

Heart Failure: Biomarkers of Diagnosis and Prognosis

OCTOBER 2010

Dear Colleagues:

Heart Failure remains a common presentation in the emergency department (ED). For the emergency physician clarifying the course of the universal complaint, shortness of breath, requires excellent clinical acumen combined with a clear understanding of the laboratory tests available to distinguish Heart Failure from other causes of dyspnea.

The natriuretic peptides (NP), including the precursor N-terminal proBNP (NT-pro-BNP) of biologically active B-type natriuretic peptide (BNP) represent the current standard for identifying Heart Failure. In addition, the troponins serve to help identify Heart Failure patients at high risk for adverse outcomes. For nearly the last decade, emergency physicians have used these biomarkers to diagnose and risk stratify these patients. In this EMCREG-International newsletter, Heart Failure expert Dr. Frank Peacock of the Cleveland Clinic authors an excellent discussion of the scientific basis for the use of these markers, with able support by Dr. Sean Collins of the University of Cincinnati who provided peer review for the article.

In addition, Dr. Peacock provides a glimpse into the future of Heart Failure biomarkers including A-type natriuretic peptide (ANP), mid-regional pro-adrenomedullin (MR-proADM), and C-terminal fragment of arginine vasopressin (CT-AVP) which is also known as "copeptin". We hope you enjoy this important discussion of Heart Failure biomarkers of the present and future and our EMCREG-International newsletters continue to help serve your clinical practice.

Sincerely,



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Educational Objectives:

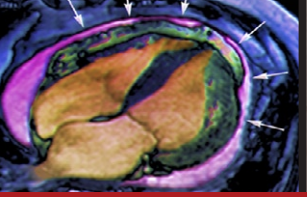
1. Identify the clinical limitations of natriuretic peptide testing in patients presenting to the emergency department with acute shortness of breath
2. Describe the outcomes associated with an elevated troponin concentration in patients hospitalized with heart failure
3. List the most important early predictors of mortality in patients presenting to the emergency department with shortness of breath
4. Identify which PCT levels have been associated with a low or high probability of bacterial infection

Introduction

When considering a heart failure diagnosis in the emergency setting, shortness of breath (SOB) is the nearly universal complaint, reported in over 90% of hospitalized heart failure (HF) patients. In some cases, a careful history may provide evidence for the presence of heart failure. On the other hand, if the patient is excessively ill, speaks another language, or is simply a poor historian, obtaining an accurate history can be challenging. Objective testing is therefore helpful to confirm or refute a suspected HF diagnosis.

The most commonly used diagnostic markers available today for suspected acute HF are the natriuretic peptides (NP). Synthesized as the precursor pro-BNP, this protein is then cleaved by the enzyme corin to the inactive metabolite N-terminal proBNP (NT-proBNP), and the biologically active B-type natriuretic peptide (BNP). The hormone BNP is predominately produced by the ventricular myocardium, and is released in response to pressure or volume stress. Active BNP causes vasodilation, natriuresis, and antagonizes the renin angiotensin system. Knowledge of its blood level can assist in differentiating chronic obstructive pulmonary disease and heart failure, two of the most common causes of SOB in emergency department (ED) patients.¹

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Both NT-proBNP and BNP can be measured rapidly enough to provide clinically useful information in the ED setting. If either is significantly elevated (>900 pg/mL if under 75 yrs, or >1800 pg/mL if older than 75 yrs for NT-proBNP, or >400 pg/mL for BNP), the positive predictive value for a HF diagnosis is approximately 90%. Conversely, very low levels (<300 pg/mL NT-proBNP, or <100 pg/mL BNP) have high negative predictive values for a HF diagnosis (approximating 90%) and strongly suggest an alternative diagnosis is responsible for the patient's presentation. Levels between the paired cutpoints result in a gray zone for both assays (300 to 900 pg/mL for NT-proBNP, and 100 to 400 pg/mL for BNP) where diagnostic uncertainty exists and additional testing may be needed.²

One method of presenting the clinical value of a diagnostic testing modality is the use of receiver operator characteristic curves, where 1-specificity is plotted against sensitivity. Figure 1 demonstrates the curves of three different performing hypothetical assays. The plotting of the curves

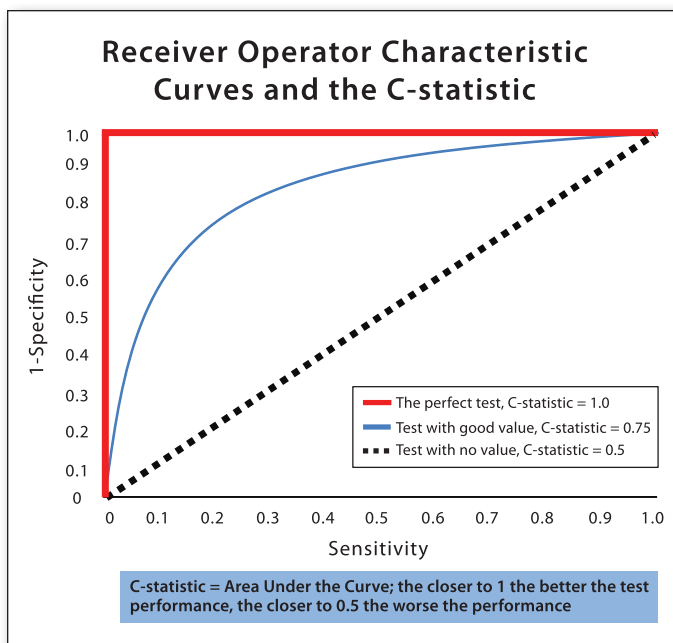


Figure 1: Receiver Operator Characteristic Curve describing diagnostic accuracy with the C-statistic. The C-statistic is the numerical value of the area underneath the curve derived from plotting 1 minus the specificity vs the sensitivity of a test (for diagnosis or predicting events). The greater the C-statistic, the better is the combination of sensitivity and specificity of a test.

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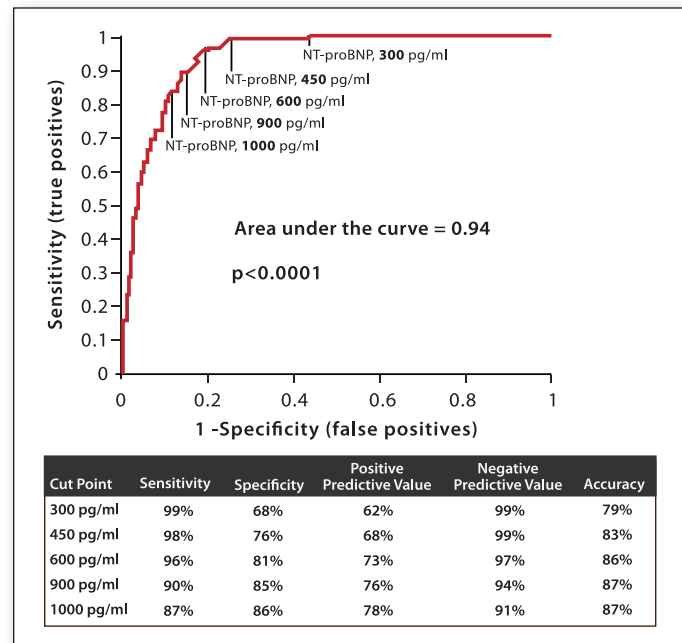


Figure 2: Receiver operator characteristic curve demonstrating the value of NT-proBNP as a diagnostic test for heart failure in patients presenting to the emergency department with acute dyspnea. The high AUC suggests this is a valuable test for diagnosing acute HF. Adapted and reprinted with permission from Januzzi JL, Camargo CA, Anwaruddin S, et al. The N-Terminal Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study. Am J Cardiol 2005; 95:948–954.

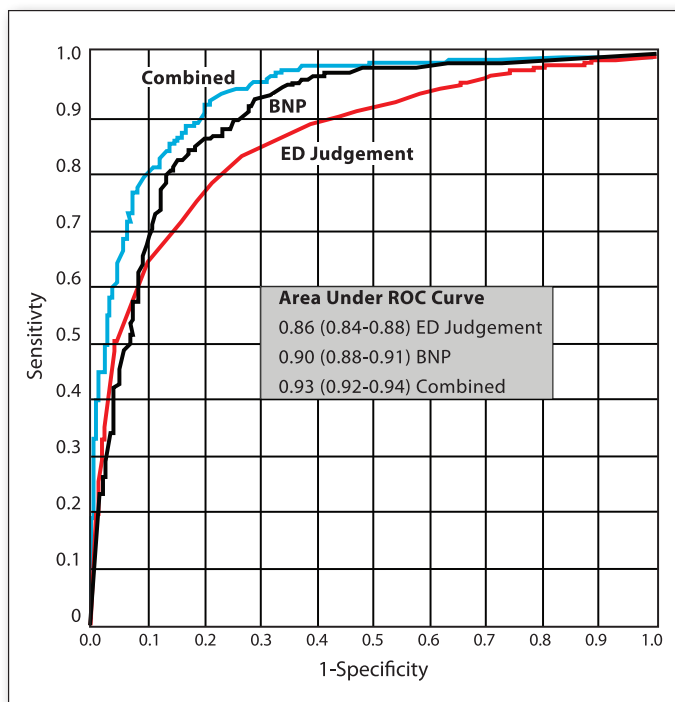
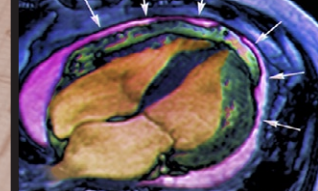


Figure 3: Receiver operator characteristic curve demonstrating the value of BNP as a diagnostic test for heart failure in patients presenting to the emergency department with acute dyspnea, compared to physician judgement alone. Combining BNP and clinical judgement provide the greatest diagnostic accuracy as demonstrated by greater AUC. Adapted and reprinted with permission from McCullough PA, Nowak RM, McCord J, et al. for the BNP Multinational Study Investigators. B-Type Natriuretic Peptide and Clinical Judgment in Emergency Diagnosis of Heart Failure: Analysis From Breathing Not Properly (BNP) Multinational Study. *Circulation* 2002;106:416-422.

allows the visual comparison of the performance of the different assays. The overall clinical value of a diagnostic strategy can then be described by the Area Under the Curve (AUC). Those tests with the greatest sensitivity and specificity will have the largest AUC. The numerical AUC value is then referred to as the C-statistic, or diagnostic accuracy. A perfect test will have a C-statistic of 1.0 where a completely useless test will have a C-statistic of 0.5. These curves have been plotted for the NPs in Figure 2 and 3. In Figure 3, diagnostic accuracy of BNP is compared with the physician's clinical impression and suggests that this biomarker significantly improves overall diagnostic accuracy at the initial ED presentation.^{3,4}

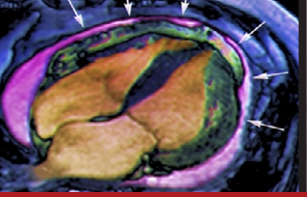
Several considerations are necessary when interpreting BNP and NT-proBNP test results. As NP levels reflect non-specific myocardial stress, non-HF causes of cardiac stress are also associated with increased levels including pulmonary embolism, primary pulmonary hypertension, and acute myocardial infarction. Natriuretic peptide levels are also increased in the setting of renal insufficiency, where a rise can be seen in direct proportion to the severity of renal dysfunction.⁵ The elevation of NP from renal insufficiency has led some authors to suggest the BNP cut point for a HF diagnosis should be increased to 200 pg/mL.

Conversely, lower than clinically predicted NP levels can occur. This is due to obesity, where there is an inverse relationship between NP levels and body mass index.⁶ In such patients, BNP should be used with caution and the understanding that the patient may have HF, even if the BNP does not meet threshold levels. For this patient presentation, a suggested correction may be employed if the body mass index exceeds 35. The measured BNP level can be doubled, which improves the sensitivity for a HF diagnosis. Most importantly, the clinical scenario must be considered to accurately interpret NP test results.

Overall, the clinical impact of ED NP testing is to improve physician's diagnostic accuracy. In the "all comers" blinded prospective 1586 patient Breathing Not Properly study, the diagnostic accuracy of clinical judgment by emergency physicians was only 74%, and may have been improved to 81.5% if BNP levels had been available and considered with clinical judgment (Figure 2).⁷ A second analysis, where physicians estimated the probability of a HF diagnosis, if BNP had been available it could have significantly decreased diagnostic uncertainty.⁷

The NP also have independent prognostic value in HF. In a 50,000 patient analysis of hospitalized HF patients in the Acute Decompensated Heart Failure Registry (ADHERE), an elevated BNP was associated with a marked increase in acute mortality.⁸ Patients with a BNP in the highest quartile at presentation (>1730 pg/mL) had a 6% in-hospital mortality, compared to those in the lowest quartile (BNP < 430 pg/mL) whose mortality was only 2.2%.

In an abstract, one large study evaluated the relationship between ED BNP, intravenous loop diuretics, and HF outcomes.⁹ In nearly 15,000 HF patients stratified by BNP quartile, delays in diuretic therapy suggested an increased



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mortality in the highest BNP cohorts (>865 pg/mL) but there were no time dependent effects with delayed treatment in the lowest BNP groups. In the highest BNP quartile (>1738 pg/mL), a diuretic delay >5 hours was associated with an acute mortality increase from 5.1% to 7.3%, suggesting that BNP identifies patients who may benefit from early therapy. Further study is necessary to confirm this relationship.

Other markers can be used for risk stratification in HF. Similar to acute coronary syndrome, a troponin level provides risk stratification information in acute HF. In one 70,000 patient analysis, the rate of coronary artery bypass grafting, balloon pump usage and mechanical ventilation was 300% higher in the 4500 patients with elevated troponin.¹⁰ Patients with a positive troponin were hospitalized one day longer and spent one half day longer in the intensive care unit. Finally, the elevated troponin cohort suffered the greatest in-hospital mortality rate (Figure 4) and there was a direct relationship between the magnitude of the troponin elevation and acute mortality (6.3% in the highest vs 1.7% in the lowest quartile).¹⁰

In addition to independent prognostic value, troponin and BNP can be used in combination. Another ADHERE analysis suggests patients with both a top quartile BNP (>840 pg/mL) and a positive troponin suffered a hospital mortality rate of 10.2%.¹¹ This compared to only 2% if the troponin was undetectable and the BNP was in the lowest quartile (<840 pg/mL). In the groups where only one of the markers was elevated, mortality approximated 4.5%. This suggests that both troponin and BNP are excellent predictors of acute mortality risk in patients presenting to the ED with acute HF.

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Markers of the Future

Although most HF studies evaluate 30 and 90 day outcomes, this is less helpful to the emergency physician in the acute setting. Emergency physician decisions regarding the need for immediate hospitalization can't be based on mortality risk predicted to occur three months into the future. Of more value to disposition decision-making is determining short term risk, such that immediate intervention could alter the near term potential for adverse outcomes. While both BNP and NT-proBNP are good predictors of mortality, and both are recommended as diagnostic and prognostic adjuncts per the guidelines of most every major medical society involved in HF care, they are poor short term outcome predictors.

Several other proteins may have prognostic value for early risk stratification, but because of their transient and unstable nature, have not been previously measurable in a clinically practical fashion. These include A-type natriuretic peptide (ANP), adrenomedullin (ADM), and arginine vasopressin (AVP). A new immunoassay strategy to determine the relative levels of these biomarkers

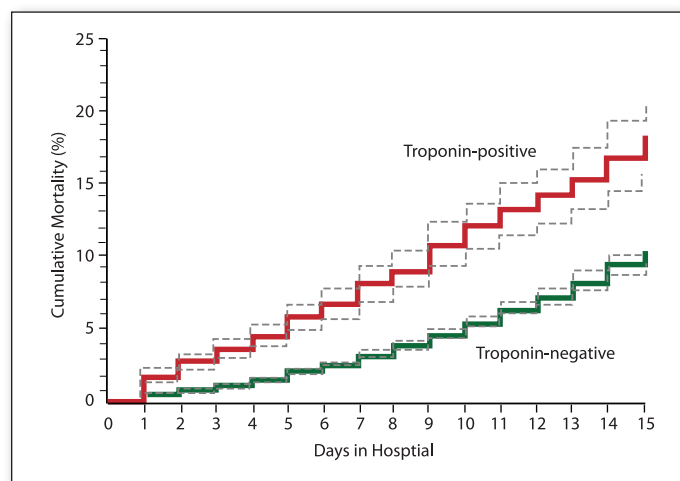
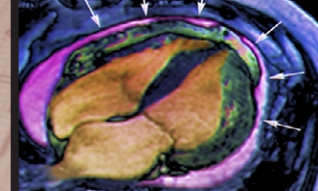


Figure 4: Kaplan Meier plot demonstrating the time dependent mortality prediction of the initial troponin level in patients hospitalized with acute heart failure. Troponin positive patients were more likely to suffer in-hospital mortality. Adapted and reprinted with permission from Peacock WF, DeMarco T, Fonarow GC, et al, for the ADHERE Investigators. Cardiac troponin and outcome in acute heart failure. N Eng J Med 2008; 358(20): 2117-2126.



has recently been developed which targets the inactive stable protein fragments released during active hormone synthesis.¹²⁻¹⁷ By this method, assays for mid-regionional proANP (MR-proANP), mid-regional pro-adrenomedullin (MR-proADM), and the C-terminal fragment of CT-AVP (also termed “copeptin”) are now available.

A-type natriuretic peptide is a peptide with physiologic characteristics similar to BNP and NT-proBNP. However, unlike BNP and NT-proBNP, which are predominately synthesized in the cardiac ventricles, most ANP is synthesized in the cardiac atria. While the impact of this unique origin requires further study, it has been suggested that this biomarker may have value in conditions of primarily atrial dysfunction such as atrial fibrillation or flutter.

Mid-regional pro-adrenomedullin is synthesized in equimolar amounts to ADM. Measures of MR-proADM reflect serum levels of ADM. A hemodynamically active vasodilatory peptide, ADM has potent hypotensive effects.¹⁷ Expressed in many different tissues, its plasma levels are elevated in chronic HF,¹⁸ and increase in proportion to heart failure severity.^{19,20} Acutely, ADM has inotropic, vasodilatory, diuretic, and natriuretic effects, and inhibits aldosterone production. Chronically, it demonstrates antihypertrophic, anti-apoptotic, antifibrotic, antioxidant, and angiogenesis effects. Most importantly for ED use, ADM levels may predict short term outcomes in acute HF as evident from the measurements of MR-proADM.

Patients with severe HF commonly present with hyponatremia, an indicator of poor prognosis, mediated in part by AVP.^{22,23} A posterior pituitary peptide hormone with antidiuretic and vasoconstrictive properties, AVP is a major regulator of sodium and free water homeostasis. Although AVP secretion increases in proportion to HF severity,²⁴ it has been difficult to accurately measure due molecular instability and rapid clearance.²⁵ Copeptin (C-terminal pre-pro-vasopressin), is synthesized and secreted in equimolar amounts to AVP. Unlike AVP, copeptin is stable in vitro, making it an ideal surrogate for AVP.²⁶ Elevated copeptin levels are associated with outcomes in sepsis, pneumonia, chronic obstructive pulmonary disease, myocardial infarction, and HF. A predictor of mortality in HF,²⁷⁻³⁰ copeptin may be a stronger predictor of acute mortality than either BNP or NT-proBNP.³¹

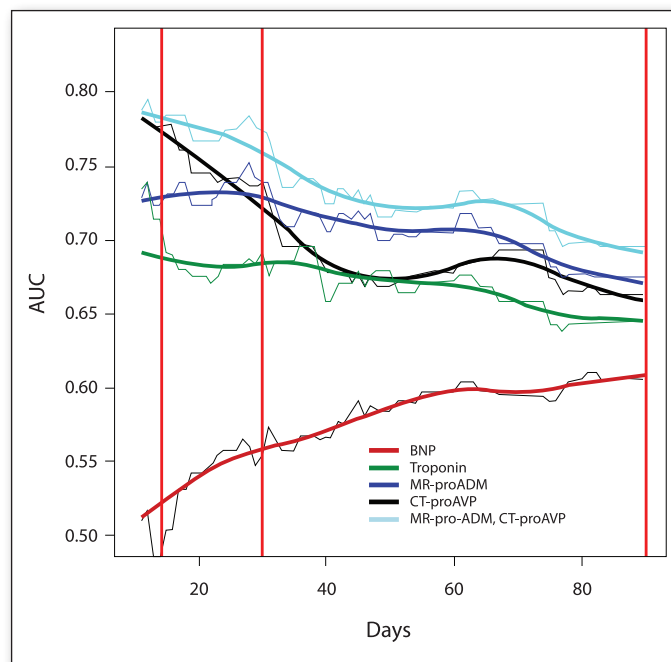
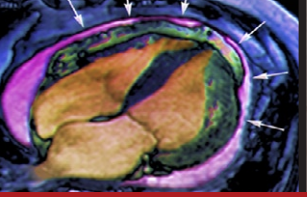


Figure 5: Time-dependent C-statistic (area under the receiver operator characteristic curve) at various times after an ED visit for acute dyspnea plot comparing MR-proADM, copeptin, BNP, troponin, and the combination of MR-proADM and CT proAVP for predicting death at various time points. MR-proADM, Copeptin, and their combination predict short term death, although after 90 days all have similar mortality prediction as troponin. Natriuretic peptides are poor short term mortality predictors. Adapted and reprinted with permission from Peacock WF, Nowak R, Neath S, et al. ED Prediction of Short Term Mortality in Acute Heart Failure: Results of the International BACH Trial. *Academic Emergency Medicine* 2009;16(4):S11.²¹

Predictive ability is not static and can change over time. For example, cholesterol is a poor short term marker of cardiovascular death, but is excellent at predicting 10 year outcomes. This is reflected by changes in the C-statistic of a test for any given time point. The recently published Biomarkers in Acute Heart Failure (BACH) trial evaluated the possible clinical utility of these new markers.³² The BACH trial was a multicenter international study which prospectively enrolled 1641 patients who presented to an ED with a chief complaint of acute dyspnea. The final gold



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... the best 14-day mortality prediction at ED presentation for acute HF was found to be the combination of ADM and copeptin (C-statistic 0.779, $p < 0.00001$).

standard diagnoses for this investigation were determined by two cardiologists reviewing all data at 90 days post ED visit. Ultimately, 568 (34.6%) patients were diagnosed with acute HF. Overall, 21 (3.5%) had died within 14 days of their ED visit. In an abstract presented at the 2009 Annual Meeting of the Society of Academic Emergency Medicine evaluating the utility of these newly available markers, the 14 day death rate prediction was described by the C-statistic (Figures 1 and 5).²¹

While NP's have excellent long term mortality predictive value, they have very little ability to predict short-term mortality. The clinical ramifications are that they do not tell emergency physicians which patients require immediate aggressive interventions. The better predictors of short term mortality were troponin, MR-proADM, and copeptin with C-statistics of 0.714, 0.723 and 0.777, respectively (all $p < 0.05$) for short-term death.³² It is important to identify mortality prediction as a dynamic process which includes the patient's condition and response to treatment at any given time point. While MR-proADM and copeptin are outstanding short term mortality predictors, their ability to predict outcomes regresses to become similar to troponin in predicting 90-day outcomes. Finally, the best 14-day mortality prediction at ED presentation for acute HF was found to be the combination of MR-proADM and copeptin (C-statistic 0.779, $p < 0.00001$). Although the BACH trial was not designed to determine the impact of intervention on outcomes in high risk cohorts, the knowledge that a patient has an excessively high 14-day mortality risk suggests a group of patients in whom aggressive investigation and possibly treatment should be considered.

Another analysis from the BACH trial, presented as an abstract at the British Thoracic Society, was performed to examine patients who present with SOB due to HF and concurrent pneumonia.³³ Although the second most common diagnosis in patients presenting to the ED with acute dyspnea,³⁴ community acquired pneumonia (CAP) can be particularly challenging to diagnose when there is concurrent acute HF. This is due to the insensitive nature of the chest x-ray and confounding clinical features. Unfortunately, the misdiagnoses of CAP may result in a delayed or incorrect treatment, and the potential for increased adverse outcomes, mortality, and costs is present.³⁵

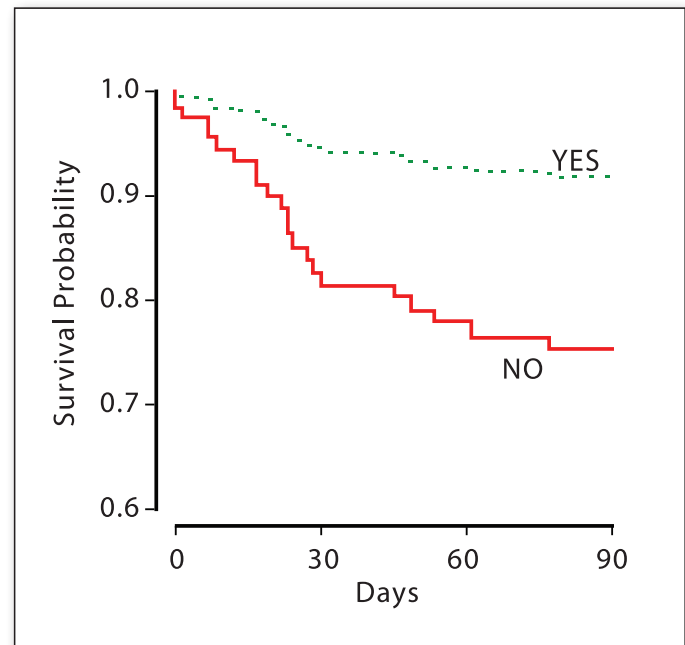
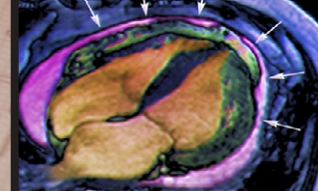


Figure 6: Adjusted acute mortality in patients presenting to the ED with heart failure and an elevated PCT, stratified by whether the patients received antibiotics (yes) or not (no). Patients with elevated PCT have lower mortality when receiving antibiotics. Adapted and reprinted with permission from Hartmann O, Landsberg J, Mueller C, et al. Procalcitonin Identifies Acute Heart Failure Biomarkers in Patients with Acute Heart Failure in Need of Antibiotic Therapy: Observational Results From the BACH (Biomarkers in Acute Heart Failure) Trial. Getting ahead in lung infection; Spoken Sessions, S123. Thorax 2009;64: A62-A64.



“If clinical studies in patients with acute HF demonstrate similar clinical utility as previous trials, PCT may be useful in determining which acute HF patients need antibiotics.”

Procalcitonin (PCT) may be used to determine the presence of clinically relevant bacterial infection requiring antibiotic therapy.³⁵⁻³⁸ Normally an intermediate product in the synthesis of calcitonin, during severe bacterial infections and sepsis, PCT blood levels rapidly rise. Procalcitonin levels can accurately differentiate sepsis and bacterial infection from viral and noninfectious inflammation.³⁹ Procalcitonin levels also can correlate with the severity of bacterial infection. In healthy patients, concentrations are < 0.05 ng/mL, while levels >0.5 ng/mL are abnormal and can be found in critically ill patients. Evidence from randomized controlled trials demonstrates that knowing the PCT level can optimize early clinical treatment. This is a result of either the early identification of those requiring antibiotics, or by matching the length of antibiotic therapy to the clinical situation, such as stopping antibiotics when PCT levels drop below 0.25 ng/mL.³⁶ Thus, the use of PCT may help improve outcomes and health-care resource utilization.³⁵⁻³⁹

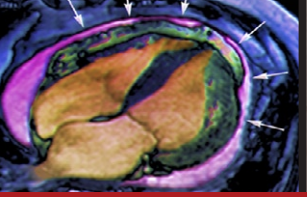
In the BACH trial, ED PCT levels were measured in 1402 patients not already on antibiotics at presentation. Of these 12% (171 of 1402) had a PCT >0.25 ng/mL and identified a cohort who would potentially benefit from antibiotics. Conversely, the PCT was < 0.1 ng/mL in 68% (949 patients), thus potentially excluding bacterial infection and antibiotic need.³² In the BACH trial, as physicians were blinded to the PCT levels, only 63% with a PCT >0.25 ng/mL received antibiotics at any time during their hospitalization. Conversely, 42% (399 patients) with a PCT <0.1 ng/mL, suggesting no need for antibiotics, received potentially unnecessary antibiotics.³³ Adjusted outcomes in the HF subset, with an admission PCT value >0.25 ng/mL, showed

that 90 day all cause mortality was significantly lower in the cohort receiving antibiotics, compared to those who did not (Figure 6). Interestingly, those HF patients with an admission PCT < 0.051 ng/mL who received potentially unnecessary antibiotics suffered an increased mortality compared to those HF patients with a low PCT who did not receive antibiotic therapy.³³ Further study is necessary to examine this relationship more closely.

Because the BACH trial was not designed to determine how unnecessary antibiotic usage was associated with increased mortality, it is not clear why this occurred. It may have been the result of the antibiotics themselves such as increased rates of pseudomembranous colitis, allergic complications, or because the cohort believed to suffer primarily from pneumonia received less aggressive HF treatment. This analysis of the BACH trial suggests a possible incremental clinical value of obtaining PCT levels in patients presenting with acute dyspnea. These results support and extend previous investigations regarding the clinical utility of PCT in the diagnosis and management of patients presenting to the ED with acute dyspnea.³⁵⁻⁴³ If clinical studies in patients with acute HF demonstrate similar clinical utility as previous trials, PCT may be useful in determining which acute HF patients need antibiotics.

Conclusion

In summary, NP are useful biomarkers in patients presenting with dyspnea where the diagnosis is unclear after the initial evaluation. While they contribute to either a “rule in”, or “rule out” HF diagnosis, consideration of the clinical scenario, body habitus, and renal function are necessary to support a correct diagnosis. Importantly, while assisting in diagnosis and providing excellent long-term prognostic value, the use of NP for predicting short-term mortality outcomes is limited. For prognosis, troponin is an excellent marker in the setting of acute HF with any elevation being associated with increased short term adverse events. In addition to troponin, other new markers reported in the BACH trial demonstrate excellent short term prognostic value. The biomarkers NP, MR-proADM and copeptin, both individually and combined, more accurately identify a cohort of HF patients at high risk of short term mortality. Finally, PCT levels may assist in diagnosing HF patients presenting with concurrent pneumonia, as well as identify patients who may benefit from early antibiotic treatment.



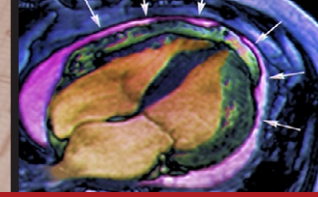
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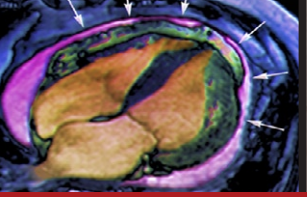
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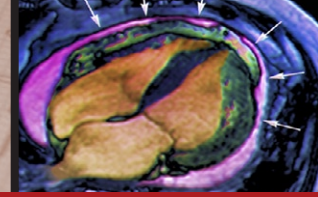
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After you have read the monograph carefully, record your answers by circling the appropriate letter answer for each question.

1. Which of the following are clinical limitations of natriuretic peptide testing in patients presenting to the emergency department with acute shortness of breath?

- A. Obesity
- B. Renal Failure
- C. African American Race
- D. Concurrent infection
- E. A and B
- F. All of the above
- G. None of the above

2. An elevated troponin concentration in patients hospitalized with heart failure portends a worse short term outcome:

- A. True
- B. False

3. The most important early predictor of mortality in patients presenting to the emergency department with shortness of breath is:

- A. Elevated troponin
- B. Elevated adrenomedullin
- C. Elevated BNP
- D. Elevated copeptin
- E. All of the above
- F. None of the above

4. Elevated PCT levels are associated with a higher probability of bacterial infection:

- A. True
- B. False

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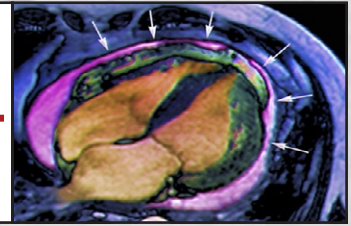
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