CARDIOLOGY Rounds®

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Heart Failure as a Neuroendocrine Syndrome: The role of natriuretic peptides in diagnosis, prognosis, and management

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Increasing recognition of heart failure (HF) as a neuroendocrine syndrome has produced remarkable progress in its management, including the development of many contemporary medical therapies with favourable neurohormonal-modulatory properties that reduce mortality and morbidity. The pathophysiological and clinical relevance of the renin-angiotensin-aldosterone and sympathetic adrenergic systems have been extensively investigated.[1,2] Over the last decade, increasing research efforts have been devoted to natriuretic peptides, some of which can now be measured by commercially-available bioassays. Preliminary human studies have shown that incorporating natriuretic peptide measurements into clinical practice increases the potential for early diagnosis, prognostication, and guidance in the management of *individual* HF patients with preserved or impaired systolic function. Although neurohormone measurements are unlikely to ever supersede informed clinical judgment, accumulating evidence suggests that they are useful biomarkers, providing independent and complementary information for an objective evaluation of cardiac function and patient clinical status that may potentially improve clinical decisions and patient care. This issue of *Cardiology Rounds* reviews the physiology of natriuretic peptides and their *potential* clinical utility to:

- **establish the diagnosis of left ventricular systolic and diastolic dysfunction, and clinical HF**
- **provide guidance to the selection and titration of therapies**
- **provide prognostic information for decompensated and chronic HF patients.**

Synthesis and regulation

The family of natriuretic peptides consists of the atrial natriuretic peptide (ANP), B-type (or brain) natriuretic peptide (BNP), and 3 other structurally similar peptides: C-type natriuretic peptide (CNP) predominantly of central nervous system and endothelial origin; urodilatin (from the kidney); and dendroaspis (a natriuretic peptide of undetermined significance at present).[3,4] Given their intrinsic cardiac origin and regulatory mechanisms, ANP and BNP are of particular relevance in cardiac diseases, including HF. Both are structurally similar molecules with the same amino-acid ring synthesized in response to the physiological stretch of myocytes, but they are regulated at different cellular levels and cardiac structures. ANP is primarily synthesized in the atria, in response to increased atrial wall stress, and regulated by controlled release from storage granules that may also contain some pre-formed BNP.[5] BNP is regulated at the level of gene transcription and is produced in bursts, predominantly from ventricular cardiomyocytes triggered by volume and transmural pressure overload.[6] Both neurohormones are initially synthesized as precursor proteins containing a signal peptide (preprohormones) that undergo intracellular

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Figure 1: Synthesis and secretion of BNP

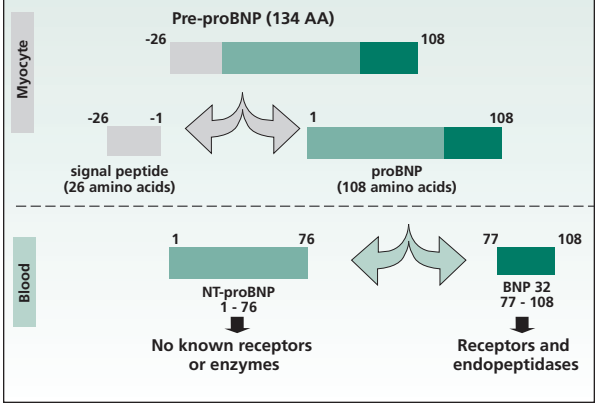
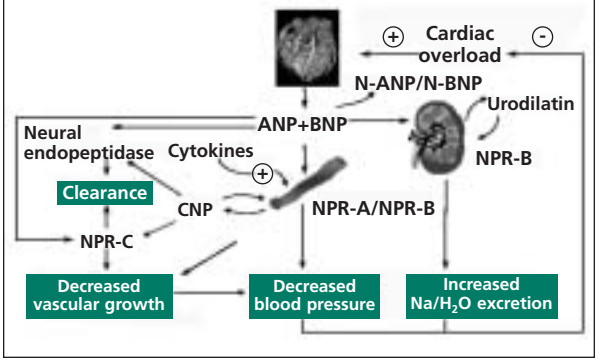


Figure 2: Biologic actions and clearance of natriuretic peptides



NPR = Natriuretic peptide receptor

modification to become prohormones. The prohormones are further cleaved into biochemically inactive N-terminal fragments (NT-ANP and NT-BNP) and active hormones (ANP and BNP) on release into the systemic circulation (Figure 1). The biologic effects of ANP and BNP are primarily mediated by the natriuretic peptide receptor (NPR-A). Both active peptides are removed by the clearance receptor (NPR-C) and inactivated by neutral endopeptidase (NEP; Figure 2).[7]

Although natriuretic peptides are primarily regulated by transmural pressure and myocardial stretch, their plasma concentrations may be elevated in other cardiac and non-cardiac conditions besides HF, including systemic and pulmonary hypertension, hypertrophic and restrictive cardiomyopathies, pulmonary embolism, chronic obstructive pulmonary disease, cor pulmonale, acute myocardial infarction, cirrhosis, and renal failure.[8] Therefore, elevated natriuretic peptides are not specific for left ventricular (LV) dysfunction or HF, and their clinical significance needs to be interpreted with appropriate considerations of clinical assessment and the presence of other confounding conditions.

Physiological effects and relationships with ventricular parameters and hemodynamics

Natriuretic peptides exert multiple effects on cardiac and vascular tissues that prevent the adverse structural remodeling and functional changes in progressive HF.[9] In addition to causing vascular smooth muscle relaxation with a reduction in venous and arterial tone, thereby decreasing preload and afterload, natriuretic peptides also exhibit antiproliferative and antifibrotic properties in the myocardium and vasculature.[10] Natriuretic peptides antagonize the actions of endothelin and vasopressin, the sympathetic and renin-angiotensin-aldosterone systems, all mediating pathological vasoconstriction, ventricular hypertrophy, and adverse vascular remodeling.[11,12] The renal actions of natriuretic peptides include natriuresis and diuresis that occur, in part, from increasing glomerular filtration rates, inhibition of renin excretion, and angiotensin II-mediated sodium reabsorption.

Despite the desirable physiology of natriuretic peptides to counteract the hemodynamic derangement and ventricular remodeling in HF, higher endogenous plasma concentrations paradoxically reflect more severe underlying hemodynamic decompensation as principal stimuli. Plasma BNP levels have been shown to correlate with pulmonary capillary wedge pressure among HF patients in decompensated states, and in response to treatment.[13] Higher plasma BNP and ANP (and NT-ANP) concentrations have also demonstrated a correlation with larger ventricular dimensions and volumes together with a lower ejection fraction among symptomatic patients with systolic HF.[14] Furthermore, changes in these natriuretic peptides on-treatment mirror concurrent changes in ventricular volumes and ejection fraction, suggesting that these natriuretic peptides may serve as potential surrogate biomarkers of LV function and remodeling.[15]

Diagnostic utilities for ventricular dysfunction and heart failure

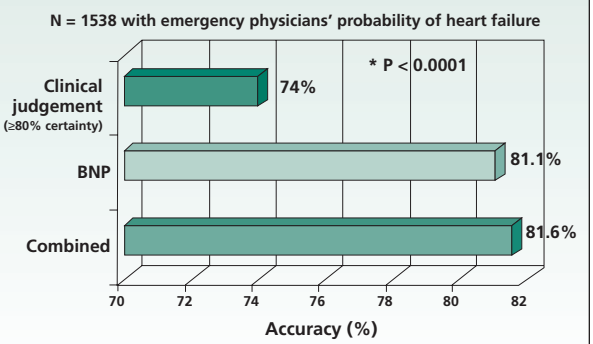
BNP has been examined as a screening tool for LV systolic dysfunction in multiple studies involving different populations, in an attempt to identify individuals at risk for HF. The Framingham Study, the largest reported to date, examined the diagnostic performance of BNP and NT-BNP for systolic dysfunction among 3177 subjects stratified by gender and pretest probability of HF, as defined by clinical criteria.[16] The area under the receiver-operating characteristic (ROC) curve indicating the discriminative power of BNP was 0.72 and 0.56 for male and female, respectively. The diagnostic performance was better among male subjects and was similar for BNP and NT-BNP. With an optimal diagnostic cut-off (maximizing sensitivity and

specificity) for males at 21 pg/mL, BNP exhibited a specificity of 84%, a sensitivity of 53%, positive (PPV) and negative (NPV) predictive values of 26% and 95%, respectively. At a similarly chosen cutoff of 34 pg/mL for females, the corresponding specificity was 89%, sensitivity 26%, PPV 6%, and NPV 98%. Overall, the poor sensitivity of BNP together with the low prevalence of systolic dysfunction in the general population suggested a limited usefulness of BNP as a mass-screening tool.

Diastolic dysfunction is an important cause of HF, accounting for up to 50% of all cases.[17,18] An accurate, reproducible, and simple means to identify and quantify diastolic dysfunction is of great clinical and research importance. Among subjects with normal systolic function and ventricular dimensions, those with abnormal diastolic function determined by transmitral Doppler on 2-D echocardiography had higher mean concentrations of plasma BNP (286 pg/mL vs 33 pg/mL).[19] Furthermore, there was a graded increase in mean plasma BNP concentrations with the degree of diastolic dysfunction, from 202 pg/mL with impaired relaxation to 408 pg/mL with restrictive filling pattern. The area under the ROC curve for BNP to detect any diastolic abnormalities was 0.91. Operating at a BNP cutoff of 62 pg/mL yielded a sensitivity of 85%, a specificity of 83%, and an overall diagnostic accuracy of 84% for any diastolic dysfunction. Although BNP concentrations cannot reliably distinguish systolic and diastolic dysfunction, since both elevate BNP, low BNP in the absence of systolic dysfunction may rule-out clinically significant diastolic inflow abnormalities and may obviate the need for investigation with echocardiography. However, in a larger study involving 2042 randomly selected residents of Olmsted County, the diagnostic performance of BNP reported as the area under its ROC curve, in identifying any diastolic dysfunction was only 0.52 to 0.68, suggesting that BNP is sub-optimal as a screening test for preclinical ventricular dysfunction.[20] Whether BNP is a potential diagnostic and surrogate marker of diastolic dysfunction awaits further investigations.

Establishing the clinical diagnosis of HF can be a challenge since the cardinal symptoms (eg, dyspnea) are often non-specific. The diagnostic utility in the acute care setting was evaluated by the prospective Breathing Not Properly (BNP) Multinational Study that involved 1586 participants presenting to an emergency department with undifferentiated dyspnea.[21] BNP measurement alone had a sensitivity of 90% and a specificity of 73% for heart failure. When complemented by clinical judgment, defined as a certainty of HF >80% by the physician, overall diagnostic accuracy was enhanced from 74% to 81% (Figure 3). BNP conferred the greatest diagnostic value with an independent diagnostic accuracy at 74% among subjects with

Figure 3: Relative diagnostic accuracy in the BNP study



intermediate clinical probability of heart failure. The utility of BNP in this clinical setting is best achieved by integration with careful history, physical examination, and conventional objective testing, as evidenced by an improved ROC of 0.93, compared to 0.86 and 0.90 with clinical judgment and BNP alone, respectively. Such an approach has demonstrated cost-effectiveness by reducing the need for hospitalization, intensive care admission, time to discharge, and cost of treatment.[22]

Prediction of therapeutic response and titration of therapies

Evidence-based treatments for HF are largely derived from clinical studies with results applicable overall to the studied *population. Individual* patients who are clinically and phenotypically similar may have highly variable neurohormonal activation and thus, differential responses to therapies with neurohormonal modulating properties. The contemporary approach to treating HF often aims to reproduce treatment strategies employed in clinical trials without any means to individualize therapies targeted to an individual patient.

In the CONSENSUS trial, enalapril reduced 6-month mortality among New York Heart Association (NYHA) class IV HF patients, but only among those with pre-treatment neurohormone (including ANP) concentrations above the group median.[23] As reported by the Australia-New Zealand Heart Failure Group, the non-selective beta-blocker, carvedilol, reduced the relative risk of death and hospitalization by 26% among subjects with NYHA III-IV HF secondary to ischemic heart disease. However, there were significant treatment interactions with both pre-treatment BNP and norepinephrine concentrations independent of patient clinical characteristics. Higher plasma norepinephrine concentrations, although predictive of worse outcome, were associated with attenuated

efficacy of carvedilol. In contrast, elevated pre-treatment ANP and BNP concentrations, while associated with a higher risk of death and hospital admission, were also predictive of increased benefits from carvedilol. Individuals with supra-median BNP and infra-median norepinephrine concentrations benefited the most from carvedilol, ie, the highest mortality and morbidity reductions.[24] Although not conclusive, these observations from post-hoc analyses of randomized controlled trials raise the interesting hypothesis that comprehensive neurohormonal profiling may predict therapeutic response and facilitate individualized medical therapies to optimize clinical outcome.

As for other chronic diseases, the main objectives in treating HF are to improve symptoms and prognosis. Changes in patient self-reported exercise tolerance, body weight, and subjective assessments of edema are commonly used to gauge symptom severity and clinical response to treatment. Contemporary practice to optimize prognosis entails the use whenever possible of therapeutic regimens with doses administered in clinical trials as tolerated. In reality, not all patients can tolerate all evidence-based medications at target doses, however, currently there is no specific or validated surrogate end-point that can be used to adjust therapies for optimizing clinical status and prognosis. Natriuretic peptides are promising candidates since they are central to the pathophysiology of heart failure and well-correlated with hemodynamics, clinical status, and prognosis.

Currently, 2 studies have specifically evaluated the clinical use of natriuretic peptides in monitoring and tailoring medical therapies in patients with heart failure. In a pilot study of patients with mild to moderate HF, patients were randomized to either titration of ACE inhibitor to achieve a predefined normal range for BNP or an empirical clinical approach. The BNP-driven approach achieved significantly greater reductions in heart rate and plasma BNP concentrations with more profound inhibition of the renin-angiotensin-aldosterone system, suggesting hemodynamic and neurohormonal effects that were more favourable.[25]

A subsequent study in patients with systolic dysfunction and NYHA II-IV HF compared the clinical outcome between pharmacotherapy titration guided by plasma NT-proBNP and empirical trial-based treatment dictated by clinical acumen. The NT-proBNP-guided approach reduced the total number of cardiovascular events, including cardiovascular death, hospital admissions, and new episodes of heart failure. These results were achieved through higher doses of ACE inhibitors and loop diuretics, and more widespread use of spironolactone.[26] The superiority of the BNP-guided approach may represent a more preventive strategy with preemptive intensification of pharmacotherapies among patients with subclinical decompensation, as identified by abnormal NT-proBNP. In recognition of the increasing complexity of medical regimens for HF with novel therapies, a validated means to optimize multiple neurohormonal strategies is imperative. The neurohormonal-guided approach is a promising option warranting further investigations.

Natriuretic peptides as prognostic markers

The prognostic value of natriuretic peptides has been consistently demonstrated in many well-designed studies involving both acutely decompensated and stable chronic HF patients.

Despite advances in treatment, the in-hospital mortality and re-admission rates for decompensated HF remain high. This may stem in part from the lack of a reliable indicator of treatment adequacy or impending risk for short-term adverse events. Among patients admitted with decompensated HF treated in the standard fashion with diuretics and vasodilators, BNP levels on admission, at discharge, and the changes during hospitalization were significant predictors of death and readmission within 30 days.[27] Only 16% of patients with a fall in BNP during admission had a subsequent cardiac event, compared with 52% of those whose BNP levels failed to decrease with treatment. Clinical improvement as defined by the change in NYHA class had no predictive value.

These results were supported by a larger study evaluating the utility of serial BNP measurements and their independent prognostic significance for death and re-admission up to 6 months.[28] The level of BNP at discharge when the patient was deemed clinically stable was an independent predictor of an event, after adjustment for patient clinical characteristics, echocardiographic parameters, and in-hospital treatment with inotropes. Moreover, the risk of adverse events increased in a stepwise fashion with increasing pre-discharge BNP concentrations. These findings suggest that patients admitted with HF may be discharged without adequate stabilization despite a clinical impression to the contrary and that BNP can complement clinical judgment in determining the timing and suitability for discharge.

Among stable, chronic HF patients, higher concentrations of BNP have been associated with

increased all-cause and cardiovascular mortality independent of validated clinical prognosticators, including age, NYHA class, LV ejection fraction, and previous myocardial infarction.[24,29] Recent data suggest that BNP is an independent predictor of sudden death in patients with EF<35% and HF, and may serve as a simple biomarker to select patients who might benefit most from an implantable cardioverter-defibrillator.[30]

The relative prognostic significance of various neurohormones activated in HF has not been evaluated until recently. Based on data from 4300 stable symptomatic HF patients randomized in the Valsartan Heart Failure Trial (Val-HeFT), baseline BNP concentration was superior to other neurohormones including norepinephrine, renin activity, aldosterone, and endothelin, in predicting mortality and morbidity after adjustment for clinical and echocardiographic parameters.[31] However, ANP, which may be differentially elevated in heart failure independent of BNP, was not included in the comparative analysis. Nevertheless, these results add to the robustness of BNP as an important prognosticator.

The validity of natriuretic peptides as surrogate risk markers of HF is further supported by studies demonstrating consistent relationships between changes in these neurohormones and changes in the risk for subsequent adverse clinical events. Changes in BNP and norepinephrine over 8 months among patients in the Val-HeFT trial predicted corresponding changes in the subsequent rate of all-cause mortality and the first morbid event, although these were not adjusted for other patient characteristics of known prognostic significance. In the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) trial,[33] the prognostic significance of temporal changes in various neurohormones was evaluated and compared after adjustment for known clinical prognosticators. Increasing plasma NT-ANP and norepinephrine concentrations over 16 weeks independently predicted an increased short-term risk of death and hospital admission for HF over the next 6 months.[34] These findings support the potential use of serial natriuretic peptide measurements for risk stratification with chronic HF patients. Further studies should determine whether such information can guide management to improve clinical outcome.

Conclusions

There is accumulating evidence that natriuretic peptides are potentially useful diagnostic and prognostic markers of HF that may guide management in the selection and titration of evidence-based therapies. Although measurement of natriuretic peptides provides complementary information from a unique pathophysiological perspective, the effective integration of this information into the overall clinical approach for managing HF and improving outcomes remains to be elucidated.

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