

Diagnostic accuracy of natriuretic peptides for acute heart failure: a review

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Abstract. – The rising incidence of and the cost associated with heart failure have made it increasingly imperative to accurately diagnose heart failure upon presentation. Correctly identifying heart failure in an Emergency Department is extremely challenging, and according to estimates, is only confirmatory in approximately 40-50% of patients. For an accurate diagnosis of heart failure and the consequent treatment, there needs to be more accurate test relying on biochemical factors as opposed to general symptoms that patients are experiencing. Natriuretic peptides are now utilized in routine tests for heart disease diagnosis in emergency departments as it is relatively low cost, easy to use and is a quick way to exclude heart failure as a reason for dyspnea. In this review, we detail the role and value of individual natriuretic peptides, particularly BNP, NT-proBNP, and MR-proANP, in diagnosing acute heart failure.

Key Words:

Acute heart failure, Natriuretic peptides, BNP, NT-proBNP, MR-proANP.

Introduction

The rising incidence and cost associated with heart failure have made it increasingly imperative to accurately diagnose heart failure upon presentation¹. There are many issues associated with diagnosing acute heart failure accurately as often it can be underdiagnosed due to asymptomatic heart damage. On the other hand, patients are often incorrectly diagnosed with heart failure as clinical presentation of other diseases can mimic symptoms of heart failure². Therefore, making a correct diagnosis in patients is extremely difficult, and according to estimates, is only confirmatory in approximately 40-50% of patients³. Generally, diagnosis is conducted through a combination of patient history, clinical examination, and investi-

gations such as chest radiography. The gold standard for the diagnosis is echocardiography, which is not always easy to obtain in Emergency Departments^{2,4}. For an accurate diagnosis of heart failure, and consequent treatment for the issue, there needs to be more accurate test relying on biochemical factors as opposed to general symptoms that patients are experiencing.

Several meta-analyses conducted on patients undergoing acute heart failure have found that natriuretic peptides were three to ten-fold higher in these patients than the normal population⁵⁻⁷. They also found that natriuretic peptides were two-fold higher in acute heart failure patients than patients that have a chronic heart failure⁸. Furthermore, natriuretic peptides were also found to be at higher levels in the plasma of patients undergoing their second or third acute heart failure as opposed to patients that experienced heart failure for the first time⁹. Therefore, measurement of natriuretic peptides increases diagnostic accuracy in patients undergoing acute heart failure.

Current guidelines, however, recommend using levels of natriuretic peptides mainly as a tool for exclusion of heart failure. As many patients present to hospitals with dyspnea, which could be attributed to a range of diseases, being able to exclude heart disease allows physicians to make the correct diagnosis. The 2012 guidelines set by the ESC (European Society of Cardiology) have suggested cutoffs for natriuretic peptides for the elimination of heart failure as a diagnosis at levels of ≤ 100 ng/L for plasma BNP (Brain Natriuretic Peptide), ≤ 300 ng/L for N-terminal proBNP, and ≤ 120 pmol/L for mid-regional proANP (Atrial Natriuretic Peptide)¹⁰.

Natriuretic peptides are now utilized in routine tests for heart disease diagnosis in Emergency Departments as it is relatively low cost, easy to use and is a quick way to exclude heart failure as a reason for dyspnea. In this review, we detailed

the function of individual natriuretic peptides in diagnosing cases of acute heart failure in an emergency setting.

Natriuretic Peptide Family

ANP, BNP, CNP (C-type Natriuretic Peptide), DNP (Dendroaspis Natriuretic Peptide), and urodilatin compose the family of natriuretic peptides¹¹. ANP was first discovered in 1981 and from animal experiments, was discovered to be primarily secreted by the atria of the heart and stored in secretory vesicles under normal conditions. ANP expression increases in response to stretching of both the atria and ventricles in heart failure¹². BNP was identified in 1988 in the brain of pigs, which is the reason it was termed brain natriuretic peptide. It was later found that BNP was synthesized in ventricular myocytes and co-expressed in secretory vesicles with ANP. Furthermore, similar to ANP, its expression increases in response to pressure and volume overload in the atria and the ventricles¹³⁻¹⁴. Another natriuretic peptide called CNP was discovered to be produced in blood vessels. CNP was discovered to have vasodilatory effects with a short half-life and in general, does not exert any natriuretic effects¹⁵. DNP was isolated from snake venom and was found to be produced in atrial cells and elevated in patients with congestive heart failure¹⁶. Finally, urodilatin, which is a hormone composed of the 32 amino acids, is structurally identical to ANP. Both ANP and urodilatin are formed from cleavage of the same peptide called proANP. From this family, primarily BNP and ANP have shown to be elevated in individuals undergoing acute heart failure, and are used as diagnostic markers¹⁷.

Role of BNP in Acute Heart Failure

Heart failure induced in animal models has resulted in an increase in the transcription of BNP mRNA in both atrial and ventricular cells, which have correlated with increases in both plasma levels and severity of heart failure¹⁸. Levels of BNP increase when cardiomyocytes are strained, thus making BNP an effective method for determining a heart attack. However, according to multiple studies, BNP levels are also upregulated in cases of renal failure, pulmonary embolism, pulmonary hypertension and chronic hypoxia, which can make it an unreliable marker in some circumstances^{19,20}.

One meta-analysis pooled data multiple studies to establish the specificity, sensitivity, positive and negative predictive value of using BNP in an

acute heart failure setting. Roberts et al²¹ analyzed 26 different studies, some of which used different concentrations as the threshold. Among studies that set BNP levels to a cutoff of ≤ 100 ng/L, the sensitivity and specificity of the 0.95 and 0.63, respectively, and the positive and negative predictive value was 0.67 and 0.94, respectively. When the threshold for BNP levels was between 100-500 ng/L, the sensitivity and specificity of the test were 0.85 and 0.86, respectively, with a positive and negative predictive value of 0.85 and 0.86, respectively. When the threshold for the BNP levels was set to ≥ 500 ng/L, which was only present in four studies, the sensitivities of the study ranged from 0.35-0.83, and the specificity was 0.78-1.0. By conducting this meta-analysis, researchers discovered that at the lower thresholds, such as less than 100 ng/L, the sensitivity was high but the specificity was variable. Therefore, decreasing the threshold lowers the false-positive rate, which leads to higher sensitivity and less missed diagnoses. However, they also leads to higher false-positive rates as there are lower specificity and greater incorrect diagnosis.

Another systematic review, which analyzed 20 studies, determined the efficiency of BNP testing in detecting heart failure. Eight of the studies used decreased left ventricular ejection by a percentage of 40% or lower to classify heart failure. They determined that using BNP levels as diagnostic test results in a pooled diagnostic odds ratio of 13, which can be classified as a moderately accurate diagnostic test. Seven studies used clinical criteria as a diagnosis of heart failure. These studies determined that BNP levels had a collective diagnostic odds ratio of 31. Furthermore, two other studies, which used echocardiographic abnormalities to diagnose heart failure, determined that using BNP levels led to a pooled diagnostic odds ratio of 38. Therefore, among the studies analyzed in this review, most studies agree on the use of BNP as a measure of heart failure, particularly diastolic heart failure²².

The outcomes of using BNP as a diagnostic test have also been investigated by several groups. One clinical trial looked at outcomes of using BNP testing as a method of heart attack detection in patients that presented with dyspnea. According to the results, when compared to patients that weren't administered a test for BNP, implementing the test decreased the length of stay as patients that were administered the test only stayed for a median of 8 days versus 11 days for people that weren't. Furthermore, the total cost of treat-

ment for patients that were administered the test was less, as it was \$5,410 for those who were and \$7,264 for those who weren't. Authors suggest that this was due to the ability of being able to rule out heart failure, which allowed physicians to diagnose other diseases, for example, COPD (chronic obstructive pulmonary disease) or pneumonia²³.

Therefore, the use of BNP is not only useful as a tool for diagnosing heart failure but also to exclude heart failure. Guidelines from the ACC (American College of Cardiology) and the AHA (American Heart Association) detail that BNP levels are valuable for patients in emergency departments that present with acute heart failure where clinical diagnosis of heart failure is often hard to make²⁴. However, the optimal threshold for diagnosing/excluding heart failure and if levels should be different depending on sex and age of patients has not yet been fully elucidated.

Role of NT-proBNP in Acute Heart Failure

An analogue of BNP, plasma NT-proBNP, is also often used a biomarker to diagnose heart failure as higher than normal NT-proBNP levels are a marker of systolic and diastolic dysfunction²⁵. ProBNP, a 108 amino acid residue, is a precursor to BNP that is stored in granules within myocytes. A protease is responsible for cleaving the inactive NT-ProBNP into an active form of BNP when there is an increase in wall tension within ventricles. NT-ProBNP has a longer half-life when compared to BNP, which makes it a more valuable diagnostic marker¹³. According to the classification of heart failure by the New York Heart Association, levels of serum proBNP and NT-proBNP are consistent with the clinical grade of the disease. Hospitalized patients tend to have higher levels of these peptides and they decrease with aggressive treatment. NT-proBNP is currently used in routine tests in emergency departments as a diagnosis of heart failure²⁶.

The role of NT-proBNP levels has been investigated by a plethora of research groups over the years. Upon evaluation of NT-proBNP levels in individuals undergoing heart failure, Ozturk et al²⁷ discovered minimum NT-proBNP levels were 712 pg/ml for clinically hospitalized patients and 245 pg/ml for outpatients. The maximum value of hospitalized and outpatients with heart failure was 35,000 pg/ml, and the average NT-proBNP levels for hospitalized heart failure patients was 11,291 pg/ml. Based on the findings of one group led by Maisel et al⁵, patients with <300 pg/ml of

NT-proBNP could rule out the probability of heart failure. For patients that were younger than 50 years old, the threshold value was >450 pg/ml. For patients between the ages of 5-75, the cutoff value was >900 pg/ml and for patients that are 75 or older, the cutoff value was >1800 pg/ml. NT-proBNP levels higher than 1000 pg/ml are associated with heart disease and an unfavorable prognosis.

In one meta-analysis, when evaluating the sensitivity and specificity of NT-proBNP, the thresholds were divided into three groups (≤ 300 , 300-1800 and ≥ 1800 ng/L). At a cutoff of ≤ 300 ng/L, the pooled sensitivity and specificity was 0.99 and 0.43, respectively. Furthermore, the positive and negative predictive value was 0.64 and 0.98, respectively. When the threshold was 300-1800 ng/L, the pooled sensitivity and specificity was 0.90 and 0.76, respectively. Additionally, the positive predictive value and the negative predictive value was 0.80 and 0.88, respectively. Only three studies applied a threshold of ≥ 1800 ng/L, and thus, the factors could not be pooled. The ranges of sensitivities with this threshold were between 0.60-0.87, and the specificities were between 0.72-0.95²¹. Once again, with regards to the applied threshold, the patterns of sensitivity and specificity were similar to that of BNP as the higher the threshold, the lower the sensitivity but the higher the specificity.

Interestingly, NT-proBNP can also be used as a diagnostic marker for chronic heart failure. According to "Tintinalli's Emergency Medicine: A Comprehensive Study Guide", using NT-proBNP to diagnose chronic heart failure, the overall specificity, sensitivity, positive predictive value and negative predictive value is 99%, 85%, 76% and 99%, respectively²⁸.

Role of MR-proANP in Acute Heart Failure

As opposed to BNP and NT-proBNP, which are released by left ventricular myocytes after a high volume of afterload, ANP is released mainly by myocytes of the atria, which are sensitive to increases in preload of the heart. Clinical observations have shown that there are high levels of plasma ANP in individuals with overt heart failure²⁹. As a precursor of ANP, the 126 amino acid NT-proANP has a lengthier life-span than ANP and is more stable under laboratory conditions. Therefore, physicians consider it a more useful and valuable biomarker than ANP³⁰. Since NT-proANP can be subject to fragmentation in the lab, a new immunoassay was established to identify the mid-regio-

nal portion of proANP, called MR-proANP, which is more stable than its counterparts³¹.

One review compiled four studies that have been conducted on the diagnostic utility of using MR-proANP in acute heart failure settings. Two studies used the ≤ 120 pmol/L threshold and the remaining the other two used >120 pmol/L threshold. At a cutoff of ≤ 120 pmol/L, the sensitivity of the studies was 0.95-0.97 while the specificity was 0.56-0.60. At a cutoff of >120 pmol/L, the sensitivity of the studies was 0.84-0.98 while the specificity was 0.4-0.84. Since such few studies have been conducted on the diagnostic utility of this specific peptide, the pattern of thresholds has not yet been elucidated. However, it was observed that sensitivity remains high across the thresholds with varying levels of specificity²¹.

The use of MR-proANP has been suggested as being more accurate when conducted alongside other natriuretic peptides. In a clinical trial with patients with acute heart failure, patients with dyspnea were analyzed for levels of MR-proANP. Results from this study showed that MR-proANP, with a threshold ≥ 120 pmol/L, had a sensitivity, specificity, and accuracy of 97%, 60%, and 73.6%, respectively. The same study found that when measuring BNP with a threshold of ≥ 100 pg/mL, the sensitivity was 95.6%, specificity was 62% and the accuracy was 72.7%. Therefore, using both MR-proANP and BNP had similar accuracies³². Furthermore, in a separate study called the PRIDE study, MR-proANP was demonstrated as being a predictor of heart failure diagnosis when conducted with NT-proBNP with an odds ratio of 4.34. These studies exhibit that using MR-proANP and BNP/NT-proBNP in conjunction could denote an increase in diagnostic accuracy of heart failure rather than either alone³³.

Conclusions

Natriuretic peptides have been shown in the context of acute heart failure to be a useful tool, not to only to diagnose heart failure but also to exclude it as a reason for a patient presenting with dyspnea. Various studies have been conducted that have studied the different aspects of using these peptides as diagnostic markers. Most studies have found that higher thresholds have lower sensitivity and higher specificity. While the thresholds might be different across studies, most researches have concluded that using peptides such as BNP, NT-proBNP, and MR-proANP are valid

diagnostic markers with good, but not excellent, accuracies. There is no consensus across the world on the correct threshold to use them, and therefore, further research needs to be conducted on determining the threshold or cutoff point for each of the natriuretic peptides which maximize both sensitivity and specificity, with varying cutoffs that take into account age and sex of patients.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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