REVIEW / SYNTHÈSE

Atrial natriuretic peptides in heart failure: pathophysiological significance, diagnostic and prognostic value

Nina Ghosh and Haissam Haddad

Abstract: Neurohormonal activation in patients with heart failure is dominated by the deleterious long-term effects of activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system. The natriuretic peptides, including brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP), are also upregulated in heart failure, and partially counteract these deleterious effects by promoting vasodilation, natriuresis, and diuresis. Although BNP has been established as an important biomarker in the diagnosis and prognosis of heart failure, growing evidence suggests that measurement of plasma ANP, specifically its metabolite mid-regional pro-ANP, has similar diagnostic and prognostic value. Furthermore, its measurement may provide incremental diagnostic value when BNP levels fall into "grey zone" levels and may be a more potent prognostic marker of mortality.

Key words: heart failure, sympathetic nervous system, renin-angiotensin-aldosterone system, atrial natriuretic peptide, brain natriuretic peptide.

Résumé : L'activation neurohormonale chez les patients atteints d'insuffisance cardiaque est dominée par les effets indésirables de longue durée de l'activation du système nerveux sympathique et du système rénine-angiotensine-aldostérone. Les peptides natriurétiques, dont le peptide natriurétique cérébral (PNC) et le peptide natriurétique auriculaire (PNA), sont régulés positivement dans l'insuffisance cardiaque et compensent partiellement les effets indésirables en favorisant la vasodilatation, la natriurèse et la diurèse. Bien que le PNC soit reconnu comme un important biomarqueur dans le diagnostic et le pronostic de l'insuffisance cardiaque, des données croissantes laissent croire que la mesure du PNA plasmatique, plus particulièrement de son métabolite MR-ProPNA, a une valeur diagnostique et pronostique similaire. Elle pourrait aussi apporter une valeur diagnostique supplémentaire lorsque les niveaux de PNC se situent dans une « zone grise » et être un marqueur pronostique plus puissant de mortalité.

Mots-clés : insuffisance cardiaque, système nerveux sympathique, système rénine-angiotensine-aldostérone, peptide natriurétique auriculaire, peptide natriurétique cérébral.

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Introduction: atrial natriuretic peptide and neurohormonal activation in heart failure

Neurohormonal activation in patients with heart failure reflects a compensatory attempt to restore cardiac output and tissue perfusion in the short-term. Several neurohormonal processes work simultaneously to increase cardiac contractility, vascular resistance, and renal sodium retention. Important mechanisms include upregulation of the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS) (Cohn 1997). Activation of the sympathetic nervous system leads to peripheral and pulmonary venoconstriction and vasoconstriction, and initially helps to maintain ventricular preload and blood pressure (Francis et al. 1984). In the long run, the increase in left ventricular afterload induced by chronic sympathetic activation accelerates deterioration of myocardial function and promotes adverse myocardial remodelling. Not surprisingly, the degree of sympathetic activation as measured by plasma norepinephrine concentration has been shown to be inversely proportional to survival (Cohn et al. 1984). Similarly, activation of the RAAS in heart failure promotes sodium reabsorption, systemic and renal vasocon-

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striction, and pathological ventricular remodeling (Dzau 1993). Other neurohormones that contribute to vasoconstriction include endothelin and vasopressin (Cohn 1997).

As a response to volume expansion due to sodium retention, natriuretic peptides are secreted and contribute to suppression of the RAAS and, in turn, to increased urinary sodium excretion (Cogan 1990). Atrial natriuretic peptide (ANP) is secreted predominantly from the atria in response to atrial stretch in the normal population and to heart failure. In more advanced heart failure, both ANP and brain natriuretic peptide (BNP) are released from ventricular cells in response to increased filling pressures in the ventricle (Yoshimura et al. 2001) (Fig. 1). In this review, the specific physiological effects and patterns of secretion of ANP and the diagnostic and prognostic value of serum ANP levels will be examined.

Atrial natriuretic peptide: secretion patterns and pathophysiological effects

Atrial natriuretic peptide derives from a prohormone which is cleaved into the biologically active form (ANP), and an inactive amino terminal fragment (NT-proANP) (Morgenthaler et al. 2004). The active form has several physiological and pathophysiological effects. These include peripheral vasodilation (and in turn, blood-pressure-lowering), natriuresis, diuresis, and inhibition of cardiac hypertrophy (Yasue et al. 1994). The natriuretic peptides are unique in their ability to reduce cardiac preload without inducing a reflex tachycardia (Suttner and Boldt 2004). This is mediated by suppression of sympathetic outflow from the central nervous system, and a resultant decrease in the release of catecholamines from the autonomic nerve endings. In the kidneys, this reduces the sympathetic nervous system drive to the juxtaglomerular cells, and in turn, renin release (Suttner and Boldt 2004). One mechanism by which ANP promotes natriuresis and diuresis is via its effect on renal hemodynamics. Natriuretic peptides can increase filtration fraction and augment natriuresis even before changes in glomerular filtration rate (GFR) can be detected. In addition, ANP is thought to increase GFR, (ie. the flow rate of filtered fluid through the kidney) by causing afferent renal arteriolar dilatation and efferent arteriolar constriction (Weidmann et al. 1986). Circulating ANP reduces sodium and water resorption by inhibiting renin secretion in the kidney, aldosterone synthesis in the adrenal cortex and in cardiac tissue, ADH-mediated water retention, and angiotensin II-induced sodium retention (Yoshimura et al. 2001) (Fig. 2).

The pattern of secretion of ANP has been shown to correlate with left ventricular dysfunction and end diastolic pressure. Yasue et al. (1994) showed that the ratio of ANP released from the heart as a whole was proportional to the pulmonary capillary wedge pressure and left ventricular end diastolic pressure. Furthermore, unlike in normal subjects where ANP is released mainly from the atria, amounts of ANP released from the left ventricle had a significant positive correlation with the severity of left ventricular dysfunction (Yasue et al. 1994). Yoshimura et al. (1993) demonstrated that measured plasma levels of ANP and BNP vary with underlying cardiac disorders of CHF. Plasma levels of ANP and BNP were measured in the aorta during cardiac catheterization in 20 subjects with mitral stenosis (MS) (predominant atrial overlaod), 30 subjects with dilated cardiomyopathy (DCM) (both atrial and ventricular overload), and 20 control subjects. The investigators found that the plasma ANP level was significantly greater in the MS and DCM groups compared with the control groups, while the plasma BNP level was significantly higher in the DCM group than in the MS group. Their results suggest that plasma levels of BNP mainly reflect the extent of ventricular overload, and that the secretion patterns of ANP and BNP vary with different degrees of overload in atria and ventricles (Yoshimura et al. 1993). Furthermore, the concentration of ANP tends to be about 10 to 50 times greater than that of BNP (Mukoyama et al. 1991). Taken together, these observations suggested that ANP may be used as a diagnostic and potentially a prognostic tool for heart failure and other cardiac pathology.

Diagnostic value of atrial natriuretic peptide measurement

A missed or delayed diagnosis of heart failure, particularly in acute settings, is associated with significantly worse prognosis (Maisel et al. 2008). Biomarkers can be a helpful adjunct to clinical history and physical examination for the diagnosis of dyspnea in the clinical setting. Although BNP has proven to be useful in this setting, its use has limitations, particularly when BNP values fall into a "gray zone" of intermediate probability values. Thus, a multimarker approach incorporating both BNP and ANP may be prove to be of incremental value. Given the observation of increased secretion of ANP in various states of atrial and ventricular pressure and volume overload, it is not surprising that recent work has elucidated its utility in the diagnosis of heart failure.

Deiplinger et al. (2009) evaluated several established and novel biomarkers including BNP, midregional pro-A-type natriuretic peptide (MR-proANP), midregional proadrenomedullin (MR-proADM), the C-terminal part of the arginine vasopressin prohormone (copeptin), the soluble isoform of a interleukin-1 receptor family member ST2 (sST2), chromogranin A, and the C-terminal endothelin-1 precursor fragment (CT-proET-1), adiponectin, chromogranin A, proguanylin, and prouroguanylin for the diagnosis of acute decompensated heart failure in 251 patients with shortness of breath presenting to an emergency department (Dieplinger et al. 2009). The reference standard of the diagnosis of acute decompensated heart failure was based on the Framingham score for HF plus echocardiographic evidence of systolic or diastolic dysfunction. Although median plasma concentrations of all measured biomarkers were greater in patients with acute destabilized HF compared with those with dyspnoea owing to other causes, areas under the curve of receiver operating curves for BNP (0.92) and MR-proANP (0.88) were significantly higher (Fig. 3) than the AUCs of the other 8 biomarkers (MR-proADM, 0.75; adiponectin, 0.73; CT-proET-1, 0.72; proguanylin, 0.68; ST2, 0.67; prouroguanylin, 0.62; copeptin, 0.62; and chromogranin A, 0.56). Furthermore, multivariate regression analysis showed that only BNP and MR-proANP concentrations functioned as diagnostic indicators of heart failure independent of clinical variables (age, sex, estimated glomerular filtration rate, history of acute destabilized heart failure, the presence of orthopnoea, paroxys-

Fig. 1. Neurohormonal activation in heart failure. The hemodynamic effects of heart failure lead to counter-regulatory activation of neurohormones including activation of the sympathetic nervous system, the renin–angiotensin–aldosterone system, and increased secretion of the vasoconstrictors, endothelin and vasopressin. These mechanisms initially help to preserve arterial blood pressure and cardiac output. In the long run, however, these mechanisms lead to the deleterious effects of salt and water retention, adverse left ventricular remodelling and dysfunction. In contrast, the natriuretic peptides, including atrial natriuretic peptide, which are also upregulated in heart failure, promote natriuresis, diuresis, and vasodilation. However, the neurohormonal effects of vasodilators tend to be overwhelmed, leading to an imbalance favoring vasoconstriction. Adapted from Cohn 1997. Reproduced with permission, from Cardiology. vol. 88, pp. 2–6. © 2011 S. Karger AG, Basel.

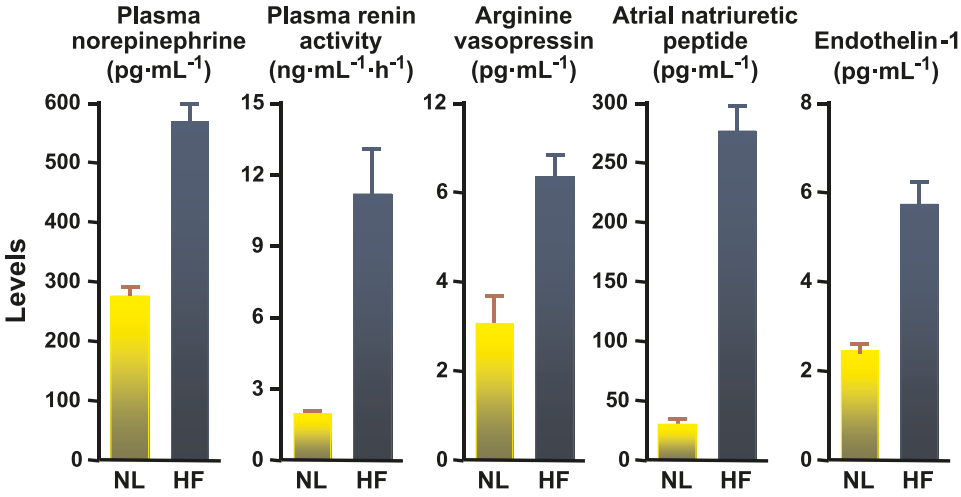
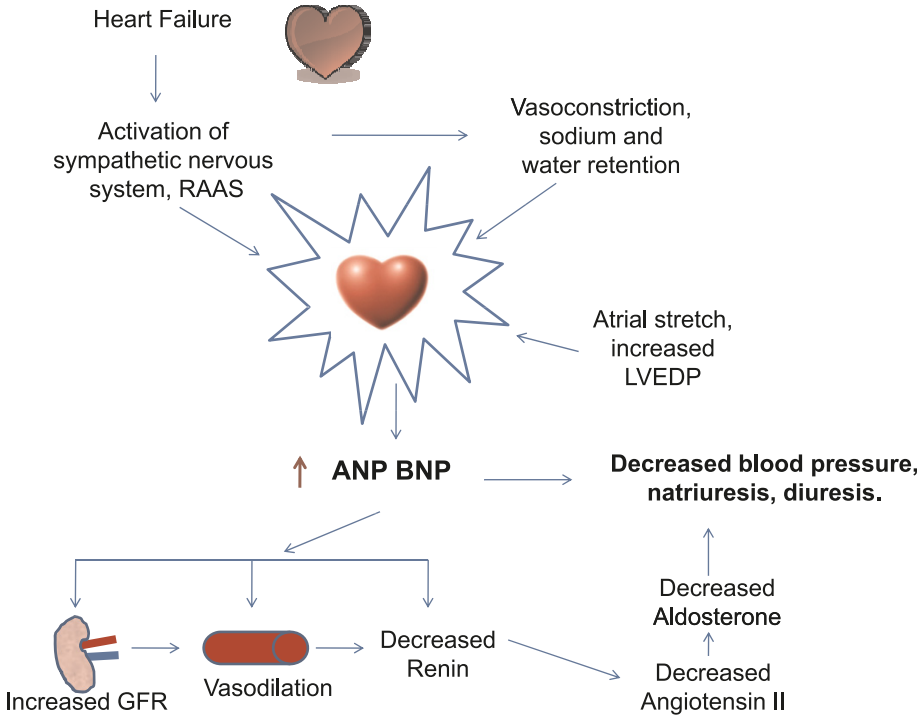


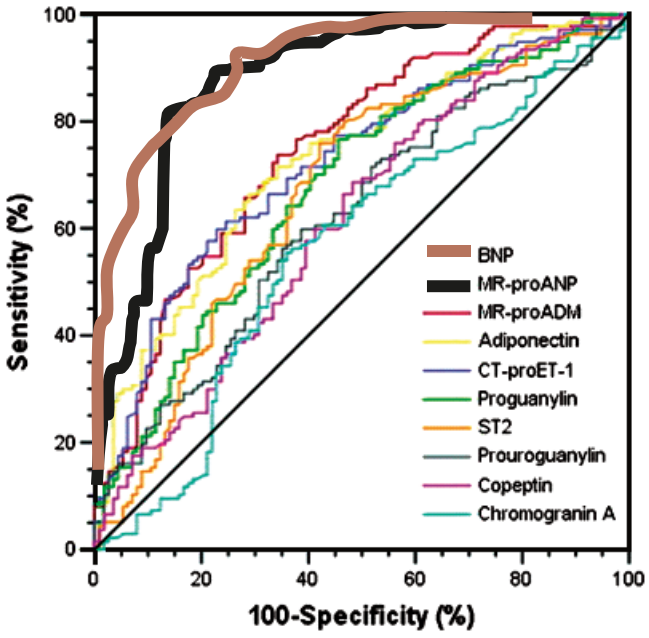
Fig. 2. The role of the natriuretic peptides in the neurohormonal cascade induced by heart failure. RAAS, renin-angiotensin-aldosterone system; LVEDP, left ventricular end diastolic pressure; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; GFR, glomerular filtration rate.



mal nocturnal dyspnoea, nocturnal cough, jugular venous distension, pulmonary rales, third heart sound, and peripheral oedema).

Potocki et al. (2010) showed that the measurement of plasma MR-proANP level may actually provide significant additional information for the diagnosis of heart failure over f BNP or NT-proBNP. The investigators measured levels of plasma MR-proANP in 287 consecutive patients presenting to the emergency departement with dyspnea, and compared the accuracy of plasma MR-proANP for the diagnosis of heart failure with that of plasma N-terminal proBNP. As demonstrated by Deiplinger et al. (2009) plasma MR-proANP had a very high area under the receiver operating curve (0,92). Furthermore, plasma MR-proANP levels added significant incremental diagnostic value in patients with BNP levels in the grey zone between 100 and 500 pg·mL^{-1}. In this

Fig. 3. Receiver operating characteristic (ROC) curves for the biochemical diagnosis of acute destabilized heart failure (HF) by established and novel biomarkers in patients with shortness of breath presenting to the emergency department. In this cohort of 137 patients with dyspnoea attributable to systolic HF or diastolic HF compared with 114 patients with dyspnoea from other causes. areas under the curve of receiver operating curves for BNP (0.92) and MR-proANP (0.88) were significantly higher (Fig. 2) than the AUCs of the other 8 biomarkers. BNP, B-type natriuretic peptide; Copeptin, C-terminal part of the arginine vasopressin prohormone; CT-proET-1, C-terminal endothelin-1 precursor fragment; MR-proADM, midregional proadrenomedullin; MR-proANP, midregional pro-A-type natriuretic peptide; NT-proBNP, amino-terminal proBNP; sST2, soluble isoform of a interleukin-1 receptor family member ST2. From Dieplinger et al. 2009. Reproduced with permission, from Heart, vol. 95, pp. 1508–1513. © 2009, BMJ Publishing Group Ltd., and the British Cardiovascular Society.



subgroup of patients, MR-proANP was added to a logistic regression model with BNP or NTproBNP to predict heart failure, and was found to confer significant additional information (OR for the diagnosis of HF = 8.9, $p = 0.022$ for BNP, and 9.8, $p = 0.042$ for NT proBNP).

The diagnostic utility of MR-proANP in heart failure was recently corroborated by the Biomarkers in Acute Heart Failure (BACH) trial: a large, prospective, multicenter study of 1641 patients presenting to the emergency depeartment with dyspnea (Maisel et al. 2010). The investigators evaluated the diagnostic non-inferiority of MR-proANP for the diagnosis of heart failure in comparison with BNP. The gold standard for heart failure diagnosis was its diagnosis by 2 independent cardiologists. MR-proANP proved to be non-inferior (sensitivity 97.0%, specificity 59.9%, accuracy 72.7%) to BNP (sensitivity 95.6%, specificity 61.9%, and accuracy 73.6%), $p < 0.001$ for non-inferiority for the diagnosis of heart failure. Furthermore, MR-proANP levels added to the utility of BNP levels in patients with intermediate BNP values and patients with obesity. Specifically, they showed that in patients with a BNP value of > 100 pg·mL^{-1}, but < 500 mg·mL^{-1}, the addition of MR-proANP conferred an odds ratio of 5.7 for the diagnosis of heart failure. Thus, when the clinical picture and BNP levels are consistent with an intermediate likelihood for the diagnosis of heart failure in a patient with dyspnea, an elevated MR-proANP suggests that heart failure is much more likely to be causing or at least to be contributing to the patient's clinical picture. This, in turn, may guide follow-up investigations and therapy.

As shown in these last 2 studies, MR-proANP may not just be as useful as BNP in the diagnosis of heart failure, but may prove to be a crucial player in the diagnosis of dyspnea in the difficult subgroup of patients who fall into the intermediate BNP "grey zone" category.

Prognostic value of atrial natriuretic peptide measurement

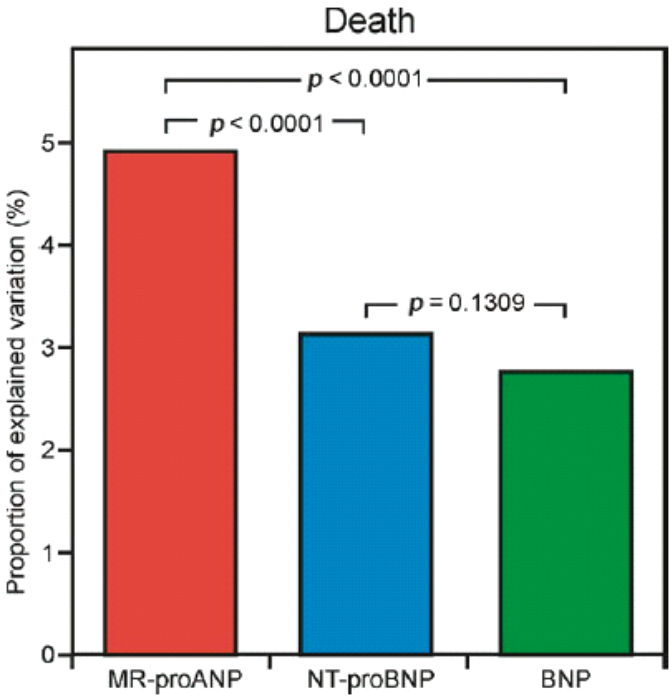
Determining prognosis in both acute and chronic heart failure settings has important clinical implications, including assisting the clinician and the patient with implementation of therapeutic interventions and, in some circumstances, appropriate preparation for end-of-life care. A mounting amount of evidence indicates that measurement of plasma MR-proANP in patients with heart failure affords reliable prognostic information.

Gegenhuber et al. (2007) compared the capability of MR-proANP to prognosticate 1-year all-cause mortality to that of BNP in 137 patients presenting to the emergency department with acute decompensated heart failure. Receiver operating curve analysis demonstrated that the areas under curve for the prediction of 1-year mortality for BNP (0.716) and MR-proANP (0.725) were similar. Kaplan-Meier analyses stratifying patients into 3 goups according to plasma MR-proANP terciles also showed that the predictive value of MR-proANP is comparable with that of BNP. Finally, multivariate regression analysis showed that an MR-proANP level of > 469 pmol·L^{-1} conferred a risk ratio of 2.71 ($p = 0.003$) for 1-year mortality.

Recent data (Moertl et al. 2009) also points to the utility of MR-proANP in the prediction of death in patients with *chronic* heart failure. Moertl et al. (2009) compared the performance of MR-proANP with that of NT-proBNP and BNP for the prediction of death in 797 patients with chronic heart failure due to systolic dysfunction (Fig. 4). Multiple Cox regression analysis showed that NT-prANP was a significantly stronger predictor of death than either BNP or NT-proBNP ($p < 0.0001$). The investigators postulate that the prognostic superiority of MR-proANP may be attributable to the higher biological stability of the molecule and the fact that it has been shown to be more robust against variability due to physical activity than BNP and NT-proBNP variability.

Thus, MR-proANP measurement has value comparable with BNP and NT-proBNP in prognostication in patients with acute decompensated heart failure and, as showed in one study, may be better than the latter 2 in predicting mortality in chronic heart failure. Further, prospective, comparative studies are required to confirm these findings and to clarify the value of MR-proANP measurement over and above current biomarker assays (Troponin, BNP, and NT-proBNP) used in clinical practice. Importantly, it will be important to establish whether measurement of MR-proANP contributes to improved patient outcomes.

Fig. 4. Relative importance of MR-proANP, NT-proBNP, and BNP to predict death as expressed by the partial proportion of explained variation in patients with chronic heart failure. In this study, MR-proANP was a significantly stronger predictor of death than NT-proBNP and BNP. MR-proANP, pro-atrial natriuretic peptide; BNP, B-type natriuretic peptide; NT-proBNP, amino-terminal pro–B-type natriuretic peptide. Adapted from Moertl et al. 2009. Reproduced with permission, from the Journal of the American College of Cardiologists, vol. 53, pp. 1783–1790. © 2009 Elsevier.



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