ATTENUATION OF ATRIAL NATRIURETIC PEPTIDE RESPONSE TO SODIUM LOADING AFTER CARDIAC OPERATION

To evaluate the role of cardiac operation and the atrial appendage in secretion of atrial natriuretic peptide in response to sodium loading, we studied 44 patients who underwent heart operations with (28 patients; group I) or without (16 patients; group II) right atrial appendectomy and 16 patients who underwent lobectomy (group III). Before and after operation 1 ml/kg of 10% NaCl was infused for 15 minutes. Blood samples were taken before NaCl infusion and immediately after infusion and at 60 minutes after infusion. There were no significant changes in hemodynamics or hematocrit level throughout the study. Plasma and urine sodium levels and the fractional excretion of sodium were significantly increased by sodium loading. Before operation, plasma mean atrial natriuretic peptide levels increased markedly in response to sodium infusion in all groups. After operation, this atrial natriuretic peptide response disappeared in groups I and II, but remained present in group III. Elution profiles of plasma atrial natriuretic peptide showed that the major peak coincided with α-atrial natriuretic peptide before sodium loading, whereas a β-atrial natriuretic peptide peak appeared 60 minutes after sodium loading in all groups both before and after operation. The mean plasma arginine vasopressin levels were significantly increased by sodium loading both before and after operation in all groups. Sodium loading decreased the mean plasma aldosterone levels in all groups before operation, but did not after operation in groups I and II. Plasma renin activity and angiotensin II concentrations were not changed by sodium loading. We conclude that atrial natriuretic peptide response to sodium loading is attenuated by cardiac operation irrespective of right appendectomy, but not by lobectomy. Sodium loading augments secretion of β-atrial natriuretic peptide even in reduced atrial natriuretic peptide response states after heart operations. (J THORAC CARDIOVASC SURG 1995;110:75-80)

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Human atrial natriuretic peptide (ANP) is a cardiac peptide that modulates acute changes in blood volume and salt balance by enhancing diuresis and natriuresis,[1] inhibiting renin and aldosterone secretion, and relaxing vascular smooth muscle.[2, 3]

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Cardiac operation increases capillary permeability and causes complex changes in sodium-water homeostasis.[4] Such operation usually involves excision of the right atrial appendage, which contains more ANP than other atrial tissue.[5, 6] Intravenous hypertonic saline solution restores cardiovascular function by displacement of tissue fluid into the blood compartment, vasodilatory effects, and direct positive inotropic actions on the myocardium in hemorrhagic shock or heart operations.[7-10] To evaluate the role of the right atrial appendage and heart operation in secretion of ANP in response to hypertonic saline solution infusion, we examined the ANP secretion responses to acute sodium loading in patients with acquired heart disease who underwent heart operation and compared these responses with those in patients who underwent pulmonary lobectomy.

Material and methods

The study group consisted of 44 patients with acquired heart disease who underwent cardiac operation and 16 patients who underwent pulmonary lobectomy because of lung cancer. Patients who underwent heart operation were divided into two groups in accordance with concomitant excision of right atrial appendage (group I) or no excision (group II). In group I, venous cannulation was done with pursestring suture of the right atrial appendage and excision of the appendage, whereas in group II venous cannulas were inserted through the free wall of the right atrium without amputation of the appendage. Group I consisted of 28 patients (15 men and 13 women, mean age 58 ± 5 years) who received 12 valvular and 16 coronary artery bypass procedures. Group II consisted of 16 patients (9 men and 7 women, mean age 60 ± 4 years) who received 6 valvular and 10 coronary artery bypass procedures. All patients in group III (10 men and 6 women, mean age 64 ± 5 years) had lung cancer (4 patients with squamous cell carcinoma, 12 patients with adenocarcinoma). Patients with congestive heart failure, metabolic disorders, or an ectopic ANP-producing tumor and those who received furosemide or angiotensin-converting enzyme inhibitors were excluded from the study. This study was approved by the Institutional Review Board of Hokushin General Hospital and written informed consent was obtained from all subjects before sodium loading and operation.

Early in the morning at 1 week before operation, with patients in the supine position without any fluid or drug intake, a balloon-tipped flow-directed catheter was positioned in the pulmonary artery via the cubital vein with the use of satisfactory local anesthesia with procaine and a urinary catheter was inserted. After control hemodynamic measurements were taken and blood sampling completed, 1 ml/kg of 10% NaCl was infused for 15 minutes, and blood samples were taken immediately and at 60 minutes after infusion. After operation, the same protocol was repeated 1 day after extubation (group I, 2.3 ± 0.5; group II, 2.2 ± 0.3; group I, 1.1 ± 0.2 postoperative days). Blood samples were withdrawn from an indwelling cannula in the cubital vein and collected in ice-chilled tubes. Plasma was separated by centrifugation at 4° C and immediately frozen and stored at −80° C.

Radioimmunoassay of ANP was done as previously described.[11] ANP profiles were obtained by gel permeation chromatography (GPC) in six patients. Briefly, GPC was done with use of a Sephadex G-75 column (Pharmacia Biotech, Tokyo, Japan). Acidified samples were loaded directly onto the column and eluted with 0.5 mol/L acetic acid at a flow rate of 5 ml/hour at 4° C. Elution positions were determined by a peptide molecular weight calibration kit and synthetic α-, β-, and γ-ANP. Samples were assayed for ANP before and after fractionation by GPC. Cyclic guanosine monophosphate (c-GMP) levels were measured with a ^{125}I-labeled radioimmunoassay.[12] Arginine vasopressin,[13] plasma renin activity,[14] and levels of angiotensin II[15] and aldosterone were analyzed with radioimmunoassays.[16]

All values were expressed as mean plus or minus the standard error. Significant differences among groups and data obtained before and after operation were determined by analysis of variance with the Bonferroni correction. Changes from control values were compared by the Wilcoxon signed-rank test or by paired Student's t test as appropriate for comparison of data. Statistical significance was accepted at a level of $p < 0.05$.

Results

Hemodynamic parameters including heart rate, right atrial pressure, mean arterial blood pressure, and hematocrit value did not show any significant change immediately and at 60 minutes after NaCl infusion compared with baseline values either before or after operation (data not shown). Both plasma and urine sodium concentrations were significantly increased by sodium loading, as was plasma osmolarity. Although there were no significant changes in urine volume and creatinine clearance, the fractional excretions of sodium increased significantly in all groups. Before operation, marked increases in plasma ANP level during sodium loading were noted, which persisted 60 minutes after sodium loading in all groups (Fig. 1). Although no changes in plasma ANP levels after sodium loading were observed in groups I and II after operation, plasma ANP levels after sodium loading increased significantly in group III (Fig. 2). Baseline urine ANP concentrations significantly increased after operation in all groups. Although sodium loading in groups I and II did not change urine ANP levels after operation, in group III urine ANP concentration increased in response to sodium loading before and after operation (data not shown). The preoperative elution profiles of plasma ANP before and after sodium loading are shown in Fig. 3. The low molecular weight peak coincided with α-ANP. A β-ANP peak appeared 60 minutes after sodium loading in all groups. This change in elution profiles of plasma ANP was also observed after operation in all groups.

There was no significant change in plasma c-GMP concentration caused by sodium loading before operation, although plasma c-GMP concentration was significantly ($p < 0.05$) decreased by sodium loading after operation in groups I and II. In contrast, plasma c-GMP concentrations significantly increased both before and after operation in group III. The plasma arginine vasopressin concentration was significantly increased by sodium loading both before and after operation in all groups. Preoperative sodium loading decreased the mean plasma aldosterone concentrations in all groups; the concentrations remained decreased 60 minutes after

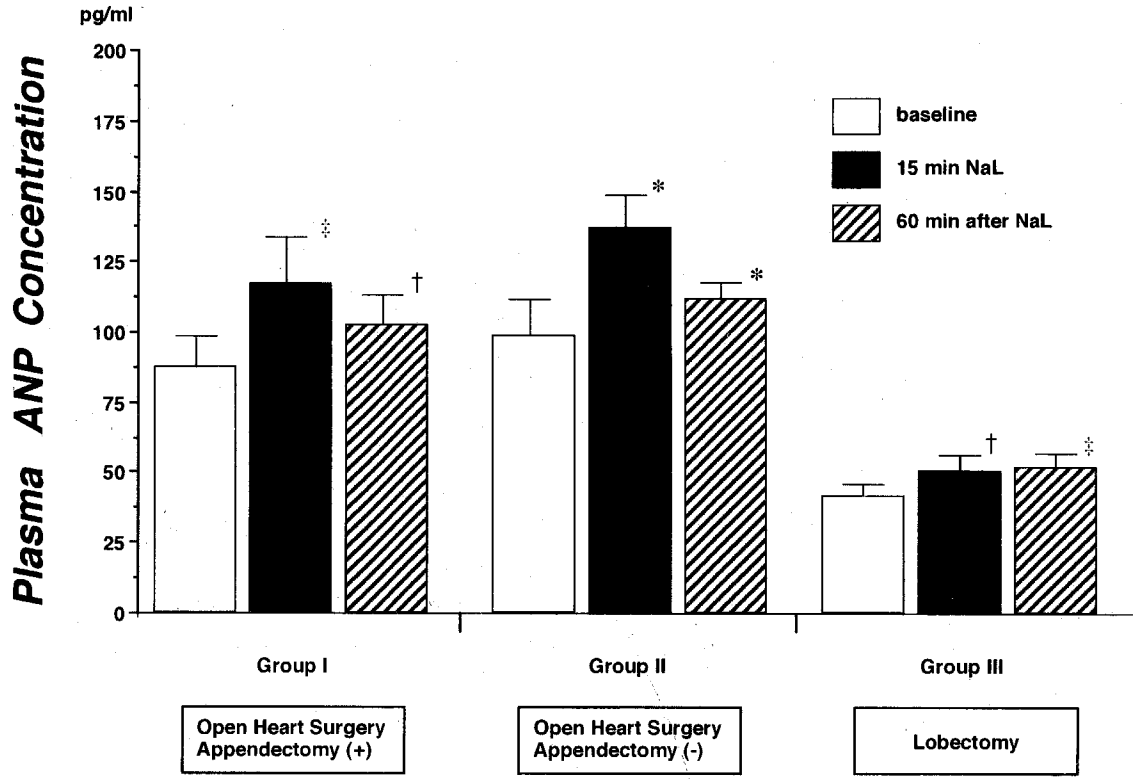

Fig. 1. Changes of plasma ANP concentration in response to sodium loading *(NaL)* before operation. Significant differences are compared with baseline values in each group as follows: $*p < 0.05$, $\ddagger p < 0.01$, $\dagger p < 0.001$.

sodium loading before operation. However, no significant change in aldosterone concentration was observed after operation in groups I and II compared with that in group III. Plasma renin activity and angiotensin II concentrations were not changed by sodium loading. Hemodynamic, renal, and hormonal responses to sodium loading were not different among patients with valvular or coronary artery diseases (data not shown).

Discussion

In this study, sodium loading increased plasma ANP concentration immediately after infusion before operation; this response was abolished after cardiac operation but was preserved after lobectomy. Furthermore, we have shown for the first time that a β-ANP peak appears after sodium loading.

Our results agree with those of previous studies showing that increases in plasma sodium concentration or hyperosmotic challenge induces rapid release of ANP.[17-20] Although we did not evaluate systemic ANP clearance in this study, the mechanism of ANP increase by sodium loading may be caused by direct stimulation of the cardiac myocytes by sodium ions and osmotic pressure.[17-19] However, because a hyperosmotic challenge increases plasma osmolarity and rapidly shifts fluid into the vascular space,[20] involvement of the atrial stretch response cannot be ruled out despite the lack of change in right atrial pressure or hematocrit value in this study.[5]

Many mechanisms may be involved in attenuation of the increase in plasma ANP concentration associated with postoperative sodium loading. Because an increase in plasma ANP concentration by sodium loading was not demonstrated in patients with an intact right atrial appendage, which contains approximately 30% of the total atrial ANP,[6] diminished secretory function caused by right atrial appendectomy is not a major factor responsible for attenuation of ANP secretion in the presence of a high baseline ANP level in the postoperative period.[5, 6] One of the possible mechanisms includes inactivation or diminished function of the renin-angiotensin-aldosterone system after operation.[21] In the present study, preoperative sodium loading sup-

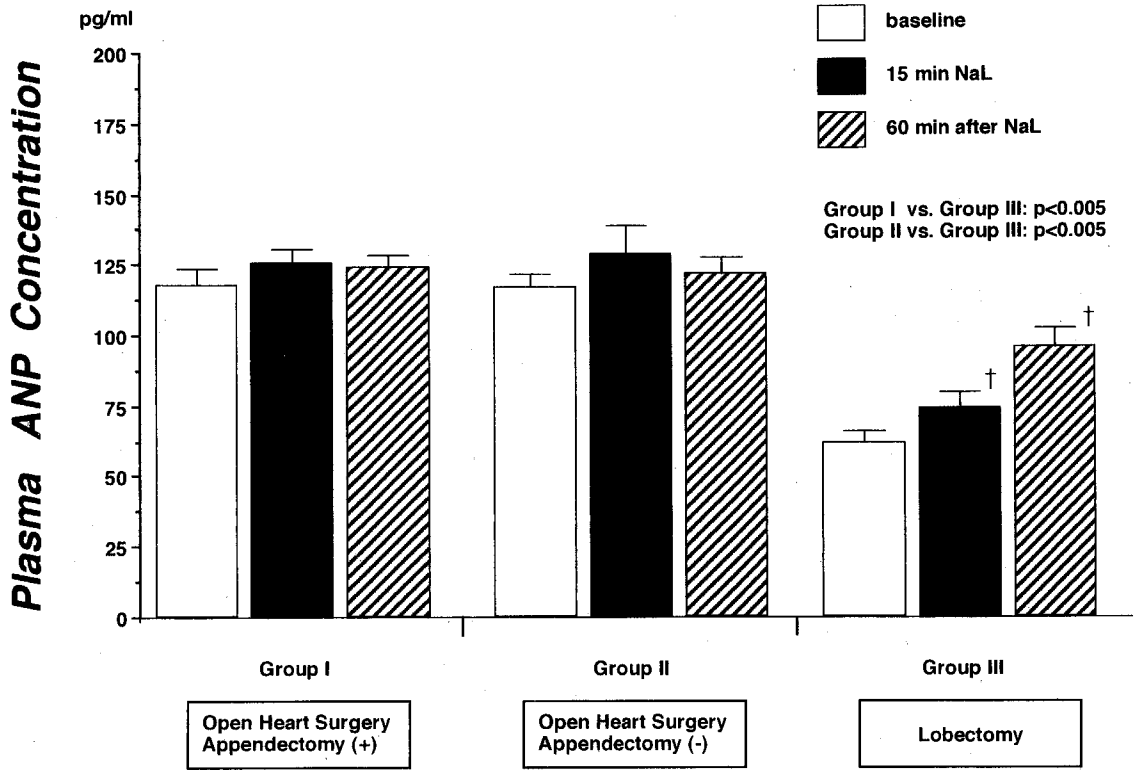

Fig. 2. Changes of plasma ANP concentration in response to sodium loading (*NaL*) after operation. Significant differences are compared with baseline values in each group as follows: †$p < 0.001$.

pressed increases in aldosterone level, whereas postoperative sodium loading did not. Thus the lack of aldosterone secretion caused by sodium loading in patients with cardiac operations after operation compared with level of secretion in patients undergoing lobectomy may play some role in attenuating increases in plasma ANP concentration. Another mechanism may be a result of high baseline preinfusion postoperative ANP concentrations in patients with cardiac operations compared with concentrations in those with pulmonary lobectomy. Other hormonal changes that we did not evaluate in this study, neural mechanisms, or physical factors may be involved in attenuation of ANP secretion in response to sodium loading in heart operations.

Comparison of the elution profiles of plasma ANP before and after sodium loading demonstrated that the major circulating form of ANP before sodium loading was α-ANP, whereas relatively large amounts of β-ANP appeared after sodium loading in all patient groups. Our previous study demonstrated that the concentration of high molecular weight ANP seen in the dehydrated state decreased after administration of saline solution.[19] Different stimuli for ANP secretion may induce different types of ANP release, and direct stimulation by sodium ion and osmotic pressure may induce β-ANP secretion from cardiac myocytes. Even though an increase in total plasma ANP after postoperative sodium loading was not seen, induction of β-ANP by sodium loading was not affected by right atrial appendectomy or lobectomy. The source of this relative increase in β-ANP may be the left atrial appendage or another part of the heart. Kato et al.[18] reported that ANP release induced by hypertonic saline solution was greater and more prolonged than that caused by glucose or isotonic saline solution. Appearance of β-ANP, which has the same diuretic, natriuretic, and vasodilatory actions as α-ANP with slower onset and longer duration,[22] or suppression of the renin-angiotensin-aldosterone system, may account for prolonged natriuresis after sodium loading.[21]

Because preoperative and postoperative sodium loading showed comparable natriuretic responses and because attenuation of ANP release in heart

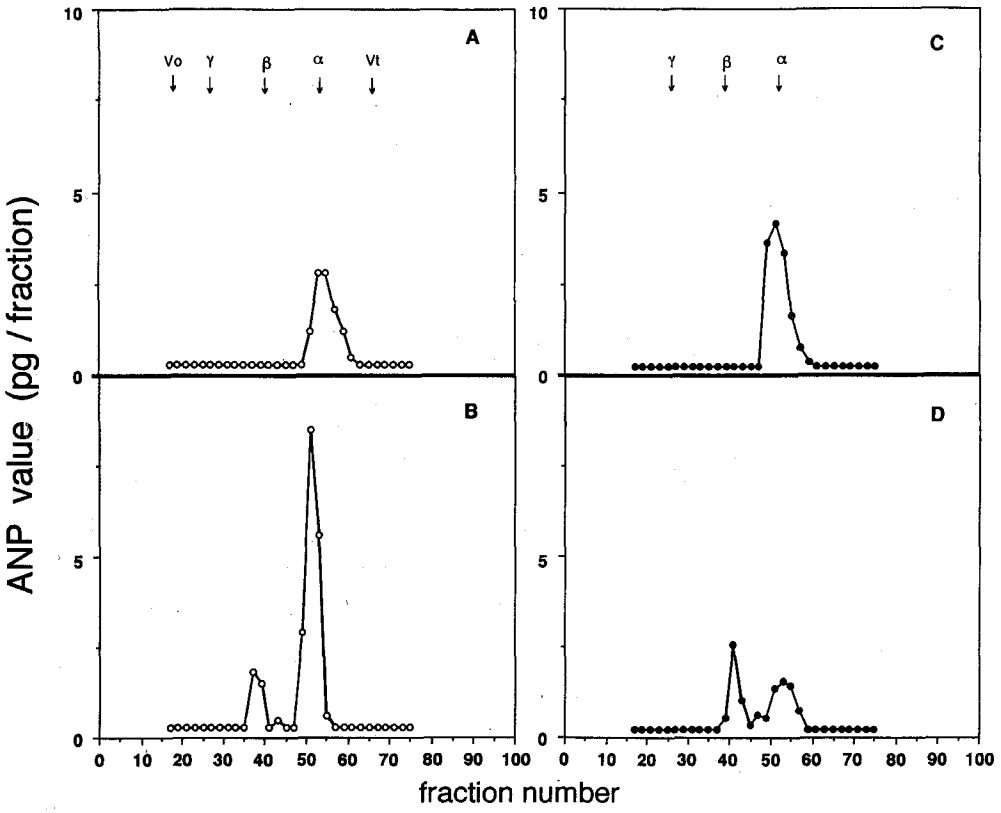

Fig. 3. GPC profiles of plasma ANP (from 48-year-old woman with mitral valve replacement for mitral stenosis). **A,** Before preoperative sodium loading. **B,** Sixty minutes after preoperative sodium loading. **C,** Before postoperative sodium loading. **D,** Sixty minutes after postoperative sodium loading. Elution positions of synthetic α-ANP, β-ANP, and γ-ANP are indicated by *arrows* for α, β, and γ, respectively. *Vo,* Void volume; *Vt,* total volume.

operations does not eliminate natriuresis completely, ANP plays a relatively small role in the regulation of sodium balance.[23] Consistent with this, levels of c-GMP, the second messenger of ANP action,[24, 25] were not increased in plasma or urine during sodium loading in patients with heart operation. Other hormones, for example, brain natriuretic peptide, may also be involved in regulation of sodium homeostasis in cardiac surgical patients.[26]

In summary, the ANP response to sodium loading is attenuated by cardiac operation but not by lobectomy. Sodium loading augments secretion of β-ANP irrespective of type of operation done. In the postoperative period, natriuresis for preservation of fluid-electrolyte metabolism in response to sodium infusion is not a result of change in ANP secretion in patients undergoing heart operation.

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