

CLINICAL RESEARCH

Clinical Trial

# Influence of Continuous Infusion of Low-Dose Human Atrial Natriuretic Peptide on Renal Function During Cardiac Surgery

## A Randomized Controlled Study

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- Objectives** The purpose of this study was to determine the effect of human atrial natriuretic peptide (hANP) in patients who underwent coronary artery bypass grafting (CABG) on renal function.
- Background** Acute renal failure after cardiac surgery is associated with high morbidity and mortality.
- Methods** A total of 504 patients who underwent CABG were divided into 2 groups: 1 group received hANP at 0.02  $\mu\text{g}/\text{kg}/\text{min}$  from the start of cardiopulmonary bypass (hANP group), and 1 group did not receive hANP (placebo group). Various parameters were measured before and after surgery.
- Results** There was no difference in mortality between the 2 groups, but post-operative complications were less frequent in the hANP group ( $p = 0.0208$ ). In the hANP group, serum creatinine (Cr) was significantly lower and urinary Cr and Cr clearance were significantly higher from post-operative day 1 to week 1. The maximum post-operative Cr level and percent increase of Cr were significantly lower in the hANP group ( $p < 0.0001$ ). Patients with Cr exceeding 2.0 mg/dl included 1 in the hANP group and 8 in the placebo group, showing a significant difference ( $p = 0.0374$ ). Four patients in the placebo group and none in the hANP group required hemodialysis, but the difference was not statistically significant.
- Conclusions** Continuous infusion of low-dose hANP from the start of cardiopulmonary bypass effectively maintained post-operative renal function. Infusion of hANP prevents early post-operative acute renal failure and helps to achieve safer cardiac surgery. (Clinical Trial registration number: UMIN00001440) (J Am Coll Cardiol 2009;54:1058–64) © 2009 by the American College of Cardiology Foundation

Acute renal failure occurs after cardiac surgery in 2.4% to 16% of patients who have normal renal function pre-operatively, and the prognosis of such patients is relatively poor, with a mortality rate of 1.3% to 30% (1–3). The mortality rate rises to 33% to 63.7% in patients requiring hemodialysis (2,4,5). Deterioration of renal function after cardiac surgery is considered to be attributable to cardiopulmonary bypass (CPB) in many cases, and it has been

reported that off-pump coronary artery bypass (OPCAB) is less frequently associated with complications such as acute renal failure and stroke (6,7). On the other hand, it has also been reported that OPCAB is associated with a lower graft patency rate and post-operative angina, and that there is no difference in post-operative renal function (8–11). The annual report of the Japanese Association for Coronary Artery Surgery stated that fewer bypasses were performed with OPCAB and that the mortality was a high 3.7% among patients who were switched from OPCAB to on-pump coronary artery bypass grafting (CABG) during surgery (12). Recent improvements of surgical techniques and progress in myocardial protection and post-operative management have led to better results of surgery. The most important factor in CABG is the quality of the grafts, and we generally perform this surgery by using CPB at our institution.

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Manuscript received January 8, 2009; revised manuscript received April 29, 2009, accepted May 25, 2009.

Human atrial natriuretic peptide (hANP) is a hormone that is secreted in response to stretching of the atrial wall. It has a vasodilatory effect and a potent natriuretic effect, it suppresses the renin-angiotensin-aldosterone system (RAAS), and it causes coronary artery dilation, and has thus been used clinically as a new drug for the treatment of cardiac failure and acute myocardial infarction (13–15). During cardiac surgery, an abnormal increase of RAAS hormones and catecholamines may result from the influence of CPB, and this can trigger a decrease of urine output and retention of water in the third space. We considered that hANP could be effective against this pathological situation, and we previously reported that continuous infusion of low-dose hANP from the start of CPB was effective compensation for the defects of CPB and suppressed left ventricular remodeling by blocking the RAAS and promoting natriuresis (16–18). All previous studies of hANP infusion have been small in scale, but we conducted a randomized, controlled, multicenter (7 institutions of Nihon University Group) study in 500 patients to assess the effect of hANP infusion during CPB on post-operative renal function.

## Methods

**Patients.** A total of 504 patients without renal impairment (evaluated by a serum creatinine [Cr] <1.3 mg/dl and a creatinine clearance [Ccr] ≥80 ml/min) underwent CABG. Those who had renal impairment pre-operatively and required hemodialysis due to pre-operative shock were excluded. The patients were randomly allocated to 2 groups by drawing lots: 1 group received infusion of hANP (Suntory Inc., Osaka, Japan, and Daiichi Sankyo Co., Ltd., Tokyo, Japan) in a blinded manner (hANP group) and 1 group received physiological saline in the same manner (placebo group). This study was approved by the ethical committee of Nihon University School of Medicine, and an explanation was given to each patient before obtaining consent. Infusion of hANP or saline was started at 0.02 μg/kg/min from the commencement of CPB. It was reduced to 0.01 μg/kg/min after the start of oral medication, and then stopped after another 12 h. In the placebo group, the saline infusion was handled in the same manner. In all patients, CABG was performed under CPB (Jostra HL-20, Jostra AG, Hirrlingen, Germany) with nonpulsatile perfusion at a reduced temperature (rectal temperature: 34°C). In all cases, the left internal thoracic artery was used for anastomosis to the left anterior descending artery, and a radial artery graft or saphenous vein graft was used for other coronary vessels.

In our study, post-operative complications were defined as central nervous system disorders, cardiovascular disorders (low output syndrome, heart failure, and refractory arrhythmias), respiratory failure, acute renal failure (necessitating hemodialysis), gastrointestinal disorders (gastrointestinal tract hemorrhage, ileus, and/or hepatic dysfunction that required parenteral hyperalimentation), infections (sepsis,

mediastinitis, and so on), and prolonged admission to the intensive care unit (ICU). The need for hemodialysis in patients with acute renal failure was determined by a nephrologist specializing in dialysis according to the following criteria: 1) urine output ≤400 ml/day despite intravenous administration of furosemide in addition to adequate post-operative fluid infusion; 2) persistent oliguria with an increase of central venous pressure or pulmonary capillary wedge pressure; 3) failure to control the serum potassium level; 4) a persistent rise of serum Cr despite a response to intravenous fluid infusion; and 5) progression of metabolic acidosis.

The levels of atrial natriuretic peptide (ANP), plasma renin activity (renin), angiotensin II, aldosterone, blood urea nitrogen, Cr, sodium (Na), and osmotic pressure (Osm) were measured before surgery, on returning to the ICU, and 1, 3, and 7 days after surgery. The maximum value and percent increase of Cr (%ΔCr = [maximum Cr – pre-operative Cr]/pre-operative Cr value × 100) were also determined. Urinary Na (U-Na), urinary creatinine (U-Cr), and osmotic pressure (U-osm) were measured before surgery, on returning to ICU, and 1, 3, and 7 days after surgery. Then the Ccr (Ccr = U-Cr × minute urine output/Cr), fractional sodium excretion (FENa = [U-Na/Na] × [Cr/U-Cr] × 100), free water clearance (C<sub>H2O</sub> = [1-U-osm/Osm] × minute urine output/body surface area), and renal failure index (RFI = [U-Na × Cr]/U-Cr) were calculated.

**Statistical analysis.** Data are expressed as mean ± SD. For parametric and nonparametric data, statistically significant differences were determined by using the Student *t* test and Fisher exact test, respectively. A *p* value of <0.05 was considered to indicate statistical significance. Other data were analyzed by using repeated measures analysis of variance. All analyses were conducted with SPSS software (SPSS Inc., Chicago, Illinois).

## Results

**Clinical characteristics.** There were no significant differences between the 2 groups with respect to pre-operative characteristics such the age, male/female ratio, body surface area, underlying diseases, emergency surgery, risk factors, and pre-operative cardiac function (ejection fraction) (Table 1).

### Abbreviations and Acronyms

<b>%ΔCr</b> = percent increase of creatinine
<b>BNP</b> = brain natriuretic peptide
<b>CABG</b> = coronary artery bypass grafting
<b>Ccr</b> = creatinine clearance
<b>C<sub>H2O</sub></b> = free water clearance
<b>CPB</b> = cardiopulmonary bypass
<b>Cr</b> = creatinine
<b>FENa</b> = fractional sodium excretion
<b>hANP</b> = human atrial natriuretic peptide
<b>ICU</b> = intensive care unit
<b>OPCAB</b> = off-pump coronary artery bypass
<b>RAAS</b> = renin-angiotensin-aldosterone system
<b>RFI</b> = renal failure index

**Table 1 Comparison of Patient Characteristics**

	hANP Group	Placebo Group	p Value
Patients (n)	251	253	0.437
Age (yrs)	65.6 ± 0.6	66.3 ± 0.6	0.255
Sex (male/female)	193/58	205/48	0.413
BSA (m <sup>2</sup> )	1.66 ± 0.01	1.65 ± 0.01	0.301
<b>Diagnosis</b>			
AMI	25	16	
OMI	100	93	
Unstable angina	94	104	
Stable angina	32	40	
Emergency	75 (29.9%)	63 (24.9%)	0.210
<b>Risk factor</b>			
DM	112 (44.6%)	110 (43.5%)	0.796
Hypertension	175 (69.7%)	179 (70.8%)	0.800
Hyperlipidemia	143 (57.0%)	151 (59.7%)	0.537
Obesity	67 (26.7%)	58 (22.9%)	0.327
Smoking	116 (46.2%)	100 (39.5%)	0.129
Ejection fraction (%)	59.5 ± 1.4	60.9 ± 1.1	0.410

AMI = acute myocardial infarction; BSA = body surface area; DM = diabetes mellitus; hANP = human atrial natriuretic peptide; OMI = old myocardial infarction.

**Post-operative results.** Table 2 shows the number of bypass grafts, the aortic cross-clamp time, and the CPB time. There were no significant differences in these variables between the hANP and placebo groups. The post-operative hospital mortality rate was 1.6% (n = 4) in the hANP group and 2.4% (n = 6) in the placebo group, and there was no significant difference between the 2 groups. The cause of death was cardiac failure in 2 patients and pneumonia in 2 patients from the hANP group, whereas it was cardiac failure in 3 patients, cerebral infarction in 1, pneumonia in 1, and hepatic failure in 1 patient from the placebo group. Complications occurred in 8 patients (3.2%) from the hANP group and 20 patients (7.9%) from the placebo group, so significantly more patients from the latter group developed complications (p = 0.0208). In the hANP group, cardiac failure, respiratory failure, and mediastinitis oc-

curred in 4, 3, and 1 of the patients, respectively. In the placebo group, the complications were cardiac failure, acute renal failure requiring hemodialysis, respiratory failure, cerebral infarction, severe arrhythmia, and hepatic failure in 7, 4, 3, 3, 2, and 1 of the patients, respectively. No patient discontinued hANP administration due to reduced blood pressure, and no rebound was observed after discontinuation of infusion. The hospital stay was significantly shorter in the hANP group (p = 0.0002).

The duration of hANP administration was 2.23 ± 0.82 days in the hANP group. In the control group, physiological saline was infused for 2.80 ± 1.90 days. The duration of infusion was significantly shorter in the hANP group (p = 0.0001).

Dopamine was administered post-operatively to 145 patients (57.8%) from the hANP group and 152 patients (60.1%) from the placebo group, showing no difference.

**Renal function.** The post-operative maximum Cr value was 0.97 ± 0.02 mg/dl in the hANP group and 1.14 ± 0.03 mg/dl in the placebo group, whereas %ΔCr was 15.7 ± 25.1% in the hANP group and 41.5 ± 80.1% in the placebo group (Table 2).

Post-operative Cr showed an increase of ≥0.3 mg/dl compared with the pre-operative value in 40 patients from the hANP group (15.9%) and 92 patients from the placebo group (36.4%), and the incidence was significantly lower in the hANP group (p < 0.0001) (Table 2).

These values were significantly higher in the placebo group (p < 0.0001). Post-operatively, Cr increased to 1.3 mg/dl or more in 20 and 61 patients from the hANP and placebo groups, respectively (p < 0.0001), and to 1.5 mg/dl or more in 9 and 35 patients, respectively (p < 0.0001). Patients with Cr exceeding 2.0 mg/dl included 1 in the hANP group and 8 in the placebo group, showing a significant difference (p = 0.0374). Four patients in the placebo group and none in the hANP group required hemodialysis, but the difference was not statistically signif-

**Table 2 Operative and Post-Operative Data**

	hANP Group	Placebo Group	p Value
Patients (n)	251	253	
Mortality	4 (1.6%)	6 (2.4%)	0.531
ACCT (min)	54.4 ± 1.4	53.3 ± 2.0	0.566
CPBT (min)	118.5 ± 2.1	118.2 ± 2.1	0.933
Bypass	3.12 ± 0.05	3.18 ± 0.05	0.331
Administering day (days)	2.23 ± 0.82	2.80 ± 1.90	0.0001
Hospital stay (days)	12.2 ± 0.4	15.1 ± 0.7	0.0002
Maximum Cr (mg/dl)	0.97 ± 0.02	1.14 ± 0.03	<0.0001
0.3 mg/dl > (pre-operative – maximum Cr)	40	92	<0.0001
Cr increase rate (%)	15.7 ± 1.6	41.5 ± 5.5	<0.0001
Cr >1.3 mg/dl	20	61	<0.0001
Cr >1.5 mg/dl	9	35	<0.0001
Cr >2.0 mg/dl	1	8	0.0374
Hemodialysis	0	4	0.123

ACCT = aortic cross clamp time; CPBT = cardiopulmonary bypass time; Cr = creatinine; hANP = human atrial natriuretic peptide.

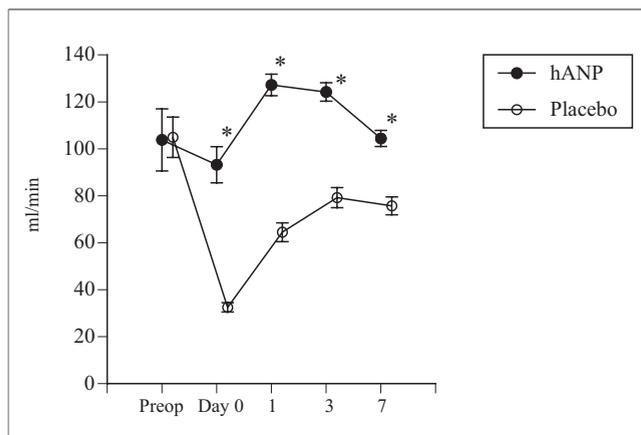
Table 3 Renal Function After Operation		Pre-Operative	Day 0	Day 1	Day 3	Week 1
BUN (mg/dl)						
hANP		15.5 ± 0.3	15.0 ± 0.8	18.5 ± 0.4	22.6 ± 0.5*	22.1 ± 0.5†
Placebo		14.7 ± 0.3	15.2 ± 0.3	18.9 ± 0.5	24.7 ± 0.7	25.0 ± 0.8
Cr (mg/dl)						
hANP		0.84 ± 0.01	0.86 ± 0.01*	0.93 ± 0.03†	0.79 ± 0.01†	0.80 ± 0.01†
Placebo		0.83 ± 0.01	0.91 ± 0.02	1.06 ± 0.03	1.00 ± 0.03	1.00 ± 0.03
U-Cr (mg/dl)						
hANP		96.2 ± 11.5	15.3 ± 1.4†	77.1 ± 2.8†	69.8 ± 2.2†	101.3 ± 2.9†
Placebo		102.4 ± 8.5	7.6 ± 0.5	47.9 ± 2.3	58.2 ± 2.4	86.4 ± 3.0
UO (ml/min)						
hANP		0.88 ± 0.01	5.65 ± 0.06†	1.56 ± 0.02†	1.41 ± 0.02†	0.82 ± 0.01*
Placebo		0.90 ± 0.01	3.69 ± 0.06	1.22 ± 0.03	1.13 ± 0.02	0.78 ± 0.01
FENa (%)						
hANP		1.02 ± 0.20	8.85 ± 0.66†	1.31 ± 0.14†	1.18 ± 0.07†	0.55 ± 0.03†
Placebo		0.99 ± 0.11	14.63 ± 1.58	2.41 ± 0.27	1.85 ± 0.16	0.78 ± 0.07
Free water clearance						
hANP		-0.34 ± 0.03	-0.57 ± 0.07*	-0.92 ± 0.05*	-0.96 ± 0.04†	-0.50 ± 0.03
Placebo		-0.37 ± 0.03	-0.41 ± 0.05	-0.69 ± 0.07	-0.67 ± 0.03	-0.45 ± 0.02
RFI						
hANP		1.63 ± 0.29	12.27 ± 0.78†	1.80 ± 0.18†	1.64 ± 1.00†	0.76 ± 0.04†
Placebo		1.12 ± 0.08	20.64 ± 2.26	3.35 ± 0.36	2.54 ± 0.22	1.09 ± 0.10

\*p > 0.05, †p < 0.01.  
BUN = blood urea nitrogen; Cr = creatinine clearance; Cr = creatinine; FENa = fractional sodium excretion; hANP = human atrial natriuretic peptide; RFI = renal failure index; U-Cr = urine creatinine; UO = urine output.

icant (p = 0.123) (Table 2). Ccr was significantly higher in the hANP group from post-operative day 0 to week 1, whereas FENa and C<sub>H20</sub> were significantly lower in the hANP group from post-operative day 0 to week 1 and days 0 to 3, respectively. RFI was significantly lower in the hANP group from post-operative day 0 to week 1 (Table 3, Fig. 1).

**ANP and RAAS.** ANP increased rapidly in the hANP group and was significantly higher than in the placebo group until post-operative day 3, but there was no significant difference between the 2 groups at post-operative week 1

(Fig. 2). The levels of renin, angiotensin-II, and aldosterone all increased post-operatively in the placebo group, and reached a peak at the time of the return to ICU. Afterwards, these parameters decreased, but did not return to the pre-operative range. On the other hand, these parameters were increased at the return to ICU in the hANP group, but improved rapidly. Angiotensin-II and aldosterone were significantly lower in the hANP group throughout the study. Renin was significantly lower in the hANP group, excluding day 1 (Figs. 2 and 3).

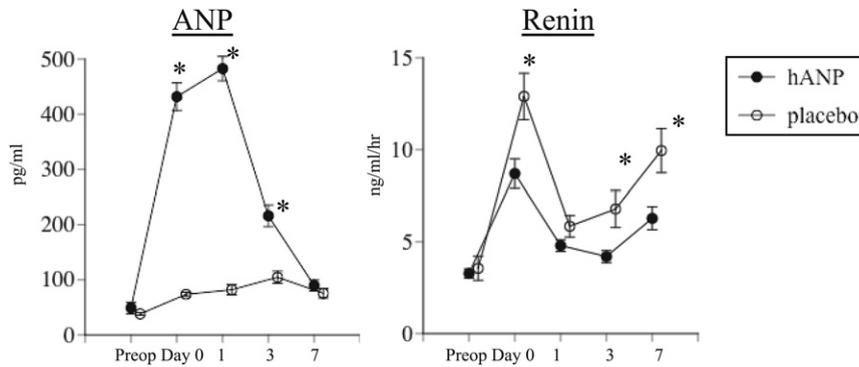


**Figure 1. Changes of Creatinine Clearance**

Creatinine clearance was significantly higher in the human atrial natriuretic peptide (hANP) group from post-operative day 0 to week 1. \*p < 0.05.

## Discussion

Deterioration of renal function after cardiac surgery is thought to be caused by nonpulsatile perfusion, renal hypoperfusion, stimulation of the inflammatory response, enhancement of RAAS activity, and renal tubular necrosis (19,20). We previously reported that continuous infusion of low-dose hANP from the start of CPB suppresses retention of water in a third space, suppresses RAAS activity, and has a potent diuretic effect, thus compensating for the adverse effects of cardiopulmonary bypass (16). The present randomized controlled study was performed to investigate the effect of hANP on post-operative renal function. The results demonstrated that post-operative transient deterioration of renal function associated with CABG can be prevented by continuous infusion of low-dose hANP during and after surgery. In the patients receiving physiological saline infusion (placebo group), Ccr showed a decline to around one-third of the pre-operative level when they returned to



**Figure 2** Changes of ANP and Plasma Renin Activity

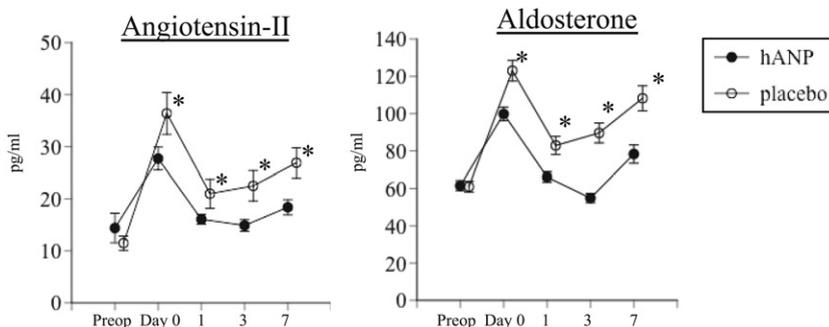
Atrial natriuretic peptide (ANP) increased rapidly in the human atrial natriuretic peptide (hANP) group and was significantly higher than in the placebo group until post-operative day 3, but there was no significant difference between the 2 groups at post-operative week 1. Renin was significantly lower in the hANP group excluding day 1. \*p < 0.05.

ICU after surgery, and it was still below the pre-operative value 1 week later. In contrast, the pre-operative Ccr could be maintained in the patients receiving hANP infusion, and none of them required hemodialysis post-operatively. Patients requiring post-operative hemodialysis showed no significant difference between the hANP and placebo groups, but patients with Cr exceeding 2.0 g/dl were significantly more common in the placebo group. In this study, it was important that post-operative hemodialysis was not required by any patients in the hANP group. When the same study is performed on patients with pre-operative decreases in renal function, it is assumed to be highly possible that the hANP administration would show a decrease in the number of patients placed on hemodialysis post-operatively. At present, the study on patients with pre-operative decreases in renal function is now in progress, and it is hoped that the efficacy of hANP administration will be shown. Analysis of FENa indicated a natriuretic effect of hANP, whereas the data on  $C_{H2O}$  supported a preventive

effect of hANP infusion against impairment of urine concentration. Because of its RAAS-suppressing effect, together with the above-mentioned activities, low-dose infusion of hANP seems to quickly improve CPB-related glomerular dysfunction, humoral imbalances, and liquidity factor impairment, and thus maintains a more physiological state.

Brown et al. (21) studied 1,391 patients with normal renal function who underwent cardiac surgery, and reported that the mortality was significantly higher in patients with a % $\Delta$ Cr of 50% or more than in those with a value of 25% or less, suggesting that it is necessary to preserve renal function perioperatively. In the present study, % $\Delta$ Cr was significantly lower in the hANP group than in the placebo group, and accordingly, we conclude that intraoperative administration of hANP prevented perioperative renal dysfunction.

Various effects of hANP on the kidneys have been reported, and it is considered to act directly on the renal tubules (exhibiting a diuretic effect) and thereby prevent



**Figure 3** Changes of Angiotensin-II and Aldosterone

The levels of angiotensin-II and aldosterone increased post-operatively in the placebo group, and reached a peak at the time of the return to intensive care unit. Angiotensin-II and aldosterone were significantly lower in the human atrial natriuretic peptide (hANP) group throughout the study. \*p < 0.05.

deterioration of the electrolyte balance, increased urinary sodium excretion, and renal parenchymal damage caused by administration of high-dose diuretics (22). However, few studies have assessed the effects of hANP in patients having cardiac surgery, including efficacy for preventing acute renal failure. Valsson et al. (23) administered hANP for 30 min to patients with acute renal failure and cardiac failure, and found that the urine output, glomerular filtration rate, and renal blood flow increased by 62%, 43%, and 38%, respectively, whereas renal vascular resistance decreased by 30%. They also performed a larger study and reported that the need for hemodialysis was decreased by hANP, and hence dialysis-free survival was improved (24). The only studies to assess prevention of acute renal failure have been our previous study (16–18) and a study by Hayashida et al. (25), both of which were small in scale. Hayashida reported that the hANP group showed significantly higher urine output than the placebo group, and had better hemodynamics and water balance. The present large-scale study demonstrated that intraoperative infusion of hANP could prevent post-operative deterioration of renal function. It is extremely difficult to predict which patients with normal renal function pre-operatively will develop acute renal failure after cardiac surgery, but the present study showed that hANP can prevent the onset of acute post-operative renal failure. Because hANP was developed in Japan, it is only available in our country so far. Brain natriuretic peptide (BNP) (nesiritide) has not been approved in Japan, but is available in Western countries. An interesting study on administration of BNP during cardiac surgery was performed in the U.S. When BNP was administered to patients with pre-operative renal dysfunction or left ventricular dysfunction, post-operative plasma levels of cystatin, aldosterone, and Cr, as well as the estimated Ccr, were better in the BNP group (26,27). A comparison of clinical efficacy between hANP and BNP has never been reported. However, it is known that hANP has a shorter elimination half-life than BNP and therefore may be safer to use. Both hANP and BNP are reported to be very effective for the improvement of renal dysfunction and cardiac dysfunction, and perioperative administration of either peptide can reduce the incidence of post-operative complications and contribute to safer cardiac surgery.

A previous large-scale multicenter study of hANP infusion after reperfusion therapy for acute myocardial infarction showed that the hANP group had a significant decrease in infarct size, better cardiac function, and significantly lower rates of cardiac death and cardiac failure compared with the placebo group (28). The present study is to our knowledge the first assessment of hANP in more than 500 patients undergoing cardiac surgery, and it demonstrates that continuous infusion of low-dose hANP from the start of CPB improves renal function post-operatively, maintains a more physiological state, and compensates for the adverse effects of CPB. Adding hANP treatment to the perioperative management of cardiac surgery can prevent deteriora-

tion of renal function and allows surgery to be performed more safely. We found that hANP was effective at a low dose of 0.02  $\mu\text{g}/\text{kg}/\text{min}$ , and no clinically significant hypotension or rebound was detected at this dose.

The present study demonstrates the efficacy of perioperative hANP infusion for protection of renal function. It seems likely that hANP administration will be more effective in patients with pre-operative renal dysfunction, cardiac dysfunction, or diabetes mellitus. Currently, we are conducting a trial in such patients to test this hypothesis.

## Conclusions

The present study evaluated the effect on renal function of continuous infusion of low-dose hANP from start of CPB. We demonstrated that hANP suppresses RAAS activity, has a potent natriuretic action, prevents post-operative renal dysfunction, and compensates for the adverse effects of CPB. Thus, hANP is a promising agent for the perioperative management of patients undergoing cardiac surgery with CPB.

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**Key Words:** human atrial natriuretic peptide ■ cardiopulmonary bypass ■ cardiac surgery ■ renal failure ■ coronary artery bypass grafting.