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Bronchodilator Effect of Infused B-Type Natriuretic Peptide in Asthma*

Michael J. Akerman, MD†; Makito Yaegashi, MD‡; Zothanmawii Khiangte, MD; Anandhi T. Murugan, MD; Olumayowa Abe, MD; and Jonathan D. Marmur, MD

Study objective: To determine the bronchodilator effect of recombinant human B-type natriuretic peptide (BNP; nesiritide) on patients with asthma.

Design: A prospective, open-label study.

Setting: Outpatient setting.

Patients: Eight adult patients with asthma confirmed by > 12% and > 200 mL increase in FEV1 after bronchodilator inhalation.

Interventions: An IV nesiritide bolus, 2 μg/kg, followed by continuous infusion for a total of 3 h at escalating doses of 0.01, 0.02, and 0.03 μg/kg/min for 1 h each as tolerated.

Measurements: Spirometry and forced oscillation technique (FOT) measurements were both obtained at baseline and every 30 min during the infusion. Two doses of albuterol, 90 μg, inhalation via metered-dose inhaler were then administered at the end of nesiritide infusion, followed by repeat spirometry and FOT measurements after 30 min. Primary end points were FEV1 and FVC changes after the nesiritide infusion for 3 h. Wilcoxon signed-ranks tests were used to compare the effects of nesiritide and albuterol.

Results: Baseline measurements (mean ± SD) were as follows: FEV1, 1.89 ± 0.87 L; FVC, 3.02 ± 0.99 L; respiratory resistance at 5 Hz (Rrs5), 10.3 ± 3.85 cm H2O · s/L; and mean respiratory resistance at 5 to 20 Hz, 7.56 ± 1.92 cm H2O/L/s. Mean baseline serum BNP level was 27 ± 27 pg/mL. After 180 min of nesiritide infusion, the following measurements showed significant changes: FEV1 increased to 2.41 ± 0.78 L (mean increase, 520 mL), p = 0.012; FVC increased to 3.65 ± 1.05 L (mean increase, 630 mL), p = 0.017; and Rrs5 decreased to 8.24 ± 4.02 cm H2O/L/s, p = 0.017. After albuterol, there were no further significant changes in these measurements.

Conclusion: IV nesiritide is an effective bronchodilator in patients with asthma.

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Key words: asthma; atrial natriuretic factor; bronchodilators; B-type natriuretic peptide; nesiritide

Abbreviations: ANP = A-type natriuretic peptide; BNP = B-type natriuretic peptide; cGMP = cyclic guanosine monophosphate; FOT = forced oscillation technique; MDI = metered-dose inhaler; Mini AQLQ = Mini Asthma Quality of Life Questionnaire; NPR = natriuretic peptide receptor; Rrs5 = respiratory resistance at 5 Hz; Rrs5–20 = respiratory resistance between 5 Hz and 20 Hz; SpO2 = oxygen saturation measured by pulse oximetry

B-type natriuretic peptide (BNP) is one of several natriuretic peptide compounds. It is similar to A-type natriuretic peptide (ANP), which is found mainly in the heart ventricle and the brain. To date, 10 human studies have shown that ANP has a significant bronchodilator effect. In these studies, the ANP was either administered IV1–5 or inhaled.6–10 Angus et al6 demonstrated that IV ANP had a comparable bronchodilator effect when compared to inhaled albuterol in a randomized double-blind crossover study. Fluge et al5 however, showed that IV ANP produced only a 50% bronchodilator effect when compared to that of salbutamol. In all of those studies, there were no side effects except for hypotension, which was immediately reversible once the ANP infusion was stopped.1–10

However, with regard to BNP, its bronchodilator effect has been examined only in an animal model, which demonstrated that BNP dilates bronchi more effectively than ANP.11 To date, no study has examined the bronchodilator effect of BNP in humans. When considering the bronchodilator effect of BNP,
there is a theoretical advantage in the concomitant use of BNP together with β-agonist inhalation. BNP increases cellular concentration of cyclic guanosine monophosphate (cGMP) secondary to a rise in intracellular Ca²⁺ concentration. This is in contrast to cyclic adenosine monophosphate-dependent stimulation of the receptor on bronchial smooth-muscle cells receptors by β-agonists. Moreover, dose-limiting side effects of β-agonists like tachycardia and arrhythmia are uncommon with IV BNP. The safety of IV nesiritide has been demonstrated in several additional studies. Currently, nesiritide is approved by the US Food and Drug Administration for the treatment of acutely decompensated congestive heart failure. It is widely used clinically for this indication and is well tolerated even in the outpatient setting.

There were no human trials of BNP in asthma previously published. Therefore, our study was designed as a pilot study to prove the concept. It was designed to detect the magnitude and time course of effect with an infusion of BNP on asthma. We choose a prospective nonrandomized open-label design because it would yield this information in the shortest time and with the least expense.

**Materials and Methods**

**Patients**

The database of outpatients who attended the Asthma Center of Excellence at the State University of New York, Downstate Medical Center was reviewed for patients who met the following inclusion criteria: age ≥ 18 years with a clinical history of asthma as defined by the National Asthma Education and Prevention Program, and documented bronchodilator response to albuterol as defined by American Thoracic Society (> 200 mL and > 12% increase in FEV₁ after bronchodilator inhalation). These inclusion criteria had to be met within previous 12 months. Patients were excluded from this study if they had a history of congestive heart failure, COPD, or other lung diseases, or if they had a > 10-pack-year history of smoking or any cigarette smoking within the past 12 months. Also excluded were pregnant women, patients who were unable to withhold inhaled bronchodilators for 12 h prior to the study; patients who were not clinically stable for 3 weeks prior to the study; and patients who had hypoxia (oxygen saturation measured by pulse oximetry [SpO₂] < 90%), tachycardia (heart rate > 100 beats/min) or hypotension (systolic BP < 100 mm Hg) at the time of the study. The study was approved by the institutional review board of State University of New York Downstate Medical Center, and each patient provided written consent to participate in the study.

**Design**

A prospective, open-label study design was employed. Prior to the study date, short-acting and long-acting inhaled bronchodilators were held for 8 h and 12 h, respectively. Patients using oral antihypertensive medications were told to withhold their dose on the morning of the study. All other medications were continued as usual. All BNP infusions were begun at 10:00 AM on the morning of the study dates. The following baseline measurements were obtained: clinical history, including asthma severity and other medical problems; height and weight (measured); Mini Asthma Quality of Life Questionnaire (Mini AQLQ); baseline serum BNP level; three acceptable spirometry measurements; and a forced oscillation technique (FOT) measurement for 60 s. The patients were asked to recline on a bed with a 45° head elevation, and ECG and pulse oximetry were monitored continuously during the study period. BP was also measured with a semiantomatic sphygmomanometer at least every 10 min, and more frequently as needed. Urine outputs were recorded as well. A 20-gauge standard IV catheter was inserted in the forearm. All spirometry and FOT measurements were obtained with the patients sitting on the edge of the bed with their legs dangling down. The flexible arms of the spirometric measuring device were adjusted in order to keep the spine and neck vertical to the ground. After obtaining baseline measurements, nesiritide was infused for a total of 3 h: a 2 μg/kg bolus was followed by a continuous infusion of 0.01, 0.02, and 0.03 μg/kg/min for 1 h each as tolerated. The dose of nesiritide was not increased if systolic BP fell > 20 mm Hg. The infusion was withheld if systolic BP fell to < 100 mm Hg in two consecutive measurements. Spirometry and FOT measurements were both obtained every 30 min during the infusion. Then, final measurements were obtained 30 min after two doses of albuterol 90 μg inhalation were administered via metered-dose inhaler (MDI). During the study, patients were not restricted from drinking water.

**Measurements**

FEV₁ and FVC were measured using an impulse oscillometry system (Masterscreen IOS; Jaeger; Wurzburg, Germany) as described previously. A disposable filter (Microgard Disposable Filters; SensorMedics; Torba Linda, CA) was connected between the mouth piece (Free Flow Spirometer Mouthpiece with oral extension; SensorMedics) and the head of the spirometer. Patients were asked to wear a nose clip (VIAYS Medical;
Hoechberg, Germany). Measurements were repeated until three acceptable results were obtained as per American Thoracic Society criteria. Among three readings, the best measurement is reported.

FOT measurements were obtained using a previously described method (Masterscreen IOS; Jaeger). Briefly, a random noise signal of 5 to 35 Hz was generated by a loudspeaker and superimposed on the subject’s spontaneous breaths. Patients were equipped with a nose clip and mouthpiece during measurements, with their tongue below the oral extension of the mouthpiece. The patients held their cheeks firmly while measurements were obtained in a sitting position with the head in a neutral position. A continuous measurement of 60 s was obtained. The respiratory resistance at 5 Hz (Rs5) and mean respiratory resistance between 5 Hz and 20 Hz (Rs5–20) were recorded each time. The Rs5–20 was calculated from the respiratory resistance at 5, 10, 15, and 20 Hz.

Pulse rate, BP, and SpO2 were measured by using a semiautomatic sphygmomanometer (Sinecust 1280; Siemens Medical Electronics; Danvers, MA). For serum BNP measurement, 3 mL of venous blood was collected into a purple-top ethylenediamine tetra-acetic acid tube. The specimens were immediately brought to the laboratory, where they were measured by fluorescence immunoassay (Triage BNP test; Biosite; San Diego, CA).

Baseline measurements are shown in Table 1. The patients were 25 to 55 years old, and asthma severity was moderate persistent as assessed both by FEV1 and Mini AQLQ scores. Six patients (75%) were of African origin, and six patients (75%) had a family history of asthma. Mean baseline serum BNP level was 27 ± 27 pg/mL, and no patients had a baseline BNP > 100 pg/mL. All female patients of reproductive age had negative urine human chorionic gonadotropin test results prior to nesiritide administration.

The result of baseline spirometry and FOT measurements are as follows (Table 2): FEV1, 1.89 ± 0.87 L; FVC, 3.02 ± 0.99 L; Rs5, 10.3 ± 3.85 cm H2O/L/s; and Rs5–20, 7.56 ± 1.92 cm H2O/L/s. After 180 min of nesiritide infusion, the two primary end points had statistically significant changes (Fig 1, 2); FEV1 increased to 2.41 ± 0.78 L (mean increase; 520 mL), p = 0.012; FVC increased to 3.65 ± 1.05 L (mean increase 630 mL), p = 0.017. Also, among secondary end points, Rs5 decreased significantly to 8.24 ± 4.02 cm H2O/L/s, p = 0.017. After albuterol administration, there was no further significant increments in these measurements (p = 0.80 for FEV1 and p = 0.50 for FVC). The increases in FEV1 and FVC reached statistical significance within 180 min of nesiritide infusion and after albuterol compared to the baseline, and after doses of albuterol. A p value < 0.05 was considered significant.

### Table 1—Baseline Characteristics of Subjects (n = 8)*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>37.8 ± 12.6</td>
</tr>
<tr>
<td>Range</td>
<td>25–55</td>
</tr>
<tr>
<td>Female/male gender, No.</td>
<td>6/2</td>
</tr>
<tr>
<td>Black/white/Hispanic race, No.</td>
<td>6/1/1</td>
</tr>
<tr>
<td>Height, inches (cm)</td>
<td>65.4 ± 3.89 (166 ± 9.88)</td>
</tr>
<tr>
<td>Weight, lb (kg)</td>
<td>208 ± 41.4 (94.1 ± 29.2)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>34.6 ± 12</td>
</tr>
<tr>
<td>Mini AQLQ (between 1 and 7)</td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>4.28 ± 1.27</td>
</tr>
<tr>
<td>Activity limitations</td>
<td>4.19 ± 1.93</td>
</tr>
<tr>
<td>Emotional function</td>
<td>2.83 ± 1.55</td>
</tr>
<tr>
<td>Environmental stimuli</td>
<td>3.05 ± 1.80</td>
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<tr>
<td>Total score</td>
<td>3.71 ± 1.18</td>
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<tr>
<td>Positive/negative family history, No.</td>
<td>6/2</td>
</tr>
<tr>
<td>Medications, No of patients</td>
<td></td>
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<tr>
<td>Short-active β2-agonists</td>
<td>5</td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
<td>6</td>
</tr>
<tr>
<td>Long-acting β2-agonists</td>
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</tr>
<tr>
<td>Oral theophylline</td>
<td>1</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>1</td>
</tr>
<tr>
<td>Baseline serum BNP level, pg/mL</td>
<td>27.8 ± 27.3 pg/mL</td>
</tr>
<tr>
<td>Range</td>
<td>&lt;5 to 72.3</td>
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<tr>
<td>Spirometry findings inclusion criteria</td>
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<tr>
<td>FEV1 (before study), L</td>
<td>1.47 ± 0.51</td>
</tr>
<tr>
<td>FEV1 increase, L (%)</td>
<td>0.45 ± 0.20 (32 ± 14)</td>
</tr>
<tr>
<td>Baseline FEV1 on study day, L</td>
<td>1.89 ± 0.87</td>
</tr>
<tr>
<td>% predicted</td>
<td>58.6 ± 20.8</td>
</tr>
<tr>
<td>Maximal dose of BNP, No. of patients</td>
<td></td>
</tr>
<tr>
<td>0.03 μg/kg/min</td>
<td>4</td>
</tr>
<tr>
<td>0.02 μg/kg/min</td>
<td>3</td>
</tr>
<tr>
<td>0.01 μg/kg/min</td>
<td>1</td>
</tr>
<tr>
<td>Urine output, mL</td>
<td>470 ± 450</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD unless otherwise indicated.
30 min after starting the nesiritide infusion (Fig 1, 2). However, it took longer for respiratory resistances to decrease significantly. FEV₁ and FVC continued to increase further during the infusion, while the respiratory resistances continued to decrease.

There was a nonsignificant decrease in both systolic BP and diastolic BP after the nesiritide infusion. BP measures prior to and after 180 min of nesiritide infusion were as follows: systolic BP decreased from 130/110 mm Hg to 117/90 mm Hg (p = 0.17), diastolic BP decreased from 81/55 mm Hg to 72/48 mm Hg (p = 0.12), and heart rate remained constant from 77.4 to 78.9 beats/min (p = 0.68). Four patients did not receive the full increment in nesiritide dose because of decreased BP. The increase in the heart rate after albuterol was not statistically significant compared to nesiritide (from 77.4 to 85.5 beats/min, p = 0.17). Urine output during the study period was highly variable between subjects, with a mean urine output of 470 ± 450 mL.

### Discussion

Our results demonstrate that human recombinant BNP (nesiritide) is a potent bronchodilator in asth-
matic patients. This is consistent with the previous reported animal model that showed a potent bronchodilator effect of infused BNP in guinea pigs.\textsuperscript{11} This bronchodilator effect is not likely to be explained by improved congestive heart failure with nesiritide, since we chose patients with no clinical history of congestive heart failure. In addition, the measured baseline serum BNP level was far less than the reported criteria for heart failure (all the patients had a BNP level \(< 100 \text{ pg/mL}\)\textsuperscript{28}). The baseline plasma BNP level did not predict the response to BNP either (Spearman correlation, \(p = 0.56\)). The mechanism of this bronchodilatation is likely to be independent from adrenergic effect, since plasma catecholamine level does not change during BNP infusion.\textsuperscript{29} After nesiritide infusion, FEV\textsubscript{1} increased by 520 mL, which is comparable to FEV\textsubscript{1} increase after ANP infusions in previous studies.\textsuperscript{1–4} This degree of the bronchodilation was not statistically different from that seen with \(\beta_2\)-agonists. The post-albuterol measurements were obtained to make a rough estimate of the degree of bronchodilation compared to \(\beta_2\)-agonist. Even though our study did not show any further significant increase in FEV\textsubscript{1} with \(\beta_2\)-agonist, this does not exclude the possibility that BNP and \(\beta_2\)-agonist have synergistic effect. A randomized cross-over study would be better suited in order to compare their direct bronchodilator effects.

In order to avoid the possibility of underestimating the bronchodilator effects of nesiritide, we excluded patients with minimal airway obstruction. There is a possibility that a ceiling effect in bronchodilation occurs with nesiritide since additional increases in FEV\textsubscript{1} or FVC were modest after initial 30 min of infusion despite increases in the dose infused.

The nesiritide infusion dose was determined based on current recommendations for patients with congestive heart failure,\textsuperscript{30} which is higher than dose of ANP used in previously published studies\textsuperscript{1–5} (between 0.035 and 0.1 \(\mu\text{g/kg/min}\)). However, as opposed to the routine clinical usage of neseritide,\textsuperscript{16–18} we were somewhat conservative by either holding or not increasing dosages depending on BP, and also by omitting the 1 \(\mu\text{g/kg bolus every time the infusion rate was increased. In addition, antihypertensive medications were held on the day of the study. As a result, there was no symptomatic or prolonged hypotension in our patients in this study.}

We included FOT measurement in this study protocol since this measurement has been shown to be more sensitive for upper airway obstruction.\textsuperscript{31} Patients with asthma show a diffuse response to bronchodilators as compared to COPD, in which bronchodilation is predominantly in the peripheral airways.\textsuperscript{32,33} In this study, bronchodilator response was more pronounced in spirometry measurements than in FOT. Therefore, it is likely that bronchodilator response was not upper airway predominant but diffuse, which would be expected in asthmatics.

BNP is a 32-amino-acid peptide found mainly in the brain and cardiac ventricles. The natriuretic peptides interact with varying affinities with the three major types of high-affinity receptors (natri-
uretic peptide receptor [NPR]-A, NPR-B, and NPR-C) on the surface of target cells. BNP binds to NPR-A and NPR-C, although those receptors are not specific for the BNP. Of those, NPR-A stimulate guanylate cyclase activity and increases intracellular concentration of cGMP, although now it is known that this increase in cGMP is secondary to a rise in intracellular Ca\(^{2+}\) concentration. This leads to natriuretic, diuretic, and vasodilatory effects, and also possibly inhibits the renin-angiotensin-aldosterone system and the endothelin pathway. BNP is then cleared by receptor removal and neutral endopeptidase cleavage mostly in the luminal surface of ventricles. In the lung, ANP plays an important role in vasodilatation, bronchorelaxation, pulmonary permeability, and surfactant production and action. However, the role of BNP in the lung is less clear. Results from animal models cannot necessarily be applied to humans since BNP structures are highly diverse among species. In this study, we were able to confirm in humans the previously seen bronchodilator effect of BNP in an animal model.

Our study of the effects of BNP in asthma may have important clinical implications. Due to the potent bronchodilator effect of BNP demonstrated in our study in stable asthmatics, it seems reasonable to further evaluate BNP in the emergency department or inpatient setting as a potential alternative or additive therapy in patients with acute asthma exacerbation who are not responding adequately to standard treatment.

There are a few limitations to this study. Although this was a prospective study, it was open labeled and nonrandomized. Therefore, a potential placebo effect is inherent in the design of the study. However, because the degree of bronchodilation observed is far above the significant level defined by the American Thoracic Society in absolute volume (FEV\(_1\) by 520 mL and FVC by 630 mL vs required > 200 mL) and in percentage of prebronchodilator value (FEV\(_1\) by 36.5% and FVC by 23.7% vs required > 12%), it is unlikely that the results we observed are the result of a placebo effect. Secondly, even though our study size was small, the number of patients was large enough to detect significant changes even with two-sided Wilcoxon test. Our study was conducted in clinically stable asthma patients in an outpatient setting. It remains to be determined whether a similar degree of bronchodilation with similar safety can be achieved during acute asthma exacerbations.

In conclusion, IV human recombinant BNP is an effective bronchodilator in patients with asthma. The clinical roles of this agent in the treatment of asthmatic patients remains to be elucidated in future clinical studies.

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