Effects of Atrial Natriuretic Peptide Infusion and Its Metabolism in Patients with Chronic Renal Failure

TOMOYUKI TAKAGI, MITSUSHIGE NISHIKAWA, YASUKIYO MORI, HIROAKI MATSUBARA AND MITSUO INADA
Second Department of Internal Medicine, Kansai Medical University, Osaka 570, Japan

Abstract. Synthetic α-human atrial natriuretic peptide (hANP) was infused continuously at a rate of 80 ng/kg/min for 20 min into normal volunteers and patients with chronic renal failure (CRF) receiving hemodialysis. Blood pressure (BP) decreased significantly both in normals and in patients with CRF. The magnitude and the duration of the decrease, however, were greater in patients with CRF. The plasma aldosterone concentration (PAC) decreased significantly in normals and only minimally in patients with CRF. The half time (T1/2) of plasma hANP in patients with CRF (M(SE): 4.5±0.5 min) was longer than that in normals (1.8±0.2 min). Moreover, the metabolic clearance rate in patients with CRF (64±7 ml/kg/min) was less than in normals (150±20 ml/kg/min). Thus, the T1/2 in plasma of hANP in patients with CRF was noticeably longer than in a normal control group. These findings suggest that hANP suppresses PAC regardless of electrocyte imbalances and/or volume change induced by kidney dysfunction and that the kidney may be important in degrading hANP.

Key words: Atrial natriuretic peptide, Chronic renal failure, Hemodialysis, Aldosterone.

THE PLASMA atrial natriuretic peptide (ANP) concentration is reported to be increased in chronic renal failure (CRF) [1–3]. It is also reported [4, 5] that in spite of this increase in human atrial natriuretic peptide (hANP), blood pressure (BP) decreases in proportion to the dose of synthetic hANP when it is infused into patients with hypertension (HT). Although hANP is known to cause diuresis and natriuresis, vasodilation and suppression of the plasma aldosterone concentration (PAC) [4–6], the PAC may be influenced secondarily by natriuresis and BP. Therefore, it is of interest to investigate the effect of α-hANP infusion on PAC in patients with CRF in whom no diuresis is observed. However, there are only a few reports [7] concerning the effects of hANP infusion on BP and PAC as well as plasma renin activity (PRA) in patients with renal dysfunction. In addition, the role of the kidneys in the clearance of hANP is not well understood.

We undertook the present clinical study to investigate the effects of hANP on vasodilation and adrenal suppression independent of its diuretic and natriuretic activities. We also studied the half time of plasma hANP in patients with CRF receiving hemodialysis (HD).

Subjects and Methods

Infusion of synthetic α-hANP

Nine normal male volunteers aged 24–38 yr (mean ± SE: 29±1 yr) and eleven male patients with CRF receiving HD aged 34–84 yr (58±5 yr) were studied. The diseases underlying CRF in these patients were diabetic nephropathy in one and chronic glomerulonephritis in ten patients.
The patients had been on HD for between one month and two years (5.5±1.7 months) and received HD regularly for 4 h two or three times a week. The patients gained 1.5-3.0 kg between HD sessions. The daily volume of urine in patients with CRF was less than 200-300 ml and their serum creatinine and urea nitrogen concentrations averaged 11.2±0.6 mg/dl and 91±5 mg/dl, respectively.

After 20 min of bed rest on the morning before the day of HD, synthetic α-hANP (Suntory, Japan) was infused continuously by vein at a rate of 80 ng/kg/min for 20 min with a continuous infusion pump (Eiko, Japan). α-hANP was dissolved in 0.9% NaCl and the injected volume was fixed to 4.0 ml. The α-hANP was injected in the peripheral vein of one arm and a blood sample was taken from the other arm with a chilled syringe containing 1 mg di-sodium EDTA and 1000 units aprotinin / ml of blood. Urine samples were collected before and 20 min after the start of the α-hANP infusion.

The heart rate (HR) and BP were recorded with a sphygmomanometer (Nippon Colin, Japan) at -10, 0, 10, 20, 30 and 40 min after initiating the α-hANP infusion. The plasma and urine sodium concentrations, PRA and PAC were measured before and 20 min after starting the α-hANP infusion. The plasma hANP concentration was measured every 10 min by radioimmunoassay (RIA) as reported previously [8]. ANP was measured after the extraction from plasma with a Sep-pak C18 cartridge (Waters Associates, Milford, MA). The intra assay variation was 5.8% and inter assay variation was 7.2%. The minimal detectable concentration was approximately 8 pg/ml plasma. The dilution curve of plasma from a normal volunteer paralleled the standard curve, and the dilution curves of plasma from two patients with CRF during the α-hANP infusion also closely paralleled the standard curve in the present RIA.

The normal ranges of PAC and plasma hANP concentrations were 39–109 pg/ml and 0–66 pg/ml [8], respectively, and the normal range of PRA was 0.3–2.9 ng/ml/h.

Pharmacokinetics of hANP in plasma

This study was performed in five normal male volunteers (ages: 27±1 yr) and in five male patients with CRF receiving HD (49±8 yr). The underlying diagnosis in each patient was chronic glomerulonephritis. Before a session of HD, the mean serum urea nitrogen concentration was 83±7 mg/dl and the serum creatinine was 10.5±1.2 mg/dl. Synthetic α-hANP was infused continuously as described above. The HR and BP were recorded at -10, -5, 0, 10, 15 and 20 min after the infusion was initiated and every 2 min, thereafter, for the succeeding 10 min. The plasma hANP concentration was measured at each time point mentioned above.

The half time (T1/2), distributional volume (Vd) and metabolic clearance rate (MCR) of plasma hANP were calculated by the one compartment method [9], according to the following formulas:

\[
\text{MCR} = \frac{\text{infusion rate}}{\text{mean steady state concentration} - \text{basal concentration}}
\]

\[
\text{Vd} = \frac{\text{MCR}}{K}
\]

\[
K = 0.693/T1/2
\]

The Vd and MCR were adjusted for 1 kg body weight.

Results

Infusion of synthetic α-hANP

Figure 1 shows the changes in BP observed during α-hANP infusion in normal volunteers (upper left) and in patients with CRF (upper right). The systolic BP in normal volunteers (115±3 mmHg) decreased significantly (p<0.01) and reached a minimum of 104±3 mmHg at 20 min after the start of the infusion. The diastolic BP also decreased from 72±3 to 57±3 mmHg at 10 min. Similarly, the systolic BP in patients with CRF decreased significantly (p<0.01) from 158±8 to 130±7 mmHg at 20 min and the diastolic BP decreased from 81±5 to 68±5 mmHg at 20 min (p<0.01). As expected, significant (p<0.01) reflex tachycardia was observed both in normal volunteers (lower left) and in patients with CRF (lower right) with the α-hANP infusion (Fig. 1; normal, 63±3 to 73±3; CRF, 72±5 to 80±5/min).

The systolic and diastolic BP in normal volunteers returned to the basal levels 10 min after the
end of the infusion. However, at 10 min after the end of the infusion the BP in patients with CRF was significantly lower than it was before the infusion and the systolic BP was still below its basal level at 20 min after the end of the infusion (Fig. 1).

The urine volume in normal volunteers increased markedly (p<0.01) from 36±7 to 311±46 ml/20 min with α-hANP infusion, but in patients with CRF any increase was too small to analyse with confidence. The urinary sodium concentrations in normal volunteers also increased markedly (p<0.01) during hANP infusion (113±17 mEq/l) as compared with before (20±1 mEq/l) the infu-
**Table 1.** Plasma renin activity and plasma aldosterone concentrations before and after α-hANP infusion

<table>
<thead>
<tr>
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<th>Before</th>
<th>After</th>
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<tbody>
<tr>
<td>Plasma renin activity (ng/ml/h)</td>
<td>normal 2.4±0.4</td>
<td>2.5±0.3</td>
</tr>
<tr>
<td></td>
<td>CRF 6.2±2.2</td>
<td>6.5±2.4</td>
</tr>
<tr>
<td>Plasma aldosterone concentration</td>
<td>normal 62±12</td>
<td>49±9*</td>
</tr>
<tr>
<td></td>
<td>CRF 144±26</td>
<td>115±16</td>
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</table>

*p<0.05 (compared to prevalue).

CRF: Chronic renal failure.

The serum sodium concentration in normal volunteers and in patients with CRF did not change appreciably (normal: 134±2 to 130±4, CRF: 132±2 to 132±2 mEq/l).

The PRA did not change during the ANP infusion in either normal volunteers (2.4±0.4 to 2.5±0.3 ng/ml/h) or patients with CRF (6.2±2.2 to 6.5±2.4 ng/ml/h) (Table 1). Despite BP being suppressed and PRA being unchanged, the PAC in normal volunteers decreased significantly (p<0.05) from 62±12 to 49±9 pg/ml during the infusion. The mean basal PAC in patients with CRF (144±26 pg/ml) was significantly (p<0.05) higher than in normal volunteers (62±12 pg/ml) and was also decreased (to 115±16 pg/ml) by the infusion.

**Pharmacokinetics of plasma hANP**

Figure 2 shows the changes which occur in plasma hANP concentrations during synthetic α-hANP infusion in normal volunteers (left) and in patients with CRF (right). The basal plasma ANP concentration in patients with CRF averaged 200±47 pg/ml, which was significantly (p<0.05) higher than that in normal volunteers (39±9 pg/ml). The plasma hANP concentration plateaued between 10 min and 20 min after the α-hANP infusion was initiated in both normal volunteers and in patients with CRF. The mean steady state concentration of hANP in patients with CRF (1300±69 pg/ml) was significantly (p<0.01) higher than that in normal volunteers (550±32 pg/ml). The ratio of the increase in the hANP concentration with infusion to the basal level tended to be higher in patients with CRF than in normal volunteers (0.05<p<0.1).

The mean Vd in normal volunteers (26±6 liters) did not differ significantly from that in patients with CRF (24±2 liters, Table 2). The T1/2 of plasma ANP in normal volunteers averaged 1.8±0.2 min (range: 1.1–2.4 min). The T1/2 in patients with CRF averaged 4.5±0.5 min (range: 3.4–6.4 min), which was significantly (p<0.01) longer than that in normal volunteers (Table 2). The MCR in normal volunteers ranged from 120 to 230 ml/kg/min and averaged 150±20 ml/kg/min. The MCR in patients with CRF ranged from 48 to 88 ml/kg/min and averaged 64±7 ml/kg/min. Thus, the mean MCR in patients with CRF decreased significantly (p<0.05) to less than

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**Fig. 2.** The hANP concentrations during α-hANP infusion in normal volunteers (left) and in patients with chronic renal failure (right). See legend to Fig. 1.
Table 2. Plasma hANP metabolism in normal volunteers and in patients with chronic renal failure (CRF)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Body weight (kg)</th>
<th>Vd (liters)</th>
<th>T1/2 (min)</th>
<th>MCR (ml/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal volunteers</td>
<td>1</td>
<td>M</td>
<td>31</td>
<td>56</td>
<td>28</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>M</td>
<td>26</td>
<td>73</td>
<td>22</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>M</td>
<td>25</td>
<td>67</td>
<td>13</td>
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<tr>
<td></td>
<td>4</td>
<td>M</td>
<td>29</td>
<td>72</td>
<td>45</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>M</td>
<td>25</td>
<td>62</td>
<td>20</td>
<td>1.7</td>
</tr>
<tr>
<td>Mean±SE</td>
<td></td>
<td></td>
<td>27±1</td>
<td>66±3</td>
<td>26±6</td>
<td>1.8±0.2</td>
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CRF Patients

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<tr>
<td>6</td>
<td>M</td>
<td>45</td>
<td>65</td>
<td>25</td>
<td>3.4</td>
<td>59</td>
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<tr>
<td>7</td>
<td>M</td>
<td>34</td>
<td>45</td>
<td>23</td>
<td>4.8</td>
<td>66</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>76</td>
<td>65</td>
<td>21</td>
<td>3.8</td>
<td>48</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>55</td>
<td>47</td>
<td>21</td>
<td>4.3</td>
<td>61</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>34</td>
<td>58</td>
<td>29</td>
<td>6.4</td>
<td>88</td>
</tr>
<tr>
<td>Mean±SE</td>
<td></td>
<td>49±8</td>
<td>56±4</td>
<td>24±2</td>
<td>4.5±0.5**</td>
<td>64±27*</td>
</tr>
</tbody>
</table>

Vd=Distributional volume, T1/2=Half time, MCR=Metabolic clearance rate.
* p<0.05 vs normal volunteers; ** p<0.01 vs normal volunteers.

Discussion

Published reports conflict on how PRA and PAC are affected by synthetic α-hANP [4, 6, 10–13]. In the present study, PAC was suppressed by α-hANP infusion in all normal volunteers and in all patients with CRF. This result agrees with those in other reports [4, 12, 13]. However, in the present study, PRA in normal volunteers and in patients with CRF did not change significantly with hANP. PRA was reported to be suppressed by ANP in some reports [6, 10, 11], and to be unaffected, or even increased in others [4, 12, 13]. Even if PRA is suppressed directly by ANP, the induced decrease in BP may stimulate PRA, thereby causing PRA to change minimally. In the present study, the patients with CRF did not have significant diuresis, so the suppression of PAC in these patients is believed to be a direct effect of ANP.

In the present study, we confirmed that the plasma hANP concentration is high in patients with CRF, and this was consistent with other reports [1–3]. The increase in ANP seen in the present study may be due to the age difference between normal volunteers and patients with CRF because ANP is reported to be increased in the elderly [14]. In that study, however, the increase was less than double and all patients but one in the present study were under sixty. Therefore, the contribution of age to the increase in ANP seen in patients with CRF seems negligible. Synthetic α-hANP infusion in patients with CRF induced a greater increase in the plasma hANP concentration than in normal volunteers. Serial dilutions of plasma obtained during the infusion from patients with CRF, however, yielded curves parallel to the standard. Furthermore, the decrease in BP and the duration of the effect were greater in patients with CRF than in normal volunteers, suggesting that in patients with CRF the plasma contains mainly α-hANP and, to a lesser degree, its metabolites. Thus, the present results suggest that the metabolism of α-hANP is prolonged in patients with CRF.

Turnover studies of plasma hANP have been performed in normal volunteers by several investigators who reported the T1/2 of hANP in plasma to be 1.7–3.2 min [15–17]. These estimates are similar to the values obtained in normal volunteers in the present study, 1.8±0.2 min. This validates the present estimates of the T1/2 in plasma of hANP.
ANP is metabolized in the liver, kidney, lung and spleen, but the relative importance of these organs, in this regard, is unclear [18–20]. Recently, Tonolo et al. [21] reported that BP and HR did not change at all with synthetic α-hANP infusion and that the T1/2 of hANP was only slightly increased in patients with CRF when compared with normal volunteers. They suggested that the kidney was not the only important organ in ANP metabolism. The reason for the discrepancy in these results is unclear, but their infusion rate of 10 pmol/kg/min was much smaller than our present infusion rate (26 pmol/kg/min). Accordingly the effects of hANP on BP and HR in our study were greater than in the study by Tonolo et al. One possible reason for the discrepancy is that, as the ANP infusion rate increases, the role of the kidney becomes more clear. We suggest that the role of the kidney is more important in patients with hypertension in whom ANP secretion is stimulated. The plasma ANP concentration in the renal arteries of dogs is reported to be significantly higher than in the renal veins, suggesting that ANP is metabolized in the kidney [22]. More recently, Webb et al. [23] reported that several processes, one being enzymatic degradation, participate in clearing ANP from the circulation. Endoprotease, in particular, is present in the kidney in high concentration and has been shown to degrade ANP [23–25]. Thus, the role of renal function in the metabolism of plasma hANP in humans remains controversial.

In the present paper, the T1/2 of ANP in patients with CRF increased more than twofold as compared with that in normal volunteers, as did the MCR. The present findings indicate that renal function is important in the metabolism of ANP. Further study is necessary to elucidate precisely the nature of hANP metabolism in the kidney.

References


