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B-TYPE NATRIURETIC PEPTIDE: BEYOND A DIAGNOSTIC

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INTRODUCTION

The concept of the heart as an endocrine organ has been an attractive one since the discovery of atrial natriuretic peptide (ANP) by DeBold in 1979. This review focuses on the second discovered natriuretic peptide from the heart – B-type natriuretic peptide (BNP) – that is widely used as a tool to aid in the diagnosis of heart failure (HF). Yet today controversy remains in regard to its use as a therapeutic agent in HF. Here we will place into perspective some of the debate as well as provide insights into the therapeutics of BNP as well as the importance of its second messenger 3'5' cyclic guanosine monophosphate (cGMP) which is also the second messenger for nitric oxide (NO) and is modulated by renal phosphodiesterases (PDEs) with a special focus on acute decompensated heart failure (ADHF).

ACUTE HEART FAILURE AND CYCLIC GMP BASED VASODILATOR THERAPY IN ACUTE HEART FAILURE AND A VIEW TOWARD THE KIDNEY

In ADHF, increases in cardiac filling pressures with resulting atrial and ventricular stretch results in the release of the natriuretic peptides (NP) both ANP and BNP which activate the particulate guanylyl cyclase (pGC) NP receptor-A (NPR-A) increasing the generation of the second messenger cyclic cGMP and the effector protein kinase G (PKG).⁽¹⁾ It should be noted that NPR-A is also activated by the natriuretic peptide urodilatin that like ANP and BNP is being developed for the treatment of ADHF. Urodilatin is a peptide that is present in urine and is excreted lumenally by the cells of the distal tubular region acting as a paracrine factor in the collecting duct, exerting its suppressing effect on sodium reabsorption by stimulating NPR-A. All three peptides when infused in animals and humans increases sodium and water excretion and in the absence of marked increases in blood pressure may increase in glomerular filtration rate (GFR).^(2,3) The NPs also suppress the renin angiotensin aldosterone system (RAAS), each with different magnitude, being BNP the most efficacious one among the other NPs. In severe experimental or human CHF, a renal hyporesponsiveness is observed to NPs which may be explained by multiple mechanisms which include excessive hypoperfusion to the kidneys and upregulation of phosphodiesterase (PDE) V activity which degrades NP generated cGMP.^(4, 5, 6) Experimental studies disrupting the NP receptors reveal a phenotype characterized by

impaired renal sodium handling and often hypertension which underscores the importance of the NPs in cardiorenal regulation.^(7,8,9)

A hallmark of ADHF is the acute elevation of plasma ANP and BNP. Studies also suggest that as a result of NP stimulation of the endothelium or by a reduction in renal perfusion pressure there may be stimulation of the intrarenal nitric oxide (NO) pathway in which NO stimulates soluble guanylyl cyclase (sGC) localized to the cell cytosol. Soluble guanylyl cyclase (sGC) activates cGMP distinct from the NPs which involves activation of pGC that is membrane bound and linked to the transmembrane NPR-A receptor to which ANP and BNP bind.

In clinical practice, sodium nitroprusside (SNP) and nitroglycerine (NTG) are used for the treatment of ADHF and both are sGC stimulators and potent vasodilators. NTG however may be associated with tolerance and non cGMP adverse actions. (Should we expand here or not?). We recently reported the cardiorenal actions of a novel direct activator of sGC BAY 41-2272 in a model of ADHF and observed potent renal vasodilation without natriuresis and diuresis or changes in GFR although BAY significantly reduced arterial pressure together with cardiac unloading.⁽¹⁰⁾ Importantly, genetic or pharmacologic disruption of the NO/cGMP system also involves alteration of physiological control of cardiorenal function most often characterized by hypertension secondary to systemic and renal vasoconstriction.^(11,12)

What we have learned is that compartmentalization of cGMP signaling occurs especially in the heart in which pGC and sGC have been demonstrated to have distinct roles in cardiomyocyte function.^(13,14) Others have reported that the pGC agonist ANP but not the sGC agonist S-nitroso-L-acetyl penicillamine stimulates the translocation of PKG to the plasma membrane of renal cells augmenting the NPR-A receptor to which ANP, BNP and urodilatin bind.⁽¹⁵⁾ We have concluded that these observations strongly support *in vitro* distinct functional roles for pGC and sGC in the kidney suggesting that NPs like BNP could have different renal actions than NTG or SNP despite both activating the second messenger cGMP.

Therefore what are the roles of the NP/cGMP and NO/cGMP pathways *in vivo* in ADHF in the regulation of renal function? We addressed this question in an experimental model of ADHF. We hypothesized that each pathway would play specific roles in the control of kidney function in ADHF consistent with distinct GC enzymes for each system.⁽¹⁶⁾ These studies revealed distinct roles for these two endogenous cGMP activating systems in ADHF whereby the endogenous NPs play a greater role in the preservation of GFR and sodium excretion while the endogenous NO system was more important in the control of renal blood flow. These studies suggest that the preservation of renal function in experimental ADHF is mediated by dual cGMP systems which activate both pGC and sGC enzymes.

Both NTG and SNP that activate sGC are used as potent vasodilators to unload the heart in ADHF. Such agents are renal vasodilators but may not enhance GFR or sodium excretion. That is the case in experimental ADHF using NTG or a direct sGC activator.⁽¹⁰⁾ An optimal renal therapeutic strategy in ADHF may be the use of non-hypotensive doses of a pGC agonist such as ANP or BNP together with a direct sGC activator. Such a strategy would

then target the glomeruli, the renal vasculature and the renal tubules. Potentiation of this dual cGMP system with a PDE V inhibitor is also an important strategy based on the observation the PDE V inhibition potentiates the renal actions of BNP in experimental CHF.⁽⁶⁾

BNP IN ACUTE DECOMPENSATED HEART FAILURE TO ENHANCE RENAL FUNCTION – IS IT POSSIBLE?

Based upon the renal actions of the endogenous natriuretic peptide / cGMP system in experimental ADHF reviewed above, BNP continues to emerge as an important renal acting vasodilating therapy for human AHF. Supporting such a therapeutic strategy has been work by Marcus et al which reported beneficial renal actions of BNP, specifically increasing sodium excretion in CHF patients.⁽¹⁷⁾ Others have reported a reduced natriuretic response without an increase in GFR in CHF after BNP administration.⁽¹⁸⁾ Also, in the Vasodilation in the Management of Acute Congestive heart failure (VMAC) study, in which BNP was administered in patients with acute CHF, a greater increase in creatinine in those patients receiving BNP was observed, although this subgroup had more severe CHF compared with the NTG groups.⁽¹⁹⁾ Recently, Wang et al also observed reduced renal responses to BNP in patients hospitalized with ADHF as demonstrated by a lack of diuretic response.⁽²⁰⁾ The mechanism of this reduced renal responsiveness may be multifactorial and be related to increased degradation of the peptides, decreased number or reduced affinity of biologic receptors or postreceptor events that lead to reduced production of cGMP, or increased cGMP degradation.

We performed a study to elucidate the actions of type V phosphodiesterase inhibition (PDEVi) in experimental CHF. Here, we also assessed the response to acute subcutaneous BNP in the presence and absence of chronic PDEVi.⁽⁶⁾ It should be noted that PDE V metabolizes cGMP and is abundant in the kidney and vasculature and has also been shown to be present in the heart. In renal disease states such as nephrotic syndrome, it has been demonstrated that PDE V contributes to renal impairment and reduced sensitivity to the natriuretic peptide system. In this recent study there were two groups, one consisting of animals received PDEVi therapy (Sildenafil 50mg orally three times daily for the 10 days of CHF) and the other one consisting of animals that received no PDEVi therapy. Despite having higher cardiac output, there was no improvement of renal function in the PDEVi group after 10 days as compared with the control group. However, the PDEVi group had significantly higher plasma and urinary cGMP than the control group. When acute subcutaneous BNP was administered at day 11, the PDEVi group had a natriuretic and diuretic response associated with an increase in GFR and that was not observed in the control group. Plasma BNP increased to a similar extent in both groups with subcutaneous BNP. In contrast, the PDEVi group had a greater urinary cGMP excretion than the control group. Even though chronic administration of PDEVi therapy did not enhance renal function despite an improvement in cardiac output, PDEVi significantly enhanced the renal hemodynamic and excretory responses to exogenous BNP. This supports the idea that there is a role for PDE V as a contributing factor to renal maladaptation in the setting of experimental overt CHF. Also, this study warrants new clinical trials that can address the

possible strategy of maximizing the renal cGMP system by combined PDEVi and natriuretic peptides therapy in CHF to improve renal function.

RENAL ACTIONS OF BNP IN HEART FAILURE AND CHRONIC RENAL INSUFFICIENCY – WHAT WE ARE LEARNING FROM RECENT HUMAN STUDIES

The recommended dose of nesiritide is a bolus of 2 µg/kg followed by infusion of 0.01 µg/kg/min. Preclinical studies have demonstrated the renal enhancing efforts of systemic intravenous (i.v.) administration of BNP. Yet, as also discussed above the clinical trials that led to the Food and Drug Administration approval of BNP for the management of acute CHF have been conflicting with regards to the renal-enhancing properties of BNP as a meta-analysis of BNP clinical trials suggest that nesiritide may be detrimental to renal function in patients with acute decompensated CHF.⁽²¹⁾ A possible mechanism for the controversy between the preclinical and clinical data could be in part that the dose used in these clinical studies resulted in significant decreases in blood pressure (BP) and hence renal perfusion pressure, attenuating the renal-enhancing effects especially in the setting of pre-existing renal disease. Indeed, in a previous study in experimental CHF, low-dose subcutaneously administered BNP, which did not lower blood pressure, had a more beneficial renal hemodynamic profile than a higher dose that lowered blood pressure.⁽²²⁾

From a clinical perspective, we performed a retrospective analysis of consecutive patients admitted to Mayo Clinic Heart Failure Hospital Service for ADHF who received BNP (nesiritide) at doses lower than the standard dose.⁽²³⁾ In this recent report we identified patients who received 0.005 µg/kg/min and 0.0025 µg/kg/min of nesiritide without bolus. We compared the results with a separate group of patients who received the standard dose of nesiritide (2 µg/kg bolus followed by 0.01 µg/kg/min) and a group of patients who received standard diuretic therapy without nesiritide, matching for ejection fraction and calculated creatinine clearance (CrCl). These studies revealed that the group that received low-dose nesiritide had lower baseline systolic blood pressure (BP) compared with patients who received standard-dose or no nesiritide. Low dose nesiritide had no significant decrease in systolic BP whereas systolic BP decreased with standard-dose and no nesiritide. The low-dose nesiritide group had improved plasma creatinine associated with a decrease in BUN. Renal function as measured by plasma creatinine and BUN did not improve in the standard-dose nesiritide and no-nesiritide groups. Patients in the low-dose nesiritide group received less furosemide compared with the standard-dose nesiritide and no-nesiritide groups while achieving similar diuresis during the i.v. therapy period.

The contributing mechanisms of efficacy of BNP in CHF with low doses are most likely multifactorial. The favorable renal response may in part be due to the fact that systolic BP was not reduced in this group. The significant reduction in systolic BP observed in the standard-nesiritide and no-nesiritide groups may have activated counter-regulatory mechanisms, such as the sympathetic and the RAAS, thus attenuating the renal enhancing properties of nesiritide. Indeed, in a human study by Brunner-La Rocca the sympatho-inhibitory effects of BNP were greatest with low-dose (0.003 µg/kg/min) infusion, which did

not alter hemodynamics, as compared with a higher dose (0.015 µg/kg/min) infusion, which reduced BP.⁽²⁴⁾ Based upon these observations a prospective randomized controlled study is warranted to test the efficacy of non-hypotensive low-dose nesiritide.

Most recently two additional prospective human studies discussed below have been reported in which nesiritide was administered perioperatively for cardiorenal protection at either low dose (0.05 µg/kg/min for 48 hours) or without the bolus in patients undergoing cardiopulmonary bypass surgery with chronic renal disease or with ventricular dysfunction.^(25,26) Both studies demonstrated improved renal function as compared to standard therapy.

A recent multicenter clinical trial, the NAPA trial (Effects of Perioperative Nesiritide in Patients with Left Ventricular Dysfunction Undergoing Cardiac Surgery) showed very interesting results with i.v. BNP infusion (nesiritide) in the setting of coronary artery bypass grafting (CABG) using cardiopulmonary bypass (CPB).⁽²⁵⁾ The NAPA investigators designed a randomized double-blinded and placebo controlled study in order to assess the effects of perioperative administration of nesiritide in heart failure patients undergoing cardiac surgery in terms of clinical outcomes and safety. The patients involved had left ventricular dysfunction with an ejection fraction of less than 40% and were NYHA Class II-IV. Nesiritide infusion (141 patients) was started after induction of anesthesia at a fixed dose of 0.01 µg/kg/min without bolus. The control group received placebo (138 patients). Intravenous infusions continued for a minimum of 24 hours up to a maximum of 96 hours. Mean pulmonary artery pressure decreased 24 hours after surgery in the nesiritide. In terms of renal function, postoperatively there was better preservation of GFR and urine output in the first 24 hours after surgery and this was significantly greater in the nesiritide group. Furthermore, in the nesiritide group fewer patients had a serum creatinine increase of more than 0.5 mg/dL by hospital discharge or study day 14, whichever came first. Important to note, these renal beneficial effects were enhanced in patients with preoperative renal dysfunction. Most importantly, there was a decrease in mortality at 180 days in the nesiritide group compared with placebo. Length of stay at hospital was also reduced in the nesiritide group. This study warrants further and larger population studies on this type of patients in this setting or in CHF. It is also interesting to note, that the most likely mechanism of action of these beneficial effect is the renal enhancing properties of nesiritide. However, concomitant cardioprotection is also a possible contributing mechanism and more studies are also needed to understand this very important and emerging concept of a cardiorenal and/or renocardiac connection.

Building on the NAPA trial and recognizing that mild to moderate renal insufficiency is associated with increased morbidity and mortality after CPB (cardiopulmonary bypass) cardiac surgery and that BNP may have a GFR enhancing properties, We recently reported the findings of a double-blinded placebo-controlled proof of concept study in patients undergoing CPB cardiac surgery with renal insufficiency determined pre-operatively (CrCl < 60 ml/min by Cockcroft-Gault formula).⁽²⁶⁾ Forty patients were randomized to i.v. BNP or placebo for 24 hours started after induction of anesthesia before CPB. The BNP dose was 0.005 µg/kg/min without bolus so as to avoid hypotension. Patients with cardiogenic shock

or hypotension with systolic blood pressure < 90 mm/Hg, acute or chronic aortic dissection were excluded from the study.

Patients that were randomized to the BNP infusion group had an increase in plasma BNP and cGMP, with a decrease in plasma cystatin levels at the end of the 24-hour infusion as compared to the placebo control group. Interestingly, there was also activation of aldosterone in the placebo group at the end of the 24-hour infusion, but not in the BNP group. Also, in the placebo group, at 48 and 72 hours, there was a decrease in estimated CrCl and an increase in plasma cystatin as compared with the values found at the end of the 24-hour infusion period. In contrast, renal function was preserved in the BNP group and there were no changes in estimated CrCl and there was a trend for plasma cystatin to increase as compared with end of the 24-hour infusion period.

This study clearly showed that a low non-hypotensive dose of BNP has renal GFR protecting properties in the setting of chronic renal insufficiency and CPB surgery. It is important to underscore that it is possible the renal effect observed in these patients may be linked to the suppression of aldosterone by BNP. Indeed, we previously observed that a combination of BNP plus furosemide can attenuate aldosterone activation in the setting of CHF.⁽²⁷⁾ This is very relevant to this setting where diuretics like furosemide are commonly used and are known to have aldosterone stimulating actions.

CD-NP: A NEW GENERATION DESIGNER NATRIURETIC PEPTIDE

Lastly, another emerging concept which builds on low dose BNP therapy is the design of novel designer peptides which are renal enhancing but less hypotensive due to targeting of NPR-B receptors in the venous system and avoiding excessive arterial vasodilation which occurs with ANP and BNP. A Phase 1 clinical trial of one such peptide, CD-NP, has recently been completed.

CD-NP represents the product of an emerging therapeutic strategy which is the engineering of proteins. This process fuses unique amino acid sequences from one peptide with sequences from separate peptides to create designer peptides which possess attractive therapeutic properties⁽²⁸⁾. Such a strategy could result in a unique peptide with a specific activity profile that could be more useful than their natural counterparts as therapeutic agents in cardiorenal disease.

We recently focused on C-type natriuretic peptide (CNP) which is a 22-amino acid (AA) peptide that shares structural homology with ANP and BNP and is a ligand for NPR-B.^(29–30) Also unlike ANP or BNP, CNP lacks a COOH-terminus (C-terminus) AA extension which may explain in part its lack of natriuretic properties.^(31,33) In isolated venous and arterial rings, CNP activates NPR-B receptors in veins while ANP and BNP bind to NPR-A receptors in both arteries and veins. The specific affinity for the venous NPR-B of CNP is consistent with the less hypotensive actions of this peptide as compared to ANP and BNP.⁽³³⁾

Schweitz and co-workers reported the *in vitro* biological actions of a newly discovered peptide *Dendroaspis* natriuretic peptide (DNP).⁽³⁴⁾ Lisy et al subsequently reported that

DNP which was originally isolated from the green mamba snake was *in vivo* potently natriuretic and diuretic and possessed cardiac unloading actions but with significant hypotensive properties.⁽³⁵⁾ Singh and coworkers recently have reported that DNP has a higher affinity for the NPR-A receptor in human myocardium as compared to ANP and BNP.⁽³⁶⁾

An important feature of DNP is that it has the longest C-terminus of the known natriuretic peptides consisting of 15-AA as compared to 5-AA for ANP, 6-AA for BNP and none for CNP. It is thought that the long C-terminus of DNP may render DNP highly resistant to degradation by neutral endopeptidase (NEP) contributing to potent natriuretic and diuretic actions.⁽³⁷⁾ Further, the absence of a C-terminus for CNP may explain that of the three known endogenous natriuretic peptides CNP is the most susceptible to NEP degradation which could limit its renal actions as NEP is expressed greatest in the kidney.

We therefore designed a peptide we call CD-NP that fuses the 15-AA C-terminus of DNP into the C-terminus position of the core 22-AA ring structure of CNP. Our studies demonstrated *in vivo* that CD-NP is natriuretic and diuretic, GFR enhancing, cardiac unloading and renin inhibiting. CD-NP also demonstrates less hypotensive properties when compared to BNP. Thus, these recent findings advance an innovative design strategy in natriuretic peptide drug discovery and development to create therapeutic peptides with favorable properties that may be preferable to those associated with native natriuretic peptides.

SUMMARY

In conclusion, we have learned a great deal from the perspective of the heart as an endocrine organ in linking the heart and kidney in cardiorenal homeostasis. The cardiac peptide BNP possesses potent cardiorenal actions and we are only beginning to understand this peptide as a therapeutic. We are still in the early stages of clinical development of the natriuretic peptides as renal therapy and clearly additional studies based upon their novel biology are warranted.

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