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Article

## Effects of Continuous Infusion of Low-dose Human Atrial Natriuretic Peptide (hANP) on the Lungs during Cardiac Surgery

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**Objective:** The objective of this study was to determine the effects of a continuous infusion of low-dose hANP on the lungs during cardiac surgery in patients under cardiopulmonary bypass (CPB).

**Methods:** We analyzed 30 consecutive cases of cardiac surgery performed at our hospital from 2007–2008. The patients were divided into a group that received hANP (hANP group) or a group that received saline and no hANP (N-hANP group). We measured various parameters before and after surgery using a PiCCO monitor.

**Result:** There were no differences in the preoperative characteristics between the groups, although urine volume during the operation was significantly greater in the hANP group. After surgery, there were no significant differences between the groups in cardiac output index (CI), global enddiastolic volume index (GEDVI), intrathoracic blood volume index (ITBI), pulmonary blood volume index (PBI), extravascular lung water index (ELWI) and pulmonary vascular permeability index (PVPI), total protein, and creatine. In contrast, interleukin-6 (IL-6) and renin were significantly lower, and albumin was significantly higher in the hANP group.

**Conclusion:** We found that low-dose hANP during open cardiac surgery inhibited the secretion and plasma activity of IL-6 and renin. Although there were no differences in lung circulatory parameters such as the amount of fluid in the pulmonary blood vessels between the two groups, we believe that the strong diuretic effect of hANP reduced third-space fluid retention caused by CPB.

**Keywords:** human atrial natriuretic peptide, cardiac surgery, PiCCO

### Introduction

Atrial natriuretic peptide (ANP), isolated and identified in 1984 by Kangawa and Matsuo,<sup>1)</sup> is predominantly

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synthesized in the atrium and has a strong diuretic effect. A hANP preparation, carperitide, was subsequently developed, and has been used mainly for the treatment of heart failure and acute myocardial infarction (AMI), because it improves preload and afterload by diuresis and vasodilatation.<sup>2-7)</sup>

ANP has been demonstrated to exert various effects, including inhibition of the renin-angiotensin-aldosterone system, reduced myocardial hypertrophy, improved cardiac function, and less remodeling, and fibrosis.<sup>8-12)</sup> During cardiac operations performed in our department, we have administered an intravenous infusion of low-dose ANP at the onset of cardiopulmonary bypass (CPB)

to overcome the disadvantages of CPB, which include complications such as decreased urinary output and third-space fluid shift.<sup>13)</sup> In addition, it has been reported that ANP decreases the demand for furosemide, inhibits potassium loss, reduces electrolyte imbalance, and prevents arrhythmia development during unstable conditions after surgery.<sup>14–18)</sup> Thus, it has become a useful drug for perioperative and postoperative management of patients treated in our department. However, the effect on the pulmonary circulation during cardiac surgery has not been examined. Therefore, the objective of this study was to elucidate the effect of a continuous infusion of low-dose hANP on fluid retention in the lungs during cardiac surgery.

## Materials and Methods

A total of 30 patients, who had cardiac surgery at Dokkyo Medical University Hospital from May 2007 to November 2008, were enrolled in this study. The patients were randomized into one of two groups: a group that received an infusion of hANP (Suntory Inc., Osaka, Japan and Daiichi-Sankyo Pharmaceutical Inc., Tokyo, Japan) at 0.025 µg/kg/min starting at the initiation of CPB (hANP group), or a placebo group that received physiological saline in the same manner (N-hANP group). In all patients, CPB was performed with non-pulsatile perfusion at a reduced temperature (rectal temperature, 34°C). The hANP or saline infusion was started just after the initiation of CPB and stopped after 24 h.

The levels of interleukin-6 (IL-6), total protein (TP), albumin (Alb), creatinine (Cr), renin activity, and aldosterone were measured before surgery, then following surgery upon return to the intensive care unit (ICU), after 6 and 12 h, and on postoperative days 1 and 3. In addition, hemodynamic data were obtained with a Swan-Ganz catheter before surgery and upon return to the intensive care unit (ICU). This catheter was used to measure cardiac output index (CI), pulmonary capillary wedge pressure (PCWP), and central venous pressure (CVP). A Pulse Index Contour Continuous Cardiac Output device (PiCCO; Pulsion Medical Systems, Munich, Germany) was used to measure, global enddiastolic volume index (GEDVI), intrathoracic blood volume index (ITBI), pulmonary blood volume index (PBI), extravascular lung water index (ELWI) and pulmonary vascular permeability index (PVPI) at the same time points.

The details of the study were explained to the patients prior to enrollment, and their consent was obtained. The

protocol was approved by the Institutional Review Board of Dokkyo Medical University Hospital.

## Statistical analysis

Data are expressed as the mean ± SD. For parametric and nonparametric data, statistically significant differences were determined using Student's *t* test and Fisher's exact test, respectively. A *p* value of <0.05 was considered significant. Other data were analyzed using repeated measures analysis of variance. All analyses were performed with SPSS software (SPSS Inc., Chicago, Illinois, USA).

## Results

### Clinical characteristics

There were no significant differences between the groups in the preoperative characteristics such as age, male/female ratio, risk factors, laboratory data (TP, Alb, Cr, IL-6, renin and aldosterone) and cardiac function (ejection fraction) (**Table 1**).

### Surgical findings

**Table 1** shows the surgical techniques. The mean CPB time was 167.8 ± 41.9 min in the hANP group and 142.7 ± 29.8 min in the N-hANP group. The aortic cross-clamp (ACC) time was longer in the hANP than the N-hANP group (126.7 ± 37.3 vs. 98.0 ± 21.0 min, *p* = 0.015). Furthermore, the perioperative urine volume was greater in the hANP than the N-hANP group (1112.2 ± 643.7 vs. 526.0 ± 492.7 ml, *p* = 0.009).

### Pre- and postoperative hemodynamic data

The preoperative hemodynamic parameters in the hANP and N-hANP groups were as follows: CVP, 6.3 ± 3.9 vs. 4.9 ± 4.4; CI, 2.3 ± 0.6 vs. 2.3 ± 0.6; GEDI, 767.9 ± 187.2 vs. 796.3 ± 192.4; ITBI, 959.8 ± 234.0 vs. 995.2 ± 240.9; PBI, 191.9 ± 46.8 vs. 199.0 ± 48.5; ELWI, 9.7 ± 3.1 vs. 9.1 ± 4.2; and PVPI, 1.9 ± 0.5 vs. 1.6 ± 0.5, respectively. The postoperative hemodynamic parameters in the two groups were as follows: 7.1 ± 3.4 vs. 8.1 ± 4.0, 2.9 ± 0.8, vs. 3.0 ± 0.7, 749.0 ± 223.7 vs. 770.2 ± 171.8, 936.3 ± 279.4 vs. 962.6 ± 214.8, 187.2 ± 55.7 vs. 192.4 ± 42.9, 8.0 ± 2.5 vs. 8.1 ± 3.0, and 1.7 ± 0.7 vs. 1.6 ± 0.8, respectively. There were no differences between the groups in any of the pre- or postoperative hemodynamic parameters (**Table 2**). Furthermore, the data on lung fluid volume and vascular permeability (GEDVI, ITBI, PBI, ELWI, PVPI) showed no changes in either group, with a positive fluid

**Table 1 Preoperative data and surgical techniques**

	hANP group	N-hANPgroup	<i>p</i>
	(n = 15)	(n = 15)	
Age (years)	63.8 ± 6.8	63.9 ± 8.8	0.963
Sex (male)	10 (66.7%)	14 (93.3%)	0.072
Risk factors			
Smoking (%)	5 (33.3%)	8 (53.3%)	0.285
Hypertension (%)	8 (53.3%)	8 (53.3%)	1.000
Hyperlipidemia (%)	8 (53.3%)	7 (46.7%)	0.726
Diabetes mellitus (%)	6 (40.0%)	4 (26.7%)	0.456
Obesity (%)	3 (20.0%)	2 (13.3%)	0.638
Lab data			
IL-6	1.8 ± 1.8	2.3 ± 3.1	0.576
Total protein	6.7 ± 0.7	6.5 ± 0.8	0.530
Albumin	3.8 ± 0.5	3.7 ± 0.5	0.806
Creatinine	0.8 ± 0.3	0.8 ± 0.2	0.884
Aldosterone	41.9 ± 30.5	54.1 ± 33.1	0.303
Renin	4.2 ± 2.8	6.2 ± 3.7	0.100
BNP	202.2 ± 355.5	165.0 ± 126.4	0.706
Left ventricular function			
EF (%)	61.4 ± 7.7	59.3 ± 10.8	0.552
CABG	9	7	
MVP	1	4	
MVR	6	2	
AVR	2	2	
TAP	3		
CPB time	167.8 ± 41.9	142.7 ± 29.8	0.069
ACC time	126.7 ± 37.3	98.0 ± 21.0	0.015
OPE time	341.8 ± 75.7	292.7 ± 65.6	0.068
Perioperative			
Urine volume	1112.2 ± 643.7	526.0 ± 492.7	0.009
Infusion volume	5553.8 ± 1327.9	4971.9 ± 2053.8	0.365

IL-6: Interleukin-6; BNP: brain natriuretic peptides; EF: ejection fraction; CABG: coronary artery bypass grafting; MVP: mitral valve repair; MVR: mitral valve replacement; TAP: tricuspid annuloplasty; AVR: aortic valve replacement; CPB: cardiopulmonary bypass; ACC: aortic cross clamp; OPE: operation

balance ranging from 5000–5500 ml after surgery in both groups.

### IL-6

In both groups, the levels of IL-6 were increased and reached a peak immediately after surgery. IL-6 in the N-hANP group was significantly higher immediately after surgery and 6 h later than in the h-ANP group ( $p < 0.05$ ). Thereafter, IL-6 in both groups decreased, but did not return to baseline levels (**Fig. 1**).

### TP and Alb

There were no significant intergroup differences in the preoperative TP or Alb levels. After surgery, those levels decreased in both groups, with the TP level significantly lower in the N-hANP than the h-ANP group ( $p < 0.05$ ).

Furthermore, Alb was significantly lower in the N-hANP group immediately and 6 h after surgery ( $p < 0.05$ ) (**Fig. 1**).

### Cr

There was no significant difference in the preoperative Cr level between the groups, whereas Cr was significantly lower in the hANP group at 12h after surgery (**Fig. 1**).

### Renin and aldosterone

In the N-hANP group, the levels of renin and aldosterone were increased after surgery. Renin reached a peak immediately after surgery, whereas aldosterone peaked at 6h after surgery. The renin level was significantly lower in the hANP than the N-hANP group after surgery and up to postoperative day 3 ( $p < 0.05$ ) (**Fig. 1**).

**Table 2** Pre and postoperative hemodynamic parameters

	hANP group	N-hANPgroup	<i>p</i>
	(n = 15)	(n = 15)	
Central venous pressure(CVP)			
Preoperative	6.3 ± 3.9	4.9 ± 4.4	0.34
Postoperative	7.1 ± 3.4	8.1 ± 4.0	0.45
Cardiac index (CI)			
(normal values: 3.0~5.0 l/min/m <sup>2</sup> )			
Preoperative	2.3 ± 0.6	2.3 ± 0.6	0.66
Postoperative	2.9 ± 0.8	3.0 ± 0.7	0.55
Global Enddiastolic Volume index (GEDI)			
(normal values: 680~800 ml/m <sup>2</sup> )			
Preoperative	767.9 ± 187.2	796.3 ± 192.4	0.92
Postoperative	749.0 ± 223.7	770.2 ± 171.8	0.33
Intrathoracic Blood Volume index (ITBI)			
(normal values: 850~1000 ml/m <sup>2</sup> )			
Preoperative	959.8 ± 234.0	995.2 ± 240.9	0.91
Postoperative	936.3 ± 279.4	962.6 ± 214.8	0.34
Pulmonary Blood Volume index (PBI)			
(normal values: 170~200ml/m <sup>2</sup> )			
Preoperative	191.9 ± 46.8	199.0 ± 48.5	0.90
Postoperative	187.2 ± 55.7	192.4 ± 42.9	0.34
Extravascular Lung Water index (ELWI)			
(normal values: 3.0~7.0 ml/kg)			
Preoperative	9.7 ± 3.1	9.1 ± 4.2	0.31
Postoperative	8.0 ± 2.5	8.1 ± 3.0	0.54
Pulmonary Vascular Pemeability index (PVPI)			
(normal values: 1.0~3.0)			
Preoperative	1.9 ± 0.5	1.6 ± 0.5	0.81
Postoperative	1.7 ± 0.7	1.6 ± 0.8	0.60

## Discussion

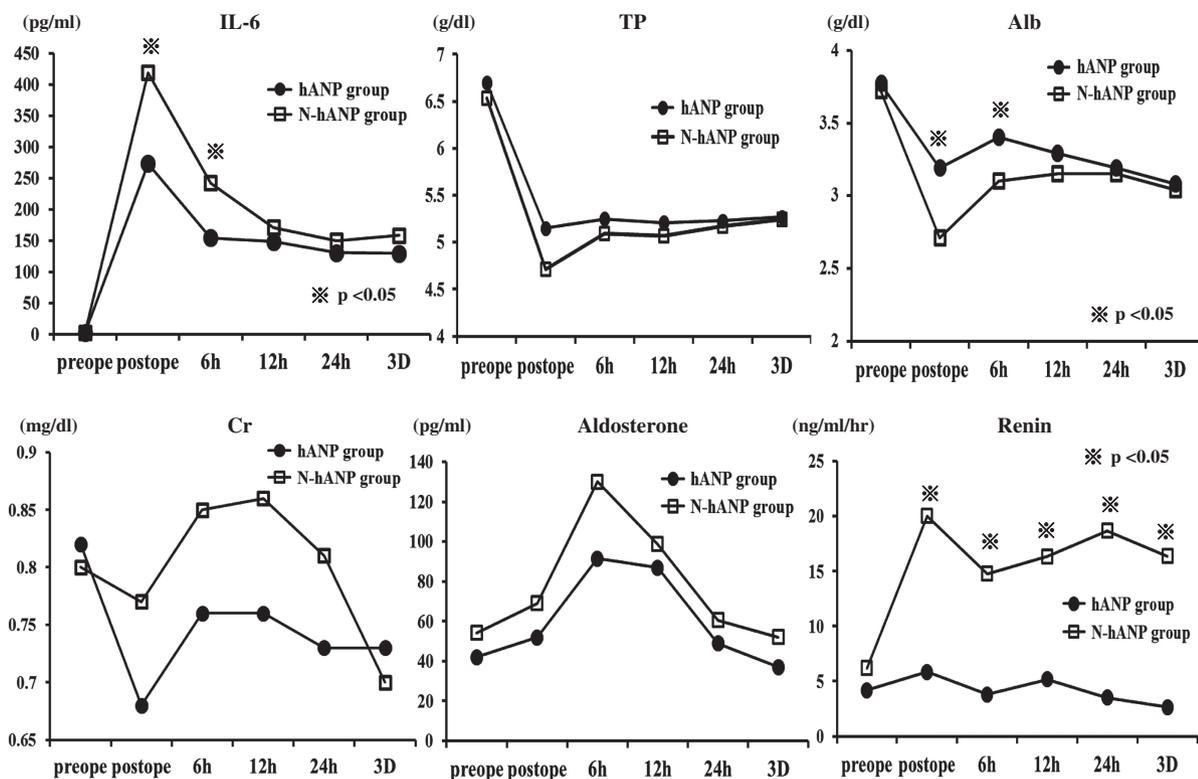
In addition to its diuretic action, h-ANP also has a vasodilatory effect, inhibits the renin-angiotensin-aldosterone system, and has an anti-inflammatory effect, which can improve the pathophysiology of heart failure.<sup>2,5-12)</sup> It is also used as a drug for acute heart failure, as it has an effect to improve acute-phase hemodynamics. Furthermore, based on clinical findings suggesting that the agent might have a cardioprotective effect in patients with acute myocardial infarction, a cardioprotective action that goes beyond hemodynamic improvement in the acute phase is also expected.<sup>3,4)</sup>

In the field of cardiovascular surgery, the use of CPB results in elevated catecholamine levels, decreased urinary output, third-space fluid retention, and renin-angiotensin-aldosterone system activation. Sezai, et al. reported that carperitide acted to reverse these changes in every aspect.<sup>13-18)</sup> They administered the drug at 0.02 µg/kg/min from the start of CPB, after taking into consideration that their patients did not have heart failure before surgery and

might become dehydrated as a result of fasting for one day prior to the operation. Their findings showed inhibition of the renin-angiotensin-aldosterone system and less fluid retention in the third space due to a strong diuretic action. Furthermore, there was a reduced incidence of cardiac dysrhythmia as a postoperative complication and inhibition of left ventricular remodeling.

In the present study, we focused on the effects of h-ANP on lung fluid volume and vascular permeability during CPB. We delivered a continuous low-dose infusion of 0.02 µg/kg/min from the initiation of CPB, as previously reported by Sezai, et al. To investigate the pathophysiological conditions of the lung, GEDI, ITBI, PBI, ELWI and PVPI were determined using a PiCCO device before and immediately after surgery. Furthermore, the levels of renin, aldosterone, IL-6, TP and Alb were also determined.

The results of blood sampling revealed that IL-6 output for the first 6 h after surgery was notably inhibited in the h-ANP group. Furthermore, the levels of TP and Alb were elevated in the h-ANP group, and Alb was significantly



**Fig. 1** Changes in interleukin-6 (IL-6), total protein (TP), albumin (Alb), creatinine (Cr), renin activity, and aldosterone preope and postope upon return to the intensive care unit (ICU), after 6 and 12 h, and on postoperative days 1 and 3.

elevated for the first 6 hours after surgery. Also, renin activity and aldosterone levels were significantly inhibited in the h-ANP group. On the basis of these findings, we conclude that carperitide inhibits the renin-angiotensin-aldosterone system and cytokine production, which results in decreased fluid retention in the third space.

It is possible that blood vessel permeability was increased due to vascular endothelial damage caused by CPB and cytokine release. Although we hypothesized that carperitide reduce pulmonary vascular permeability inhibiting Cytokines produced, there were no changes in TIBI, PBI, ELWI or PVPI before and after CPB in either group. Thus, despite cytokine release, the interstitial space outside of the pulmonary blood vessels did not accumulate fluid and there was no effect of hANP on the lung fluid parameters. These findings confirmed that there was no effect exerted until lung gas exchange.

Carperitide has been frequently reported to have a strong diuretic effect on the kidneys, as it acts directly on the glomerulus and renal tubules.<sup>19)</sup> From the present results, we considered that carperitide may have a strong diuretic action, as urinary output was significantly greater during surgery in the hANP group than in N-hANP, whereas Cr was lower in the h-ANP group. Therefore, it

is highly likely that its administration is effective for patients with renal failure in the pre-dialysis stage.

### Conclusion

In the present study, low-dose continuous h-ANP administration during open heart surgery inhibited cytokine secretion and plasma renin activity. The infusion of h-ANP did not affect lung fluid volume or pulmonary vascular permeability. Thus, it is considered that the diuretic effect of carperitide can relieve fluid retention in the third space induced by CPB.

### Disclosure Statement

There are no conflicts of interest.

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