Molecular and physiological effects of nesiritide

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BACKGROUND: Nesiritide (Natrecor, Janssen-Ortho Inc, Canada), or recombinant human B-type natriuretic peptide (BNP), is a molecule identical in structure to endogenous BNP-32. This peptide is secreted from cardiac myocytes in response to volume and pressure overload. While high levels of circulating BNP are measured by commercially available assays during acute decompensated heart failure (ADHF), the detection of alternate, potentially more active, but undermeasured forms of BNP needs to be considered.

AIM: The present review summarizes the molecular and physiological effects of nesiritide in the setting of hospitalized patients with ADHF. In particular, an overview of the molecular structure and circulating isoforms of BNP is given, followed by a discussion of the vasodilatory, renal, antagonistic neurohormonal, pulmonary, anti-inflammatory and cardiac remodelling effects of recombinant human BNP.

SUMMARY: Nesiritide has beneficial effects in the treatment of ADHF that go beyond the traditional goals of reducing pulmonary capillary wedge pressure, preload and afterload, and relieving symptoms of dyspnea. Therefore, the unique pharmacological profile of this medication provides an additional treatment option for Canadian patients with ADHF.

Key Words: Acute decompensated heart failure; BNP; Nesiritide

Nesiritide (Natrecor, Janssen-Ortho Inc, Canada) has recently been approved in Canada for the treatment of hospitalized patients with acute decompensated heart failure (ADHF). The molecular structure is identical to the 32 amino acid isoform of endogenously secreted B-type natriuretic peptide (BNP), giving it a unique pharmacological profile that allows for rapid relief of ADHF symptoms (dyspnea), reducing preload, afterload and pulmonary capillary wedge pressure (PCWP) without increasing heart rate. In addition, it reduces neurohormonal activation and has a beneficial effect on cardiac remodelling. The present review not only summarizes the molecular and physiological effects of this therapeutic agent, but gives insight into the rationale of giving more BNP in the form of recombinant human BNP (shBNP) to the already overloaded BNP condition of ADHF.

BASIC MOLECULAR SCIENCE

In response to increased atrial and ventricular pressure and volume stimuli that occurs during ADHF, cardiac myocytes synthesize natriuretic peptides (NPs). While there are several types of NPs that all share a common amino acid ring structure, eg, atrial NP, BNP, C-type, D-type, V-type and the renal peptide urodilatin (1), the present review will primarily focus on BNP.

Secreted primarily from the ventricles at the transcriptional level, BNP serves the neurohormonal function of counteracting the detrimental effects of heart failure (HF). Before BNP circulates in its active form (BNP-32), the prohormone (proBNP-108) is cleaved by an endoprotease within the myocyte into BNP-32 and NT-proBNP-76 (2). Beyond having different molecular weights – BNP-32: low molecular weight; proBNP-108: high molecular weight – they also behave in different biochemical ways. BNP-32 has a half-life of only 22 min, while NT-proBNP-76 circulates for 1 h to 2 h (3). Despite initially being secreted in equal amounts by the heart, proBNP-108, rather than the more active BNP-32, appears to be the peptide that is measured in greater quantities by commercial assays (4).

Herein lies the debate as to the significance of assays being more sensitive to high molecular weight than low molecular weight peptides. While discussion still continues as to what represents a clinically relevant BNP cutoff value for the diagnosis of ADHF (5), and while it seems intuitive that higher levels of assay-measured BNP would correlate with greater burden of HF, one must probe deeper. Recall that what is measured may in fact actually be the less active peptide, or in other words, the NP that perhaps offers less physiological benefit to end organs.

The present review will highlight the potential physiological effects of nesiritide in ADHF patients. This includes a more detailed discussion of the molecular and physiological effects of recombinant human BNP, and the potential benefits of giving BNP in the form of recombinant human BNP (shBNP).

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Hemodynamic (vasodilation)
- veins
- arteries
- coronary arteries

Neurohormonal
- aldosterone
- endothelin
- noradrenaline

Renal
- sodium/water excretion

Pulmonary
- bronchodilation

Cardiac
- lusitropy
- antifibrinolytic
- remodeling

**Figure 1** Summary diagram of the physiological effects of nesiritide. BNP B-type natriuretic peptide

appears to become resistant to persistently high levels of BNP, as evidence gathered from animal studies suggests. Finally, the upregulation of phosphodiesterase during severe HF may impair cGMP activity, and increased clearance of BNP by the ectoenzyme neutral endopeptidase may result in even further BNP reduction (8).

Therefore, while produced in response to HF overload states, and ideally designed to offer the cardiorenal and vascular system protection from failure, the reality may be that there is a relative deficiency of active BNP, and matters are further complicated by potential receptor resistance (9). In recognition of these issues, the hypothesis that offering patients rhBNP such as nesiritide (Natrecor, Janssen-Ortho Inc, Canada) during ADHF has been proposed. Experimental studies suggest clinical benefit to hospitalized patients, the mechanisms of which will be discussed in the following section.

**PHYSIOLOGICAL SUMMARY**

In the presence of HF, BNP acts at various locations within the body (Figure 1). BNP targets the vasculature, influences which hormones are secreted and recognized, and influences the functioning of the kidneys, lungs and even the heart, all with the aim of minimizing the effects and, ultimately, the symptoms of ADHF.

**Vasodilation**

While the exact mechanisms are not yet fully understood, NPs appear to promote nitric oxide release (10). Additionally, as described in detail in the previous section, activation of NP receptors signals cGMP, thereby activating calcium/potassium channels, resulting in vasodilatation in both endothelial and vascular smooth muscle cells.

One of the first studies to examine BNP effects on human arteries and veins was completed by Potter et al (11), in which isolated internal mammary artery and saphenous vein samples were exposed to BNP. This study concluded that BNP was a more potent dilator of constricted arteries than veins. Studying several different NPs, Schmitt and colleagues (12) examined forearm blood flow and vascular volume in control subjects and in patients with HF. The results challenged Potter's findings by proposing that in HF, venous, but not necessarily arterial relaxation is conserved. Attenuation of NPs on the arterial system, but not venous system was further reviewed by Houben et al (10).

Clinically, these theories were explored when 127 patients hospitalized for ADHF requiring the placement of Swan-Ganz catheters were given either an intravenous infusion of nesiritide or standard medical therapy. Subjects receiving nesiritide significantly decreased their PCWP, right atrial pressures and systemic vascular resistance. Slight increases (+0.4±0.69 L/min/m²) in cardiac index were also reported in patients receiving an infusion of 0.30 µg/kg/min compared with controls (P<0.001) (13). The Vasodilation in the Management of Acute CHF (VMAC) study was a randomized, double-blind trial that assigned patients to receive either intravenous nesiritide (n=204) or nitroglycerin (n=142) for 3 h in addition to standard care (14). Main outcome measures included PCWP and self-evaluated dyspnea. At 3 h, patients receiving nesiritide had lower PCWP values and decreased dyspnea when compared with controls (14). Finally, both animal (15) and human trials (16) have demonstrated the direct effect of nesiritide infusion on increasing coronary artery blood flow and reducing coronary resistance, ultimately lowering wall stress and myocardial oxygen demands. Additional research will be required to elucidate whether nesiritide is truly a balanced systemic vasodilator.

**Antagonization of neurohormones**

It is accepted practice to prescribe angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and even spironolactone to patients in HF with the goal of decreasing the effects of the renin-angiotensin-aldosterone system (17). Neurohormonal activation initially serves to augment low cardiac output by increasing contractility and low blood pressure by increasing systemic vascular resistance. Furthermore, the kidneys retain sodium with the goal of increasing free water. However, if the renin-angiotensin-aldosterone system remains activated and left unchecked, it results in a state of tachycardia, increased afterload and excessive fluid, eventually leading to increased myocardial wall stress, cardiac remodelling, hypertrophy and debilitating symptoms such as decreased exercise tolerance and dyspnea (18).

BNP is intended to endogenously antagonize, in a multifactorial manner, the harmful effects of long-term neurohormonal activation. Specifically, BNP appears to overcome the vasoconstrictive effects of endothelin-1 (19), leading to both venous and arterial dilation as described above. Furthermore, BNP suppresses the activity of the renin, aldosterone, noradrenaline system (20), and possibly even the renal Akt, tumour necrosis factor-alpha and interleukin-6 (21). Clinical trials have supported these ideas, including a randomized study in which patients received either placebo or a short (4 h) nesiritide infusion (0.25 µg/kg/min to 0.5 µg/kg/min). While only a small sample size was recruited to receive nesiritide (n=12), reductions in preload, systemic vascular resistance, noradrenaline and aldosterone levels with an accompanying slight increase in cardiac output (but without tachycardia) were reported (13). Furthermore, Colluci et al (13) also described significant reductions in plasma aldosterone levels with nesiritide treatment compared with patients in ADHF receiving placebo infusion.

Significant renal dysfunction is common in patients hospitalized for HF (22). Acutely, HF decreases renal blood flow with resultant decreases in glomerular filtration rates. If allowed to persist, clinical evidence of renal failure in the form of proteinuria, glomerulosclerosis and tubulointerstitial fibrosis and increased creatinine eventually appear (21). While rhBNP promotes natriuresis (23), conflicting study results have questioned the degree of nesiritide’s action on the renal system during HF. In a more recent study in patients receiving perioperative nesiritide infusion versus placebo, Metzner et al (24) observed that nesiritide might play a role in the maintenance of glomerular filtration rates by enhancing renal vasodilatation. Knowing that BNP reduces angiotensin II and aldosterone levels, it is quite plausible that BNP can also cause a direct augmentation of diuresis. Indeed, this was described clinically in the VMAC trial. While urinary output did not increase in this trial, patients receiving nesiritide required fewer diuretics than standard-of-care patients (14). Similarly, two other trials (19,25), also studying
patients in HF, were able to show that nesiritide increased urinary sodium excretion and urine output. Again, further study is required to clarify these issues.

Effects of BNP on the pulmonary and cardiac systems
In both the earlier, nonrandomized trial conducted by Colucci et al (13) and the subsequent randomized VMAC trial (14), measures of improved global clinical status and dyspnea were described following the use of nesiritide. While VMAC subjects receiving nesiritide infusion reported reductions in dyspnea at 3 h compared with patients receiving placebo (P=0.03), this effect was not sustained at 24 h. To further explore this topic, the action of BNP on bronchodilatation was studied in eight subjects with asthma, but not HF. Protocol involved intravenous nesiritide bolus (2 μg/kg) followed by continuous infusion over 3 h with increasing doses of 0.01 μg/kg/min, 0.02 μg/kg/min and 0.03 μg/kg/min every hour. Both forced expiratory volume in 1 s and forced vital capacity statistically increased (P=0.012 and P=0.017, respectively) (26). From the above data, it would seem that BNP also acts directly on bronchioles; however, further confirmatory studies are required to better elucidate exact mechanisms before definitive conclusions may be offered.

Thus far, our discussion has focused on BNP’s ability to vasodilate, suppress endothc function and promote renal homeostasis, but the role of the NPs on suppressing excessive collagen production and fibrosis during cardiac remodelling must also be mentioned. If allowed to continue unimpeded, remodelling may eventually lead to impaired cardiac histotpy and diastolic dysfunction (23). Tamura et al (27) created genetically modified mice to exhibit BNP deficit. Not only did these mice have increased numbers of fibrotic lesions, but when exposed to ventricular pressure overload these lesions were further increased in both number and size. Furthermore, mice created to lack NP receptor type-A also demonstrated increased fibrotic burden (28). Fibrosis not only requires fibroblast proliferation, which secretes transforming growth factor-beta, but also increased deposition of extracellular matrix proteins. Using cardiac fibroblasts obtained from two human male subjects, and analysed using Western blot analysis, Kapoun et al (28) demonstrated that BNP indeed reduced transforming growth factor-beta-induced cell proliferation, as well as collagen and fibronectin proteins.

CONCLUSIONS
HF is a complex syndrome affecting multiple organs, and no longer is considered just a state of hemodynamic compromise. Although BNP and nesiritide effectively reduce both preload and afterload, therefore reducing symptoms of ADHF, they also have demonstrated additional benefits such as decreasing neurohormonal activation, decreasing inflammation and ultimately reducing cardiac remodelling. The suppression of these mechanisms is import to protect the myocardium from further HF insult, and ultimately to improve long-term patient survival.

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REFERENCES
Hemodynamic and renal excretory effects of human brain 
natriuretic peptide infusion in patients with congestive heart 
failure. A double-blind, placebo-controlled, randomized crossover 
26. Akerman MJ, Yaegashi M, Khiangte Z, Murugan AT, Abe O, 
Marmur JD. Bronchodilator effect of infused B-type natriuretic 
peptide in asthma. Chest 2006;130:66-72.
lacking brain natriuretic peptide. Proc Natl Acad Sci USA 
2000;97:4239-44.
exerts broad functional opposition to transforming growth factor- 
beta in primary human cardiac fibroblast fibrosis, myofibroblast 
conversion, proliferation, and inflammation. Circ Res 