Continuous Low-Dose Infusion of Human Atrial Natriuretic Peptide in Patients With Left Ventricular Dysfunction Undergoing Coronary Artery Bypass Grafting

The NU-HIT (Nihon University working group study of low-dose Human ANP Infusion Therapy during cardiac surgery) for Left Ventricular Dysfunction

Akira Sezai, MD, PhD,* Mitsumasa Hata, MD, PhD,* Tetsuya Niino, MD, PhD,* Isamu Yoshitake, MD, PhD,* Satoshi Unosawa, MD, PhD,* Shinji Wakui, MD, PhD,* Kishu Fujita, MD,* Tadateru Takayama, MD, PhD,† Yuji Kasamaki, MD, PhD,† Atsushi Hirayama, MD, PhD,† Kazutomo Minami, MD, PhD*

Tokyo, Japan

**Objectives**
Continuous low-dose infusion of human atrial natriuretic peptide (hANP) in patients undergoing cardiac surgery on cardiopulmonary bypass (CPB) inhibits the renin-angiotensin-aldosterone system and compensates for the adverse effects of CPB.

**Background**
We examined the influence of hANP infusion on cardiac and renal function in patients with left ventricular dysfunction undergoing coronary artery bypass grafting (CABG).

**Methods**
The subjects were 133 patients who underwent CABG and had a pre-operative ejection fraction ≤35%. They were randomized to receive 0.02 μg/kg/min of hANP from the initiation of CPB (hANP group) or placebo (saline) infusion.

**Results**
Early post-operative mortality did not show a significant difference between the 2 groups, but perioperative complications were significantly less frequent in the hANP group (p = 0.015). Long-term all-cause mortality showed no difference, but the cardiac death-free rate at 5 or 8 years post-operatively was 98.5% in the hANP group and 85.5% in the placebo group (p = 0.0285). Post-operative ejection fraction was significantly larger and the post-operative brain natriuretic peptide level was significantly lower in the hANP group. Serum creatinine was significantly lower in the hANP group than the placebo group at 1 month, 6 months, and 1 year post-operatively, whereas the estimated glomerular filtration rate was significantly higher in the hANP group at these times.

**Conclusions**
In patients with left ventricular dysfunction undergoing CABG, hANP showed renal- and cardio-protective effects and reduced post-operative complications. It also improved the long-term prognosis. We suggest that hANP should be considered as part of perioperative management of patients with cardiac dysfunction undergoing cardiac surgery. (NU-HIT trial for LVD; UMIN000001652) (J Am Coll Cardiol 2010;55:1844–51) © 2010 by the American College of Cardiology Foundation

The results of coronary artery bypass grafting (CABG) have improved in recent years due to advances in operative techniques and post-operative management, but the operative mortality of patients with left ventricular dysfunction (LVD) undergoing CABG is still high at 4.4% to 11.6% (1–4). These patients also tend to require prolonged post-operative hospital stay for heart failure or serious arrhythmias, and the long-term prognosis is still unsatisfactory. In patients with LVD undergoing CABG, Nardi et al. (5) reported a cardiac death rate of 20.4% and a cardiac...
death-free rate of 63% at 10 years post-operatively. Appoo et al. (1) classified patients into 3 groups according to their pre-operative left ventricular ejection fraction (LVEF) (i.e., low EF [EF <30%], medium EF [EF 30% to 50%], and normal EF [EF >50%] groups) and reported that the 5-year survival rate was significantly lower in the low EF (77.7%) and medium EF groups (85.5%) than in the normal EF group (91.2%). Therefore, careful interdisciplinary care during the perioperative period is required in these patients.

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 (6,7). It is used clinically in Japan to treat heart failure. Heart surgery with cardiopulmonary bypass (CPB) leads to an increase of circulating hormones from the RAAS and catecholamines as well as decreased urine output and accumulation of water in the third space. Administration of hANP might counter such changes, and continuous low-dose infusion of hANP from the start of CPB has been reported to inhibit the RAAS and show a potent natriuretic effect, thus compensating for the adverse influence of CPB (8). In subsequent research, hANP has been shown to inhibit left ventricular (LV) remodeling and ischemia-reperfusion injury as well as have a myocardial protective effect (9–11). The NU-HIT (Nihon University working group study of low-dose Human ANP Infusion Therapy during cardiac surgery) was designed to examine the efficacy of hANP in patients undergoing cardiac surgery. The present research enrolled patients with LVD and a poor prognosis who were undergoing CABG with CPB (NU-HIT trial for LVD). This is the first study to investigate the effects of hANP in patients with LVD undergoing cardiac surgery.

Methods

Study protocol. The NU–HIT trial for LVD was a randomized, double-blind, placebo-controlled study of patients who had LVD and underwent CABG with CPB. The patients with cardiogenic shock and hemodialysis and having off-pump CABG were excluded. Among patients undergoing CABG at Nihon University Itabashi Hospital from March 1997 to March 2008, 135 were enrolled in the NU–HIT trial for LVD, and they had LVD with an LVEF ≥35% on pre-operative LV angiography. The EF was measured by center-line method on LV angiography. The patients were randomized into 2 groups, which were a hANP group that received an infusion of hANP (Suntory, Inc., Osaka, Japan; and Daiichi-Sankyo Pharmaceutical, Inc., Tokyo, Japan) from initiation of CPB and a placebo group that was administered physiological saline (Fig. 1). Treatment was done in a blinded manner. Because hANP is approved for acute cardiac failure but not for administration during cardiac surgery, approval for this study was received from the Ethics Committee of Nihon University Itabashi Hospital, the details of the study were explained to subjects, and informed consent was obtained. This study was registered with the University Hospital Medical Information Network (UMIN000001652).

Approval was obtained for a starting dose of 0.1 μg/kg/min for acute cardiac failure, but the initial low dose of 0.02 μg/kg/min was selected for this study because the subjects of this study did not have acute cardiac failure. Administration of hANP or placebo was initiated at the start of CPB, with the dosage decreased to 0.01 μg/kg/min at the commencement of oral medication and then discontinued after 12 h. Isosorbide dinitrate was administered to all subjects from before CPB withdrawal until commencement of oral medication. The CPB was performed by nonpulsatile perfusion at a low temperature (target rectal temperature: 34°). The bypass was connected to the left internal thoracic artery in patients undergoing surgery on the territory of the left anterior descending artery and a radial arterial and/or great saphenous venous graft for other sites. The levels of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and creatine kinase isoenzyme-myocardial band (CPK-MB) were measured by center-line method on LV angiography. The EF was measured by center-line method on LV angiography. The patients were randomized into 2 groups, which were a hANP group that received an infusion of hANP (Suntory, Inc., Osaka, Japan; and Daiichi-Sankyo Pharmaceutical, Inc., Tokyo, Japan) from initiation of CPB and a placebo group that was administered physiological saline (Fig. 1). Treatment was done in a blinded manner. Because hANP is approved for acute cardiac failure but not for administration during cardiac surgery, approval for this study was received from the Ethics Committee of Nihon University Itabashi Hospital, the details of the study were explained to subjects, and informed consent was obtained. This study was registered with the University Hospital Medical Information Network (UMIN000001652).

Approval was obtained for a starting dose of 0.1 μg/kg/min for acute cardiac failure, but the initial low dose of 0.02 μg/kg/min was selected for this study because the subjects of this study did not have acute cardiac failure. Administration of hANP or placebo was initiated at the start of CPB, with the dosage decreased to 0.01 μg/kg/min at the commencement of oral medication and then discontinued after 12 h. Isosorbide dinitrate was administered to all subjects from before CPB withdrawal until commencement of oral medication. The CPB was performed by nonpulsatile perfusion at a low temperature (target rectal temperature: 34°). The bypass was connected to the left internal thoracic artery in patients undergoing surgery on the territory of the left anterior descending artery and a radial arterial and/or great saphenous venous graft for other sites. The levels of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and creatine kinase isoenzyme-myocardial band (CPK-MB) were measured by center-line method on LV angiography. The EF was measured by center-line method on LV angiography. The patients were randomized into 2 groups, which were a hANP group that received an infusion of hANP (Suntory, Inc., Osaka, Japan; and Daiichi-Sankyo Pharmaceutical, Inc., Tokyo, Japan) from initiation of CPB and a placebo group that was administered physiological saline (Fig. 1). Treatment was done in a blinded manner. Because hANP is approved for acute cardiac failure but not for administration during cardiac surgery, approval for this study was received from the Ethics Committee of Nihon University Itabashi Hospital, the details of the study were explained to subjects, and informed consent was obtained. This study was registered with the University Hospital Medical Information Network (UMIN000001652).
peptide (BNP), plasma renin activity, angiotensin II, aldosterone, and serum creatinine (sCr) as well as the estimated glomerular filtration rate (eGFR) were measured pre-operatively, on return to the intensive care unit (ICU) after surgery and at 1 and 3 days and 1 week post-operatively. The creatine kinase isoenzyme-myocardial band (CPK-MB), BNP, sCr, and eGFR were also assessed at 1 and 6 months and 1 year post-operatively. The eGFR was calculated by the method proposed for Japanese persons by the Japanese Society of Nephrology (men: $194 \times Cr^{-1.094} \times age^{-0.287}$, women: $194 \times Cr^{-1.094} \times age^{-0.287} \times 0.739$) (12). The LVEF was measured pre-operatively and post-operatively (1 week, 1 month, and 1 year) by echocardiography, with experienced echocardiographers using Simpson’s method.

**End points.** The primary end points were: 1) early post-operative outcome (operative mortality and complications); and 2) long-term results (cardiac death- and event-free rate, overall survival rate after surgery). Post-operative complications were categorized as central nervous system disorders, cardiovascular disorders (low output syndrome, heart failure, perioperative myocardial infarction, and refractory arrhythmia), respiratory failure, acute renal failure (requiring dialysis), gastrointestinal disorders (a requirement for high calorie alimentation such as in patients with gastrointestinal bleeding, ileus, liver dysfunction), infections (sepsis, pneumonia, mediastinitis, and so forth), and other disorders requiring long-term ICU management. Cardiac events in this study were defined as: cardiac failure requiring treatment with cardiotonic agents or assisted circulation for 1 week or longer after surgery, cardiac failure requiring hospital treatment after discharge, perioperative myocardial infarction, recurrent ischemic heart disease after discharge, arrhythmia requiring treatment due to effect on post-operative hemodynamic status, and arrhythmia requiring hospital treatment after discharge. The secondary end points were: 1) cardiac function (EF, BNP); 2) post-operative CPK-MB (immediately after surgery; 3 h after surgery; and on the first, second, and third days after surgery); 3) renal function (sCr, eGFR, the maximum value and rate of increase of sCr $[\%\Delta Cr + (\text{maximum}\ sCr - \text{pre-operative}\ sCr} \times \text{pre-operative}\ sCr} \times 100])$, an increase of sCr by $\geq 0.3$ mg/dl compared with the pre-operative value; and 4) ANP, renin activity, angiotensin-II, aldosterone.

**Statistical analysis.** Data are expressed as the mean $\pm$ SD. Baseline comparisons between the groups and all other statistical analyses were performed with Student unpaired $t$ test and Fisher exact test where appropriate for categorical data. A $p$ value $< 0.05$ was considered to indicate statistical significance. Data with a skewed distribution (BNP, EF, ANP, RAAS, serum Cr, and eGFR) were analyzed by repeated measures analysis of variance, and Scheffe’s test was performed as a post hoc test.

All-cause mortality, the cardiac death-free rate, and the cardiac event-free rate were analyzed by the Kaplan-Meier method, and significance of differences was assessed by the log-rank test.

**Results**

**Patient enrollment.** Initially, 135 patients were enrolled in the NU-HIT trial for LVD, but 2 of these patients were switched to off-pump CABG during the operation and thus were excluded from the trial, leaving 133 patients. Among these 133 patients, 68 were assigned to the hANP group and 65 were assigned to the placebo group (Fig. 1). All patients were followed in our institute. Completion of follow-up was possible in all patients.

**Baseline characteristics.** Pre-operative patient characteristics showed no significant differences between the 2 groups (Table 1).

**Surgical procedures and post-operative management.** Table 2 shows the number of bypasses, aortic cross-clamping time, extracorporeal circulation time, mechanical support, and post-operative oral medications. No significant differences were observed between the hANP and placebo groups. Routine perioperative management of the blood pressure response was conducted. The duration of hANP infusion was $2.8 \pm 1.1$ days in the hANP group, whereas physiological saline was infused for $3.4 \pm 1.8$ days in the placebo group, and the period was significantly shorter in

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical Profile of the 2 Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>hANP Group (n = 68)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>65.9 ± 10.4</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>57/11</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.67 ± 0.17</td>
</tr>
<tr>
<td>EuroSCORE</td>
<td>5.8 ± 3.9</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>AMI</td>
</tr>
<tr>
<td></td>
<td>OMI</td>
</tr>
<tr>
<td></td>
<td>Unstable angina</td>
</tr>
<tr>
<td></td>
<td>Stable angina</td>
</tr>
<tr>
<td>Risk factor</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td></td>
<td>Obesity</td>
</tr>
<tr>
<td></td>
<td>Smoking</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td></td>
<td>Chronic renal failure</td>
</tr>
<tr>
<td>Oral medication</td>
<td>ARB</td>
</tr>
<tr>
<td></td>
<td>ACE-I</td>
</tr>
<tr>
<td></td>
<td>Calcium antagonist</td>
</tr>
<tr>
<td></td>
<td>Beta-blocker</td>
</tr>
<tr>
<td></td>
<td>Aldosterone blocker</td>
</tr>
<tr>
<td></td>
<td>Statin</td>
</tr>
<tr>
<td></td>
<td>Average follow-up (yrs)</td>
</tr>
</tbody>
</table>

Values are mean $\pm$ SD or n (%).

ACE-I = angiotensin-converting enzyme inhibitor; AMI = acute myocardial infarction; ARB = angiotensin receptor blocker; Ca = calcium; EuroSCORE = European System for Cardiac Operative Risk Evaluation; hANP = human atrial natriuretic peptide; OMI = old myocardial infarction.
Primary end points. EARLY POST-OPERATIVE OUTCOME.

No significant differences were observed in the 30- and 180-day mortality rate between groups, although the incidence of post-operative complications including arrhythmia was significantly lower in the hANP group. The time in ICU and the hospital stay were both significantly shorter in the hANP group (ICU time: p = 0.0393, hospital study: p = 0.0434) (Table 3).

LONG-TERM RESULTS. Late post-operative death occurred in 6 patients from the hANP group and in 5 from the placebo group (Table 3). The overall survival rate (including noncardiac death) in the hANP group and the placebo group was 97.0% and 90.8% at 2 years post-operatively; 87.0% and 84.1% at 5 years post-operatively; and 87.0% and 84.1%, respectively, at 8 years post-operatively. There were no significant differences between the 2 groups (p = 0.0578) (Fig. 2). However, the cardiac death-free rate in the hANP group and the placebo group was 98.5% and 92.3% at 2 years post-operatively, 98.5% and 85.5% at 5 years post-operatively, and 98.5% and 85.5%, respectively, at 8 years post-operatively. These rates were significantly higher in the hANP group than in the placebo group (p = 0.0285) (Fig. 2). Cardiac events occurred in 15 patients from the hANP group and in 38 from the placebo group (Table 3). The cardiac event-free rate in the hANP group and the placebo group was 82.1% and 49.0% at 2 years post-operatively, 82.1% and 41.5% at 5 years post-operatively, and 72.7% and

### Table 2: Operative and Post-Operative Data

<table>
<thead>
<tr>
<th></th>
<th>hANP Group (n = 68)</th>
<th>Placebo Group (n = 65)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCT (min)</td>
<td>28.1 ± 12.0</td>
<td>28.0 ± 13.7</td>
<td>0.963</td>
</tr>
<tr>
<td>CPBT (min)</td>
<td>97.0 ± 21.7</td>
<td>96.8 ± 24.0</td>
<td>0.945</td>
</tr>
<tr>
<td>Emergency</td>
<td>15 (22.1%)</td>
<td>14 (21.5%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Bypass</td>
<td>3.1 ± 0.8</td>
<td>3.1 ± 0.9</td>
<td>0.823</td>
</tr>
<tr>
<td>Arterial graft use</td>
<td>61 (89.7%)</td>
<td>58 (89.2%)</td>
<td>1.00</td>
</tr>
<tr>
<td>IABP support</td>
<td>1</td>
<td>3</td>
<td>0.358</td>
</tr>
<tr>
<td>Venoarterial bypass</td>
<td>0</td>
<td>2</td>
<td>0.237</td>
</tr>
<tr>
<td>Inotropic support</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td>33 (48.5%)</td>
<td>30 (46.2%)</td>
<td>0.863</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>20 (29.4%)</td>
<td>17 (26.2%)</td>
<td>0.847</td>
</tr>
<tr>
<td>PDE-III Inhibitor</td>
<td>21 (30.9%)</td>
<td>21 (32.3%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Furosemide</td>
<td>14 (20.6%)</td>
<td>28 (43.1%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Dosage of furosemide (mg)</td>
<td>11.7 ± 24.3</td>
<td>31.5 ± 42.8</td>
<td>0.0014</td>
</tr>
<tr>
<td>Dosage of potassium (mEq)</td>
<td>104.0 ± 66.1</td>
<td>211.7 ± 140.2</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are mean ± SD, n (%), or n.

ACCT = aortic cross-clamp time; CPBT = cardiopulmonary bypass time; CPK-MB = creatine kinase isoenzyme-myocardial band; Cr = creatinine; IABP = intra aortic balloon pumping; Max = maximum; PDE = phosphodiesterase; Preop = pre-operative; other abbreviations as in Table 1.

The hANP group (p = 0.027). Both hANP and saline were infused continuously, and administration was not discontinued for reasons such as hypotension in any of the patients. In the ICU, significantly fewer patients from the hANP group required intravenous administration of furosemide, and the dose was significantly lower. Potassium supplementation was also required less frequently in the hANP group (Table 2).

### Table 3: Post-Operative Data

<table>
<thead>
<tr>
<th></th>
<th>hANP Group</th>
<th>Placebo Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early post-operative outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>68</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>30-day death</td>
<td>0 (0%)</td>
<td>2 (3.1%)</td>
<td>0.237</td>
</tr>
<tr>
<td>Cause of death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hepatic insufficiency</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>180-day death</td>
<td>0 (0%)</td>
<td>3 (4.6%)</td>
<td>0.114</td>
</tr>
<tr>
<td>Cause of death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Hepatic insufficiency</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Complications</td>
<td>4 (5.9%)</td>
<td>10 (15.4%)</td>
<td>0.015</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mediastinitis</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hepatic insufficiency</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Post-operative arrhythmias</td>
<td>14</td>
<td>33</td>
<td>0.0003</td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td>2</td>
<td>10</td>
<td>0.0151</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>12</td>
<td>23</td>
<td>0.0296</td>
</tr>
<tr>
<td>ICU stay (days)</td>
<td>3.6 ± 1.9</td>
<td>4.4 ± 2.6</td>
<td>0.0393</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>13.7 ± 7.6</td>
<td>19.3 ± 21.0</td>
<td>0.0434</td>
</tr>
</tbody>
</table>

Values are n, n (%), or mean ± SD.

hANP = human atrial natriuretic peptide; ICU = intensive care unit.
The overall survival rate showed no significant difference between the 2 groups. The cardiac death-free rate was significantly higher in the hANP group than in the placebo group from Day 1 until 1 year post-operatively. Compared with the pre-operative value, the level in the hANP group was significantly lower from 1 month after surgery. In the placebo group, the levels on days 1 and 3 post-operatively were significantly higher than the pre-operative value. Although BNP decreased thereafter, it did not show a significant decline compared with the pre-operative value throughout the entire post-operative course (Table 4). No significant differences were observed in immediate post-operative CPK-MB levels between groups, although CPK-MB levels were significantly lower in the hANP group than the placebo group from day 1 post-operatively (Table 2).

RENAL FUNCTION. The pre-operative sCr was higher in the hANP group than the placebo group, because there were 4 patients with chronic renal failure (CRF) in the former group, although the difference was not significant (p = 0.1454). At 1 month, 6 months, and 1 year post-operatively, sCr was significantly lower in the hANP group than the placebo group. When CRF patients were excluded from both groups, the hANP group showed a significantly lower sCr than the placebo group throughout the entire post-operative course (from return to ICU until 1 year post-operatively) (Fig. 3). The pre-operative eGFR was lower in the hANP group than the placebo group, although the difference was not significant (p = 0.051). At 1 month, 6 months, and 1 year post-operatively, the hANP group had a significantly higher eGFR than the placebo group. When CRF patients were excluded from both groups, the hANP group had a significantly higher eGFR than the placebo group throughout the entire post-operative course (from return to ICU until 1 year post-operatively) (Fig. 4). The CRF patients had a pre-operative sCr ≥1.5 mg/dl and were not receiving dialysis. The peak sCr and the rate of Cr increase until 1 month post-operatively were significantly lower in the hANP group, and the number of subjects with a 0.3-mg/dl or higher increase in sCr over the pre-operative value was significantly smaller in the hANP group (Table 2). Only 1 patient from the hANP group required dialysis over the long term. In the placebo group, 2 patients started dialysis within 2 years post-operatively, and 1 each did so after 3 and 5 years, for a total of 4 patients (p = 0.054). One of these 4 patients had CRF pre-operatively, but the other 3 patients had normal sCr values pre-operatively.

ANP and RAAS. In the hANP group, the ANP level increased rapidly to approximately 10 times the pre-operative value. Renin was significantly higher in the hANP group on return to the ICU but tended to be lower
after that, although the difference was not significant. Angiotensin-II was significantly lower in the hANP group on return to the ICU and at 1 day and 1 week post-operatively. Aldosterone was significantly lower in the hANP group on return to the ICU and at 1 week post-operatively (Table 4).

**Discussion**

This study showed that administration of hANP to CABG patients with poor cardiac function was effective for improving both renal and cardiac function in the early post-operative period and also over the long term. Even though hANP was only administered for a few days in the acute stage, a potent cardio- and renal-protective effect was demonstrated. The preventive effect of hANP on ischemic recirculatory disorder, which we reported in our previous study, was also demonstrated by the results of post-operative CPK-MB in this study. During the early post-operative
period, BNP was significantly increased in the placebo group but not in the hANP group. The cardio-protective effect of hANP was also evident in BNP values over the long term, and the rates of cardiac death and cardiac events were reduced. The renal-protective effect of hANP was clear from the sCr and eGFR data in the acute post-operative period and also over the long term. Angiotensin-II and aldosterone levels at 1 week post-operatively were, upon examination of the RAAS, significantly lower in the hANP group. In addition, they recovered to the pre-operative levels in the hANP group but did not recover in the placebo group even 1 week post-operatively. These results showed that hANP exerted an early effect countering the adverse influences of extracorporeal circulation. This study is the first investigation of CABG patients with LVD that has assessed cardiac function over the long term post-operatively. We suggest, because of the results of this study, that hANP should be considered as part of perioperative management for protection of cardiac and renal function.

Both hANP (carperitide) and BNP (nesiritide) are already used to treat heart failure and have recently been reported to be effective for acute myocardial infarction. A large-scale multicenter study (J-WIND [Japan-Working Groups of Acute Myocardial Infarction for the Reduction of Necrotic Damage by ANP or Nicorandil] study) on administration of hANP after reperfusion therapy for acute myocardial infarction showed that the infarct size was significantly reduced, cardiac function was improved, and cardiac death and heart failure rates were significantly lower in the hANP group than in the placebo group (13). In addition, Kasama et al. (14) reported that administration of hANP for 48 h after percutaneous coronary intervention in patients with acute myocardial infarction improves cardiac sympathetic activity and prevents LV remodeling.

Small-scale studies of hANP in heart surgery have already been reported, but there have been few randomized controlled trials. Valsson et al. (15) administered hANP for 30 min post-operatively to patients who had acute renal failure associated with heart failure and reported a 62% increase of urine volume, 43% increase of GFR, and 38% increase of renal blood flow, along with a 30% decrease of renal vascular resistance. The same group also reported a larger study that showed less need for dialysis and a higher dialysis-free survival rate (16). Hayashida et al. (17) studied patients undergoing mitral valve surgery with extracorporeal circulation and reported that their hANP group had a significantly higher urine output as well as better hemodynamic status and fluid balance. Human atrial natriuretic peptide has a diuretic effect, due to a direct action on the glomeruli and renal tubules. It prevents worsening of the electrolyte balance after high-dose administration of diuretics, increases urinary sodium excretion, and prevents renal parenchymal damage (18). From our results and those of Valsson et al. (15), Swärd et al. (16), and Hayashida et al. (17), it is clear that hANP both inhibits the RAAS and stimulates renal function.

Human atrial natriuretic peptide is only used in Japan at present, whereas BNP has not been approved in Japan but is used in Western countries. The NAPA (Nesiritide Administered Peri-Anesthesia) trial on use of BNP during heart surgery was performed in the U.S. (19), with subjects similar to those of the present study. In the BNP group, the peak sCr was lower and GFR was higher, whereas the survival rate at 180 days post-operatively was significantly higher in the BNP group than the placebo group (19). Our study of hANP obtained results comparable to those of the NAPA trial.

In the NAPA trial, early post-operative (until discharge) renal function and mortality until 180 days after surgery were investigated, whereas in our trial we evaluated not only early post-operative but also until 1 year post-operative renal and cardiac function and examined the RAAS, which has been reported to be affected more by hANP. Moreover, the
mean observation period of this study was as long as 4 years. This study yielded the interesting finding that several days of post-operative administration can affect the long-term prognosis.

We showed that hANP improve both renal and cardiac function in the acute post-operative period as well as over the long term. A trial of BNP in patients with pre-operative renal dysfunction (eGFR <60 ml/min) was reported by the Mayo Clinic (20), showing better post-operative results in the BNP group.

Few reports have been published about the use of hANP and BNP in heart surgery, and there have been no comparisons of these 2 peptides. From the results of our study, the NAPA trial, and the Mayo Clinic study, it seems that use of hANP or BNP during heart surgery can improve post-operative renal function and cardiac function in patients with renal or cardiac dysfunction, that the incidence of post-operative complications is reduced, and that long-term improvement is also obtained.

Accordingly, we suggest that perioperative use of hANP or BNP should be considered in patients with cardiac dysfunction undergoing cardiac surgery. Study limitations. In this study, we demonstrated the efficacy of hANP in patients with cardiac dysfunction undergoing CABG, and we suggest that hANP treatment be considered as a new method of perioperative management. However, there are limitations to the conclusions that can be drawn from this study, because of the low subject numbers, with only 133 cases. A large-scale future study should verify our results and clarify the efficacy of hANP therapy and associated problems.

Conclusions

In patients with LV dysfunction undergoing CABG, hANP showed renal- and cardio-protective effects and reduced post-operative complications. It also improved the long-term prognosis. We suggest that hANP should be considered as part of perioperative management of patients with cardiac dysfunction undergoing cardiac surgery.

Reprint requests and correspondence: Dr. Akira Sezai, Department of Cardiovascular Surgery, Nihon University School of Medicine, 30-1 Oyaguchi-kamimachi Itabashi-ku, Tokyo 173-8610, Japan. E-mail: address: asezai@med.nihon-u.ac.jp.

REFERENCES


Key Words: atrial natriuretic factor ● cardiopulmonary bypass ● coronary artery bypass grafting ● left ventricular dysfunction ● natriuretic peptides.