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B-type natriuretic peptide: Is there a place in the critical care setting?

Anthony S. McLean, Stephen J. Huang, Iris Ting

Abstract

B-type natriuretic peptide (BNP) is a 32 amino-acids peptide that is synthesized and released predominantly from the ventricular myocardium. The triggers for BNP release are increased ventricular preload and/or afterload. Circulating BNP possesses several physiological activities including vasodilation, inhibition of the renin-angiotensin-aldosterone system (RAAS), inhibition of sympathetic nervous activity as well as promoting natriuresis and diuresis. Together these activities not only counteract the deleterious effects of the RAAS and sympathetic system in heart failure but also reduce the ventricular preload and afterload. The potential therapeutic effect of BNP was tested when a recombinant hBNP (nesiritide) was released. The outcomes of nesiritide therapy in heart failure have so far been positive. BNP has also been promoted as a diagnostic tool for cardiac failure. Given the wide range of cardiac diseases encountered in the intensive care setting, and the recent observations that BNP levels could be affected by age and gender, its use as a diagnostic tool for cardiac dysfunction in this particular setting should however be cautioned. Nevertheless, this should not discourage the use of BNP in the intensive care unit, in particularly the potential use of nesiritide in acute heart failure and the use of plasma BNP as an index in guided therapy.

Keywords: B-type natriuretic peptide, Intensive Care Unit, Cardiac dysfunction

Introduction

Brain natriuretic peptide (BNP) is a member of the natriuretic peptide family which also include atrial natriuretic peptide (ANP), C-type natriuretic peptide (CNP) and urodilatin. It was first isolated from porcine brain and subsequently found in human brain, heart and other organ [1-5]. Although it is secreted by both atrial and ventricular myocytes, the ventricles are the predominant site of synthesis and secretion in human. The misleading nature of the nomenclature leads to the adoption of the new name - *B-type natriuretic peptide*, which reflects the current view of it as a cardiovascular and not a neural factor.

When first secreted, BNP is a 108 amino acid precursor protein (pro-BNP). Pro-BNP is cleaved into the biologically active 32 amino acids carboxyl-terminal peptide (BNP), and a 76 amino acid amino-terminal fragment (N-terminal BNP). BNP contains a 17 amino acid ring structure which is common to all the natriuretic peptides and is highly conserved in the family. This ring structure is necessary for the binding to its receptors (**Figure 1**). The BNP gene contains the destabilizing

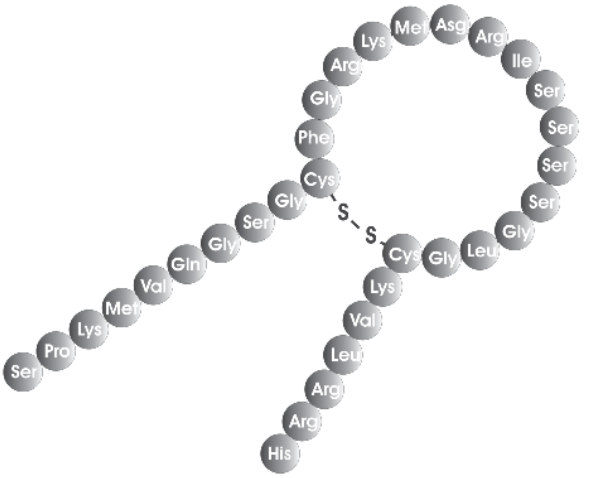

FIGURE 1. STRUCTURE OF BNP.

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TATTTAT*f* sequence, suggesting a high turnover rate of the BNP mRNA, and spontaneous synthesis of BNP, in response to physiological stimuli. This gene sequence also implies rapid degradation of the mRNA after the loss of stimuli [6].

Physiology

Physiologic effects

The main physiological stimuli for BNP secretion is volume expansion and pressure overload of the ventricles [7, 8]. In contrast to ANP, where secretion is effected by exocytosis of storage granules, the secretion of BNP is controlled at the transcription level in response to the stimuli. Once secreted and cleaved into the active form, BNP binds to the natriuretic peptide receptor A (NPR-A) and natriuretic peptide receptor B (NPR-B) [9]. These receptors are coupled to guanylate cyclase, via a protein kinase moiety, and lead to the formation of the second messenger cyclic guanosine monophosphate (cGMP). A NPR-C type receptor is also present on cell surface but is believed to be responsible for the clearance of the natriuretic peptides (**Figure 2**) [10].

BNP plays an important role in the maintenance of circulatory homeostasis and serves to protect the cardiovascular system from volume overload. This is brought forth mainly by vasodilation (including both venous and arterial trees) and promoting natriuresis and diuresis (**Figure 3**). BNP has been recognized to be one of the protective mediators against the deleterious effects of prolonged activation of the renin-angiotensin-aldosterone system (RAAS), partly due to its inhibitory actions on renin or aldosterone release [11,12]. The inhibition of the endothelin and noradrenaline may also contribute to a favourable hemodynamic response [13]. The release of BNP has been shown to be associated with an improvement in cardiovascular hemodynamics, including reductions in both cardiac preload and systemic vascular resistance, which occur without an associated reflex tachycardia [14]. The resulting vasodilatory effect has been shown to be beneficial to the coronary circulation, and may improve oxygen supply to the myocardium [15].

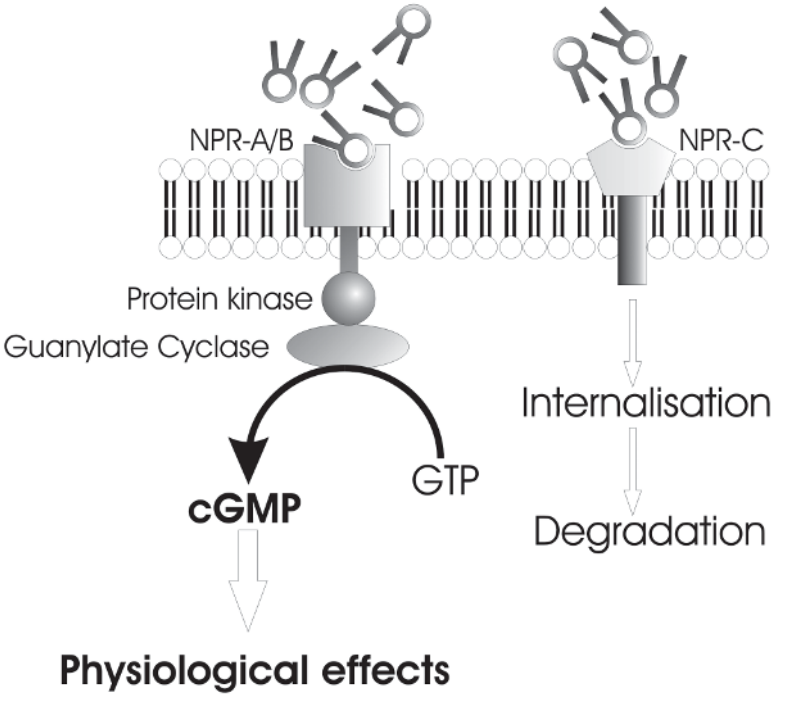

Figure 2. Signal transduction pathway for BNP. *BNP binds either to the natriuretic peptide type A or type B receptor (NPR-A/B) and activates the guanylate cyclase which in turn catalyses the conversion of GTP to cyclic GMP (cGMP). BNP clearance is effected by binding to the type C (NPR-C) receptor, which leads to internalisation and degradation of the peptide.*

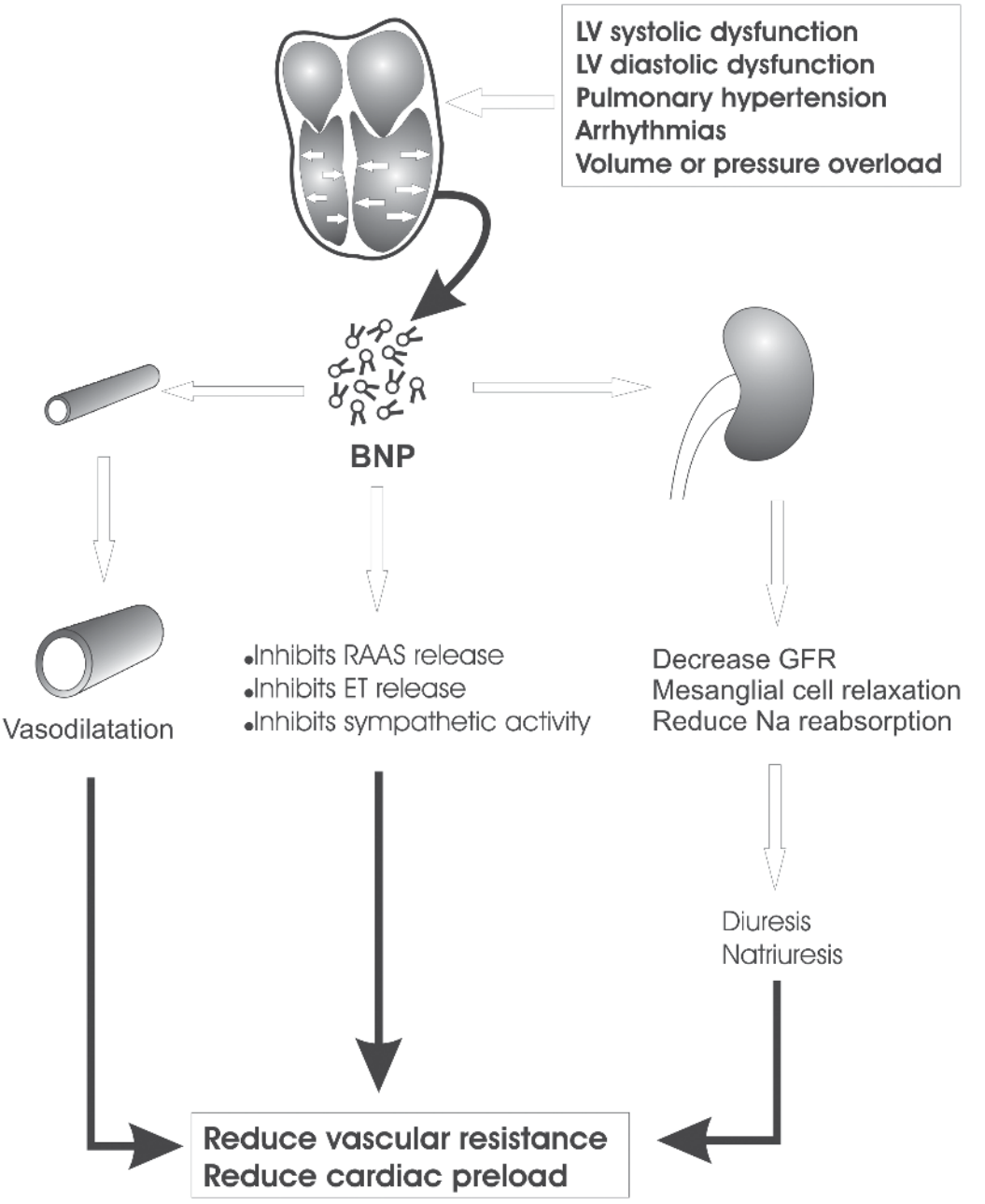

FIGURE 3. ACTIONS OF BNP. *IN RESPONSE TO CARDIAC STRESSES, THE VENTRICULAR MYOCARDIUM SYNTHESIZES AND SECRETES BNP. BNP CAUSES (A) VASODILATATION; (B) INHIBITION OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS), ENDOTHELIN-1 (ET) RELEASE AND THE SYMPATHETIC SYSTEM; AND (C) PROMOTION OF DIURESIS AND NATRIURESIS. AS A RESULT, THE VASCULAR RESISTANCE AND CARDIAC PRELOAD IS REDUCED.*

Neurohumoral maladaptation in heart failure and BNP

The low output state of heart failure (HF) leads to the adaptive activation of the RAAS and the sympathetic nervous system. Although the activation of both systems help providing a short term favourable haemodynamic response in these patients, their activations unfortunately also promote the symptoms and progression of the disease. Tachycardia, increased peripheral resistance, and

volume overload are common amongst the HF population and are due in part to the activation of the RAAS and the sympathetic system. Other deleterious effects include rendering patients refractory to diuretics as a result of angiotensin II-induced increased Na^+ reabsorption, down regulation of cardiac β_1-adrenoceptor which leads to reduced contractility, tachycardia-induced cardiomyopathy, and myocardial remodeling [16-18]. Numerous studies have shown that blocking of the RAAS and the sympathetic effects by angiotensin-converting enzymes inhibitors and by β-blockers, respectively, are accompanied by an improvement in clinical outcomes in HF patients [19, 20].

It is now believed that the activation of the natriuretic peptide systems (ANP and BNP) is an intrinsic mechanism to counter-regulate the maladaptive response of the RAAS and sympathetic system. This notion is supported by studies which demonstrate that natriuretic peptide antagonism promotes RAAS activation and Na^+ retention [21]. A recent animal model study also demonstrated inhibition of natriuretic peptide degradation improves renal hemodynamic and tubular responses, whereas administration of a natriuretic peptide receptor antagonist attenuated such responses in mild HF [22]. The beneficial effects of the natriuretic peptides are partly effected via their abilities to decrease renin release, inhibit endothelin-1 response to angiotensin II, inhibit sympathetic activity and decrease aldosterone production [23-25].

Applications of BNP measurement

BNP as a diagnostic tool

The increased release of BNP in response to cardiac overload stress has encouraged the use of BNP as a diagnostic tool of heart failure. Such application of BNP was made possible with the release of a commercial portable BNP meter, which provides results within 20 minutes [26]. The use of BNP in the diagnosis of heart failure has been proven to be useful in the outpatient as well as in the emergency settings [27, 28]. BNP levels were found to be proportional to New York Heart Association class [28]. In the Breathing Not Properly (BNP) study, which was conducted in the emergency setting, it was found using a plasma BNP cutoff of 100 pg/ml yielded a sensitivity of 90% and a specificity of 76% in diagnosing of heart failure [29]. It has also been demonstrated that BNP was significantly more accurate than clinical judgement and traditional diagnostic methods in identifying HF patients [30]. BNP has also been used for the diagnosis of left ventricular hypertrophy and diastolic dysfunction [31-33].

BNP has also been found to be increased in the intensive care setting [34]. The mean plasma BNP concentration is found to be higher in the intensive care patients than the normal population. The BNP concentration is significantly higher in patients with cardiac dysfunction (**Figure 4**). At a cutoff value at 144 pg/ml, BNP offers a 92% sensitivity and 86% specificity in predict-

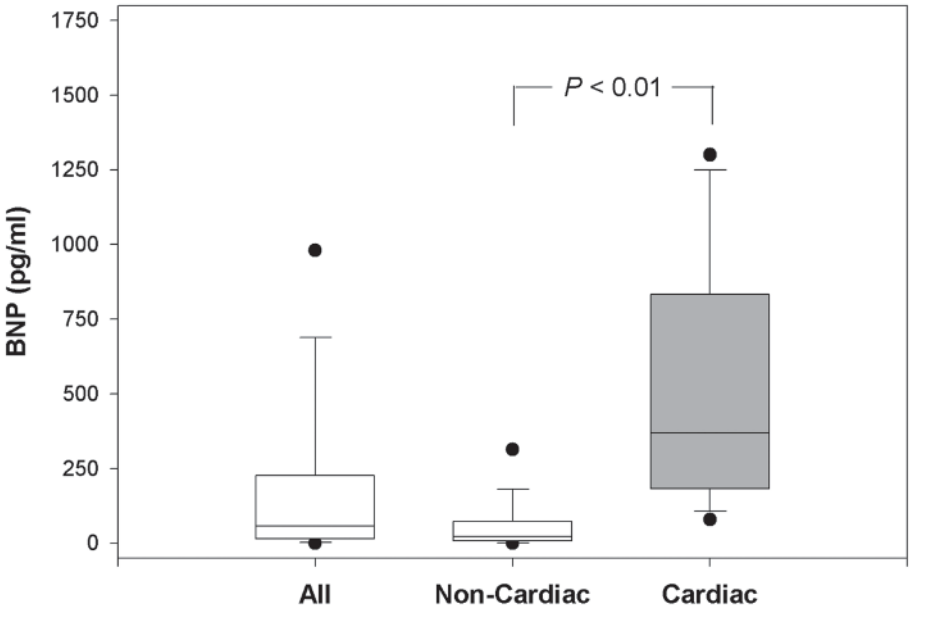

FIGURE 4. DIFFERENCES IN THE BNP LEVELS IN INTENSIVE CARE PATIENTS WITH AND WITHOUT CARDIAC DYSFUNCTION (N = 121).

ing the presence of cardiac dysfunction. Of note, BNP is increased in a variety of cardiac abnormalities and may include left ventricular systolic and/or diastolic dysfunction, hypertrophy, right ventricular volume or pressure overload, arrhythmias and valvular lesions. As there are substantial overlaps of plasma BNP concentrations between different classes of cardiac abnormality, the attempt to use BNP to diagnose and differentiate different types of cardiac abnormality will be futile in the intensive care settings. Instead, an increased BNP concentration should alert the intensivist and initiate further cardiac investigations, such as echocardiography.

Plasma BNP concentration is found to be affected by other confounding factors, the most important ones appear to be age and gender, which together can account for 30% of the variations in BNP concentrations [35]. A positive correlation is seen with age and is higher in female than in male. The cutoffs for male and female are 100 pg/ml and 200 pg/ml, respectively, for diagnosis of cardiac abnormality. The results imply that different cutoffs may be required for different age group. However, the findings do not preclude the use of BNP as a guide for therapy or monitoring cardiovascular progress in patients.

Other sources or conditions are claimed to be responsible for an increase in plasma BNP in some situations, for example in brain disorders/injury (*e.g.* subarachnoid haemorrhage) and renal failure, which are common in the intensive care setting. An earlier study involving surgical critical care patients showed that brain disorder patients exhibited higher BNP levels and speculated that this was due to the release of BNP from damaged brain cells [36]. However, it is now known that although BNP is expressed in the brain, the level of gene transcripts are at least 1 to 2 orders of magnitude less than the cardiac ventricles and makes if fairly impossible to sustain the high plasma BNP concentrations observed [37]. Other studies instead support the notion that BNP was mainly of cardiac origin as a results of brain injury-induced myocardial depression [38-40].

BNP levels are often elevated in chronic renal failure [41]. Although it is believed that such increase is due to decreased renal clearance, so far there is no direct evidence available to prove the notion. On the other hand, the lack of correlation between BNP and creatinine in non-cardiac intensive care patients suggests strongly that renal clearance plays a minor role, if any, in elevating plasma BNP levels [35]. Further, BNP levels are only elevated in renal failure patients with cardiac dysfunction [35,42,43]. These results suggest that the elevation of BNP level in renal disease is, at least in part, mediated via its effect on the cardiovascular system. For example, renal dysfunction may lead to LV hypertrophy and eventually to LV diastolic dysfunction, both of which are capable of increasing BNP concentration.

BNP as a marker for guided therapy

BNP is known to fall rapidly on treatment of patients with heart failure [44]. Although preliminary data have suggested that treatment with vasodilator can be titrated against plasma BNP concentrations in patient with mild to moderate heart failure, the monitoring of therapy by measuring BNP level is in fact complicated by the wide variation of BNP concentrations in the patients [45]. This has made the titration to a target plasma level of BNP difficult. That said, the use of BNP as a guide in combined ACE inhibitor-diuretics therapy for symptomatic heart failure has demonstrated some benefits. Fewer cardiovascular events resulted in the group of patients whose treatments were guided by plasma BNP levels [46]. At present, there is insufficient data available to support the use of BNP as a guide in therapy, especially where the target level remains arbitrary. However, rising BNP concentrations should alert the clinician to decompensation.

BNP therapy

Decompensated heart failure (DHF) commonly refers to the worsening of chronic heart failure or exacerbation of heart failure by an acute incident. The clinical presentation of DHF ranges from sudden onset of dyspnoea to cardiogenic shock. Current pharmacological treatment options for DHF include diuretics, vasodilators, and/or inotropic agents. While diuretics and vasodilators may provide effective symptomatic relief, inotropes are required to stabilize the patient and provide short term symptomatic and haemodynamic improvements. The prolonged use of classic inotropes, such as dobutamine, is discouraged due to the long term adverse mortality [47, 48].

Although BNP in elevated in such patients, the concentrations is often not enough to offers the necessary protective effects. Recombinant hBNP (nesiritide) has recently been used to treat DHF with success. In the early phase II trials, nesiritide therapy (intravenous = 24 hours infusion) was associated with dose-dependent reduction in pulmonary capillary wedge pressure, systemic vascular resistance, pulmonary artery pressure and increased cardiac index [49]. Unlike dobutamine, the increase in cardiac index is not associated with tachycardia or proarrhythmias [23, 50, 51]. The outcomes for patients treated with dobutamine, in terms of readmission rate and 6-month mortality, also compare unfavourable

with low-dose nesiritide treatment [52]. Therefore, nesiritide is an effective and safe agent for improving haemodynamic profiles and symptoms in acute DHF patients. Whether or not its use could be extended to more severe form of DHF or other pathology such as sepsis remains to be investigated.

Prediction of future cardiac events

The synthesis and release of BNP is acute in response to cardiac stress. Theoretically, the increase in plasma BNP level should take precedent before any adverse changes in the cardiovascular system. If this is true, then the measurement of BNP in ICU may provide a promising predictive tool for future cardiac events.

Conclusion

BNP is now recognized as a protective agent against the maladaptation of the RAAS and the sympathetic system in heart failure. The latter two systems, if left unchecked, would be deleterious to the patients with cardiovascular overloading. In response to such overloading, the ventricles release BNP which results in vasodilation, natriuresis and diuresis. As a consequence there is a reduction in vascular resistance and cardiac preload. BNP can inhibit the release of vasoconstrictors and aldosterone in addition to inhibiting sympathetic activity which also contribute to its beneficial effects.

Since BNP is specifically elevated in cardiac overloading, its level is proven to be valuable in the diagnosis of cardiac dysfunction. At the reported cutoffs, BNP shows high sensitivity and negative predictive value for diagnostic purpose. A high sensitivity will include patients with probable cardiac dysfunction whereas a high negative predictive value will exclude patients that are unlikely to have underlying cardiac dysfunction. However, the fact that BNP is increased in diverse pathophysiological conditions precludes its application in discriminating different cardiac pathology. Further, the presence of other confounders, especially age and gender, has made the choice of BNP cutoff difficult. Therefore, BNP measurement should not be used in replace of formal cardiac assessments or in isolation from the clinical context.

The prompt change in plasma BNP levels in response to cardiac overload stress renders it a *thermometer* that reflects the *á la mode* cardiovascular condition. The potential of BNP as a marker for guided therapy in ICU setting deserve further investigations. Although preliminary results are promising, the great variability of baseline BNP levels amongst the patients remains an obstacle before BNP can be used as a guide for therapy.

Given the relative low cost and less time-consuming of BNP measurement, compared to other methods of cardiac assessments, it is a most convenient and cost-effective tool for screening cardiac dysfunction. However, BNP measurement interpretation should not be taken out from the clinical context.

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