ESC HEART FAILURE
ESC Heart Failure 2017; **4**: 203–208
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12189

REVIEW

The role of procalcitonin in acute heart failure patients

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Abstract

Acute dyspnoea is a common chief complaint in the emergency department and is mainly caused by cardiac and pulmonary underlying diagnoses. In patients with acute heart failure (AHF), an early initiation of adequate therapy is important to improve patient outcome. Clinical differentiation of pulmonary and cardiac underlying causes and of concomitant pathologies determines which therapeutic strategy is chosen.

Procalcitonin is a marker of bacterial infection, which is markedly increased in AHF patients with concomitant bacterial infection and thus has the potential to guide the early initiation of adequate antibiotic therapy. The IMPACT-EU trial is a multicenter randomized controlled trial designed to test this hypothesis.

This mini-review summarizes the current literature on procalcitonin in AHF and explains the design of the IMPACT-EU trial.

Keywords Procalcitonin; Acute heart failure; Bacterial infection; Inflammation; Antibiotic therapy

Received: 7 February 2017; Revised: 24 April 2017; Accepted: 2 June 2017
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Introduction

Acute dyspnoea is one of the most common and, more importantly, most detrimental symptoms in emergency medicine, as it is associated with a high mortality. Acute dyspnoea can be caused by an array of underlying diagnoses, including mainly cardiac and pulmonary diseases.[1] Independent of the underlying pathology, a fast containment of the most likely differential diagnoses and consequently, a fast and adequate initiation of therapy in the emergency department (ED) can be life-saving. Additionally, identification of high-risk patients, who most profit from intensive monitoring and therapy, is important to support treatment and management decisions. Acute heart failure (AHF) is one of the most important differential diagnoses in these patients. Recent guidelines[2,3] define AHF as a time critical disease comparable to acute coronary syndrome and support the concept to identify the underlying trigger factors or precipitants as soon as possible.

Increasingly, patients in emergency medicine are characterized by old age and multi-morbidity and rarely present with a single disease and its typical clinical pattern. The challenge in AHF is to identify the underlying cause or precipitant, i.e. the most important of a number of co-existing diagnoses, which requires immediate attention and intervention. Maisel *et al*. were recently able to show that adequate prescription of antibiotics in heart failure influences patient outcome. Patients with bacterial infection, who did not receive an antibiotic, had an impaired prognosis. Surprisingly, also patients without bacterial infection who did receive an antibiotic had a worse outcome than patients without antibiotic therapy.[2] Procalcitonin (PCT) is a precursor peptide of the hormone calcitonin, and levels increase particularly following bacterial infection. A more rapid rise and fall in blood with a very strong signal with 10^5-fold increase as compared with other molecules like C-reactive proteine showing only a 10- to 100-fold increase is observed. The half-life is around 24 h, and the molecule is stable *in vivo* and *in vitro*.[11] Therefore, PCT is a marker of bacterial infection, and recent evidence suggests that it can be used to guide decision-making with respect to antibiotic therapy in patients with AHF by identifying patients with concomitant or triggering bacterial infection. On the other hand, evidence suggests that inflammation may be an important pathophysiological factor in heart failure, which may impact patient prognosis. PCT is therefore studied from two perspectives, as a prognostic marker in heart failure as well as a guiding biomarker for adequate medical therapy. This article summarizes the current evidence to help clinicians in their judgement and use of PCT in routine practice.

Procalcitonin as a prognostic marker in heart failure

It has long been known that severe or worsening heart failure is associated with systematic inflammation. Levine *et al.* published their article on 'Elevated Circulating Levels of Tumor Necrosis Factor in Severe Chronic Heart Failure' over 25 years ago in an attempt to evaluate the pathogenesis of cardiac cachexia.[3] Interestingly, they found that tumor necrosis factor alpha levels were markedly increased in patients with end-stage heart failure and renal impairment without being correlated to cardiac output or ventricular filling pressure, thus indicating prognosis rather than cardiac function. Several studies were since able to show that increased cytokine levels were related to a poor prognosis in patients with heart failure.[4–7]

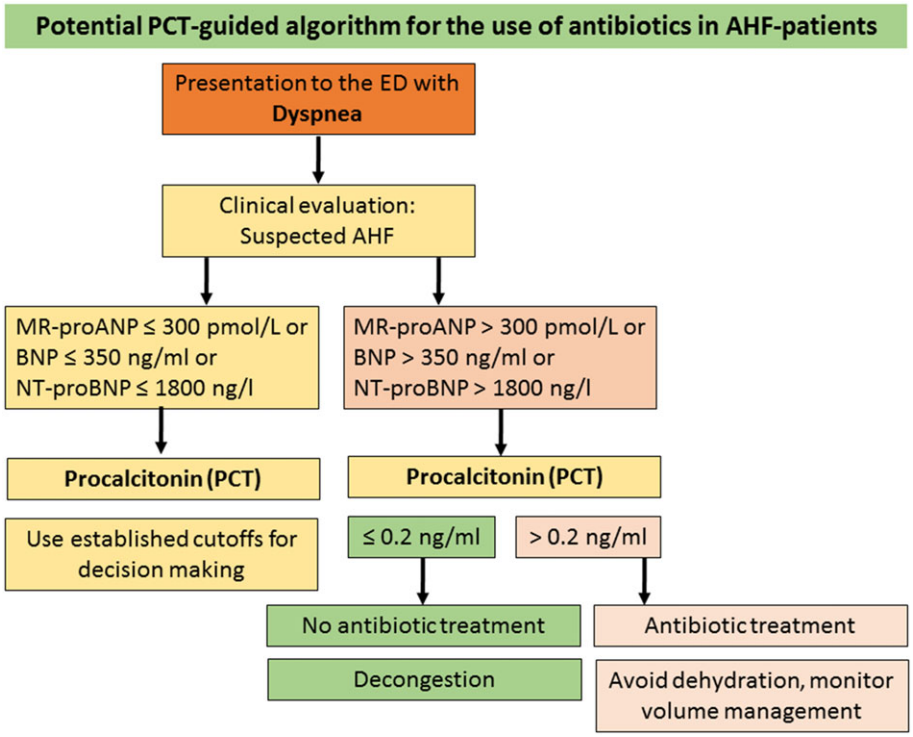
Anker *et al.* developed the hypothesis that the inflammation in AHF might be caused by mesenteric congestion, leading to bacterial translocation from the intestinal lumen into the blood stream, thereby causing endotoxemia and, consequently, immune activation.[8]

In this context, PCT was first investigated by Niebauer *et al.* who were able to show that endotoxin and inflammatory cytokine levels increased during the oedematous state of AHF. PCT was reported to show higher levels in patients with oedematous heart failure as compared with patients with compensated heart failure and to controls without heart failure.[9] Mollar *et al*. studied the role of PCT in patients with heart failure and confirmed absence of bacterial infection to evaluate the role of PCT in patients with AHF admitted to an ED. Their results support the role of PCT as an indicator of endotoxin-immune activation, as PCT levels correlated with markers of inflammation, including endotoxin, as well as markers of venous congestion.[10]

A large study from China compared PCT levels in patients with isolated AHF, patients with isolated bacterial infections, patients with AHF complicated by bacterial infection, and healthy controls. Their findings confirm a role of PCT in AHF in the absence of bacterial infection, as patients with isolated AHF compared with healthy controls had higher PCT levels. Patients with isolated bacterial infection had lower PCT levels than patients with bacterial infection complicated by heart failure.[11]

Recently, Boulogne *et al.* investigated biomarkers of inflammation and of mechanical stress in patients with acute and chronic heart failure. Patients with active or recent infection, inflammatory disease, or active cancer were excluded. The authors were able to show that markers of inflammation and of mechanical stress were highest in patients with AHF,

Figure 1 Proposed future use of procalcitonin in acute heart failure (AHF) using the cut-offs currently investigated in the IMPACT study. Established cut-offs are listed in *Table 1*. BNP, brain natriuretic peptide; ED, emergency department; MR-proANP, midregional pro-atrial natriuretic peptide; NT-proBNP, N terminal pro brain natriuretic peptide.



but whilst markers of mechanical stress decreased with clinical improvement, markers of inflammation remained high for up to 1 month after re-compensation. Interestingly, PCT levels did not differ between patients with AHF and chronic heart failure. PCT levels were above 0.05 ng/mL but below the cut-off for systemic infection (<0.50 ng/mL) in the majority of patients.[12]

Even though plenty of evidence suggests the important role of inflammation in the pathogenesis of AHF and in the prognosis of heart failure patients, the prognostic value of PCT in patients with isolated heart failure remains unclear, as evidence is sparse. Maisel *et al.* reported a significant association of PCT with the 90-day mortality of ED dyspnoea patients diagnosed with AHF with a reduced survival rate of patients in the fifth PCT quintile (>0.21 ng/mL) of 80.5% as opposed to 92% for patients in the first PCT quintile (<0.05 ng/mL),[2] but this included patients with concomitant pulmonary infection. In a trial by Travaglino *et al.*, PCT was a modest predictor for 30- and 90-day mortality in ED patients with acute dyspnoea, but sub-analysis revealed that this was true for patients without heart failure only.[13]

Villanueva *et al.* on the other hand reported increased long-term mortality rates of AHF patients with increased PCT levels independent of white blood cell count, C-reactive protein, endotoxin, and different interleukin levels.[14] In a trial by Loncar *et al.*, PCT had a significant but modest prognostic value in AHF patients without clinical signs of infection at admission.[15]

In the PROTECT trial, which included AHF patients without clinical signs of infection, patients with elevated PCT levels had a higher 30-day mortality and were more often classified as treatment failures, although they did not differ in disease severity.[16]

Table 1 Overview of the different PCT cut-off values and of mean/median PCT values in different studies and study groups

Publication	PCT-assay	Patients	Predetermined cut-off values or PCT results
Boulogne *et al.*[12]	Kryptor, Thermofisher	Patients with AHF and CHF	AHF admission value median: 0.14 (0.09–0.21) ng/mL CHF admission value median: 0.13 (0.10–0.21) ng/mL
Christ-Crain *et al.*[18]	Kryptor, Thermofisher	Patients with LRTI	Use of antibiotics Discouraged: PCT <0.1 ng/mL (strong advice) or <0.25 ng/mL (advice) Encouraged: PCT ≥0.5 ng/mL (strong advice) or ≥0.25 ng/mL (advice)
Demissei *et al.*[16]	Alere	Patients with AHF without clinical signs of infection	Significant elevation of PCT was considered present when baseline levels exceeded 0.20 ng/mL. Patients with levels <0.20 ng/mL were considered to have low PCT levels. Baseline PCT levels ≥0.20 ng/mL in 6% of analysed patients.
Maisel *et al.*[2]	Kryptor, Thermofisher	Patients with acute dyspnoea	AHF patients: PCT concentration >0.21 ng/mL (upper quintile): Significantly worse survival if not treated with antibiotics. PCT concentrations between 0.05 and 0.21 ng/mL: Antibiotic treatment did not affect survival. PCT values <0.05 ng/mL: Increased mortality if they were treated with antibiotics All patients: Patients in the first quintile (PCT <0.05 ng/mL): 90-day survival rate 92.0%, patients in the fifth quintile (PCT >0.21 ng/mL): 90-day survival rate 80.5%
Mollar *et al.*[10]	Elecsys BRAHMS PCT	Patients with AHF without clinical signs of infection	Mean PCT 0.06 (±0.06) ng/mL
Schütz *et al.* ProHosp sub-analysis[21]	Kryptor Thermofisher	Patients with LRTI and AHF	Use of antibiotics Discouraged: PCT <0.1 ng/mL (strong advice) or <0.25 ng/mL (advice) Encouraged: PCT ≥0.5 ng/mL (strong advice) or ≥0.25 ng/mL (advice)
Travaglino *et al.*[13]	Kryptor Thermofisher	Patients with acute dyspnoea	PCT in AHF: 0.09 (0.05–0.19) ng/mL PCT in no AHF: 0.09 (0.05–0.28) ng/mL PCT in AHF + no AHF: 0.13 (0.075–0.62) ng/mL
Villanueva *et al.*[14]	Elecsys BRAHMS PCT	Patients with AHF without clinical signs of infection	Median PCT 0.06 (0.04–0.10) ng/mL
Wang *et al.*[11]	Cobas, Roche	Comparison of four study groups	Simple infection median: 0.28 (0.06–0.49) ng/mL Simple heart failure median: 0.13 (0.05–0.22) ng/mL Infection complicated by HF median: 0.45 (0.12–2.59) ng/mL Healthy controls median: 0.04 (0.05–0.12) ng/mL

AHF, acute heart failure; CHF, chronic heart failure; HF, heart failure; LRTI, lower respiratory tract infection; PCT, procalcitonin.
Kryptor, Thermofisher: Normal value according to manufacturer PCT <0.05 ng/mL, diagnosis of systemic infection PCT >0.50 ng/mL.

DOI: 10.1002/ehf2.12189

Procalcitonin as a marker to guide antibiotic therapy in acute heart failure

The idea of using PCT as a marker to guide antibiotic treatment in patients with AHF stems from studies testing PCT in patients with lower respiratory tract infections (LRTI), all showing a reduction of antibiotic prescriptions in PCT-guided patient management.[17–20] In times of increasing antibiotic oversubscription and of antibiotic resistance, this is an extremely valuable achievement. Christ-Crain *et al.* used PCT to guide antibiotic treatment in a cohort of patients presenting to the ED with LRTI. They were able to show that confirmation or exclusion of bacterial infection with PCT before treatment initiation led to a significant reduction of antibiotic prescriptions.[18] In the ProHosp Trial, a large randomized clinical trial also set in EDs and recruiting patients with LRTI, the mean duration of antibiotic exposure and, consequently, the rates of antibiotic-related side effects were significantly lower in the PCT-guided group. Notably, the rate of adverse outcomes did not differ between the two study groups.[19]

In 2012, Maisel *et al.* published a sub-analysis of the BACH trial, a large multicenter diagnostic biomarker study in ED patients with acute dyspnoea. This analysis evaluated the diagnostic value of PCT in patients with a diagnosis of AHF and surprisingly not only showed that patients with confirmed AHF and increased PCT levels had a worse outcome if they did not receive antibiotic treatment but also that patients with confirmed AHF and low PCT levels had a worse outcome if they—inadequately—received antibiotic treatment.[2]

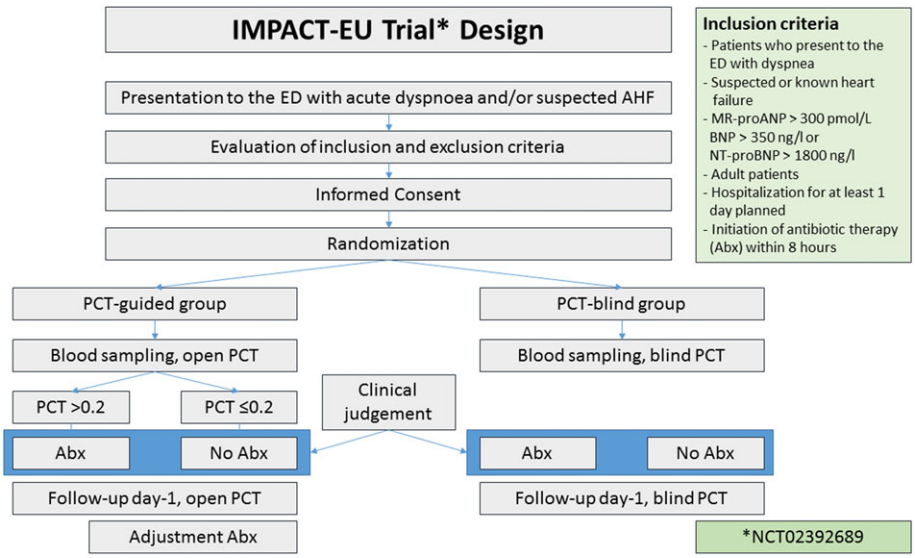
Two years later, Schuetz *et al.* published a sub-analysis from the above-mentioned ProHOSP trial, including only the 233 patients with heart failure. As was already reported in the original trial, the primary endpoint (mortality and intensive care unit admission) did not significantly differ between the two study groups (PCT-guided vs. standard management), but antibiotic exposure was significantly shorter in the PCT-guided group, as were antibiotic side effects. Even more compelling was that in the group of patients with low PCT ($<$0.05 ng/mL), patients with PCT guidance had better outcome.[21] Recently, a study on intensive care unit patients confirmed that antibiotic treatment can be safely guided by repetitive PCT measurements and that this transfers into a lower mortality.[22]

The concept to use PCT in heart failure has also been adopted in the recent ESC guidelines.[23] *Figure 1* shows how PCT could potentially be used in this setting. *Table 1* gives an overview of the different PCT cut-off values and of mean/median PCT values in different studies and study groups.

The IMPACT trial and its future implications

Even though sub-analyses from large trials show promising results for PCT-guided antibiotic therapy in AHF, current evidence is insufficient to allow for implementation into routine clinical practice. The IMPACT-EU study (clinicaltrials.gov; NCT02392689) is a large, multicenter, randomized controlled trial comparing PCT-guided patient management with standard management in the ED. The trial was initiated in 2014 and is ongoing. Patients are enrolled if they present to the

Figure 2 Protocol flow chart of the IMPACT study and key inclusion criteria. AHF, acute heart failure; BNP, brain natriuretic peptide; ED, emergency department; MR-proANP, midregional pro-atrial natriuretic peptide; NT-proBNP, N terminal pro brain natriuretic peptide; PCT, procalcitonin.



DOI: 10.1002/ehf2.12189

ED with dyspnoea and suspected heart failure as indicated by increased levels of natriuretic peptides as outlined in *Figure 2*. A cut-off level of 0.2 ng/mL will be used to support decision on antibiotic therapy initiation in the PCT-guided group, whereas antibiotic treatment is solely based on clinical judgement in the control group.

Patients will be followed up 30 and 90 days after randomization to evaluate the survival status, rehospitalizations, and antibiotic therapy variables.

Conclusions

Evidence regarding the role of PCT in heart failure is promising. Even though data clearly suggests inflammation as an important pathophysiological contributor to severe heart failure, the prognostic value of PCT seems to be related to concomitant infection rather than systemic inflammation in isolated AHF. Adequate therapy is of utmost importance in AHF, and in this respect, correct judgement of the underlying diagnosis in patients presenting with dyspnoea seems to be an important factor determining patient outcome. PCT-guided antibiotic therapy has been proven useful in LRTI and might improve patient outcome by early identification of patients with AHF who will profit from antibiotic treatment. The IMPACT-EU trial is currently testing this hypothesis in a prospective randomized study.

Conflict of interest

M. M. received research grants and lecture fees from Novartis, Thermofisher BRAHMS, and Roche Diagnostics. J. S. reports research grants from Novartis, Thermofisher BRAHMS, and Roche Diagnostics.

The authors declare that the submitted work is original and has not been published before (neither in English nor in any other language) and that the work is not under consideration for publication elsewhere.

Funding

This current work received no funding. The open access fees for the publication were covered by Thermofisher BRAHMS.

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