Natriuretic Peptides, Respiratory Disease, and the Right Heart*

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It is well-recognized that atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) are raised in conditions with ventricular volume and pressure overload. In addition to this established role in left ventricular congestive cardiac failure, there is good evidence that BNP has a diagnostic role in right ventricular (RV) dysfunction and pulmonary arterial hypertension (PAH). For example, BNP levels can be used to differentiate between dyspneic patients with pure respiratory defects and those with RV dysfunction. Studies in patients with PAH have demonstrated significant correlations between BNP levels and mean pulmonary arterial pressure as well as pulmonary vascular resistance. Additionally, BNP has a prognostic role in patients with RV pressure overload and pulmonary hypertension, and it offers a noninvasive test that can be used to guide therapy in patients with PAH. However, although measured plasma proBNP levels are raised in conditions with RV overload, its biological significance is still not well-understood. In this article, we review the general physiologic and potential therapeutic role of natriuretic peptides in respiratory disease, RV dysfunction, and PAH. Furthermore, we assess the various clues toward natriuretic peptide action coming from laboratory studies. ANP and BNP knockout mice develop cardiac fibrosis and hypertrophy. Potentiation of the natriuretic pathway has been shown to reduce cardiac hypertrophy and PAH. This is likely to take place as a result of increased intracellular cyclic guanosine monophosphate levels and subsequent pulmonary vasorelaxant activity. In view of this evidence, there may be a rationale for the therapeutic use of recombinant BNP or neutral endopeptidase inhibitors under conditions of RV dysfunction and PAH.

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Key words: natriuretic peptide; pulmonary arterial hypertension; right ventricular dysfunction

Abbreviations: ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; cGMP = cyclic guanosine monophosphate; CHF = congestive heart failure; DMPPO = 1,3-dimethyl-6-(2-propoxy-5-methanesulfonylamidophenyl)-pyrazol[3,4-d]pyrimidin-4-(5H)-one; LV = left ventricle, ventricular; mPAP = mean pulmonary arterial pressure; NEP = neutral endopeptidase; NPR = natriuretic peptide receptor; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PPH = primary pulmonary hypertension; RV = right ventricle, ventricular; TPR = total pulmonary resistance

Learning objectives:
1. To recognize that plasma BNP is a useful marker for right ventricular dysfunction and correlates with the severity of pulmonary arterial hypertension and/or right ventricular overload.
2. To understand that ANP and BNP play a role in cardiac fibrosis and ventricular hypertrophy and may have a role in both monitoring and treating conditions associated with right ventricular overload.

Atrial natriuretic peptide (ANP) was first isolated from cardiac tissue following the identification and purification of granules within atrial muscle cells.1 Subsequently, other peptides, brain or B-type natriuretic peptide (BNP) and C-type natriuretic peptide, also have been isolated. ANP and BNP are both are synthesized by cardiac myocytes, and it is now dogma that their production is increased by factors that increase cardiac pressure and volume overload.2

The diagnostic and therapeutic potential of ANP and BNP in the context of ischemic heart disease and congestive heart failure (CHF) are well-documented.3–5 However, in stark contrast to the extensive

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number of studies on natriuretic peptides among patients with left ventricular (LV) dysfunction, there are few studies on patients with right ventricular (RV) dysfunction. Isolating the cause of natriuretic peptide release in RV dysfunction is interesting for two reasons. The first is that there may be a potential for natriuretic peptides in the diagnosis of RV dysfunction and PAH. These conditions often involve invasive forms of investigation such as cardiac catheterization, and hence a noninvasive test would be invaluable. The second is that understanding the mechanisms of the natriuretic peptide pathway in RV pressure overload may help develop treatment strategies in patients with pulmonary arterial hypertension (PAH). The aim of this article is therefore to collate the physiologic, diagnostic, and therapeutic roles of natriuretic peptides in the context of respiratory disease, RV dysfunction, and PAH, and to relate these to its possible future roles in RV disease. The structure and physiology of natriuretic peptides relevant to its role in the diagnosis of diseases with RV dysfunction and PAH is discussed in the first part of the review. The second half of the review concentrates on the role of natriuretic peptides in the pathophysiology of cardiac fibrosis and hypertrophy because of its future implications in PAH therapy.

Structure and Physiology

The natriuretic peptides are a family of peptides consisting of molecules that share a 17-amino acid ring structure. All three natriuretic peptides are synthesized as distinct high-molecular-weight precursors, which are cleaved in two to give N-terminal segments and biologically active low-molecular-weight peptides. For example, BNP 1–108 is cleaved into the active C-terminal BNP 32 and N-terminal proBNP 1–76 by enzymes within cardiac myocytes such as Corin and prohormone convertase (PC1/3). ProBNP 1–76 is not known to have an active intracellular role. Increasingly, newer assays measure the nonactive proBNP form instead of the active BNP 32 molecule.

Three main natriuretic peptide receptors (NPRs) also have been cloned. NPR-A and NPR-B are guanylyl cyclase-linked, and they utilize cyclic guanosine monophosphate (cGMP) as the intracellular messenger. Both ANP and BNP bind to NPR-A. A third receptor, known as NPR-C, is not linked to guanylyl cyclase but may act to clear the natriuretic peptides from the circulation. ANP and BNP both cause salt loss (ie, natriuresis) and diuresis, conditions in which there is myocardial stretch and pressure overload in both cardiac ventricles may cause raised plasma levels of natriuretic peptides. In patients with CHF, increased ANP release corresponds more to atrial filling volume than ventricular filling pressures, suggesting that atrial stretch is the major determinant for ANP release. Raised levels of plasma ANP are associated not only with raised central venous pressure related to volume (ie, salt and water) overload, but are also easily influenced by BP, age, sodium intake, and renal function. For this reason, ANP and BNP levels are increased in patients with renal impairment. Elevated plasma BNP levels are found in patients with LV dysfunction, acute myocardial infarction, unstable angina, hypertension, and LV hypertrophy. Higher BNP values are also found among women compared to men, and among the elderly.

BNP in Respiratory Disease

BNP has better prognostic potential than ANP because of the rapidity and low cost of the assay, hence most clinical studies have focused on BNP for diagnostic purposes. The predominant theme has been the differentiation of heart failure and obstructive lung disease as a cause of breathlessness. Initially, it was shown that plasma BNP concentration
was increased in patients with hypoxic COPD when compared to healthy control subjects. This was thought to diminish its potential discriminative value in distinguishing between CHF and COPD. However, the severity of the COPD in these patients (FEV1, 27% predicted) predicted that they would have some degree of right heart strain, which may have contributed to the raised BNP levels. This was supported by the observation that both ANP and BNP levels are significantly increased in patients with cor pulmonale when compared to patients with chronic pulmonary disease alone.

Patients with COPD and worsening of their cor pulmonale with signs of RV volume overload (including edema and ascites) manifested increased BNP levels, and, indeed, these patients had increased mortality. Therefore, BNP also has been shown to be useful in discriminating between respiratory disease and LV dysfunction in determining the causes of dyspnea. It has been particularly effective in discriminating between CHF from asthma or COPD in the emergency setting. Within the context of severe respiratory disease, it may be that elevated BNP levels are due to RV pressure overload and that they may predict the prognosis within this group.

Although useful in differentiating between patients with dyspnea due to respiratory disease and those with respiratory disease with RV overload and CHF, additional investigation (ie, by echocardiography or hemodynamic studies) may be necessary to differentiate the latter two groups. Nevertheless, the accumulated evidence supports a role for natriuretic peptides in differentiating obstructive lung disease from CHF in a clinical setting.

**RV Pressure Overload and PAH**

In patients with RV pressure overload due to primary pulmonary hypertension (PPH) and thromboembolism, ANP and BNP levels are higher in those patients with RV volume overload due to atrial septal defect. ANP and BNP levels correlated with mean pulmonary artery pressure (mPAP), right atrial pressure, RV end-diastolic pressure, and total pulmonary resistance (TPR) in these patients. After long-term vasodilator treatment, there was a reduction in TPR and a subsequent reduction in BNP levels. In a different study of PPH patients, ANP levels correlated with the severity of RV dysfunction, as indicated by mPAP. The ANP levels decreased along with mPAP when therapy with inhaled iloprost was given. In PPH patients, plasma BNP levels also have been shown to be a prognostic indicator.

BNP levels also have been shown to be higher in patients with acute pulmonary embolism, especially among those with echocardiographic evidence of RV dysfunction when compared to control patients. RV overload measured by echocardiography (ie, RV/LV ratio and inferior vena cava dimensions) is associated with higher BNP levels, suggesting myocardial stretch as the physiologic cause. This suggests that in pulmonary embolism, BNP can be used to help identify patients with increased RV strain and, hence, in higher risk patients. Higher BNP levels at presentation with pulmonary embolism also was found to be associated with increased mortality in two other recent studies with large cohorts of patients. In patients with chronic thromboembolic pulmonary hypertension, BNP levels have been used as markers of PAH. Following thromboembolectomy and rectification of RV strain, BNP levels decreased along with TPR.

These studies demonstrated that in different pathologies causing right heart strain, both ventricular and atrial pressure overload are likely to be the cause of natriuretic peptide release. They also showed that the severity of PAH or right heart strain, as measured by hemodynamic data, could be estimated by a biochemical assay that could be used as an indicator of treatment efficacy (eg, correlation with RV end-diastolic pressure) to guide therapy. Importantly, the measurement of BNP levels offers a noninvasive test that may be used in conjunction with the 6-min walk test and right heart catheterization in the monitoring of PAH.

**Comparison of Values in RV and LV Dysfunction**

There are few studies involving the measurement of BNP levels and RV systolic function. A study using gated blood pool scintigraphy has shown that patients with both right-sided and left-sided heart failure, as defined by an ejection fraction of < 40%, had significantly higher BNP levels when compared to those with left-sided heart failure alone. In patients with congenital heart disease who have chronic RV pressure overload, cardiac MRI measuring RV ejection fraction showed a negative correlation with plasma BNP levels, suggesting that BNP levels are raised in patients with RV systolic dysfunction.

A direct comparison of LV dysfunction and RV dysfunction shows little evidence that the plasma levels are different. Comparing BNP levels assessed with either of two assays (Shionoria BNP kit; Shionogi & Co, Ltd; Tokyo, Japan; or Triage assay; Biosite Diagnostics; San Diego, CA [both measure C-terminal BNP]) and show good correlation) in patients with CHF in the New York Heart Association functional class II had an average BNP value of 389 pg/mL, and those in New York Heart Association class III had a value of 640 pg/mL, while patients with RV pressure overload, assessed using a
similar assay, had an average value of 260 pg/mL. Although direct comparison is difficult, the BNP levels may not be vastly different in studies of patients with RV and LV dysfunction. In CHF, the biventricular release of BNP may contribute to raised plasma levels.

Possible Underlying Mechanisms of Natriuretic Peptide Secretion

At present, there is still a lot that is not understood with regard to the mechanism of natriuretic peptide secretion from the RV. There are, however, clues regarding signaling cascades that are dependent on myocyte cell surface integrins and mitogen-activated protein kinases, which increase BNP gene expression. We are beginning to understand the differences in the biological activation of ANP and BNP. Within atrial myocytes, secretory granules store ANP, but ventricular myocytes do not have secretory granules, and thus secretion is constitutive. This process is affected in the ventricular myocytes of CHF patients, and hence patients may have increased concentrations of precursors while lacking biologically active peptides. One point to note is that the nonactive form proBNP1–76 is increasingly being measured in newer generation plasma assays. This form is much more stable in plasma and serves better as a plasma marker, but these do not necessarily reflect the level of BNP32 activity, which requires more time-consuming radio-immunoassay methods.

Natriuretic Peptides in the Modulation of Cardiac Hypertrophy and PAH

ANP and BNP have been implicated in the pathogenesis of cardiac hypertrophy and fibrosis. This is of great interest because the natriuretic peptide pathway may be involved in modulating the development of PAH.

There are multiple studies on mice demonstrating that ANP and BNP action are essential in preventing cardiac fibrosis and hypertrophy. ANP has been shown to inhibit collagen synthesis in cardiac fibroblasts, and BNP knockout mice have been shown to be susceptible to cardiac fibrosis and hypertrophy. Cardiac myocytes with inhibited ANP responses also demonstrate significant cardiac hypertrophy. When exposed to hypoxia, mice with disrupted ANP genes developed increased levels of RV pressures. NPR-A disruption in mice also worsens RV and LV hypertrophy during chronic hypoxia, indicating a possible NPR-A-mediated antihypertrophic action in the heart.

Hyoxia causes the induction of ANP and BNP production. An increase in ANP levels following hypoxia may act as an endogenous pulmonary vasodilator that could modulate the response (ie, the development of PAH or cardiac hypertrophy) to hypoxia. Mice exposed to an hypoxic hypobaric environment also show increased expression of ANP and BNP messenger RNA in both the LV and the RV.

Rats exposed to hypoxic conditions are protected against developing PAH when given infusions of ANP and BNP. Similarly, in mice exposed to a hypoxic environment, ANP and BNP delivery reduced mPAP in mice with functioning NPR-A compared to those with deficient NPR-A.

Various agents have been studied with respect to this. Urodilatin (renal natriuretic peptide type A) causes vasodilation and reduction of mPAP in rabbits with thromboxane mimetic induced pulmonary hypertension. PDE 5 inhibitors such as 1,3-dimethyl-6-(2-propoxy-5-methanesulfonylamido(phenyl)pyrazol-[3,4-d]pyrimidin-4-(5H)-one (DMPO), E4010, and sildenafil have been studied along similar lines. DMPO reduced hypoxia-induced PAH, while E4010 also suppressed RV hypertrophy in rats.

Sildenafil has been shown to decrease pulmonary vascular resistance and increase exercise tolerance among patients with PAH. The mechanism of action may result in an increase in intracellular cGMP levels leading toward pulmonary vasorelaxation (Fig 3). In mice, sildenafil reduced RV hypertrophy under hypoxic conditions, and the effect was enhanced by ANP in NPR-A homozygous mice, but not in NPR-A knockout mice. This suggests that natriuretic peptide activity enhancement may be adjunctive to the effect of other agents that increase intracellular cGMP levels or even nitric oxide as a pulmonary vasodilator.

Clinical trials among human subjects have shown that mPAP and pulmonary vascular resistance increase in response to hypoxia. This response is attenuated by BNP infusion. Similar findings have

![Figure 3. Enhancement of cGMP within endothelial cells leading to pulmonary vessel relaxation. Natriuretic peptides and prostaglandins enhance cGMP production, while sildenafil inhibits phosphodiesterase, which breaks down cGMP. GTP = guanosine triphosphate.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/22017/ on 06/21/2017)
been demonstrated among patients with cor pulmonale, with both ANP and BNP infusion causing a favored neurohumoral pulmonary vasodilator response. These studies suggest that there is a potential therapeutic use for natriuretic pathway-enhancing drugs in the treatment of PAH.

Enhancement of Natriuretic Peptide Activity

There are two predominant ways of enhancing natriuretic peptide activity. One way is by using natriuretic peptide analogues (eg, nesiritide), and the other way is by reducing breakdown via the inhibition of neutral endopeptidase (NEP) [eg, candoxatril or omapatrilat].

Nesiritide may have therapeutic potential in slowing the progression of RV dysfunction. The drug binds to receptors in the vasculature, kidney, adrenal gland, and brain, and helps to overcome resistance to endogenous BNP that is present in patients with CHF. Nesiritide administration leads to a rapid and balanced vasodilatory effect, which results in a significant decrease in RV and LV filling pressures, a decrease in pulmonary capillary wedge pressure (PCWP), and also an increase in stroke volume and cardiac output. Patients with CHF have reduced PCWP following nesiritide infusion when compared to patients receiving nitroglycerin infusion. Similarly, omapatrilat has been shown to be as effective as lisinopril or enalapril in lowering PCWP and improving cardiac output among CHF patients.

These agents provide an avenue toward natriuretic peptide activity manipulation that is still underexplored.

Possible Future Areas of Research and Clinical Implications

Although still speculative, the effect of NEP inhibitors or recombinant natriuretic peptides on the reduction of ventricular hypertrophy indicate their possible potential as therapeutic agents for the treatment of PAH. As yet, there are no ongoing trials along these lines, but they may prove to be effective adjunctive therapy with more established agents such as iloprost, epoprostenol, bosentan, and sildenafil.

In theory, the enhancement of pulmonary vasorelaxation or vasodilatation via natriuretic peptide action would result in a reduction of pulmonary arterial pressure. If we were to see similar effects to those demonstrated in laboratory studies, then enhancing natriuretic peptide activity may slow the progression of RV hypertrophy in such patients. Hence, future trials involving agents that enhance natriuretic peptide action, such as nesiritide or omapatrilat, under conditions of PAH and RV overload may reveal their therapeutic potential.

There also may be subgroups of patients who are more responsive to agents enhancing natriuretic peptides compared to prostacyclins, nitric oxide, or endothelin receptor modulators. Studies looking at the response from the different subgroups (ie, patients with PPH, collagen vascular disease, and hypoxemia-induced thromboembolism) that may respond to these agents are important.

Conclusion

Although it has been accepted that plasma BNP has a high negative predictive value for LV dysfunction and heart failure, there is increasing evidence that BNP may also prove to be a clinically useful marker for RV dysfunction and PAH. This is important for the identification and risk stratification of patients for further investigations such as those with cardiac catheterization. Measured plasma C-terminal BNP or N-terminal pro-BNP levels may be used to guide therapy in patients with the conditions associated with RV overload and PAH. The potentiation of natriuretic peptide action may have beneficial effects in reducing cardiac fibrosis or hypertrophy. These findings also provide the first tantalizing evidence for the need for trials using natriuretic peptides generated via NEP inhibitors and recombinant BNP under conditions of RV overload and PAH.

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