Clinical Implications of Defective B-Type Natriuretic Peptide

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ABSTRACT

Our understanding of the natriuretic peptide system continues to evolve rapidly. B-type natriuretic peptide (BNP), originally thought to be a simple volume-regulating hormone that is produced in response to cardiac stretch, has been shown to also play important roles in modulating bronchodilation, endothelial function, and cardiac remodeling. Recent data demonstrate that elevated levels of BNP in patients with heart failure do not represent a simple ratcheting up of normal production in response to increased stimulus. Instead, we now know that chronic stimulation of BNP synthesis induces a reversion to fetal gene expression, resulting in production of high molecular weight forms of BNP that are functionally deficient. Standard point-of-care BNP assays are immunoassays that will detect any molecule containing the target epitopes. Consequently, these assays cannot distinguish between defective, high molecular weight forms of BNP and normal, physiologically active BNP. In 2 separate evaluations, mass spectroscopy detected little, if any, normal BNP in patients with heart failure, despite the appearance of high circulating levels of immunoreactive BNP (iBNP) using commercial assays. Therefore, these commercial assays should be considered to be only an indication of myocardial stress. They do not measure physiologic BNP activity. This accounts for the "BNP paradox," namely, that administration of exogenous recombinant human BNP (rhBNP, nesiritide) has substantial clinical and hemodynamic impact in the presence of high levels of circulating iBNP using commercial assays. In addition to its short-term hemodynamic impact, rhBNP may have other important effects in this setting, and further investigation is warranted.

Introduction

Over the past decade, our understanding of both atrial, or A-type, and B-type natriuretic peptides (ANP/BNP) has expanded rapidly. These peptides, discovered nearly a quarter century ago, are no longer seen as simply volume-regulating atrial and ventricular hormones.[1] They play important roles in a wide variety of physiologic states where, in addition to volume regulation, they influence endothelial function, cardiac ischemia, and myocardial remodeling.[1]

During early cardiac development, both atrial and ventricular tissue produce natriuretic peptides and this production is a marker for the formation of working myocardium.[2] Shortly after birth, however, ventricular production of natriuretic peptides ceases and the atria become the primary source for both ANP and BNP.[2] Under normal circumstances, release of these peptides occurs almost instantaneously in response to atrial muscle stretch. Data from patients with cardiac tamponade confirms that stretch, not increased intracardiac pressure, is responsible for this release.[2]

This normal physiologic response, however, is altered in patients with prolonged hemodynamic overload. Both chronic hypertension and heart failure stimulate changes in ventricular myocytes that cause a reversion toward fetal gene expression.[3] As a result, ventricular production of fetal isoforms of myosin and natriuretic peptides increase dramatically.[1] We originally believed that the increased levels of BNP measured in clinical heart failure represented a simple ratcheting up of normal production. However, nothing could be farther from the truth. Recent data demonstrates that this reversion to ventricular production results in BNP that is both structurally altered and functionally deficient.[4–9] This article considers the clinical implications of this defective production and offers a potential rational basis for the administration of exogenous recombinant human BNP (rhBNP, Nesiritide) in decompensated heart failure patients.

Activity of BNP

B-type natriuretic peptide has a very diverse physiologic profile that, in addition to volume regulation, includes modulation of cardiac hypertrophy and fibrosis, antiproliferative activity, endothelin inhibition, vasodilation, bronchodilation, and sympathoinhibitory effects (Figure 1).[10] These later responses may be as, if not more, important than the role of BNP as a volume regulator.

Aldosterone is a potent stimulus for myocardial fibrosis. B-type natriuretic peptide has been shown to inhibit

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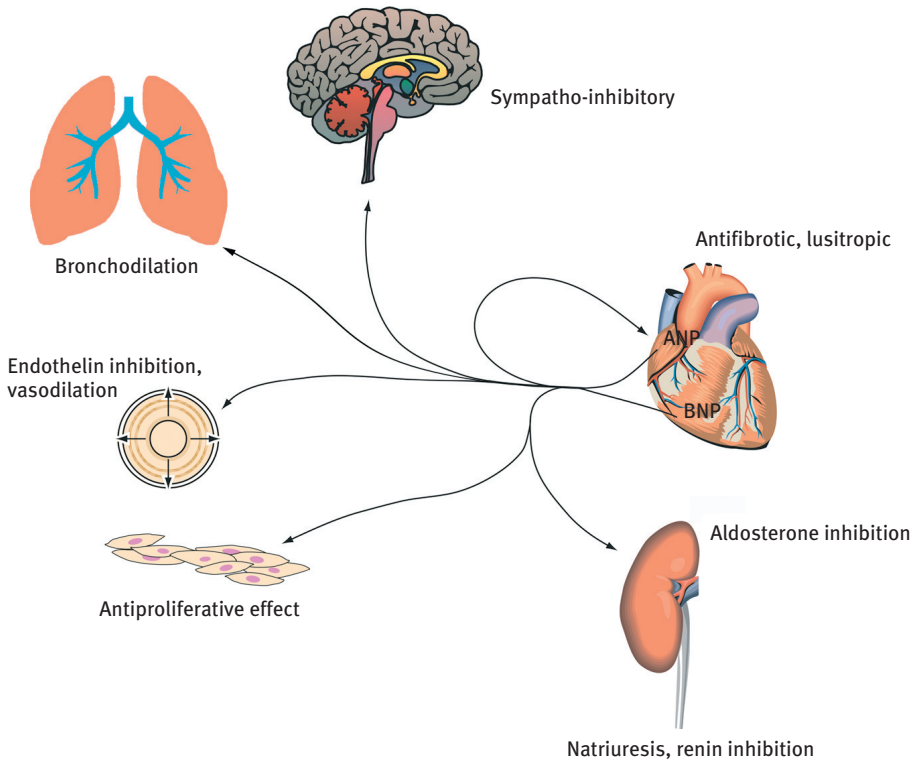

Figure 1. Physiologic activity of B-type natriuretic peptide (BNP). Adapted with permission from John C. Burnett and Informa Healthcare.[10]

aldosterone secretion in primary human adrenal cortex cells, in experimental heart failure, and in clinical heart failure, indirectly curtailing myocardial fibrosis.[11–13] However, recent data demonstrates that ANP and BNP also have direct effects on cardiac hypertrophy and fibrosis. Peaks in natriuretic peptide production occur concurrently with significant events in cardiac organogenesis, suggesting that ANP and BNP play an important role in this development.[5] In tissue culture studies using primary human cardiac fibroblasts, BNP inhibited expression of several profibrotic genes including collagen 1, fibronectin, and connective tissue growth factor in response to transforming growth factor-β.[14] This suggests that at least some antifibrotic effects of BNP are mediated by direct actions on cardiac fibroblasts. In a canine model, Tsuruda et al showed that cardiac fibroblasts produced BNP that inhibited collagen synthesis and stimulated collagen breakdown through the production of matrix metalloproteases.[15] Likewise, murine knockout models have shown that absence of the natriuretic peptide receptor A (NPRA) gene is associated with marked cardiac hypertrophy and fibrosis with impaired diastolic relaxation.[5] Human trials have now confirmed these animal findings. In an early randomized evaluation of patients presenting with a first anterior acute myocardial infarction, ANP infusion was more effective than nitroglycerin in preventing adverse ventricular remodeling.[16] Similarly, in the Japan working group studies on acute myocardial infarction for the reduction of necrotic damage by human ANP or nicorandil (J-WIND), patients who received ANP had significantly lower infarct size, fewer reperfusion injuries, and better outcomes.[17] A recent abstract from the BNP and post myocardial infarction: left ventricular remodeling (BELIEVE) trial demonstrated a similar beneficial effect with nesiritide (rhBNP) infusions.[18]

Defective BNP

These beneficial effects require natriuretic peptides that are structurally and functionally normal. However, chronic overstimulation of BNP production produces consistent, predictable malfunctions in the generation of this peptide that diminishes these effects.

B-type natriuretic peptide is synthesized as a 134-amino acid pre-prohormone that is subsequently processed into a 108-amino acid prohormone (proBNP).[1,19] Under normal conditions, proBNP is then cleaved, perhaps by corin, into the 32-amino acid, biologically-active peptide and a 76-amino acid, nonbiologically active N-terminal chain (NT-proBNP). Analyses of plasma taken from patients with heart failure, however, demonstrate predominantly

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high molecular weight forms of BNP with little, if any, normal 32-amino acid peptide.[8,19,20] In one evaluation, Western blot analysis identified high molecular BNP as the predominating form of the peptide in plasma samples from 4 out of 5 patients with heart failure.[8] In another, nano-liquid chromatography electrospray ionization Fourier transform ion cyclotron resonance mass spectroscopy did not detect any endogenous 32-amino acid BNP in plasma samples from 4 patients with severe heart failure despite the appearance of high levels of circulating BNP utilizing a standard commercial assay (Triage BNP assay, Biosite, San Diego, CA).[19] Similarly, in 12 patients with heart failure, plasma concentration of endogenous 32-amino acid BNP was undetectable in 1 and ranged from 25 pg/mL to 43 pg/mL in the remaining 11 using matrix-assisted laser desorption/ionization time-of-flight mass spectroscopy despite parallel BNP concentrations ranging from 900 pg/mL to 5000 pg/mL using the Triage BNP assay (U.S., unpublished data, 2007).

In contrast to the normal peptide, these high molecular weight forms of BNP have reduced biologic activity. In one evaluation, high molecular weight BNP was 6-fold to 8-fold less potent than normal BNP in stimulating cyclic guanosine monophosphate (cGMP) production in human endothelial and smooth muscle cells[8] while in another, the cGMP response to high molecular weight BNP in human cardiac fibroblasts and myocytes did not differ significantly from that of no treatment.[7]

Commercial BNP Assays

The standard commercial BNP assays are immunoassays that will detect any molecule containing their target epitopes. They are not specific for any individual peptide. In one evaluation, neither the Triage BNP assay nor the Advia Centaur BNP test (Bayer Diagnostics, Tarrytown, NY) could discriminate between normal 32-amino acid BNP and high molecular weight proBNP (Figure 2)[8] and in another, the Elecsys NT-proBNP assay (Roche Diagnostics, Indianapolis, IN), could not distinguish between the 76-amino acid NT-proBNP molecule and the 108-amino acid proBNP molecule.[7]

As a result, these assays provide a measure of the amount of immunoreactive BNP (iBNP) present. They do not assess functional activity. This concept is crucial in explaining the apparent BNP paradox; namely, why does administration of exogenous rhBNP produce significant clinical and hemodynamic effects in patients who already have high circulating levels of endogenous BNP? High circulating levels of iBNP indicate myocardial stress, but the BNP produced in response to this stimulus is typically defective, minimally active, high molecular weight peptide instead of the normal peptide. In this setting, administration of exogenous rhBNP provides the normal, fully functional, 32-amino acid peptide.

Nesiritide or Exogenous rhBNP

Therapeutic administration of nesiritide, or exogenous rhBNP, should be governed by appropriate indications and safety vs efficacy considerations. Similar to other neurohormonal blocking agents, nesiritide administration may be associated with an increased risk of acute serum creatinine elevation.[21,22] In 2005, questions were raised about the impact of nesiritide therapy on renal function and on mortality risk.[23] However, more recent prospective randomized trial data, as well as a new retrospective analysis, make this an unlikely scenario. Administration of nesiritide over a 12-week period was not associated with an increased risk of renal adverse events in either of the Follow-up Serial Infusions of Nesiritide (FUSION) trials, although these trials were conducted in chronic, not acute, heart failure patients.[24,25] In the FUSION I trial, the subset of patients with renal insufficiency at baseline, showed

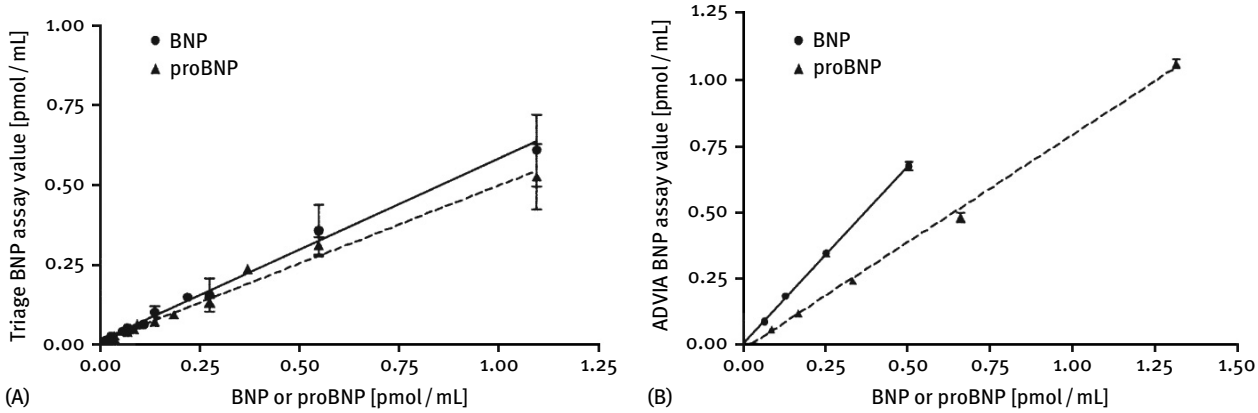

Figure 2. Failure of the Triage (A) and Advia (B) assays to distinguish between normal 32-amino acid B-type natriuretic peptide (BNP) and a high molecular weight precursor (proBNP). Reprinted with permission from Andrew P. Protter and Elsevier.[8]

a trend toward decreased mortality, although the comparator group received positive inotropes.[26] In heart failure patients undergoing on-pump coronary bypass graft surgery (with or without mitral valve procedures) administration of nesiritide was associated with significant attenuation of postoperative renal dysfunction in the Nesiritide Administered Peri-Anesthesia (NAPA) trial.[27] Furthermore, a recent retrospective analysis of data from the Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) trial, found that nesiritide-associated increases in serum creatinine were strongly associated with concomitant use of high dose diuretics. High dose diuretics, not nesiritide, appeared to account for significantly increased 30-day mortality risks (R.M.M., unpublished data, 2007).

These new data increase the importance of considering all effects of nesiritide when contemplating therapy. In the management of patients with acute decompensated heart failure, the immediate clinical goals are symptom relief and rapid institution of oral maintenance therapy.[28] Extensive clinical trial data have confirmed that administration of nesiritide rapidly improves hemodynamic abnormalities in volume-overloaded patients.[29–31] Improvement in hemodynamics alone, however, may not be sufficient justification for the use of nesiritide in these patients. Clinicians should bear in mind that the severity of dyspnea correlates only moderately with hemodynamic status; producing rapid improvement in heart failure symptoms requires more than simply reducing pulmonary capillary wedge pressure (Figure 3).[31,32]

Although initial evaluations of nesiritide concentrated on hemodynamic effects, more recent studies suggest that other properties may prove to be as, if not more, important than these hemodynamic effects. Elevated pulmonary artery pressure can induce reflex bronchoconstriction, contributing to symptoms of dyspnea[33]; in a small series of cases, nesiritide showed potent bronchodilator activity, comparable to that of a β_2-agonist.[34] Similarly, thirst and cachexia frequently accompany advanced decompensated heart failure and nesiritide appears to relieve thirst and stimulate appetite, potentially contributing to improved volume and nutritional status in these patients.[35] Additionally, nesiritide has been shown to improve myocardial perfusion. In a prospective evaluation of 10 patients undergoing coronary angiography, coronary artery diameter increased by 15% and coronary blood flow increased by 35% (both $P = .007$) following a 30 minute infusion of nesiritide.[36] Finally, nesiritide decreases deleterious myocardial remodeling, one of the major causes of heart failure and its progression. Neurohormones have a direct toxic effect on the myocardium[37] and nesiritide reduces these neurohormones.[24,30] In a small, open-label, randomized evaluation, initiation of low-dose nesiritide infusion (0.006 μ g/kg/min) within 24 hours of anterior myocardial infarction was associated with significant reduction in left ventricular end-systolic volume (65 ± 9 to 45 ± 9 mL/m^2) and significant improvement in left ventricular ejection fraction ($39\% \pm 4\%$ to $53\% \pm 5\%$) at 1 month.[18]

Conclusions

Natriuretic peptides are an essential component of the physiologic response to both cardiac ischemia and myocardial dysfunction. They regulate volume, modulate cardiac

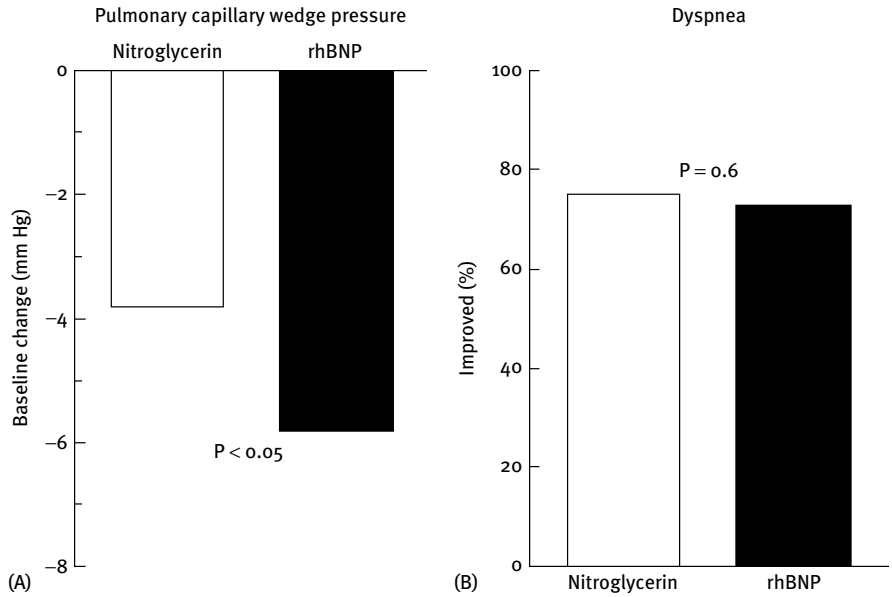

Figure 3. Effect of intravenous nitroglycerin and recombinant human B-type natriuretic peptide (rhBNP) on hemodynamics (A) and symptoms (B) at 3 hours in the Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) trial. Adapted from Publication Committee for the VMAC Investigators.[31]

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hypertrophy and fibrosis, suppress endothelin, and inhibit the renin-angiotensin-aldosterone and sympathetic nervous systems. However, chronic stimulation of natriuretic peptide production leads to synthesis of structurally altered and functionally deficient BNP, diminishing these effects at the time of greatest physiologic need. Commercial point-of-care assays cannot distinguish between normal 32-amino acid BNP and these defective forms, leading to a gross overestimation of the amount of functionally active peptide present. Consequently, BNP levels reflect physiologic need, not biological activity. This fact may help to account for the observed effects of administering exogenous rhBNP as nesiritide in patients who already have high circulating levels of iBNP.

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