Procalcitonin-based indication of bacterial infection identifies high risk acute heart failure patients. *Int J Cardiol* 2016; 204:164-171. doi: 10.1016/j.ijcard.2015.11.141. PubMed PMID: 26666342.
 16. Aissou L, Sorbets E, Lallmahomed E, et al. Prognostic and diagnostic value of elevated serum concentration of procalcitonin in patients with suspected heart failure. A review and meta-analysis. *Biomarkers* 2018; 23:407-413. doi: 10.1080/1354750X.2018.1443511. PubMed PMID: 29465002.
 17. Schuetz P, Kutz A, Grolimund E, et al. Excluding infection through procalcitonin testing improves outcomes of congestive heart failure patients presenting with acute respiratory symptoms: results from the randomized ProHOSP trial. *Int J Cardiol* 2014; 175:464-472. doi: 10.1016/j.ijcard.2014.06.022. PubMed PMID: 25005339.
 18. Berge K, Lyngbakken MN, Einvik G, et al. Diagnostic and prognostic properties of procalcitonin in patients with acute dyspnea: Data from the ACE 2 Study. *Clin Biochem* 2018;59:62-68. doi: 10.1016/j.clinbiochem.2018.07.006. PubMed PMID: 30028971.
 19. Möckel M. IMPACT - BIC - 18: Procalcitonin-guided antibiotic therapy does not improve mortality in patients with shortness of breath and suspected AHF. <https://www.escardio.org/Congresses-&-Events/Heart-Failure/Congress-resources/News/impact-bic-18-procalcitonin-guided-antibiotic-therapy-does-not-improve-mort>.