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Natriuretic Peptides in Clinical Practice: A Current Review

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ABSTRACT

Heart failure is a major clinical problem affecting 64 million people worldwide with a 5-year mortality rate of around 50%. Patients present to the emergency department with inability to breathe properly. Heart failure is an important condition not to be missed as accurate and early diagnosis or exclusion is crucial for timely intervention. Conventionally heart failure was regarded as congestion consequent to fluid accumulation. Currently heart failure is viewed as a complex heterogeneous entity encompassing severity (clinical versus sub-clinical), onset (acute versus chronic), vascular compartment involved (intra- versus extra-vascular), besides fluid accumulation (cardiopulmonary versus generalized). There is a myriad of biomarkers that reflect different parts of heart failure pathophysiology. However, only natriuretic peptides remain as the "gold standard" against which other biomarkers are compared. This review provides a current update on the utility of natriuretic peptides in clinical practice. We will provide a brief overview of natriuretic peptides, the assays, their clinical use in heart failure, some caveats for their use (age, chronic kidney disease, obesity, heart failure with preserved ejection fraction) and highlight some emerging applications.

Introduction

In patients who present to the emergency department with inability to breathe properly, acute heart failure (HF) is an important condition not to be missed. Accurate and early diagnosis or exclusion of HF is crucial for timely intervention in a dyspneic patient. Conventionally HF was regarded as congestion consequent to fluid accumulation[1]. The current view is that HF is a complex heterogeneous entity encompassing severity (clinical versus sub-clinical), onset (acute versus chronic), fluid distribution (cardiopulmonary versus generalized), and vascular compartment involved (intra- versus extra-vascular)[1]. The myriad of biomarkers that reflect different parts of HF pathophysiology exist[2]. However, only natriuretic peptides remain as the "gold standard" against which other biomarkers are compared[3]. This review provides a current update on the utility of natriuretic peptides in clinical practice.

Natriuretic Peptide Overview

Natriuretic peptides are more accurate than patient history, physical findings, or any other laboratory test in differentiating acute heart failure from other causes[4]. Heart failure affects 64 million people worldwide with a 5-year mortality rate of around 50%[5,6]. The role of natriuretic peptides spans heart failure screening, diagnosis, management, prognostication, to risk stratification.

There are 2 well-known cardiac natriuretic peptides – atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP). These are released in response to myocardial stretching[7]. Expression of the bnp gene occurs in response to sustained cardiac stretching and results in a 134 amino acid pre-proBNP product which is then processed to $proBNP_{1-108}$. $ProBNP_{1-108}$ is cleaved by furin or corin in the cardiomyocyte or peripherally to release equimolar portions of the biologically active C-terminal peptide BNP and its N-terminal peptide by-product NT-proBNP[7-9]. Conversely, the ANP gene is expressed over time and ANP is stored in secretory granules which are released in response to myocardial stretch[10]. The half-life of ANP is extremely short (3mins), limiting its reliability as a measurable biomarker[11].

The main functions of BNP include natriuresis and diuresis via the kidneys and the renin-angiotensin-aldosterone system (RAAS), reduction of vascular tone and inhibition of cardiac remodeling[12]. They exert these effects through membrane-bound natriuretic peptide receptors (NPRs) A and B which are guanylyl-cyclase receptors with cGMP as the intracellular messenger. Natriuretic peptide receptor C is involved in the clearance of BNP. BNP is also metabolized by enzymes such as neprilysin[13]. NT-proBNP is cleared by the kidneys and other organs[14].

BNP and NT-proBNP are useful biomarkers in heart failure as their blood concentrations correlate with left ventricular function as well as the severity of heart failure symptoms[4,15-17].

Cardiac Natriuretic Peptide Assays

Since the early 2000s, BNP and NT-proBNP have been evaluated as cardiac biomarkers for heart failure[4,17]. Both BNP and NT-proBNP are non-competitive (sandwich) immunoassays using capture and detector antibodies. The BNP assays detect BNP as well as its precursor, proBNP, and any fragments containing regions that the BNP assay capture and detector antibodies can bind to (though only BNP_{1-32} is biologically active). Different capture and detection antibodies are used on each assay platform and different epitopes may be absent depending on the BNP fragment[18]. Furthermore, proBNP and its derivatives also undergo glycosylation[19]. Glycosylation blocks the peptide from cleavage by enzymes and inhibits binding by the assay antibodies at the glycated regions, effectively creating more variance in the measured concentrations with between-method imprecision (CV) of up to 43%[20-23]. Similarly, the NT-proBNP assays detect NT-proBNP, proBNP and any fragments containing regions that the NT-proBNP assay capture and detector antibodies can bind to. They are susceptible to the same variation due to the heterogeneity of fragments and glycation of peptides. Fortunately, most NT-proBNP assays are based on the same antibodies so results are more comparable with between method CV of 8.7%[23]. As the half-life of NT-proBNP (70 minutes) is longer than BNP (22 minutes), NT-proBNP is a more stable biomarker and concentrations between the two are not interchangeable[24].

BNP assays require EDTA samples for stability, whereas NT-proBNP can be analyzed from plasma or serum samples with minimal bias. NT-proBNP also has longer storage stability with a less than 10% decrease in more than 90% of samples after 2 years when stored at -20 degrees Celsius, whereas BNP concentrations decreased to less than 50% after 2 to 4 months of storage under the same conditions[25,26]. Thus, there are many advantages of using NT-proBNP over BNP such as lower between method variation, longer half-life, diversity of specimen types, and better storage stability. However, the biggest advantage is in its use to monitor patients receiving angiotensin receptor-neprilysin inhibitors (ARNIs), a newly introduced heart failure therapy. In the PARADIGM-HF trial, an ARNI (Sacubitril/Valsartan), was overwhelmingly effective in reducing risk of death and hospitalization for Sacubitril/Valsartan patients with chronic heart failure compared to established treatment with an ACE-inhibitor (enalapril). The trial was stopped early as it was unethical to continue withholding an ARNI from the control group[27]. However, participants in the intervention group had a paradoxical increase in BNP due to inhibition of BNP degradation by neprilysin in the initial 8–10 weeks after initiation of Sacubitril/Valsartan from 202 ng/L to 235 ng/L while NT-proBNP reflected an expected fall in these participants. As ARNIs are now recommended as part of first-line treatment for chronic heart failure, NT-proBNP is the cardiac biomarker of choice in monitoring treatment response in patients on neprilysin inhibitor therapy. Even Abbott Diagnostics, the pioneer in BNP assays, has launched an NT-proBNP assay. Given that each laboratory is likely to offer either BNP or NT-proBNP only, NT-proBNP seems to be the preferred option.

Clinical Use of BNP and NT-proBNP

The most established use for natriuretic peptides in clinical practice is in the assessment for acute heart failure in dyspneic patients presenting to the emergency department. The Breathing Not Properly (BNP) study in 2002 established the role of the natriuretic peptide BNP in participants with acute dyspnea (n=1586)[4]. BNP level was the single most accurate predictor of the absence of congestive heart failure using 100pg/ml as the cut off (sensitivity 90%, specificity 76%). In addition, BNP increased with the severity of congestive heart failure in relation to the New York Heart Association (NYHA) functional class.

A similarly designed study (PRIDE) using NT-proBNP soon followed in 2004[28]. This was the first large study using

NT-proBNP (n=600). It reinforced the role of natriuretic peptides in ruling out congestive heart failure (300pg/ml: sensitivity 99%, specificity 68%) and the positive association with increasing severity of heart failure. In addition, it demonstrated that the sensitivity and specificity of NT-proBNP was improved and could additionally be used to rule-in heart failure with age-stratified cut offs. The optimal rule-in cutoffs of NT-proBNP for acute congestive heart failure were 450 pg/ml for age <50 years (sensitivity 93%, specificity 95%) and 900 pg/ml for age ≥50 years (sensitivity 91%, specificity 80%). While NT-proBNP was the single most accurate modality to diagnose acute congestive heart failure (AUC 0.94), it performed even better when combined with clinical judgement (AUC 0.96), supporting the use of the biomarker in conjunction with clinical assessment.

Thereafter a larger NTproBNP study emerged. The ICON study published in 2006 was an international, multicenter analysis of 1256 dyspneic patients to establish optimal NT-proBNP cut offs for diagnosis or exclusion of acute heart failure and to evaluate the prognostic significance of elevated NT-proBNP in the setting of acute heart failure[17]. Using bootstrapping methods, the most optimal strategy was an age-independent NTproBNP cut off of 300 pg/ml (sensitivity 99%, specificity 60%, NPV 98%) for ruling out acute heart failure. For ruling in heart failure there were age-dependent NTproBNP cut offs: 450 pg/ml for < 50 years (sensitivity 97%, specificity 93%, PPV 76%), 900 pg/ml for 50–75 years (sensitivity 90%, specificity 82%, PPV 83%), and 1800 pg/ml for >75 years (sensitivity 85%, specificity 73%, PPV 92%). These are the thresholds that were incorporated into the 2013 AHA guidelines and again in the 2022 AHA guidelines[29,30]. Prognostic significance of natriuretic peptides in patients with acute heart failure was also established with marked elevations of NT-proBNP (>5180 pg/ml) outperforming other markers such as age and NYHA classification as predictors of short-term mortality[17].

More than a decade later ICON-RELOADED, a multicenter clinical trial in USA and Canada, validated that the NT-proBNP cut offs identified in ICON study for the rule in and rule out of heart failure[31]. In 1461 patients presenting to the emergency department with dyspnea NTproBNP performed well (AUC 0.91) with the single rule-out at 300 pg/ml - sensitivity 93.9%, specificity 71.7%, NPV 98%. The age-stratified rule-in cut offs were: 450 pg/ml for < 50 years (sensitivity 85.7%, specificity 93.9%, PPV 53.6%); 900 pg/ml for 50–75 years (sensitivity 79.3%, specificity 84.0%, PPV 58.4%); and 1800 pg/ml for >75years (sensitivity 75.9%, specificity 75.0%, PPV 62.0%).

Natriuretic peptides should be interpreted as continuous biomarkers with prognostic implications. Patients with NT-proBNP values between the rule-in and rule-out cut offs, known as the intermediate or grey zone, typically have better diagnostic outcomes than those with values above the diagnostic cut offs for heart failure[32,33]. However, patients in the grey zone fared worse than those with NT-proBNP values below the rule-out cut-offs. It must be remembered that there are other causes of mild elevations in NT-proBNP - impaired renal function, ischemic heart disease, atrial fibrillation, valvular disease, heart muscle disorders, severe infectious or inflammatory diseases, lung cancer, and other cardiac diseases that elevate right ventricular pressures (e.g., pulmonary hypertension and pulmonary embolism). However, these conditions per se even in the absence of heart failure also carry a poorer prognosis.

Higher natriuretic peptide levels are associated with greater risk of adverse short-term and long-term outcomes, including death (all-cause and cardiovascular) and major cardiovascular events[29,34-38]. In addition to its use in the diagnosis or exclusion of heart failure, the American Heart Association also recommends the measurement of natriuretic peptides in a few other settings. Natriuretic peptide measurement in the ambulatory setting also enables risk stratification of patients with chronic heart failure. At the beginning of a heart failure admission, measurement of NT-proBNP provides prognostic information. Pre-discharge levels are also strong predictors of risk of death and hospital readmission for heart failure. The relative change of natriuretic peptide levels from the beginning of admission tend to correlate with better outcomes in those with a reduction in levels after treatment compared to those with unchanging or increased levels. Measurement of natriuretic peptides for screening in patients at risk of developing heart failure also facilitates the identification of asymptomatic patients and for more aggressive management of risk factors for preventing development of LV dysfunction with or without heart failure[39].

Until recently, natriuretic peptide guided therapy has had mixed evidence due to issues such as poor compliance with the intervention[40]. The recent STRONG-HF trial was overwhelmingly supportive of rapid up-titration of treatment guided by clinical assessment and NT-proBNP such that it terminated early[41]. STRONG-HF was a multinational, randomized trial (n=1078) that assessed the efficacy and safety of rapid up-titration of guideline-recommended heart failure therapy (beta-blockers, ACE-I/ARBS/ARNIs, mineralocorticoid receptor antagonists, SGLT-2 inhibitors, intravenous iron) before discharge from an acute heart failure admission and during the following weeks on morbidity and mortality. In the arm with rapid up-titration, the 180-day heart failure readmission or all-cause death was 8.1% lower than the control arm with an adjusted RR of 0.66, supporting natriuretic peptide guided therapy for more rapid up-titration of heart failure medications after an acute heart failure admission.

Another recent medication that was incorporated as one of the first-line drugs for heart failure management are the SGLT-2 inhibitors. SGLT-2 inhibitors are effective in both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). Empagliflozin, a popular SGLT-2 inhibitor, significantly reduced NT-proBNP concentrations and HF events in patients with HFrEF in the EMPEROR-Reduced trial. Compared to pre-treatment NT-proBNP values, those patients with improved post-treatment NT-proBNP concentrations had better otcomes[42]. Dapagliflozin similarly reduced the risk of worsening heart failure or HF death in patients with mildly reduced ejection fraction or HFpEF in the DELIVER trial[43]. However, in the CANVAS trial, NT-proBNP only explained 10.4% of Canagliflozin's effect on reducing HF events[44]. This raises the importance of understanding how each drug exerts its therapeutic effects and their relationship to natriuretic peptides – class effect versus specific individual drug effect.

Considerations in natriuretic peptide use

Comorbidities and heart failure drugs are potential confounders that may influence the interpretation of natriuretic peptide values (refer to Table 1). Natriuretic peptides may be raised in certain disease states or comorbidities (e.g. acute coronary syndrome, anemia, atrial fibrillation, impaired renal function, mitral regurgitation, older age, pulmonary embolism, pulmonary hypertension, right ventricular dysfunction, sepsis) and lower in others (e.g. obesity, flash pulmonary edema, constrictive pericarditis, end-stage cardiomyopathy, or genetic variation)[45].

Medications can affect the concentration of circulating natriuretic peptides through influencing their secretion or clearance. Many drugs used in heart failure such as ARNI's, SGLT-2 inhibitors, diuretics, renin-aldosterone-angiotensin system blockers, vasodilators, dopamine agonists, amiodarone and some statins suppress natriuretic peptides, whereas certain drugs such as beta-blockers, digitalis, aspirin may increase natriuretic peptides[46,47].

We discuss some established confounders of natriuretic peptides here.

Table 1. Some confounders of natriuretic peptide values

Older age
Impaired renal function
Obesity
HFpEF
Gender
Comorbidities (vide supra)
Genetic variation
Drugs

Age and Chronic Kidney Disease

Age and chronic kidney disease are known to cause elevation in natriuretic peptide levels. European guidelines recommend age-specific diagnostic thresholds[48]. The cause of increasing natriuretic peptides with age is not fully understood. It is thought to be contributed by deteriorating renal function and the accumulation of age-related structural cardiac changes such as diastolic abnormalities, valvular disease, and arrhythmias. The inverse relationship between natriuretic peptides and eGFR is well-documented but does not fully account for the natriuretic peptide elevation associated with age[49-51]. Our previous study on 388 subjects with eGFR > 90 ml/min/1.73mm^2 demonstrated that there was a significant difference between median (43.0, 95.1, 173.1 pg/ml) NT-proBNP levels in those aged <50 years , 50–75 years and > 75 years, supporting the case that there are factors other than declining renal function that raise natriuretic peptides with age. The use of natriuretic peptides in the very old can result in a larger range of values which can add to diagnostic uncertainty[52]. This should be taken into account when interpreting natriuretic peptide values in this group.

Obesity

Patients with obesity tend to have lower natriuretic peptide levels[53]. BNP binds to natriuretic peptide receptors in adipocytes and BNP concentrations are thought to be lower in obesity due to the increased receptor binding[54]. NT-proBNP does not bind to these receptors but are also lower in this group. Other mechanisms such as impaired processing of proBNP are being explored as better explanations for lower natriuretic peptide concentrations in patients with obesity. In the Dallas Heart study of community dwelling subjects without known heart failure, NT-proBNP levels decreased by 0.109 in women and 0.314 in men for every 5kg/m^2 increase in BMI[55]. In ICON-RELOADED, patients with a BMI less than and greater than or equal to 30 had different AUCs (0.946 vs 0.896) with p=0.001[31]. A separate study looking at BNP levels in obese subjects with heart failure found obese subjects to have significantly lower BNP levels than non-obese subjects (205 pg/ml versus 335 pg/ml, p =0.0007)[56]. In patients with obesity and heart failure with preserved ejection fraction (HFpEF), both conditions concomitantly have the potential to depress NT-proBNP levels below clinical decision points. In fact, using NT-proBNP alone missed the diagnosis of heart failure in more than 50% of patients with obesity and HFpEF[57]. The guidance on use of natriuretic peptides from the Heart Failure Association of the European Society of Cardiology recommends using lower cut offs (up to 50% lower) in this population[51]. Clinical acumen is vital in this group; an NT-proBNP level below rule-out cut-offs should not be used alone to exclude HFpEF in obese patients.

HFpEF

Approximately 50% of heart failure patients are those with heart failure preserved with ejection fraction (HFpEF)[58]. While natriuretic peptides tend to be lower in HFpEF (EF ≥ 50%) compared to levels in HFrEF[59,60], natriuretic peptides are still raised in HFpEF and correlate with the severity of cardiac dysfunction[61]. For any given level of BNP, the prognosis in patients with HFpEF and HFrEF are comparable[60]. However, there are currently no separate guideline-recommended natriuretic peptide cut offs for HFpEF.

Gender

Although current guidelines have not recommend gender-specific natriuretic peptide thresholds, most studies have found that natriuretic peptides are higher in females than males[62-64]. Differences around 10 pg/ml in BNP and 100% in NT-proBNP between genders have been observed[62,63]. This difference is not well understood but some that explanations have been proposed: ranging from hormonal influence on gene expression and gender differences in obesity to extra-cardiac sources of natriuretic peptides within the female productive system[63,64]. Higher NT-proBNP values in transgender women support hormonal differences as a driver for this difference[65]. Despite higher natriuretic peptide levels in females, current evidence does not support gender-specific thresholds as natriuretic peptides perform similarly to diagnose HF and as a prognostic marker in both sexes.

Next Frontiers

Cardiovascular disease is one of the main causes of death in diabetes and the presence of diabetes doubles the incidence of the heart failure (RR 2.14)[66]. The PONTIAC study (n=300) in 2008 used an elevated NT-proBNP > 125 pg/ml to identify at risk patients for primary prevention of cardiac disease with intensified medical treatment using renin-angiotensin system antagonists and beta-blockers[39]. Intensified treatment in the at-risk group reduced hospitalization or death due to cardiac disease.

The ESC released a position statement in 2022 on biomarkers for prediction of heart failure and cardiovascular events in patients with type 2 diabetes[67]. Natriuretic peptides outperform other biomarkers for cardiovascular risk and heart failure risk prediction in diabetes and the current natriuretic peptide thresholds used for non-diabetics seem to perform adequately in diabetic patients.

Natriuretic peptides are also increasingly used in community screening. A review of natriuretic peptide use in a large UK primary care cohort (n=7,212,013) revealed that there is still room for further uptake in the community setting to identify undiagnosed heart failure before an acute heart failure hospital admission[68]. A Canadian review determined that natriuretic peptide testing improved diagnostic accuracy of heart failure and was cost effective in the community setting[69].

Uses of natriuretic peptides in other conditions such as atrial fibrillation, aortic stenosis are also being explored[70-73].

Conclusion

Natriuretic peptides have made the diagnosis of heart failure more accurate and accessible besides enabling prognostication, risk stratification and screening of at-risk populations. More recently their monitoring has facilitated further optimized management for heart failure treatment. Although there are established uses of natriuretic peptides, its use in special populations such as patients with obesity and HFpEF need to be examined further.

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Conflict of interest

Nil

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