Original Article

The Efficacy of Human Atrial Natriuretic Peptide in Patients with Renal Dysfunction Undergoing Cardiac Surgery

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Objectives: The purpose of this study was to investigate the efficacy of carperitide (human atrial natriuretic peptide [h-ANP]) in perioperative management in patients with renal dysfunction, especially its kidney-protecting effects.

Patients and Methods: The subjects were 18 patients who underwent elective cardiac surgery using cardiopulmonary bypass (CPB) with a preoperative serum creatinine (Cr) level of 1.2 mg/dl or more. The subjects were prospectively assigned to 2 groups: an h-ANP-treated group (Group H, n = 10) and a non-h-ANP-treated group (Group N, n = 8). At the beginning of surgery, h-ANP administration was initiated and continued for 5 days or more. The central dose was 0.02 μg/kg/min. The primary end point included the serum Cr level and creatinine clearance (Ccr).

Results: In Group H, Cr level significantly decreased after surgery compared to the preoperative level. The Ccr values were significantly higher 2 and 3 days after surgery than the preoperative values. And the intraoperative urine volume significantly increased. In Group H, an increase in urinary N-acetyl-beta-D-glucosaminidase (NAG) level the day after surgery was significantly inhibited in comparison with Group N.

Conclusion: The results of this study suggest that in patients with renal dysfunction before cardiac surgery, continuous low-dose h-ANP therapy maintains renal function, preventing its deterioration. (Ann Thorac Cardiovasc Surg 2008; 14: 294–302)

Key words: renal dysfunction, human atrial natriuretic peptide, cardiac surgery, creatinine, creatinine clearance

Introduction

It is known that acute renal failure develops in 1% to 10% of patients after cardiovascular surgery. In patients requiring dialysis, the mortality rate ranges from 30% to 60%.[1–5] The main etiological factors include renal hypoperfusion during extracorporeal circulation and postoperative heart failure. Risk factors for acute renal failure include preoperative heart/kidney functions, the type of heart disease, techniques, intraoperative hypotension/hypoxemia, prolonged cardiopulmonary bypass (CPB) time, hemolysis, and massive blood transfusion.[1–5] Acute renal failure may frequently cause failure of other organs, markedly influencing the outcome; it is very important to prevent renal dysfunction during and after surgery. The diuretic effects of human atrial natriuretic peptide (h-ANP) appear via an increase in the glomerular filtration rate, an increase in renal medullary blood flow, and the inhibition of passive water/natrium (Na) reabsorption in the ascending limb of Henle's loop. The kidney may be protected from ischemia via the renal medullary blood-flow-increasing effects, preventing postoperative renal

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dysfunction. Furthermore, cardiovascular surgery with CPB enhances the renin-angiotensin-aldosterone system (RAA) and the sympathetic nervous systems, decreasing the urine volume and inducing water retention in the third space.[2,6,7] It is known that h-ANP exhibits various pharmacological actions, such as inhibition of the RAA/sympathetic nervous systems and diuretic actions.[6–8] This agent may reduce the complications of surgery with CPB, protecting the kidney.

In this study, we initiated the continuous administration of h-ANP at the beginning of surgery in renal dysfunction patients with a serum creatinine (Cr) level of 1.2 mg/dl or more, and investigated its protective effects on the kidney during and after surgery.

Patients and Methods

We conducted a prospective randomized comparative study involving h-ANP-treated (Group H, n = 10) and non-h-ANP-treated (Group N, n = 8) groups. The subjects were 18 patients who underwent palliative cardiac surgery using a CPB from May 2005 to December 2006 with a preoperative serum Cr level of 1.2 mg/dl or more. The results were compared between the 2 groups. Our exclusion criteria included patients chronically undergoing dialysis, those in whom therapy with an angiotensin-converting enzyme (ACE) inhibitor was newly started within 1 week before surgery, those to whom contrast medium was administered within 3 days before surgery, those with a left ventricular ejection fraction (LVEF) of less than 35%, those less than 20 years old, and those considered ineligible by attending physicians. Before registration, written informed consent was obtained from the patients or their families. The protocol was approved by the Ethics Review Board of our hospital.

Administration methods

Dose of h-ANP: To prevent a decrease in blood pressure, the initial dose of h-ANP was established as 0.01 μg/kg/min. The central dose was 0.02 μg/kg/min and was changed if necessary. Concerning the administration period, administration was initiated at the start of surgery and as a rule was continued for 5 days or more. Its prolongation was evaluated by attending physicians. Concerning combined agents, there was no restriction other than the following contraindicated agents. However, cardiotonic agents and replenisher solution were administered to maintain renal blood flow/renal perfusion pressure and systolic blood pressure. Aminoglycoside antibiotics and prostaglandin preparations were contraindicated.

Cardiopulmonary bypass

CPB was initiated at a perfusion index of 2.4 L/min/m^2. An adequate perfusion pressure (40–60 mmHg) and moderate controlled systemic hypothermia (28°C–32°C) were maintained. For myocardial protection, antegrade hypothermic (4°C) crystalloid cardioplegia was applied.

Primary evaluation items

The primary evaluation items included the serum Cr level and creatinine clearance (Ccr). The accessory evaluation items included the urine volume per hour, blood urea nitrogen (BUN) level, urinary N-acetyl-beta-D-glucosaminidase (NAG) level, urinary liver-type fatty acid-binding protein (L-FABP) level, blood levels of proinflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor-alpha (TNF-α), a dose of furosemide, and CHDF transfer.

Data on measurement

The serum Cr and BUN levels were measured before surgery, after admission to the intensive care unit (ICU), and 1, 2, 3, 4, 5, 7, and 14 days after surgery. Ccr was calculated before surgery and 1, 2, 3, and 7 days after. The urine volume per hour was measured before surgery, during surgery, and 1, 2, 3, 4, 5, and 7 days after. The urinary NAG and L-FABP levels were measured before surgery and 1, 2, and 3 days after. The TNF-α and IL-6 levels were measured before surgery, immediately and 6 hours after admission to the ICU, and the day after surgery. Continuous hemodiafiltration (CHDF) transfer was evaluated until discharge.

Statistical analysis

A statistical analysis was performed using the SPSS® software package, version 11.0 (SPSS Inc., Chicago, IL, USA). All variables were expressed as the mean ± standard deviation (SD). The results were compared between the 2 groups using the Mann-Whitney test for unpaired data and Wilcoxon's test for paired data. $P < 0.05$ was regarded as significant.

Results

There were no significant differences in age, height, body weight, preoperative Cr, Ccr, BUN, LVEF, or urine volume between the 2 groups (Table 1). In Group

Table 1. Preoperative patient characteristics

	Group H	Group N	P value
No. of patients	10	8	
Age (years)	74.7 ± 7.5	70.6 ± 12.1	ns
Weight (kg)	54.2 ± 8.3	61.9 ± 15.5	ns
Height (cm)	155.1 ± 6.8	158.4 ± 12.2	ns
Serum Cr (mg/dl)	1.41 ± 0.30	1.32 ± 0.07	ns
Ccr (ml/min)	32.4 ± 6.2	43.1 ± 23.8	ns
BUN (mg/dl)	29.9 ± 6.4	23.4 ± 9.0	ns
LVEF (%)	63.8 ± 18.4	72.8 ± 11.1	ns
Urinary volume (ml/h)	66.9 ± 19.4	67.0 ± 27.6	ns

Cr, creatinine; Ccr, creatinine clearance; BUN, blood urea nitrogen; LVEF, left ventricule ejection fraction; ns, not significant.

H, the techniques consisted of surgery for cardiac valvular disease in 7 patients and coronary aortic bypass graft (CABG) with surgery for valvular disease in 3 patients. In Group N, surgery for cardiac valvular disease and for CABG were each performed in 4 patients. There were no significant differences in the operation time, CPB time, aortic cross-clamp (AXC) time, duration required for intubation, ICU stay, or hospital stay (Table 2). The period of h-ANP administration was 5.2 ± 0.6 days. During surgery, dopamine (DOA) was combined in the 2 groups. However, there were no significant differences in the doses or administration periods between them. There was also no significant difference in the doses of furosemide between the 2 groups (Table 3). There was no patient in whom h-ANP administration was discontinued because of a decrease in blood pressure or arrhythmia. Concerning blood pressure, a systolic blood pressure value of 80 mm Hg or more was maintained in the 2 groups, and there was no significant difference between them. Groups H and N included 2 diabetics each (Group H: 20%; Group N: 25%). After surgery, no patient in either group required CHDF. In Group H, the postoperative complications consisted of atrial fibrillation in 1 patient and complete AV block in another. No patients died. In Group N, atrial fibrillation was observed in 2 patients. No patients died.

Serum Cr and Ccr

In Group H, the serum Cr level significantly decreased after admission to the ICU (Cr: 1.06 ± 0.24 mg/dl, p = 0.001) compared to the preoperative level (1.41 ± 0.30 mg/dl). The value increased the day after surgery (1.28 ± 0.24 mg/dl), but was significantly lower than the preoperative value (p = 0.009). Thereafter it gradually and significantly decreased until 5 days (2 postoperative days [POD]) 1.18 ± 0.29, p = 0.01; 3 POD 1.08 ± 0.25, p = 0.001; 4 POD 1.04 ± 0.22, p = 0.001; 5 POD 1.02 ± 0.26 mg/dl, p = 0.001) after surgery (during the h-ANP administration period), but it then increased again 7 (1.12 ± 0.25 mg/dl) and 14 days (1.12 ± 0.31 mg/dl) after surgery. However, the value was significantly lower than the preoperative value (p = 0.006 and p = 0.001, respectively). In Group N, the serum Cr levels were higher than those in Group H at all measurement points after surgery (ICU arrival; 1.18 ± 0.19, 1 POD; 1.29 ± 0.19, 2 POD; 1.21 ± 0.26, 3 POD; 1.11 ± 0.15, 4 POD; 1.12 ± 0.15, 5 POD; 1.10 ± 0.16, 7 POD; 1.17 ± 0.20, 14 POD; 1.23 ± 0.19) (Fig. 1). There were no significant differences between Group H and Group N.

In Group H, Ccr serially increased 1, 2, and 3 days after surgery (39.3 ± 14.5 ml/min, p = 0.08; 46.6 ± 15.0 ml/min, p = 0.004; and 50.3 ± 13.6 ml/min, p = 0.002, respectively) in comparison with the preoperative value (32.4 ± 6.2 ml/min), but returned to the preoperative value 7 days after surgery (36.8 ± 19.2 ml/min, p = 0.48). There were significant increases 2 and 3 days after surgery. In Group N, the Ccr values were higher than those in Group H at all measurement points (preoperative 43.1 ± 23.8; 1 POD 53.6 ± 17.1; 2 POD 60.3 ± 16.5; 3 POD 53.0 ± 17.5 ml/min). Ccr increased in this group 1 and 2 days after surgery and reached a peak, but it then decreased. There were no significant changes in comparison with the preoperative value (Fig. 2).

BUN

In Group H, the BUN level significantly decreased after admission to the ICU (22.5 ± 5.5 mg/dl, p = 0.001) compared to the preoperative level (29.9 ± 6.4 mg/dl). It increased again 1 and 2 days after surgery, but then

Table 2. Operative and postoperative data

	Group H	Group N	P value
Operation			
CABG	0	4	
S-CABG	0	0	
D-CABG	0	0	
T-CABG	0	0	
Q-CABG	0	4	
Valve surgery	7	4	
AVR	5	1	
MVR	1	1	
MP	1	1	
AVR + MVR	0	1	
CABG + valve surgery	3	0	
AVR + S-CABG	1	0	
AVR + MP + D-CABG	1	0	
Bentall's operation	1	0	
Bypass graft (CABG)			
LITA	0	3	
RITA	0	3	
GEA	0	1	
RA	0	0	
SVG	3	5	
Operation time (min)	268.9 ± 65.9	304.5 ± 92.6	ns
CPB time (min)	114.7 ± 24.0	118.4 ± 45.5	ns
AXC time (min)	64.6 ± 18.2	69.4 ± 33.1	ns
Ventilation time (min)	11.6 ± 11.6	10.8 ± 6.4	ns
ICU stay (days)	4.0 ± 1.2	3.3 ± 1.3	ns
Hospital stay (days)	23.8 ± 5.6	25.1 ± 5.7	ns

CABG, coronary artery bypass grafting; AVR, aortic valve replacement; MVR, mitral valve replacement; MP, mitral valve plasty; LITA, left internal thoracic artery; RITA, right internal thoracic artery; GEA, right gastroepiploic artery; RA, radial artery; SVG, saphenous vein graft; CPB, cardiopulmonary bypass; AXC, aortic cross-clamp; ICU, intensive care unit; ns, not significant.

Table 3. The dose and administration period of dopamine and furosemide

	Intra-op		1 POD		2 POD		3 POD		4 POD		5 POD		6 POD		7 POD	
	GH	GN	GH	GN	GH	GN	GH	GN	GH	GN	GH	GN	GH	GN	GH	GN
Dopamine (ug/kg/min)	6.3 ± 2.2	5.8 ± 2.0	6.1 ± 3.1	4.5 ± 2.6	3.4 ± 2.8	2.0 ± 1.6	0.9 ± 1.5	1.1 ± 1.2	0.4 ± 0.8	0	0	0	0	0	0	0
Furosemide (mg)	0	0	8.5 ± 31.0	0	11.1 ± 24.2	6.3 ± 9.2	12.2 ± 23.0	2.5 ± 7.1	8.2 ± 16.9	2.5 ± 7.1	7.3 ± 32.7	2.5 ± 7.1	9.4 ± 28.4	5.0 ± 9.3	11.6 ± 30.1	5.0 ± 9.3

intra-op, intraoperation; GH, Group H; GN, Group N; POD, postoperative day.

decreased until 14 days after surgery. At all measurement points, the values were lower than the preoperative value. In Group N, the BUN level decreased after admission to the ICU, but increased again until 3 days after surgery. It remained higher than the preoperative value (23.4 ± 9.0 mg/dl) until 7 days after surgery. However, there were no significant differences (Fig. 3).

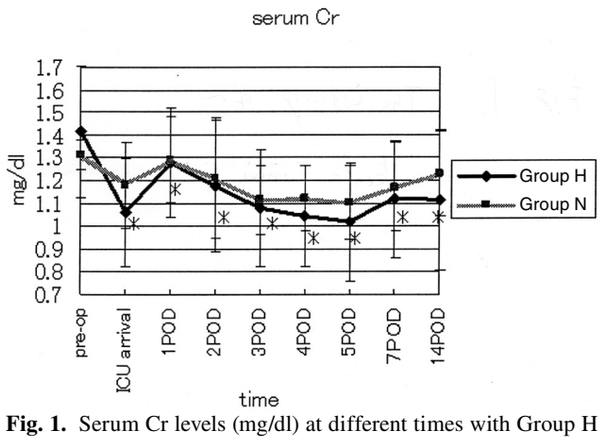

Fig. 1. Serum Cr levels (mg/dl) at different times with Group H and Group N.
Data are mean ± SD.
*, p <0.05 compared to preoperative value in Group H.
Cr, creatinine; pre-op, preoperation; ICU, intensive care unit; POD, postoperative day.

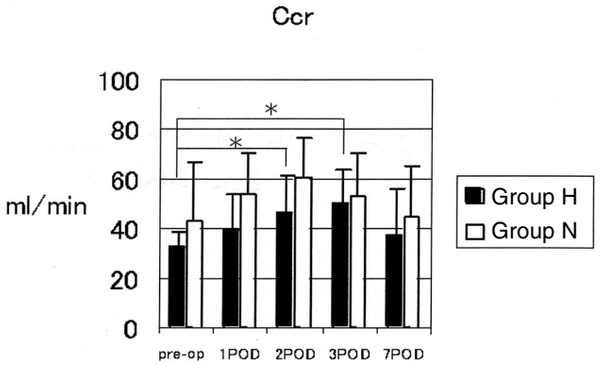

Fig. 2. Ccr levels (ml/min) at different times with Group H and Group N.
Data are mean ± SD.
*, p <0.05 compared to preoperative value in Group H.
Ccr, creatinine clearance; pre-op, preoperation; POD, postoperative day.

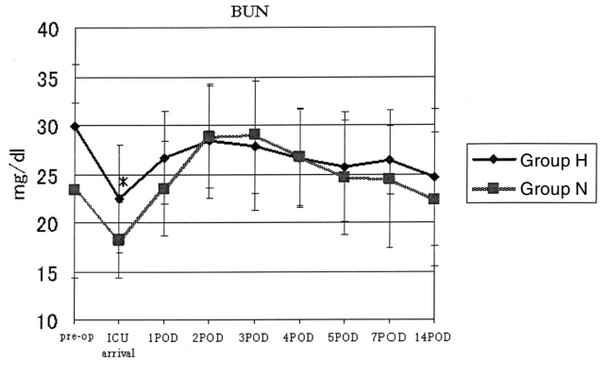

Fig. 3. BUN levels (mg/dl) at different times with Group H and Group N.
Data are mean ± SD.
*, p <0.05 compared to preoperative value in Group H.
BUN, blood urea nitrogen; pre-op, preoperation; ICU, intensive care unit; POD, postoperative day.

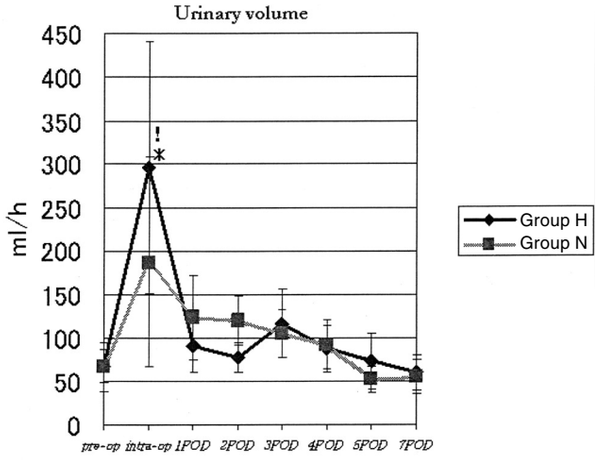

Fig. 4. Urinary volume levels (ml/h) at different times with Group H and Group N.
Data are mean ± SD.
*, p <0.05 compared to preoperative value in Group H.
! , Differences between groups are significant (p = 0.04).
pre-op, preoperation; intra-op, intraoperation; POD, postoperative day.

Urine volume per hour

In Groups H and N, the intraoperative urine volume increased. In Group H, the increase was more marked (Group H: 297.0 ± 145 ml/h; Group N: 187.2 ± 120.7 ml/h, p = 0.001). One and 2 days after surgery, the urine volume was higher in Group N (1 POD 123.6 ± 48.9; 2 POD 120.2 ± 27.4 ml/h) than in Group H (1 POD 90.9 ± 31.1; 2 POD 77.6 ± 17.7 ml/h), and from 3 until 7 days after surgery, it was higher in Group H (Group H vs. Group N: 3 POD 116.6 ± 39.8 vs. 104.9 ± 27.2; 4 POD 92.4 ± 28.5 vs. 87.8 ± 26.9; 5 POD 73.7 ± 32.3 vs. 52.1 ± 14.2; 7 POD 59.8 ± 19.9 vs. 55.3 ± 18.9 ml/h). However, there were no significant differences (Fig. 4).

Urinary NAG and L-FABP

In Group H, an increase in the urinary NAG level was significantly inhibited in comparison with Group N the day after surgery (Group H: 4.7 ± 2.9 U/l; Group N: 7.4 ± 4.1 U/l, p = 0.004). In Group H, the urinary NAG level

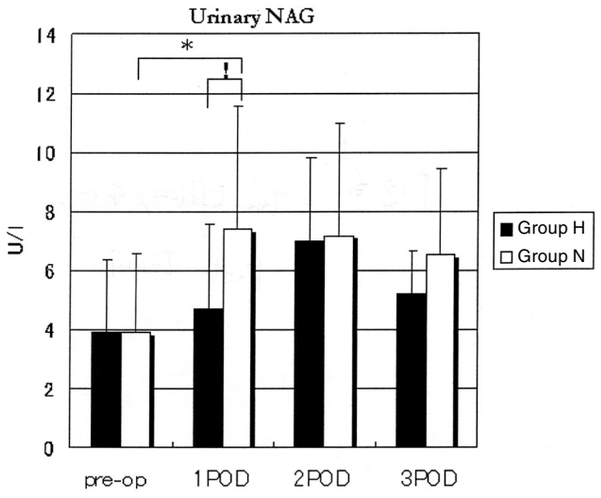

Fig. 5. Urinary NAG levels (U/l) at different times with Group H and Group N.
Data are mean ± SD.
*, p <0.05 compared to preoperative value in Group N.
! , Differences between groups are significant (p = 0.004).
NAG, N-acetyl-beta-D-glucosaminidase; pre-op, preoperation; POD, postoperative day.

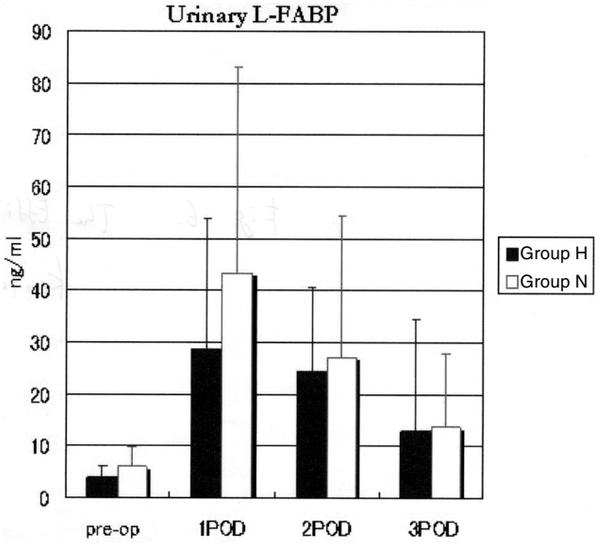

Fig. 6. Urinary L-FABP level (ng/ml) at different times with Group H and Group N.
Data are mean ± SD.
L-FABP, liver-type fatty acid-binding protein; pre-op, preoperation; POD, postoperative day.

Table 4. IL-6 and TNF-α levels at different times

		Pre-op	ICU arrival	6 hours after ICU arrival	1 POD
IL-6 (pg/ml)	Group H	6.0 ± 8.5	142.1 ± 48.5	77.4 ± 20.4	46.7 ± 19.5
	Group N	6.1 ± 7.0	141.7 ± 67.1	100.25 ± 41.1	53.4 ± 30.4
TNF-α (pg/ml)	Group H	<5	<5	<5	<5
	Group N	<5	<5	<5	<5

IL, interleukin; TNF, tumor necrosis factor; pre-op, preoperation; ICU, intensive care unit; POD, postoperative day.

was lower than that in Group N 2 and 3 days after surgery (2 POD: Group H 6.9 ± 2.9 and Group N 7.2 ± 3.8; 3 POD: Group H 5.2 ± 1.5 and Group N 6.5 ± 2.9 U/l), though there were no significant differences (Fig. 5).

In Group H, the urinary L-FABP level was lower than that in Group N 1 to 3 days after surgery (Group H vs. Group N pre-op: 4.1 ± 0.2 vs. 6.1 ± 3.8; 1 POD: 28.7 ± 25.3 vs. 43.3 ± 39.8; 2 POD: 24.6 ± 16.0 vs. 27.2 ± 27.2; 3 POD: 12.9 ± 21.7 vs. 13.8 ± 14.3 ng/ml). The peak value was inhibited the day after surgery, though there was no significant difference (Group H: 28.7 ± 25.3 ng/ml; Group N: 43.3 ± 39.8 ng/ml, p = 0.36) (Fig. 6).

IL-6 and TNF-α

There were no significant differences in the IL-6 level between the 2 groups. There were also no significant differences in the TNF-α level (Table 4).

Discussion

The results of this study showed that in patients with renal dysfunction before cardiac surgery, continuous low-dose h-ANP therapy from the beginning of surgery (central dose: 0.02 μg/kg/min) maintained renal function, preventing its deterioration. In Group H, the serum Cr level was significantly lower than the preoperative value from admission to the ICU until 14 days after surgery (Fig. 1). The Ccr value the day after surgery (39.3 ± 14.5 ml/min, p = 0.08) was higher than the preoperative value (32.4 ± 6.2 ml/min), and then it significantly increased 2 and 3 days after surgery (46.6 ± 15.0 ml/min, p = 0.004, and 50.3 ± 13.6 ml/min, p = 0.002,

respectively). Seven days after surgery, the value returned to the preoperative value (36.8 ± 19.2 ml/min, p = 0.48). A Ccr elevation was achieved during the administration period (Fig. 2). The primary evaluation items such as Cr and Ccr suggested the protective effects of h-ANP on the kidney.

Concerning secondary evaluation items, the BUN level in Group H significantly decreased after admission to the ICU. Thereafter it was also lower than the preoperative value (Fig. 3), though there were no significant differences. In particular, a high level of NAG is contained in the proximal uriniferous tubule, and its molecular weight is relatively high. Usually, serum NAG is not excreted in urine. In the presence of uriniferous tubule/glomerular disorders, NAG appears in urine, and this parameter is useful for detecting renal disorders in the early stages.[9] In this study, in Group H an increase in the urinary NAG level the day after surgery was significantly inhibited (Group H: 4.7 ± 2.9 U/l, and Group N: 7.4 ± 4.1 U/l, p = 0.004). In Group H, the value was also lower 2 and 3 days after surgery. In Group N, the urinary NAG level (6.5 ± 2.9 U/l) 3 days after surgery was significantly higher than the preoperative value (3.9 ± 2.7 U/l) (p = 0.005) (Fig. 5).

The urinary L-FABP level reflects the grade of stress in the proximal uriniferous tubule and is useful for predicting the severity of renal disorders. Also, this marker is used to monitor renal disorders.[10,11] In this study, there were no significant differences in the urinary L-FABP level between the 2 groups. However, in Group H the peak (28.7 ± 25.3 ng/ml, 1 POD) was lower than that in Group N (43.3 ± 39.8 ng/ml, p = 0.36). The value was also lower in this group 2 and 3 days after surgery (Fig. 6).

Concerning the urine volume per hour, the intraoperative urine volume in Group H (297.0 ± 145 ml/h) was markedly higher than that in Group N (187.2 ± 120.7 ml/h, p = 0.001). In Group N, the urine volume per hour was higher than that in Group H 1 and 2 days after surgery (Fig. 4). This was possibly because fluid reserved in the third space had returned into blood vessels in Group N. These results suggest that h-ANP protects the kidney.

Some studies have reported the usefulness of h-ANP administration during and after cardiovascular surgery with a CPB. Bergman et al. administered h-ANP for 3 hours after cardiac surgery in patients with normal renal function and reported that this agent increased the urine volume, inulin clearance, glomerular filtration rate, and Na excretion, protecting the kidney.[12] Cardiovascular surgery with a CPB enhances the RAA and sympathetic nervous systems, decreasing the urine volume and inducing water retention in the third space.[2] It is known that h-ANP exhibits various pharmacological actions such as an inhibition of the RAA/sympathetic nervous systems and diuretic activities.[6–8] According to several studies, continuous intraoperative/postoperative low-dose h-ANP therapy inhibited RAA system activity, reduced peripheral vascular resistance, and exhibited potent diuretic activities, suggesting its usefulness in postoperative water balance control.[6,7] Various studies have reported the effects of h-ANP administration on acute renal failure after cardiovascular surgery. Valsson et al. administered h-ANP to acute renal failure patients with heart failure after open heart surgery. They reported that the urine volume, glomerular filtration rate, and renal blood flow increased by 62%, 43%, and 38%, respectively, and that renal vascular resistance decreased by 30%, improving renal function.[13] Swärd et al. conducted a randomized placebo-controlled trial in 61 acute renal failure patients with an increase of more than 50% in the serum Cr level after cardiovascular surgery (open heart surgery).[14] The protocol consisted of h-ANP administration at 0.05 μg/kg/min. Twenty-one days after surgery, 21% of the patients in the h-ANP-treated group and 47% of those in the control group required dialysis; h-ANP administration significantly decreased the proportion of patients requiring dialysis. In the h-ANP-treated group, Ccr significantly increased in comparison with the pretreatment value until 3 days after the start of treatment. However, in the control group there were no marked changes. Furthermore, the dialysis-free survival rates 21 days after surgery were 72% and 43% in the h-ANP-treated and control groups, respectively, showing a significant difference.[14]

Some studies have reported h-ANP administration for acute renal failure in patients after non–open heart surgery. Rahman et al. examined patients with acute renal failure and reported that h-ANP administration increased the glomerular filtration rate, reducing the necessity of dialysis.[15] In 1997, the results of a multicenter large-scale prospective study were reported.[16] The subjects were 504 patients with acute renal failure. There were no significant differences in the serum Cr level after 24-hour h-ANP administration, dialysis-free rate, or mortality rate between the h-ANP-treated and control groups. These renal failure patients were

divided into 2 groups (oliguria and nonoliguria), and stratified analysis was performed. In the oliguria group, the serum Cr level decreased after 21 days, and the dialysis-free survival rate significantly increased (h-ANP-treated group: 23%, control group: 8%), but the rate decreased in the nonoliguria group. There was no marked difference in the mortality rate between the 2 groups. However, in another multicenter double-blind study involving oliguria-related acute renal failure patients, there were no marked differences in the dialysis introduction or survival rates.[17] In the h-ANP-treated group, the blood pressure value was significantly lower than in the control group, suggesting that h-ANP is not effective. Thus several studies have indicated the association between h-ANP administration and blood pressure. With respect to renal blood flow and the glomerular filtration rate, the optimal dose of h-ANP is 0.1 μg/kg/min or less.[13,15] However, a study reported that at a dose exceeding 0.1 μg/kg/min, the glomerular filtration rate and renal blood flow both decreased to the pretreatment values with the reduction of the mean arterial pressure.[15] Furthermore, another study suggested that h-ANP administration in the presence of a blood-pressure drop increases oxygen consumption in the kidney, causing ischemia.[18] To achieve the protective effects of h-ANP on the kidney, blood pressure maintenance and pulmonary oxygenation may be important. In this study, continuous h-ANP administration at a low dose, at which the mean arterial pressure is maintained, for 5 days or more from the start of surgery achieved protective effects on the kidney. With respect to the long-term administration of h-ANP, a study reported that in patients with ischemic acute renal failure, the efficacy of h-ANP (0.05 μg/kg/min) for renal blood flow and the glomerular filtration rate was maintained after 9 days of treatment.[19] Thus there may be no issue of h-ANP resistance.

Extracorporeal circulation causes the exposure of blood to foreign substances, activating the coagulation system, complements, leukocytes, and various cytokines. This condition is reported as systemic inflammatory response syndrome (SIRS).[20] The inflammatory response may influence complications such as respiratory failure, renal dysfunction, and hemorrhage after surgery. IL-6 is a high-sensitivity parameter of the acute inflammatory response.[21] TNF-α is considered to be a more sensitive marker of systemic inflammation related to the use of a CPB.[22] A recent study reported that heart failure induced inflammatory cytokines. In particular, the IL-6/TNF-α-mediated modification of heart failure has been shown; increases in the IL-6 and TNF-α levels may be involved in the progression of cardiovascular remodeling associated with reduced myocardial contractions, apoptosis, and myocardial fibrosis. Several studies examined the association between the prognosis of chronic heart failure and IL-6 and reported that patients with an IL-6 level of 4.6 pg/ml or more showed a poor prognosis.[23] Another study indicated that h-ANP administration inhibited increases in the IL-6 and TNF-α levels.[24,25] Considering this, we measured the IL-6 and TNF-α levels in the study. We could not obtain a finding that h-ANP administration inhibited increases in the levels of cytokines (IL-6 and TNF-α). This was possibly because the dose of h-ANP was low (0.02 μg/kg/min). In the future, high-dose h-ANP administration should be investigated.

The limitation of this study was the relatively small number of subjects. Therefore its results must be confirmed in a large-scale multicenter cooperative study.

In conclusion, the results of the study suggest that in patients with renal dysfunction before cardiovascular surgery, continuous low-dose h-ANP administration (central dose: 0.02 μg/kg/min) from the start of surgery maintains renal function, preventing its deterioration.

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