Elevated Brain Natriuretic Peptide Predicts Blood Pressure Response After Stent Revascularization in Patients With Renal Artery Stenosis

Jose A. Silva, MD; Albert W. Chan, MD; Christopher J. White, MD; Tyrone J. Collins, MD; J. Stephen Jenkins, MD; John P. Reilly, MD; Stephen R. Ramee, MD

**Background**—A significant number (20% to 40%) of hypertensive patients with renal artery stenosis will not have blood pressure improvement after successful percutaneous revascularization. Identifying a group of patients with refractory hypertension and renal artery stenosis who are likely to respond to renal stent placement would be beneficial.

**Methods and Results**—Brain natriuretic peptide (BNP) was measured in 27 patients with refractory hypertension and significant renal artery stenosis before and after successful renal artery stent placement. This neuropeptide was elevated (median, 187 pg/mL; 25th to 75th percentiles, 89 to 306 pg/mL) before stent placement and fell within 24 hours of the successful stent procedure (96 pg/mL; 25th to 75th percentiles, 61 to 182 pg/mL; \( P = 0.002 \)), remaining low (85 pg/mL; 25th to 75th percentiles, 43 to 171 pg/mL) at follow-up. Clinical improvement in hypertension was observed in the patients with a baseline BNP \( > 80 \) pg/mL (n = 22) in 17 patients (77%) compared with 0% of the patients with a baseline BNP \( \leq 80 \) pg/mL (n = 5) (\( P = 0.001 \)). After correction for glomerular filtration rate, BNP was strongly correlated with improvement in hypertension.

**Conclusions**—BNP is increased in patients with severe renal artery stenosis and decreases after successful stent revascularization. In addition, an elevated baseline BNP level of \( > 80 \) pg/mL appears to be a good predictor of a blood pressure response after successful stent revascularization. (Circulation. 2005;111:328-333.)

**Key Words:** hypertension, renal natriuretic peptides stents

Use of percutaneous transluminal renal angioplasty and stenting to treat refractory hypertension secondary to renal artery stenosis has increased dramatically. In Medicare beneficiaries, between 1996 and 2000, the number of renal interventions increased from 7660 to 18 520; half of these were performed by cardiologists.1 Approximately one third of the treated patients failed to show improvement in hypertension after the procedure.2 Biomarkers that would identify patients likely to respond to revascularization would enhance patient selection and improve cost effectiveness.

Brain natriuretic peptide (BNP) is a neurohormone released from the ventricular myocardium in conditions that cause myocardial cell stretching such as congestive heart failure and pulmonary embolism.3-5 This neurohormone, which has a serum half-life of \( \approx 20 \) minutes, has been shown to directly correlate with pulmonary capillary wedge pressure.6,7 BNP is also considered a good predictor of major cardiovascular events and sudden death in patients with unstable angina, myocardial infarction, and ischemic cardiomyopathy.8-10

Although most of the circulating BNP is synthesized and released from ventricular myocytes, its most important physiological actions occur at the kidney level not only during conditions of health but also in pathological states.11,12 BNP promotes diuresis, natriuresis, and arterial vasodilation and antagonizes renin activity.3 In vitro data have also shown that angiotensin II may directly induce the synthesis and release of BNP, and an animal study has suggested that BNP mRNA is significantly upregulated 6 hours after clipping of the renal artery.13,14 Theoretically, BNP may be increased in patients with renovascular hypertension, a condition known to promote activation of the renal angiotensin system and the release of angiotensin II.15-17

The aims of the present investigation were to determine whether BNP may be increased in patients with renal artery stenosis, whether successful renal artery revascularization would affect BNP levels, and whether elevated BNP levels might predict which patients would have a blood pressure response after successful renal artery revascularization with a stent.

**Methods**

**Patient Selection**

Thirty-four consecutive patients with significant renal artery stenosis (\( \geq 70\% \) diameter stenosis) by angiography were prospectively included in the study. Seven initially screened patients were excluded.
from the protocol because of (1) congestive heart failure exacerbation and left ventricular dysfunction (ejection fraction <40%; n=3), (2) recent (within 6 months) myocardial infarction and/or acute coronary syndromes (n=2), and (3) chronic renal insufficiency (creatinine ≥2 mg/dL; n=2).

All renal artery stenoses were atherosclerotic ostial stenoses (within 5 mm of the origin of the vessel). Eighteen patients had unilateral renal artery stenosis; 9 patients had bilateral renal artery stenosis. The investigators enrolled all patients in the protocol without knowledge of the patients’ BNP levels. The study was approved by the Investigational Review Board of the Ochsner Clinic Foundation. All patients enrolled in the protocol signed informed consent.

Procedure
All patients were pretreated with aspirin for ≥24 hours before the procedure, and aspirin was continued indefinitely. The renal stent placement procedure has been described previously. All patients had BNP measured on 4 occasions: 2 to 7 days before the procedure (n=23), within 24 hours of the intervention (n=27), 1 day after the intervention (n=27), and 7 days to 2 months after the intervention (n=25). Serum creatinine was measured 24 to 48 hours before and within 1 week after the renal artery intervention. Blood pressures were measured according to the guidelines proposed by the AHA, and the number of antihypertensive medications before the procedure, at hospital discharge, and at follow-up was recorded.

The operator performing the procedure visually estimated diameter stenosis. Kidney length was calculated by measuring the pole-to-pole kidney shadow during the parenchymal phase of renal angiography with computerized quantitative angiography (Image.Com, Inc). The estimated glomerular filtration rate (eGFR) was calculated with the Cockcroft-Gault equation and standardized in each patient to 1.73 m² body surface. The investigators obtained these measurements without knowledge of the patients’ BNP levels or blood pressures.

For determination of BNP, all blood samples were collected by venipuncture into EDTA tubes. The blood samples were kept at room temperature and analyzed within 4 hours with the Biosite assay (Biosite Diagnostics). For the present investigation and similar to previous studies, BNP levels were dichotomized through the use of published criteria for BNP normality at ≤80 pg/mL.9,21

Definitions
Hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg. Refractory hypertension was defined as a blood pressure that could not be reduced to <140/90 mm Hg with a 3-drug regimen. Improvement in hypertension (blood pressure responders) was defined as diastolic blood pressure <90 mm Hg and systolic blood pressure <140 mm Hg on the same or reduced number of antihypertensive medications or a reduction in diastolic blood pressure of ≥15 mm Hg on the same or reduced number of antihypertensive medications. These definitions follow the guidelines for reporting clinical trials in renal artery revascularization.22

Angiographic success was defined as a residual diameter stenosis of <30% after stent placement. Procedural success was defined as angiographic success and the absence of a major complication during hospitalization. Major complications included death, myocardial infarction, stroke, bleeding requiring transfusion, and need for hemodialysis or surgery. A significant decrease in BNP was defined as a decline in this peptide of >30% from baseline in patients with an elevated baseline BNP of >80 pg/mL.

Study End Points
The primary end point of this study was to compare the baseline and posttreatment BNP levels. The secondary end point was to determine whether the baseline BNP level correlated with clinical improvement in hypertension at follow-up.

Table 1. Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Age (mean±SD), y</th>
<th>74±3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male), n (%)</td>
<td>8 (30)</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>22 (81)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>9 (33)</td>
</tr>
<tr>
<td>Current tobacco abuse, n (%)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>CAD, n (%)</td>
<td>21 (78)</td>
</tr>
<tr>
<td>Prior MI, n (%)</td>
<td>4 (15)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>57±7</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>1.1±0.3</td>
</tr>
<tr>
<td>eGFR, ml·min⁻¹·1.73m⁻²</td>
<td>61±14</td>
</tr>
<tr>
<td>eGFR &lt;60 ml·min⁻¹·1.73m⁻², n (%)</td>
<td>12 (44)</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>173±19</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>89±13</td>
</tr>
<tr>
<td>Antihypertensives, n (%)</td>
<td>3.8±0.8</td>
</tr>
<tr>
<td>ACE/ARB</td>
<td>20 (74)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>18 (67)</td>
</tr>
<tr>
<td>CCB</td>
<td>11 (41)</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>20 (74)</td>
</tr>
<tr>
<td>α-Blocker</td>
<td>4 (15)</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; MI, myocardial infarction; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure; ARB, angiotensin receptor blocker; and CCB, calcium channel blocker. n=27.

Statistical Analysis
Categorical variables are reported as frequencies and percentages; continuous variables, as mean±SD. However, when the variable was significantly skewed or had extreme values, the median (25th to 75th percentiles) was reported. Student’s t tests or Wilcoxon’s 2-sample tests were used to compare continuous variables; χ² tests were used to compare categorical variables.

Bivariate correlation analysis was performed with Pearson’s or φ coefficients to investigate whether percent diameter stenosis was correlated with BNP and with hypertension improvement and whether BNP and eGFR were correlated with hypertension improvement. The correlation of BNP with hypertension improvement at follow-up was then assessed independently of multivariate analysis (partial correlation analysis), with correction for eGFR (a continuous variable), eGFR <60 ml·min⁻¹·m⁻² (a categorical variable), creatinine, and preprocedural diastolic blood pressure (SPSS version 11.0, SPSS Inc). Differences at the level of P<0.05 (2 tailed) were considered statistically significant.

Results
The baseline clinical characteristics of the patient population are shown in Table 1. The angiographic and procedural success rates were 100%. There were no procedural complications or in-hospital major cardiovascular events. After successful renal stent revascularization, the serum levels of BNP fell from 187 pg/mL (25th to 75th percentiles, 89 to 306 pg/mL) to 96 pg/mL (25th to 75th percentiles, 61 to 182 pg/mL; P=0.002) and remained low at follow-up (Figure 1). Systolic and diastolic blood pressures decreased from baseline values of 172±18 and 89±13 mm Hg before intervention to 144±24 and 72±12 mm Hg after renal stent placement at 3.5±1.3 months of follow-up (range, 2 to 7 months) (P<0.001 for both systolic and diastolic blood pressures). The number of antihypertensive medications decreased from
3.8 ± 0.8 before intervention to 3.2 ± 1 at follow-up (P = 0.02).

For the entire group, hypertension improved in 70% of the patients (19 of 27) at hospital discharge. Blood pressure improvement was sustained in 63% of patients (17 of 27) at 3.5 ± 1.3 months of follow-up.

Twenty-two patients (81%) with renal artery stenosis had a baseline BNP ≥ 80 pg/mL. In this group, hypertension improvement occurred in 77% of the patients (n = 17) compared with 0% of the 5 patients with a baseline BNP < 80 pg/mL (P = 0.001) (Figure 2). The sensitivities, specificities, and positive and negative predictive values of using a baseline BNP ≥ 80 pg/mL to predict hypertension improvement at 3.5 ± 1.3 months of follow-up were 100%, 50%, 77%, and 100%, respectively. After renal stent placement, BNP decreased by >30% of the baseline value in 17 patients (63%). In those patients whose posttreatment BNP fell by >30%, blood pressure improved at follow-up in 94% (16 of 17 patients). In patients whose BNP fell by ≤30%, only 1 patient (10%) had improved blood pressure (P < 0.001) (Figure 2).

After renal stent placement, there was a significantly greater decrease in BNP in blood pressure responders compared with blood pressure nonresponders (Figure 3).

Influence of GFR and Severity of Renal Artery Stenosis
Fifteen patients had eGFR ≥ 60 mL · min⁻¹ · 1.73 m⁻² (71 ± 8 mL · min⁻¹ · 1.73 m⁻²), and 12 patients had eGFR < 60 mL · min⁻¹ · 1.73 m⁻². eGFR was unchanged after renal stent placement (from 61 ± 13 to 63 ± 13 mL · min⁻¹ · 1.73 m⁻²; P = 0.058). Improvement in eGFR was observed only in the 9 patients with bilateral renal artery stenosis (from 57 ± 11 to 64 ± 10 mL · min⁻¹ · 1.73 m⁻²; P = 0.018), not in patients with unilateral renal artery stenosis (from 61.7 ± 14 to 62 ± 12 mL · min⁻¹ · 1.73 m⁻²; P = 0.42). Differences between patients with eGFR < 60 and ≥ 60 mL · min⁻¹ · 1.73 m⁻² are shown in Table 2.

We found no correlation between the severity of the renal artery stenosis and preprocedural BNP levels (as a continuous variable) (P = 0.51), BNP ≥ 80 pg/mL (as a categorical variable) (P = 0.30), or blood pressure response (P = 0.24).

Blood Pressure Responders Versus Nonresponders
The baseline clinical characteristics, including the BNP and eGFR before and after intervention, for blood pressure responders compared with nonresponders are shown in Table 3. Six blood pressure responders (35%) and 3 nonresponders (30%) had bilateral renal artery stenosis (P = 0.56). Blood pressure responders after renal stent placement had a higher preprocedural diastolic blood pressure and lower eGFR. Additionally, blood pressure responders were more likely to have an elevated baseline BNP ≥ 80 pg/mL.

There was a good correlation between baseline BNP ≥ 80 pg/mL, postprocedural BNP drop, and GFR with blood pressure response to treatment (Table 4). Using a multivariate correlation analysis, we found that preprocedural BNP...
preprocedural diastolic blood pressure. From glomerular mesangial and epithelial cells. Renal artery circulating BNP is the ventricular myocardium. However, peptide (ANP) and BNP is upregulated in the 2-kidney, 1-clip renin-angiotensin-aldosterone system. The main source of increases the GFR, promotes natriuresis, and antagonizes the revascularization. Stenosis do not have a blood pressure reduction after renal revascularization. 40% of patients with refractory hypertension and renal artery stenosis is important for clinicians, because 20% to strongly suggests a cause-and-effect relationship for renal revascularization. Patients with clinical evidence of congestive heart failure or an acute coronary syndrome were excluded, so the baseline elevation of BNP in our study cannot be attributed to these conditions. The significant decline in BNP after renal artery revascularization strongly suggests a cause-and-effect relationship for renal artery stenosis and BNP elevation. Identifying patients who are likely to have blood pressure improvement after renal revascularization is important for clinicians, because 20% to 40% of patients with refractory hypertension and renal artery stenosis do not have a blood pressure reduction after renal revascularization.

BNP plays an important role in renal physiology. It increases the GFR, promotes natriuresis, and antagonizes the renin-angiotensin-aldosterone system. The main source of circulating BNP is the ventricular myocardium. However, BNP has also been shown to be synthesized and released from glomerular mesangial and epithelial cells. Renal artery stenosis induces the activation of the renin-angiotensin system with increased levels of angiotensin II. Recent animal data have shown that angiotensin II directly stimulates the synthesis and release of BNP independently of cell stretching and that the mRNA for both atrial natriuretic peptide (ANP) and BNP is upregulated in the 2-kidney, 1-clip renal artery stenosis model. Our data support the results of these experimental studies in that we found an elevated BNP (>80 pg/mL) in 81% (22 of 27) of our hypertensive patients with renal artery stenosis. BNP may represent a biochemical marker for activation of the renin-angiotensin system and thus may be a useful clinical assay to help identify patients who will benefit from revascularization.

In agreement with previous studies, eGFR increased only in patients with bilateral renal artery stenosis after stent revascularization. In unilateral renal artery stenosis, the unobstructed kidney is capable of compensating for the contralateral stenotic kidney by increasing its GFR. After revascularization, however, the compensatory increase in GFR of the nonobstructed kidney returns to baseline, and the overall GFR remains unaltered. Although BNP has been reported to be elevated in patients with a GFR <60 mL · min⁻¹ · 1.73 m⁻², serum creatinine, and preprocedural diastolic blood pressure.

<table>
<thead>
<tr>
<th>TABLE 2. Blood Pressure and BNP Comparison Between Patients With eGFR &lt;60 and ≥60 mL · min⁻¹ · 1.73 m⁻²</th>
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</thead>
<tbody>
<tr>
<td>eGFR &lt;60 (n=12)</td>
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<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Age (mean±SD), y</td>
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<tr>
<td>BNP prestent, pg/mL</td>
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<tr>
<td>BNP poststent, pg/mL</td>
</tr>
<tr>
<td>BNP &gt;80 pg/mL, n (%)</td>
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<tr>
<td>BNP drop &gt;30%, n (%)</td>
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<td>BNP drop, %</td>
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<tr>
<td>SBP prestent, mm Hg</td>
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<tr>
<td>DBP prestent, mm Hg</td>
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<tr>
<td>Mean BP prestent, mm Hg</td>
</tr>
<tr>
<td>SBP at follow-up, mm Hg</td>
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<tr>
<td>DBP at follow-up, mm Hg</td>
</tr>
<tr>
<td>Mean BP at follow-up, mm Hg</td>
</tr>
<tr>
<td>Hypertension improvement, n (%)</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure. Values in parentheses are 25th and 75th percentiles. *P<0.001 vs BNP after stent placement.

Discussion
We have demonstrated that BNP is increased in patients with refractory hypertension and renal artery stenosis and that this peptide may be useful for predicting which patients will have clinically improved blood pressure after successful renal revascularization. Patients with clinical evidence of congestive heart failure or an acute coronary syndrome were excluded, so the baseline elevation of BNP in our study cannot be attributed to these conditions. The significant decline in BNP after renal artery revascularization strongly suggests a cause-and-effect relationship for renal artery stenosis and BNP elevation. Identifying patients who are likely to have blood pressure improvement after renal revascularization is important for clinicians, because 20% to 40% of patients with refractory hypertension and renal artery stenosis do not have a blood pressure reduction after renal revascularization.

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We have demonstrated a strong correlation between BNP and hypertension improvement that is independent of eGFR, serum creatinine, and baseline blood pressure. An elevated baseline BNP of >80 pg/mL was a strong predictor of hypertension improvement at follow-up (100% sensitivity, 77% positive predictive value, and 100% negative predictive value), with a specificity of 50%. There was no correlation between severity of the renal artery stenosis on angiography and blood pressure improvement or elevated BNP. Angiography suffers from limited precision.
when trying to image aorto-ostial renal artery lesions. These vessels arise at unpredictable angles from the aorta and may not be seen well with 2D angiographic imaging. Previous reports have also failed to show this correlation.27,29 and 1 study found that a reduction in renal cortical perfusion was not directly related to the severity of renal artery stenosis.30

**Study Limitations**

Our study is limited by the relatively small number of patients; the likelihood of a type I statistical error is increased. Because we do not have a control group of refractory hypertensive patients without renal artery stenosis, it remains speculative whether other potential factors such as older age or the presence of coronary artery disease may have contributed to the elevated BNP in this group of patients with renal artery stenosis.31–33

**Conclusions**

We report that BNP is increased in patients with medically refractory hypertension and significant renal artery stenosis and that the elevated BNP level falls after revascularization. An elevated preprocedural BNP level correlates strongly with clinical improvement in blood pressure after successful percutaneous renal revascularization. A BNP-guided strategy may improve patient selection for the revascularization procedure and clinical outcomes.

**References**


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