Plasma Concentration of Atrial Natriuretic Polypeptide in Patients with Atrial Tachycardia

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SUMMARY

To investigate the mechanisms of polyuria associated with tachycardia, we measured plasma concentrations of α -human atrial natriuretic polypeptide (α -hANP) and cGMP in 6 patients with paroxysmal tachycardia. Plasma concentrations of immunoreactive α -hANP and cGMP increased by +69% ($p < 0.05$) and +100% ($p < 0.05$), respectively, during both paroxysmal atrial tachycardia and atrial fibrillation. To examine whether tachycardia per se raises the secretion of α -hANP, we also determined plasma concentrations of α -hANP and cGMP in 5 patients during rapid atrial pacing. The pacing-induced tachycardia also increased both of the plasma concentrations. Further, the examinations of cardiac and renal functions in patients with complete atrioventricular block during rapid pacing revealed that each of the increases in atrial pressures, urinary sodium excretion and creatinine clearance were in parallel with the change in plasma concentration of α -hANP. These results suggest that an increase in plasma concentration of α -hANP during paroxysmal tachycardia is mainly due to elevation of atrial pressure and that this increase in α -hANP contributes to tachycardia polyuria.

Additional Indexing Words:

Cyclic GMP Pacing Polyuria Atrial pressure
Sodium excretion Creatinine clearance

TACHYCARDIA polyuria is a well-known phenomenon; 20 to 50% of patients with paroxysmal atrial tachycardia show an increase in urine

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output.^{1),2)} Although Henry et al³⁾ suggested that cardiac atria may influence renal function in 1956, the mechanisms underlying polyuria are unknown. During tachycardia, both urinary sodium excretion and urine flow increase, while urinary specific gravity decreases.^{1),2),4)} A decrease in anti-diuretic hormone (ADH) has been considered to be involved in this polyuria because urinary osmolarity falls.^{1),4),5)} However, a decrease in ADH alone cannot fully explain the natriuresis accompanied by the polyuria. Recent studies on atrial natriuretic polypeptide (ANP) have raised the possibility that this peptide may be a causal factor in polyuria because the plasma concentration of ANP is elevated during paroxysmal tachycardia.^{6),7)} In addition, intravenous infusion of ANP has been shown to increase urinary output and sodium excretion.⁸⁾⁻¹⁰⁾ However, the mechanisms by which plasma concentration of ANP is elevated during paroxysmal tachycardia are still unclear. Furthermore, it is also unclear whether the elevated ANP concentration is sufficient to cause polyuria.

Since ANP stimulates the production of cGMP in vascular smooth muscle, the kidneys, and adrenal glomerulosa cells,¹¹⁾⁻¹³⁾ cGMP may be involved in the effects of ANP. Thus, if ANP plays a role in patients with tachycardia, the cGMP level in plasma is expected to change. In the present study, we measured the plasma concentrations of immunoreactive α -human ANP (α -hANP) and cGMP during paroxysmal atrial tachycardia and rapid atrial pacing, and determined both cardiac and renal function in patients with complete atrioventricular block during rapid pacing.

SUBJECTS AND METHODS

Study I

Plasma concentrations of α -hANP and cGMP were measured in patients with paroxysmal tachycardia (mean age 58.3 ± 3.4 (SE) years; atrial tachycardia in 3 and atrial fibrillation in 3 patients). Venous blood samples were obtained from supine patients during tachycardia and normal sinus rhythm (before or after paroxysmal tachycardia). When paroxysmal tachycardia returned to normal sinus rhythm, blood specimens were drawn at least 20 min after the cessation of tachycardia. To examine whether or not tachycardia itself raises the plasma concentrations of α -hANP and cGMP, rapid atrial pacing was conducted in 5 patients (50.0 ± 10.8 years old; complete atrioventricular block in 1, paroxysmal supraventricular tachycardia in 1, sick sinus syndrome in 1 and paroxysmal ventricular tachycardia in 2 patients). Pacing was set at a rate of 150 beats/min and continued for 10 min. Blood was taken at 0, 2, 5 and 10 min during pacing and 10 min after the cessation of

pacing.

Study II

Cardiac and renal function and the plasma concentration of $\text{i}\alpha\text{-hANP}$ were examined in 2 patients with complete atrioventricular block during rapid atrial and/or ventricular pacing. The study was performed in a supine position after 6 hours of fasting. Pacing electrodes were placed at the right atrium and right ventricle and a Swan-Ganz catheter was introduced into the pulmonary artery through the femoral vein. Pressures in the right atrium and pulmonary artery and pulmonary capillary wedge pressure (PCWP) were determined using a Swan-Ganz catheter. Arterial pressure was measured through a catheter introduced into the radial artery and cardiac output was assessed by the thermodilution method. Urine was collected using a bladder catheter and analyzed for volume and concentrations of sodium and creatinine. The urinary excretion rate of sodium (U_{NaV}) and endogenous creatinine clearance (C_{Cr}) were calculated.

Following the measurement of atrial pressures, mean arterial pressure and cardiac output, and sampling of blood and urine specimens during the control period, atrial pacing was started at a rate of 100 or 150 beats/min and continued for 10 min. Hemodynamic parameters were determined between 7 and 10 min after starting the pacing. Blood and urine were collected at the end of pacing. The atrial electrical pacing was then followed by ventricular pacing and atrioventricular sequential pacing at a rate of 100 beats/min. The parameters for cardiac and renal function were also obtained during a recovery period after cessation of pacing.

The plasma concentration of immunoreactive $\alpha\text{-hANP}$ was measured by radioimmunoassay according to the method of Miyata et al.¹⁴⁾ The antiserum showed 100% cross reactivity with β -, γ -, $\alpha\text{-hANP}$ (1-26) and $\alpha\text{-hANP}$ (1-27), but only 40% with $\alpha\text{-rat ANP}$. The sensitivity was 2 pg/tube and the 50% intercept was 40 pg/tube. The intraassay variation was 7.2% ($n=6$) and the interassay variation was 13.0% ($n=4$). Plasma cGMP concentration was measured by radioimmunoassay after succinylation (Yamasa assay kit, Chiba, Japan).¹⁵⁾ The intraassay variation was 3.7% ($n=10$) and the interassay variation was 10.0% ($n=6$). Urinary sodium concentration was measured by a flame photometer and creatinine concentration in urine and plasma by an autoanalyzer.

Statistical analysis

Data were expressed in terms of means $\pm$ SE. The differences in parameters between at rest and during tachycardia or rapid pacing were as-

essed using paired Student's *t*-test. When a *p*-value was less than 0.05, the difference was considered to be significant.

RESULTS

Study I

Fig. 1 shows the plasma concentrations of α -hANP and cGMP during paroxysmal tachycardia (mean heart rate 143 ± 10 beats/min) and normal sinus rhythm (75 ± 3 beats/min). The plasma concentrations of both α -hANP and cGMP increased significantly during tachycardia by +69% ($p < 0.05$) and +100% ($p < 0.05$), respectively. The increases in plasma concentrations of α -hANP and cGMP during paroxysmal atrial tachycardia were comparable to findings during paroxysmal atrial fibrillation. As shown in Fig. 2, the plasma concentrations of both α -hANP and cGMP increased between 2 and 5 min after initiation of rapid atrial pacing. Both the time course and the degree of changes were similar in both conditions.

Study II

Figs. 3 and 4 demonstrate the heart rate (atrial rate and ventricular rate), PCWP, cardiac output, plasma concentration of α -hANP, U_{NaV} and C_{Cr} in 2 patients with complete atrioventricular block before, during and after rapid pacing. Case 1 was an 81 year old woman. As shown in Fig. 3, rapid pac-

Fig. 1. Plasma concentrations of immunoreactive α -human atrial natriuretic polypeptide (α -hANP) and cGMP during paroxysmal tachycardia and normal sinus rhythm (before or after paroxysms). Open circles indicate paroxysmal atrial tachycardia and closed circles paroxysmal atrial fibrillation.

Fig. 2. Plasma concentrations of immunoreactive α -human atrial natriuretic polypeptide (α -hANP) and cGMP before, during and after rapid atrial pacing.

Fig. 3. Cardiac and renal function and plasma concentrations of immunoreactive α -human atrial natriuretic polypeptide (α -hANP) during rapid atrial and/or ventricular pacing in a patient with complete atrioventricular block (case 1).

AP=atrial pacing; VP=ventricular pacing; AVP=sequential atrioventricular pacing; PCWP=pulmonary capillary wedge pressure; CO=cardiac output; $U_{Na}V$ =urinary sodium excretion; C_{Cr} =creatinine clearance.

Fig. 4. Cardiac and renal function and plasma concentrations of immunoreactive α -human atrial natriuretic polypeptide (α -hANP) during rapid atrial and/or ventricular pacing in a patient with complete atrioventricular block (case 2).

AP=atrial pacing; VP=ventricular pacing; AVP=sequential atrioventricular pacing; PCWP=pulmonary capillary wedge pressure; CO=cardiac output; $U_{Na}V$ =urinary sodium excretion; C_{Cr} =creatinine clearance.

ing increased PCWP, α -hANP, $U_{Na}V$ and C_{Cr} concomitantly. The mean arterial pressure did not change throughout the pacing while the pulse pressure tended to decrease during ventricular and sequential atrioventricular pacings. The mean right atrial pressure increased from 4 to 6 mmHg and the mean pulmonary arterial pressure also increased from 12 to 20 mmHg during atrial and ventricular pacings. An increase in cardiac output was associated with increases in $U_{Na}V$ and C_{Cr} when the ventricular rate was increased by the ventricular and atrioventricular pacing. However, increases in $U_{Na}V$ and C_{Cr} were also observed during atrial pacing, and were not accompanied by an increase in cardiac output. Furthermore, despite the similar levels of PCWP, the plasma concentration of α -hANP was elevated when the rate of atrial pacing was increased from 100 to 150 beats/min.

Case 2 was a 62 year old man with complete atrioventricular block (Fig. 4). In this case, atrial pacing at 150 beats/min did not increase either PCWP or the plasma concentration of α -hANP. Only when the right ventricle was

paced at 120 beats/min were PCWP, cardiac output and $U_{Na}V$ substantially increased. These increases were associated with a rise in the plasma concentration of α -hANP.

DISCUSSION

In the present study, the plasma concentration of α -hANP was elevated during paroxysmal atrial tachycardia, paroxysmal atrial fibrillation and rapid atrial pacing. Similar results have already been reported.^{6),7)} The most potent stimulus for the secretion of ANP is considered to be a change in atrial pressure. Lang et al¹⁶⁾ reported that large intravenous saline infusion increases the plasma ANP concentration in rats. This increase in ANP was associated with a rise in the central venous pressure. In humans, the higher the right atrial pressure, the higher the plasma ANP concentration.¹⁷⁾ We have also found that the plasma concentration of ANP is well correlated with both right atrial pressure and pulmonary capillary wedge pressure (unpublished observations). Canepa-Anson et al⁵⁾ found elevated atrial pressure in a patient during tachycardia associated with polyuria. Rapid atrial pacing is also known to increase atrial pressure.¹⁸⁾ Accordingly, the increase in plasma concentration of α -hANP during atrial tachycardia and rapid atrial pacing in study I is probably due to a rise in atrial pressure.

To confirm this suggestion, we measured both the atrial pressure and the plasma concentration of α -hANP during rapid atrial pacing in study II. It was found that an increase in plasma concentration of α -hANP was associated with a rise in atrial pressure. Moreover, atrial pacing which did not elevate the PCWP failed to increase the plasma concentration of α -hANP. However, in case 1, an increase in a pacing rate from 100 to 150 beats/min, which did not further elevate PCWP, raised the plasma concentration of ANP. These findings suggest that the elevation in plasma concentration of ANP during tachycardia is mainly due to a rise in atrial pressure, but that the rapid contraction of the atrial walls may play a secondary role.

Goetz et al¹⁹⁾ showed that increases in urine flow and sodium excretion were produced by rapid ventricular pacing, but not by atrial pacing, in dogs with atrioventricular block. They concluded that receptors in the carotid sinus and the aortic arch were more important for diuresis during tachycardia than atrial receptors because sinoaortic denervation diminished the diuresis induced by rapid ventricular pacing. The reason why rapid atrial pacing did not induce polyuria in their study may also reflect a lack of an increase in central venous pressure.

Wood¹⁾ pointed out, in his first report about tachycardia-induced poly-

uria, that urine output and urinary sodium excretion increased, while urinary specific gravity decreased during tachycardia. This was explained by suppression of ADH.^{5),18)} However, the concomitant natriuresis observed during tachycardia cannot be explained by this assumption. When synthesized ANP is administered to animals and humans, it increases sodium excretion and decreases osmolar clearance.²⁰⁾ These effects of ANP on urine composition are considered to be mainly due to increases in the glomerular filtration rate and medullary blood flow.²⁰⁾⁻²³⁾ In the present study, rapid atrial pacing, which increased atrial pressure but did not change blood pressure or cardiac output, tended to increase urinary sodium excretion and creatinine clearance. In our experience, α -hANP infusion at 0.025 μ g/kg/min into patients with essential hypertension increased the plasma concentration of α -hANP to about 400 pg/ml, and induced a 3-fold increase in urinary sodium excretion and a 5% decrease in blood pressure.²³⁾ Thus, it seems likely that an increase in secretion of ANP contributes to tachycardia-induced polyuria.

Cyclic GMP in plasma was elevated in parallel with α -hANP during tachycardia. This is in agreement with the report by Mizuno et al²⁴⁾ that the plasma concentration of cGMP was increased in patients with paroxysmal atrial fibrillation. Several researchers have suggested that cGMP is an intracellular second messenger for ANP because ANP increases cGMP levels in target organs in a receptor-mediated manner.¹¹⁾⁻¹³⁾ This is interpreted to mean that the plasma concentration of cGMP reflects the intrinsic activity of ANP, and if so, ANP may play some role during tachycardia.

In conclusion, secretion of α -hANP was increased during paroxysmal tachycardia and rapid pacing. This increase was caused mainly by a rise in atrial pressures. The plasma concentration of cGMP was also elevated at the same time, and this was probably due to the effects of ANP. The observed rise in secretion of ANP may explain, at least in part, the phenomenon called "tachycardia polyuria".

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