Does Brain Natriuretic Peptide Have a Direct Renal Effect in Human Hypertensives?


Abstract—Systemic infusion of brain natriuretic peptide (BNP) stimulates natriuresis and diuresis but has variable effects on the renal vasculature. In this study, we investigated whether BNP has any direct effects on the kidney in hypertensive patients. Three stepwise increasing doses of BNP (60, 120, and 180 pmol/min) or placebo were infused into the renal artery of 26 hypertensive patients. Renal blood flow was determined with the $^{133}$Xenon washout technique. Before and after infusion of BNP, arterial and venous blood samples were taken for cGMP, renin, and creatinine concentration. Intra-arterial blood pressure and heart rate were monitored continuously. Intrarenal BNP infusion did not induce significant changes in renal blood flow despite increases in circulating levels of cGMP. The latter, however, was not associated with changes in the cGMP gradient across the kidney. In addition, we did not find any BNP-related changes in the secretion of active renin and in creatinine extraction. At the highest dose, heart rate increased after BNP infusion without a change in mean intra-arterial blood pressure. In conclusion, this study suggests that at least in hypertensive subjects, BNP has no direct intrarenal hemodynamic effects and that the rise in circulating cGMP without changes in net renal extraction of this second messenger is related to a primary extrarenal target of BNP. (Hypertension. 2003;41:119-123.)

Key Words: natriuretic peptides ■ vasodilation ■ hypertension, renal ■ human ■ kidney ■ hemodynamics ■ vasoconstriction ■ hormones

Systemic infusion of brain natriuretic peptide (BNP) stimulates natriuresis and diuresis1–6 and inhibits plasma renin activity1–3,7,8 but has variable effects on the renal vasculature. Although most but not all studies in healthy humans reported that BNP infusion increases glomerular filtration rate,1,5–7 renal plasma flow has been found to decrease,1,7 to increase,5 or to remain unchanged.3,8 Variations in the renovascular effects of BNP could be related to differences in BNP levels reached during the experiments, but it is equally possible that the renal changes are, in part, secondary to systemic effects. Indeed, BNP not only acts on the kidney but also affects blood pressure, heart rate, cardiac output, and systemic vascular resistance.2,3,5,6,8,9 In those studies in which changes in renal plasma flow are reported, it is important to keep in mind that such alterations may simply be due to concurrent changes in cardiac output. If, for instance, renal fraction (that is, the proportion of cardiac output perfusing the kidneys) remains unaltered during systemic BNP infusion, it is unlikely that the peptide has exerted a direct effect on the renal vasculature. If, on the other hand, renal fraction increases, relative renal vasodilation must have occurred. In most studies, this has not been taken into account.

Local administration of BNP in a regional vascular bed in amounts that will not have systemic effects allows for assessing whether BNP has any direct effects on certain parts of the circulation. With this approach, we and others have demonstrated previously that BNP induces a dose-dependent vasodilation in forearm vasculature.10,11 In the present study, we investigated whether BNP has any direct effects on the renal circulation. To this end, we infused BNP into the renal artery of hypertensive patients who were scheduled for renal angiography. Before and during the infusion, we measured renal blood flow, renin release, and the extraction of creatinine, the latter being taken as a marker of glomerular filtration. We also measured concentrations of cGMP, since this second messenger may reflect BNP activity.

Methods

Subjects
This study was performed in 26 hypertensive patients in whom renal artery stenosis was suspected on the basis of one or more of the following criteria: treatment-resistant hypertension despite the use of at least two adequately dosed antihypertensive agents, overt peripheral vascular disease, the presence of an abdominal bruit or an increase in serum creatinine during ACE inhibitor treatment. Anti-hypertensive medication, if any, was discontinued for 3 weeks before
the measurements. Before hospital admission, patients were randomly allocated to a placebo group and a BNP group. Because the effects of BNP are dependent on sodium intake, we instructed half of the patients from the BNP group to follow a salt-restricted diet (55 mmol of sodium per day) and the other half to adhere to a high-salt diet containing 220 mmol of sodium per day during the last week before the study. Compliance with the diet was checked by measuring sodium and creatinine output in 24-hour urine collections obtained during the last day before angiography. Patients were also instructed to refrain from smoking and drinking caffeine or alcohol containing beverages for at least 48 hours before the investigations. The Medical Ethics Committee of the Maastricht University Hospital approved the study, and all participants gave written informed consent. The investigations conformed to the principles outlined in the Declaration of Helsinki.12

Experimental Design
Experiments were performed in the angiography suite of the Department of Radiology, which is equipped with a radiographic system and a gamma camera. After selective catheterization of the renal artery and vein and before any administration of contrast material, blood samples were drawn simultaneously from the renal artery and both renal veins for determination of active plasma renin concentration (APRC), BNP, cGMP, and creatinine levels. Subsequently, mean renal blood flow (MRBF) was measured, first in the left kidney and then in the right, by means of the 133Xenon washout technique as described earlier.13,14 Next, BNP in incremental doses of 60, 120, and 180 pmol/min or placebo (glucose 5%) was infused into the right renal artery. Each dose was continued for 10 minutes. MRBF was measured at the end of each dosing interval. At the end of the highest dose of BNP, blood samples for determination of APRC, BNP, cGMP, and creatinine levels were drawn again from the right renal vein and the femoral artery. The latter was necessary to avoid contamination of blood by BNP from the infusion line. Blood samples were spun immediately and plasma was stored at a temperature of −80°C until assay. Heart rate and intra-arterial blood pressure were monitored continuously during each MRBF measurement. Angiography was performed only after all measurements had been completed.

Assay Methods
APRC was measured by the IRMA method (Nichols Institute Diagnostics, Wijchen, The Netherlands). BNP and cGMP levels were measured by means of a competitive protein-binding radioimmunoassay (Peninsula Laboratories Inc, RIK 9086, and IBL Hamburg RE 29071, respectively). Before the assay, plasma samples of BNP were acidified and extracted with the use of a SEP-Pak C18 column (Waters-Millipore). In our hands, the intra-assay and inter-assay variability of 8% for repeated measurements. Therefore, this study is able to demonstrate a 10% difference in MRBF in 10 control and 16 experimental subjects, with a power of 85%

Results
Baseline clinical characteristics of the study participants are summarized in Table 1. Although 8 patients had some degree of renal artery stenosis, hemodynamically significant lesions existed in none.

Effect of BNP or Placebo Infusion on Renal Blood Flow
At baseline, MRBF did not differ significantly between the placebo and the BNP groups (P=0.262; Table 2). Likewise, no differences in flow could be detected between patients receiving a low-salt diet and those receiving a high-salt diet. Responses did not differ either between kidneys with or without renal artery stenosis. Infusion of placebo did not induce significant changes in MRBF (P=0.976; Table 2). However, MRBF was not altered by BNP, either (P=0.204; Table 2). The latter was true both in the low-salt and in the high-salt group (P=0.308, and P=0.366, respectively). Furthermore, changes in 1VR during BNP infusion (1.8 [−11.3 to 37.0]) did not differ significantly from zero (P=0.234). In addition, there was no difference in IVR between the BNP and placebo groups (P=0.856). No relation was seen between IVR and baseline renal flow.

### Table 1. Characteristics of the Study Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo</th>
<th>BNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (male/female)</td>
<td>10 (6/4)</td>
<td>16 (11/5)</td>
</tr>
<tr>
<td>Age, y</td>
<td>56 (37–67)</td>
<td>53 (46–68)</td>
</tr>
<tr>
<td>Diagnosis, EH/RAS</td>
<td>10/4</td>
<td>12/4</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.7 (22.6–28.0)</td>
<td>25.3 (23.3–27.2)</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>136 (120–144)</td>
<td>140 (123–149)</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>77 (66–85)</td>
<td>70 (60–75)</td>
</tr>
<tr>
<td>Urinary sodium excretion, mmol/24 hours</td>
<td>65 (41–80)</td>
<td>LS: 68 (48–83)</td>
</tr>
<tr>
<td>creatinine</td>
<td>HS: 204 (161–244)</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as median and interquartile range.

### Table 2. Absolute Flow (ml/100 g/min) at Baseline and After BNP (or Placebo) Infusion

<table>
<thead>
<tr>
<th>Infusion of</th>
<th>Baseline</th>
<th>60 pmol/min</th>
<th>120 pmol/min</th>
<th>180 pmol/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>241 (163–290)</td>
<td>233 (156–297)</td>
<td>263 (162–314)</td>
<td>251 (172–305)</td>
</tr>
<tr>
<td>BNP</td>
<td>166 (111–248)</td>
<td>190 (137–236)</td>
<td>176 (166–260)</td>
<td>184 (137–206)</td>
</tr>
</tbody>
</table>

Data are presented as median and interquartile range.
Plasma Levels of BNP, cGMP, Renin, and Creatinine

Placebo infusion did not alter any of the measured variables or their gradients across the kidney. Intrarenal BNP infusion not only caused the expected increase in venous levels of this peptide but enhanced arterial BNP levels (both \(P < 0.01\); Table 3). Parallel with the increase in plasma BNP, we observed a rise in cGMP, both in arterial and in venous renal blood samples (both \(P < 0.01\)). The net BNP and cGMP gradients across the kidney, however, did not change during BNP infusion (\(P = 0.182\) and \(P = 0.875\), respectively). Moreover, BNP infusion did not induce significant changes in net APRC production and creatinine extraction (Figure 1). Fractional creatinine extraction did not change, either (Table 3). When the placebo and BNP groups were compared, no differences were observed in APRC production or (fractional) creatinine extraction between both groups.

Blood Pressure and Heart Rate

Mean intra-arterial pressure did not change during either placebo or BNP infusion (\(P = 0.475\) and \(P = 0.650\), respectively; Figure 2). Whereas heart rate did not change during placebo infusion (\(P = 0.505\)), it increased significantly from 67 beats per minute at baseline to 72 beats per minute at the highest dose of BNP infusion (\(P = 0.011\); Figure 2). The difference in heart rate responses between the placebo and the BNP group was, however, not statistically significant (0.05 < \(P < 0.10\)).

**Discussion**

The present study shows that intrarenal BNP infusion in supine hypertensive patients does not induce significant changes in renal blood flow despite increases in circulating levels of cGMP. In addition, we did not find BNP-related changes in the secretion of active renin and in creatinine extraction.

At baseline, median BNP levels of our hypertensive patients were almost 3 times higher than those we measured before in the forearm of healthy subjects. This difference corroborates previous studies that demonstrated elevated

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**TABLE 3. Plasma Levels of BNP, cGMP, APRC, and Creatinine at Baseline and After BNP Infusion**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline Arterial (pg/mL)</th>
<th>Baseline Venous (pg/mL)</th>
<th>After BNP Infusion Arterial (pg/mL)</th>
<th>After BNP Infusion Venous (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP</td>
<td>83.6 (60.0–149.6)</td>
<td>82.1 (53.8–132.1)</td>
<td>510.8 (318.6–761.0)*</td>
<td>577.3 (271.0–880.5)*</td>
</tr>
<tr>
<td>cGMP</td>
<td>6.8 (5.7–9.3)</td>
<td>5.6 (2.9–7.3)</td>
<td>10.3 (6.5–15.8)*</td>
<td>7.9 (5.2–9.7)*</td>
</tr>
<tr>
<td>APRC, µU/mL</td>
<td>19.0 (13.4–40.1)</td>
<td>26.5 (17.2–39.1)</td>
<td>26.9 (14.5–36.8)</td>
<td>26.4 (17.1–38.1)</td>
</tr>
<tr>
<td>Creatinine, mmol/mL</td>
<td>79.5 (61.5–113.3)</td>
<td>70.5 (57.0–89.3)</td>
<td>78.5 (58.3–108.5)</td>
<td>68.0 (58.8–81.3)</td>
</tr>
<tr>
<td>Fractional creatinine extraction</td>
<td>0.20 (0.13–0.26)</td>
<td>0.20 (0.13–0.26)</td>
<td>0.20 (0.13–0.26)</td>
<td>0.20 (0.13–0.26)</td>
</tr>
</tbody>
</table>

*Data are presented as median and interquartile range. *\(P < 0.01\) vs baseline.

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**Figure 1.** Net renal renin (A) and creatinine (B) production/extraction at baseline and after placebo or BNP infusion. Data are presented as median and interquartile ranges. No changes were observed.

**Figure 2.** Heart rate (HR, A) and mean intra-arterial blood pressure (MAP, B) at baseline and after infusion of placebo or BNP. Data are presented as median and interquartile ranges. *\(P < 0.02\), BNP infusion vs baseline.
plasma BNP concentrations in hypertension and which may be related to left ventricular hypertrophy and/or diastolic dysfunction.16,17

Intra-arterial infusion of BNP caused an $\approx 7$-fold increase in renal venous BNP levels. Although this increase is to be expected, we also observed a comparable rise in arterial plasma BNP levels, indicating overflow of BNP into the systemic circulation. The slight increase in heart rate at the highest dose of BNP is compatible with this notion, and, in the absence of changes in mean arterial blood pressure, may point toward mild baroreceptor activation. The elevated BNP levels at the end of the infusion period approached but mostly exceeded the venous levels reached in systemic infusion studies.1–3,8 However, in this respect, a simple comparison is not justified because the BNP levels reported here were obtained at the end of a dose-response study. Thus, in our experiment, the systemic vasculature must have been exposed to lower concentrations of BNP during the greater part of the study. Despite higher circulating BNP, the gradient of BNP across the kidney did not change. In fact, we found no evidence for renal extraction of BNP, neither at baseline nor during BNP infusion. This casts doubt on the supposition of a direct renal effect of BNP.

In a previous study, we demonstrated that intra-arterial BNP infusion into the human forearm induces a dose-dependent vasodilatation through an increase in cGMP and c-type natriuretic peptide levels.15 The second messenger cGMP is thought to be generated by activation of the natriuretic peptide receptor A and/or through nitric oxide production. The present study shows that BNP infusion, indeed induced cGMP release in our patients. Both renal venous and arterial cGMP plasma levels rose significantly after BNP infusion, but there was no change in the net renal cGMP gradient, with even a tendency for uptake rather than release. Taken together, these observations suggest that BNP by itself is not able to trigger cGMP release intrarenally, and this may explain why we failed to observe renal vasodilatation. In addition, it suggests that cGMP was produced somewhere else in the cardiovascular system. Other variables to assess the effect of BNP, for example, creatinine extraction (as marker for filtrating capacity) and renin secretion, also showed no differences after BNP infusion.

Another explanation for the lack of variation in MRBF may be that BNP, except for inducing vasodilatation, simultaneously stimulates a vasoconstrictor mechanism within the kidney and that any locally produced cGMP is excreted into the urine. Indeed, it has been demonstrated before that there is no evidence for renal extraction of BNP, neither at baseline nor during BNP infusion. This casts doubt on the supposition of a direct renal effect of BNP.

Induced vasodilation in human and rat tissue. In phenylephrine-preconstricted human omental and pericardial resistance arteries, and rat mesenteric, renal, saphenal, and uterine arteries, in only 4 of 14 experiments 10 nmol/L BNP (human BNP-32 and rat BNP-45) caused a relaxation. On the contrary, 10 μmol/L acetylcholine induced dilation in all experiments (unpublished observations).

Limitations

One could argue that the Xenon-washout technique is not sensitive enough to detect increases in renal blood flow. However, in earlier studies we showed that both acetylcholine and adenosine induce renal vasodilatation, and that this was adequately detected with our method.19,20 So, if there was any (net) effect of BNP, it must have been very small. Another limitation of the present study is that for ethical reasons, we could not study healthy subjects. It is well known that in diseases such as hypertension, several mechanisms may be altered and dysfunctional. Therefore, it is possible that BNP produces greater renal vasodilatation in normal subjects and that our patients merely exhibited decreased sensitivity for this peptide. In addition, we cannot exclude the possibility that BNP-induced changes may be more pronounced in the upright position. Furthermore, creatinine extraction may not be the best marker for evaluating changes in glomerular filtration rate. Finally, we want to stress that thus far, our findings are only applicable to those hypertensive patients who fulfilled our selection criteria, that is, the ones with treatment-resistant hypertension and/or target organ damage.

Perspectives

Further investigations are needed to determine BNP binding sites in the kidney and the role of urinary cGMP excretion. In addition, more research is needed to investigate the role of ET-1 as a mediator of BNP-induced renal effects. Finally, the hypothesis needs to be tested that renal effects of BNP can only be elicited in the face of systemic hemodynamic changes.

Acknowledgments

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References


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