Low-dose Atrial Natriuretic Peptide for Chronic Kidney Disease in Coronary Surgery

Isamu Yoshitake, MD, Akira Sezai, MD, Mitsumasa Hata, MD, Tetsuya Niino, MD, Satoshi Unosawa, MD, Shinji Wakui, MD, and Motomi Shiono, MD

Department of Cardiovascular Surgery, Nihon University School of Medicine, Tokyo, Japan

Received: August 25, 2010; Accepted: September 8, 2010
Corresponding author: Isamu Yoshitake, MD. Department of Cardiovascular Surgery, Nihon University School of Medicine, Ohyaguchi kami-machi 30-1, Itabashi-ku, Tokyo 173-8610, Japan
Email: iyoshita@med.nihon-u.ac.jp
©2011 The Editorial Committee of Annals of Thoracic and Cardiovascular Surgery. All rights reserved.

Purpose: Chronic kidney disease (CKD) is an independent risk factor for cardiovascular disease. We investigated the effectiveness of human atrial natriuretic peptide (hANP) infusion in CKD patients undergoing coronary artery bypass grafting (CABG).

Patients and Methods: We analyzed 134 consecutive cases in which CABG had been performed in our hospital from 2002 to 2005. They were divided into four groups: Group A (n = 19) was CKD + placebo, Group B (n = 30) was non-CKD + placebo, Group C (n = 22) was CKD + hANP, and Group D (n = 63) was non-CKD + hANP. The serum creatinine (mg/dl) and estimated glomerular filtration rate (ml/min/1.73 m²) were measured as evaluation values.

Results: The value of sCr changed preoperatively and at 1 year postoperatively from 1.09 ± 0.09, 51.3 ± 4.4 to 1.26±0.42, 49.4±14.4 in Group A, from 0.77 ± 0.14, 75.5 ± 12.1 to 0.91 ± 0.40, 72.3 ± 19.5 in Group B, from 0.99 ± 0.12, 54.8 ± 3.0 to 0.93 ± 0.16, 64.2 ± 12.3 in Group C and from 0.77 ± 0.13, 77.7 ± 13.4 to 0.83 ± 0.17, 75.9 ± 16.2 in Group D, respectively. There was a significant difference between Group A and Group C regarding the change of creatinine (p = 0.0022)

Conclusion: Our study has confirmed that an infusion of hANP during CABG in patients with CKD not only improves perioperative renal function, but also prevents the progression of CKD.

Key words: chronic kidney disease, human atrial natriuretic peptide, coronary artery bypass grafting, cardiovascular disease

Introduction

Research and experience has gradually established chronic kidney disease (CKD) as an independent risk factor for cardiovascular disease (CVD) through mechanisms including volume overload, cardiac remodeling, worsened blood pressure control, and inflammation.1, 2) Moderate renal dysfunction is also recognized as a reliable indicator of systemic arterial sclerosis and a risk factor for cerebrovascular and cardiovascular disease.3) For these reasons, early diagnosis and treatment of CKD are believed to be important for improving the long-term prognosis of CVD. Acute renal failure occurs in 1% to 31% of patients after cardiac surgery4–8) and the prognosis of such patients is relatively poor with a mortality rate of 1.3% to 30%.5, 9, 10) Thus, CKD is one of the major risk factors for cardiac surgery. Cooper et al. previously reported that the mortality rate of CKD patients having coronary artery bypass grafting (CABG) is 1.8% in stage 3, 4.3% in stage 4, and 9.3% in stage 5.11)

Human atrial natriuretic peptide (hANP) is a hormone that is secreted in response to expansion of the atrial wall, hANP has a vasodilator action, a potent natriuretic effect,
inhibits the renin-angiotensin-aldosterone system (RAAS), and dilates the coronary arteries.\textsuperscript{12, 13} It is used clinically in Japan to treat heart failure. Cardiac surgery with cardiopulmonary bypass (CPB) leads to an increase in circulating hormones from the RAAS and catecholamines, as well as a decrease in urine output and accumulation of water in the third space. We considered that hANP could be useful in this pathological situation, and we have shown that continuous infusion of low-dose hANP from the start of CPB suppresses left ventricular remodeling by blocking the RAAS and promoting natriuresis.\textsuperscript{14–16)}

hANP is usually administered for heart failure through continuous infusion at a starting dose of 0.05 to 0.1 μg/kg/min or through bolus injection. Because of our knowledge about past studies, we also suggested that efficacy of low dose hANP was obtained at a dose of only 0.02 μg/kg/min without the problems of hypotension and rebound associated with hANP administration.\textsuperscript{14, 15)}

In this study, we hypothesized that the administration of hANP during CABG would be beneficial for CKD due to RAAS inhibition and it would be tends to prevent the renal function, and we investigated the effect of hANP by retrospective analysis.

**Patients and Methods**

A total of 347 patients were enrolled in a previous CABG study and randomized to receive hANP at Nihon University Itabashi Hospital from 2002 to 2005. The patients were randomized to two groups, which were a hANP group that received an infusion of hANP (Suntory Inc., Osaka Japan and Daiichi-Sankyo Pharmaceutical Inc., Tokyo, Japan) from the initiation of CPB and a placebo group that was administered physiological saline. Treatment was done in a blinded manner. But cases of an age over 81 years, poorly controlled diabetes mellitus (hemoglobin A1C ≥ 7.5), left ventricular dysfunction with a left ventricular ejection fraction of less than 35%, maintenance hemodialysis, and preoperative circulatory assist were excluded from this study. The remaining 134 patients were enrolled in the present study and were divided them into four groups, which were Group A (CKD + placebo: 19 patients), Group B (non-CKD + placebo: 30 patients), Group C (CKD + hANP: 22 patients), and Group D (non-CKD + hANP: 63 patients) (Fig. 1). We conducted two inter-group comparisons, one with CKD complicated group between Group A and Group C and one without CKD complicated group between Group B and Group D, to evaluate the effect of hANP administering in each inter-groups, and all patients were followed up for one year.

CKD was classified into five stages based on the estimated glomerular filtration rate (eGFR): Stage 1, ≥ 90 mL/min/1.73 m\(^2\); Stage 2, 60–89 mL/min/1.73 m\(^2\); Stage 3, 30–59 mL/min/1.73 m\(^2\); Stage 4, 15–29 mL/min/1.73 m\(^2\); and Stage 5, < 15 mL/min/1.73 m\(^2\). The eGFR was calculated by the following formula provided in the Japanese Society of Nephrology CKD Practice Guide: eGFR (mL/min/1.73 m\(^2\)) = 194 × (Serum creatinine (sCr) [mg/dl])\(^{-1.094}\) × (Age [years])\(^{-0.287}\). The result was multiplied by a correction factor of 0.739 for women. In this study, CKD was defined as a preoperative eGFR ≤ 60 mL/min/1.73 m\(^2\).

**hANP therapy and Surgical procedures**

Infusion of hANP or saline was started at 0.02 μg/kg/min from the initiation of CPB. When the diet was started after operation, the infusion rate of hANP was reduced to 0.01 μg/kg/min and was discontinued at 12 hours later (Administering day of hANP: 2.39 ± 0.80 days). Conventional CABG was performed under cardiac arrest with cardioplegia and CPB was done by nonpulsatile perfusion at a tepid temperature (target rectal temperature: 34°C).

**Assessment of renal function**

sCr is generally thought to be a poor indicator of renal function, while GFR is a more accurate parameter\textsuperscript{17} that identifies patients with mild renal impairment who have normal or nearly normal sCr levels. In this study, we measured sCr and eGFR at preoperatively and 1 week (post 1W), 1 month (post 1M) and 1 year postoperatively (post 1Y) and compared the 1-year postoperative sCr and eGFR values with the respective preoperative values to
assess preventive effect of hANP therapy as follows. Preoperative eGFR was calculated by using the last measured preoperative sCr value.

1) The recovery value of sCr at 1Y
   : post 1Y sCr - Pre sCr (mg/dl)
2) The recovery value of eGFR at 1Y
   : post 1Y eGFR - Pre eGFR (ml/min/1.73m²)
3) The recovery ratio of sCr at 1Y
   : post 1Y sCr / Pre sCr (%)
4) The recovery ratio of eGFR at 1Y
   : post 1Y eGFR / Pre eGFR (%)

Statistical analysis
Results are presented as the mean ± standard deviation, and a probability (p) value of less than 0.05 was defined as indicating significance. Patient characteristics were analyzed with one-way analysis of variance (ANOVA) for continuous variables and the \( \chi^2 \) test for categorical variables. Values were compared by ANOVA with the Turkey-Kramer multiple comparison test, respectively. All analyses were conducted with SPSS software (SPSS Inc. IL, USA).

Table 1 Clinical profiles of the four groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>group A (CKD + placebo) (n = 19)</th>
<th>group B (non-CKD + placebo) (n = 30)</th>
<th>group C (CKD + hANP) (n = 22)</th>
<th>group D (non-CKD + hANP) (n = 63)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, years</td>
<td>67.7 ± 7.4</td>
<td>64.3 ± 10.3</td>
<td>69.3 ± 4.9</td>
<td>62.3 ± 8.1</td>
<td>0.017</td>
</tr>
<tr>
<td>Gender (%female)</td>
<td>2 (10.5)</td>
<td>7 (23.3)</td>
<td>5 (22.7)</td>
<td>9 (14.3)</td>
<td>0.817</td>
</tr>
<tr>
<td>BMI, mean ± SD</td>
<td>24.6 ± 3.2</td>
<td>24.3 ± 2.7</td>
<td>23.8 ± 2.7</td>
<td>24.4 ± 3.0</td>
<td>0.866</td>
</tr>
<tr>
<td>Diagnosis (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMI</td>
<td>0 (0)</td>
<td>3 (10)</td>
<td>3 (13.6)</td>
<td>2 (3.2)</td>
<td>0.819</td>
</tr>
<tr>
<td>OMI</td>
<td>6 (31.6)</td>
<td>5 (16.7)</td>
<td>3 (13.6)</td>
<td>15 (23.8)</td>
<td>0.865</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>10 (52.6)</td>
<td>17 (56.7)</td>
<td>14 (63.6)</td>
<td>42 (66.7)</td>
<td>0.206</td>
</tr>
<tr>
<td>Stable angina</td>
<td>3 (15.8)</td>
<td>5 (16.7)</td>
<td>2 (9)</td>
<td>4 (6.3)</td>
<td>0.107</td>
</tr>
<tr>
<td>Risk factor (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (52.6)</td>
<td>10 (33.3)</td>
<td>11 (50)</td>
<td>19 (30.2)</td>
<td>0.229</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (89.5)</td>
<td>23 (76.7)</td>
<td>20 (90.9)</td>
<td>47 (74.6)</td>
<td>0.599</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>15 (78.9)</td>
<td>27 (90)</td>
<td>14 (63.6)</td>
<td>45 (71.4)</td>
<td>0.354</td>
</tr>
<tr>
<td>Smoking</td>
<td>11 (57.9)</td>
<td>15 (50)</td>
<td>18 (81.8)</td>
<td>42 (66.7)</td>
<td>0.087</td>
</tr>
<tr>
<td>Ejection fraction, mean ± SD, %</td>
<td>68.4 ± 15.6</td>
<td>70.3 ± 12.5</td>
<td>64.3 ± 13.1</td>
<td>64.6 ± 11.5</td>
<td>0.146</td>
</tr>
<tr>
<td>sCr, mean ± SD, mg/dl</td>
<td>1.09 ± 0.09</td>
<td>0.77 ± 0.14</td>
<td>0.99 ± 0.12</td>
<td>0.77 ± 0.13</td>
<td>0.001</td>
</tr>
<tr>
<td>eGFR, mean ± SD, ml/min/1.73m²</td>
<td>51.3 ± 4.4</td>
<td>75.5 ± 12.1</td>
<td>54.8 ± 3.0</td>
<td>77.7 ± 13.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Emergent operation (%)</td>
<td>0 (0)</td>
<td>5 (16.7)</td>
<td>6 (27.2)</td>
<td>13 (14.3)</td>
<td>0.101</td>
</tr>
<tr>
<td>Number of graft, mean ± SD</td>
<td>2.9 ± 0.8</td>
<td>3.1 ± 0.8</td>
<td>3.0 ± 0.7</td>
<td>3.2 ± 0.9</td>
<td>0.395</td>
</tr>
<tr>
<td>ACCT, mean ± SD, min</td>
<td>65.5 ± 24.0</td>
<td>72.0 ± 42.1</td>
<td>76.0 ± 20.2</td>
<td>81.4 ± 31.5</td>
<td>0.059</td>
</tr>
<tr>
<td>ECCT, mean ± SD, min</td>
<td>124.3 ± 37.6</td>
<td>134.9 ± 53.7</td>
<td>126.3 ± 29.3</td>
<td>143.8 ± 44.8</td>
<td>0.137</td>
</tr>
<tr>
<td>30-day mortality (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
</tbody>
</table>

*p one-way analysis of variance (ANOVA) for continuous variables and \( \chi^2 \) test for categorical variables.

BMI: body mass index; AMI: acute myocardial infarction; OMI: old myocardial infarction; sCr: serum creatinine; eGFR: estimated glomerular filtration rate; ACCT: aortic cross clamp time; ECCT: extracorporeal circulation time

Results
Preoperative characteristics showed no significant differences among the four groups, apart from the age and preoperative renal function (sCr and eGFR) (Table 1). The number of the patients in each stage of CKD as follows: Group A and Group C contained only stage 3 patients (Group A: n = 19, Group C: n = 22), Group B included 5 patients (16.7%) of stage 1 and 25 patients (83.3%) of stage 2, Group D included 14 patients (22.2%) of stage 1 and 49 patients (77.8%) of stage 2.

Isosorbide dinitrate was used by all patients postoperatively. Treatment with dopamine (17% of hANP use, 16% of non-hANP use), dobutamine (9.2% of hANP use, 10.4% of non-hANP use) and norepinephrine (5.6% of hANP use, 9.7% of non-hANP use) during the perioperative period showed no significant differences regardless of hANP use. And the actual numbers of inotropic support (over 5\( \gamma \) of DOA or combination with DOA and NA) over 24 hours were 3 cases (15.8%) in group A, 3 cases (10%) in group B, 4 cases (18.2%) in group C and 4 cases (6.3%) in group D, respectively. Both hANP and saline were infused continuously, and the administration was not
discontinued for reasons such as hypotension in any of the patients. There weren’t the patients who have any cardiovascular events that might have influenced renal function, i.e. recurrent angina, need for repeat revascularization and need for repeat catheterization during follow up period.

**Effect on CKD**

The sCr (mg/dl) and e-GFR (mL/min/1.73 m²) values changed as shown in the table after the operation (Table 2). The value of sCr changed preoperatively and at 1 year postoperatively from 1.09 ± 0.09 to 1.26 ± 0.42 in Group A, from 0.77 ± 0.14 to 0.91 ± 0.40 in Group B, from 0.99 ± 0.12 to 0.93 ± 0.16 in Group C and from 0.77 ± 0.13 to 0.83 ± 0.17 in Group D, respectively. And the value of eGFR changed from 51.3 ± 4.4 to 49.4 ± 14.4 in Group A, from 75.5 ± 12.1 to 72.3 ± 19.5 in Group B, from 54.8 ± 3.0 to 64.2 ± 12.3 in Group C and from 77.7 ± 13.4 to 75.9 ± 16.2 in Group D, respectively. Even a little improvement of sCr and eGFR were found in group C by one year after surgery.

Table 2  Assessment of renal function

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group A (CKD + placebo)</th>
<th>Group C (CKD + hANP)</th>
<th>Group B (non-CKD + placebo)</th>
<th>Group D (non-CKD + hANP)</th>
<th>p valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCr (pre), mean ± SD, mg/dl</td>
<td>1.09 ± 0.09</td>
<td>0.99 ± 0.12</td>
<td>0.77 ± 0.14</td>
<td>0.77 ± 0.13</td>
<td>0.997</td>
</tr>
<tr>
<td>sCr (post 1W), mean ± SD, mg/dl</td>
<td>1.30 ± 0.41</td>
<td>0.99 ± 0.22</td>
<td>&lt; 0.001</td>
<td>0.78 ± 0.16</td>
<td>0.994</td>
</tr>
<tr>
<td>sCr (post 1M), mean ± SD, mg/dl</td>
<td>1.08 ± 0.20</td>
<td>0.95 ± 0.16</td>
<td>0.069</td>
<td>0.79 ± 0.15</td>
<td>1.0</td>
</tr>
<tr>
<td>eGFR (pre), mean ± SD, ml/min/1.73m²</td>
<td>46.5 ± 14.1</td>
<td>56.9 ± 12.5</td>
<td>0.178</td>
<td>75.3 ± 16.0</td>
<td>0.962</td>
</tr>
<tr>
<td>eGFR (post 1W), mean ± SD, ml/min/1.73m²</td>
<td>53.5 ± 9.1</td>
<td>58.4 ± 9.4</td>
<td>0.706</td>
<td>73.8 ± 13.3</td>
<td>0.645</td>
</tr>
<tr>
<td>eGFR (post 1Y), mean ± SD, ml/min/1.73m²</td>
<td>49.4 ± 14.4</td>
<td>64.2 ± 12.3</td>
<td>0.022</td>
<td>72.3 ± 19.5</td>
<td>0.755</td>
</tr>
<tr>
<td>recovery value of sCr at 1Y, mean ± SD, mg/dl</td>
<td>1.15 ± 0.39</td>
<td>0.94 ± 0.14</td>
<td>0.057</td>
<td>1.17 ± 0.36</td>
<td>1.08 ± 0.18</td>
</tr>
<tr>
<td>recovery ratio of eGFR at 1Y, mean ± SD, mg/dl</td>
<td>0.16 ± 0.41</td>
<td>0.14 ± 0.38</td>
<td>0.022</td>
<td>0.14 ± 0.38</td>
<td>0.06 ± 0.14</td>
</tr>
</tbody>
</table>

*aANOVA with the Turkey-Kramer multiple comparisons test.

* sCr: serum creatinine; eGFR: estimated glomerular filtration rate

were also significant difference with regard to the recovery value of sCr (p = 0.022) (Fig. 2) and recovery ratio of eGFR (p = 0.024), respectively. The number of the patients required dialysis or renal replacement therapy during follow up period were only one case (5.3%) which required dialysis 3 days after operation in group A.

**Discussion**

CKD is a new concept of kidney disease that was first described by the American National Kidney Foundation in 2002, as a disease entity including mild to end-stage renal disease (ESRD) due to any etiology, which was defined as an eGFR < 60 ml/min/1.73m² and/or the presence of proteinuria. There is evidence that CKD is an independent risk factor for CVD outcomes and all-cause mortality in the highest-risk populations. Go et al. assumed that a GFR of 60 ml/min/1.73 m² corresponded to 1.0 for the relative risk of cardiovascular events and all-cause death, and calculated that a GFR of 45–59 ml/min/1.73 m², 30–44 ml/min/1.73 m², 15–29 ml/min/1.73 m², and < 15 ml/min/1.73 m² increased the relative risk to 1.4–1.2 times, 2.0–1.8 times, 2.8–3.2 times, and 3.4–5.9 times, respectively. Taken together with the 30.6% rate of patients with CKD classified as Stage 3 in our study, it can be suggested that improving the long-term prognosis after CABG depends on early diagnosis and early
treatment of CKD.

We have previously reported findings for patients treated with hANP in a study that commenced in 1997. We have demonstrated that low-dose hANP during cardiac surgery not only compensates for problems induced by CPB (hemodilution, electrolyte abnormalities, etc.), but also protects the myocardium, inhibits arrhythmia, suppresses left ventricular remodeling, and protects against ischemia-reperfusion injury. Furthermore, our randomized controlled trial in 504 patients without renal impairment undergoing CABG demonstrated that hANP suppresses RAAS activity, has a potent natriuretic action, prevents postoperative renal dysfunction, and compensates for the adverse effects of CPB. However, we have not examined the effect of hANP in CKD patients. In light of these earlier findings, we hypothesized that the administration of hANP during CABG would also be effective for patients with CKD.

In this study, the renal function deteriorated by all groups except group C after the operation, then, we did the evaluation for comparison between groups so that the effect of hANP administering might verify whether there was a difference by the presence of the CKD. As a result, we noted that the infusion of hANP during CABG in patients with CKD not only improves perioperative renal function, but also prevents the progression of the CKD in this study.

ANP has a strong diuretic effect and also antagonizes the RAAS. It is known to have a renoprotective effect in acute renal insufficiency, chronic nephritis, and other models of nephropathy, as it protects against disorders of the renal tubules and stroma in addition to disorders of the glomeruli. ANP seems to maintain renal function and avoid dialysis by increasing medullary blood flow in the kidney, even in patients with acute renal insufficiency. Patients with CVD and CKD tend to be hypertensive due to the progression of systemic arteriosclerosis. Kidney damage in this clinical setting is presumed to initially affect the juxtamedullary glomerulus and outer medulla. Given that ANP dilates the vasa recta and increases medullary blood flow, hANP may be especially effective in patients with CKD and advanced arterial sclerosis.

Brown et al. have reported that an eGFR of less than 60 mL/min/1.73 m² was associated with worse 5-year survival and that eGFR is an adequate parameter for identifying acute kidney injury and the subsequent risk of mortality. Our findings also suggest that the eGFR is a useful parameter for risk management of coronary surgery.

However, the present study was retrospective. In the future, it will be necessary to conduct a prospective randomized study of hANP in CABG patients with CKD in order to confirm its effectiveness for improving renal function and long-term survival, and for reducing the incidence of major cardiovascular events.

References

2) Menon V, Sarnak MJ. The epidemiology of chronic