The effect of short-lasting atrial pacing on the release of atrial natriuretic peptide, vasopressin, and methionine enkephalin in man

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Abstract. In order to study the effect of atrial tachycardia on the release of atrial natriuretic peptide (ANP), AVP, and methionine enkephalin (M-Enk), plasma concentrations of these peptides in the right ventricle were determined in patients with various arrhythmias (N = 10) during cardiac catheterization and incremental atrial pacing. Each pacing (100 per min, the maximum rate for 1:1 atrioventricular conduction, and 200 per min) lasted 4 to 5 min. Plasma ANP was significantly increased from 53.1 ± 12.2 in the resting condition to 168.9 ± 59.9 pmol/l at a pacing rate of 200 beats per min (P < 0.05); plasma AVP tended to decrease, but not significantly, and plasma M-Enk did not change at all. Pulse pressure in the right atrium (PPRA) and mean right atrial pressure (MRAP) tended to increase during the pacing, and at the rate of 200 beats per min PPRA was significantly higher than at the rate of 100 beats per min. Mean arterial blood pressure, plasma osmolality, and plasma sodium and potassium concentrations did not change significantly. There were significant correlations between plasma ANP and PPRA, MRAP and heart rate. These results indicate that atrial pacing stimulates ANP release with a rise in right atrial pressure, but does not influence M-Enk and AVP releases.

The polyuria associated with paroxysmal tachycardia, partly explained by the inhibition of AVP release (Boykin et al. 1975; Canepa-Anson et al. 1984), has recently been proposed to be related to the release of atrial natriuretic peptide (ANP) which elicits natriuresis and diuresis (DeBold et al. 1981). Indeed, tachycardia by atrial pacing has been shown strongly to stimulate ANP release from the heart accompanied by a rise in atrial pressure (Rankin et al. 1986). Moreover, a rise in atrial pressure and distention of the atria were documented to stimulate ANP release (Katsube et al. 1985; Ogawa et al. 1986) or to attenuate AVP release (Fater et al. 1982; Ledsome & Wilson 1984) via volume receptor. Methionine enkephalin (M-Enk), an endogenous opioid peptide, has been reported to be present in the atrium (Lang et al. 1983) and to affect heart rate and cardiac contractility (Yukimura et al. 1981).

Therefore, it is plausible that atrial tachycardia affects the release of these hormones causing changes in cardiovascular and renal functions thus providing natriuresis and diuresis. However, so far, changes in plasma ANP, AVP and M-Enk levels during atrial tachycardia and the mutual relationships between these hormones and cardiac functions have never been explored in man.

In the present study, in patients with cardiac arrhythmia undergoing cardiac catheterization and electrophysiological study, changes in plasma ANP, AVP and M-Enk levels were determined simultaneously with changes in cardiovascular functions.
Patients and Methods

Ten patients, five males and five females aged 20 to 68 years (44.8 ± 16.7 years, mean ± sd), were studied during diagnostic atrial pacing. They had various arrhythmias such as paroxysmal atrial fibrillation (2), paroxysmal supraventricular tachycardia (2), ventricular tachycardia (1), second degree atroventricular block (1), and sick sinus syndrome (4), but not any cardiac valvular diseases. None of the patients took any drugs before the study. An electrode catheter (Multi-electrode catheter, Webster, USA) was inserted from the femoral vein and was located at the right atrial wall for pacing. The rate of pacing was increased step-wise from basal heart rate (HR) to 200 beats/min with 10 beats/min increments by cardiac stimulator (RM6000, Nihon Koden, Japan). Blood samples were collected four times through another catheter located in the right ventricle during pacing at the following rates: 1) basal HR; 2) 100 beats/min; 3) the maximum rate for 1:1 atroventricular conduction, and 4) 200 beats/min. The duration of each pacing was 4 to 5 min. In four patients, whose maximum rate for 1:1 atroventricular conduction was equal to 100 beats/min, blood samples were taken three times. Blood pressure, heart rate and right atrial pressure were recorded simultaneously with blood collection. Blood pressure was carefully measured by sphygmomanometer, HR by electrocardiogram (RM6000, Nihon Koden), and right atrial pressure (RAP) by pressure transducer (SCK601, Gould, USA) through the catheter in the right atrium. Mean arterial blood pressure (MAP) was calculated as diastolic blood pressure plus one third of pulse pressure. Twelve ml of blood were taken into heparinized syringes and immediately transferred into chilled tubes on ice. After centrifugation at 3000 rpm for 15 min at 4°C, 3 ml of plasma with addition of 3.6 ml of 0.1 mol/l HCl was immediately frozen and kept until extraction for ANP. Plasma, 1½ ml, was kept frozen for extraction for AVP. One ml of plasma with addition of 1.2 ml of 0.1 mol/l HCl was also kept frozen until extraction for M-Enk.

Extraction and RIA for ANP, AVP and M-Enk were reported elsewhere (Kimura et al. 1980, 1986; Ota et al. 1986). Briefly, ANP was extracted with Sep-Pak C18 cartridge (Waters Associates Inc, Milford, Mass.). Synthetic α-human ANP (α-hANP, Protein Institute, Osaka, Japan), 200 µl, or extracted sample, 50 µl of antiserum (final dilution 1:42 000) against α-hANP, and 50 µl of 125I-α-hANP (Amersham, Japan Co) were incubated using a non-equilibrium method. Separation of bound from free was performed by the PEG method. Detection limit was 2.5 fmol/tube and 50% inhibition of total binding occurred at 29.2 fmol/tube. Recovery rate of added 25.9 fmol of synthetic α-hANP in this experiment was 83.0 ± 7.1% (mean ± sd). Inter- and intra-assay coefficients were 10.8 and 2.6%, respectively. AVP was extracted with microcolumn of CG-50 resin. Sensitivity of this RIA was 0.38 fmol/tube and the half maximal binding dose was 3.8 fmol/tube. Recovery rate of added 9.8 fmol of AVP was 67.0 ± 6.0% and inter- and intra-assay coefficients were 13.8 and 9.9%, respectively. M-Enk was extracted with Sep-Pak C18 cartridge. M-Enk (Protein Institute, Osaka, Japan), 200 µl, or extracted samples oxidized by hydrogen peroxide, 50 µl of diluted antiserum (1:360 000) and 50 µl of 125I-Met-Enk (NEN Co, Boston, Mass.) were incubated using a non-equilibrium method. Detective limit and half maximal binding dose were 0.44 and 5.23 fmol/
tube. Recovery rate of added 17.4 fmol M-Enk was 62.4 ± 13.7%. Inter- and intra-assay coefficients were 16.8 and 5.1%. Plasma sodium and potassium were measured by flame photometry (Hitachi flame photometer 205D, Tokyo, Japan) and plasma osmolality was measured by Advanced Osmometer (Model 3D2, Advanced Instruments Inc, Needham Heights, Mass.). Statistical analysis was performed by an analysis of variance for the repeated measurements for the same variable followed by Newman-Keuls test. Correlation analyses were also applied to each measured variable. Because of non-homogeneity of variance, the values of α-hANP, AVP and M-Enk were subjected to logarithmic transformation before statistical analyses. Result was expressed as mean ± SEM.

Results

As shown in Table 1, atrial electrical stimulation at a rate of 100 beats/min was well conducted to the ventricle in all patients. HR at the pacing rate of 100 beats/min was significantly higher than the basal heart rate (63.2 ± 3.0 beats/min) (P < 0.05). At this pacing rate, there were an increase in MAP and decreases in both mean right atrial pressure (MRAP) and pulse pressure in the right atrium (PPRA), but these changes were not statistically significant. At the maximum rate for 1:1 atrioventricular conduction (Max 1:1, 125.0 ± 9.7 beats/min), HR was significantly increased relative to the basal value, but MAP did not change significantly. Both MRAP and PPRA were slightly increased, but the increase was not statistically significant. At the pacing rate of 200 beats/min, 1:1 conduction through the atrioventricular node was never observed in any of the ten patients, but HR (102.7 ± 15.6 beats/min) at this pacing rate was significantly higher than the basal HR. During this atrial pacing, MAP and MRAP tended to decrease and increase, respectively, but these changes were not statistically significant. PPRA was significantly increased to 7.8 ± 0.7 mmHg at the pacing rate of 200 beats/min relative to that of 100 beats/min, but this value was not significantly different from the basal value. Plasma osmolality, plasma sodium and potassium concentrations did not change significantly throughout the step-wise pacing. Fig. 1 shows changes in plasma α-hANP (A), AVP (B) and M-Enk concentrations (C) during the pacings. In each patients, plasma α-hANP was increased or decreased at a pacing rate of 100

Fig. 1.
Changes in plasma α-hANP (Pa-hANP) (A), plasma AVP (P_AVP) (B), and plasma M-Enk concentrations (P_M-Enk) (C) during incremental atrial pacing. Each symbol denotes a value from a patient with the following diseases: ◆ paroxysmal atrial fibrillation, □: ventricular tachycardia, Δ and V: paroxysmal supraventricular tachycardia, ●, △, ▽ and ■: sick sinus syndrome, ×: second degree atrioventricular block.

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beats/min and then started to increase at the maximum 1:1 atrioventricular conducting rate of pacing. These changes, however, were statistically insignificant as shown in Table 2. At 200 beats/min of atrial pacing, plasma α-hANP was increased in all patients except one with sick sinus syndrome, who showed a fall in RAP at this pacing, and its average increase was statistically significant compared with both the basal state and the pacing rate of 100 beats/min (Table 2). Plasma AVP and M-Enk concentrations did not change significantly throughout the study, but at the

### Table 2.

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<th>Pacing rate (beats/min)</th>
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<tr>
<td></td>
<td>0</td>
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<tr>
<td>Pα-hANP (pmol/l)</td>
<td>53.1 ± 12.2</td>
</tr>
<tr>
<td>PAVP (pmol/l)</td>
<td>5.9 ± 1.7</td>
</tr>
<tr>
<td>PM-Enk (pmol/l)</td>
<td>9.0 ± 0.6</td>
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Max 1:1: maximum pacing rate for 1:1 A-V conduction.
* P < 0.05 vs 0/min. ** P < 0.05 vs 100/min.

![Figure 2](https://example.com/figure2.png)

**Fig. 2.**

The respective correlations between plasma α-hANP concentration (Pα-hANP) and either MRAP (A) or PPRA (B). The symbols are the same as in Fig. 1. Plasma α-hANP correlates positively with PPRA (log Pα-hANP = 0.0774 PPRA + 1.2642, r = 0.5486, P < 0.01) and with MRAP (log Pα-hANP = 0.0903 MRAP + 1.5104, r = 0.4172, P < 0.05), respectively.
pacing rate of 200 beats/min the former tended to decrease compared with the basal value (Table 2). There were no significant correlations between plasma concentrations of these peptides (ANP vs AVP, AVP vs M-Enk and ANP vs M-Enk).

Fig. 2 depicts the respective correlations between plasma α-hANP concentration and either MRAP (A) or PPRA (B). Plasma α-hANP concentration correlated with PPRA (log Pa-hANP = 0.0774 PPRA + 1.2642, r = 0.5486, P < 0.01) as well as with MRAP (log Pa-hANP = 0.0903 MRAP + 1.5104, r = 0.4172, P < 0.05) and with HR (log Pa-hANP = 0.0044 HR + 1.8603, r = 0.4146, P < 0.05). Changes in PPRA showed a more potent correlation to changes in plasma α-hANP compared with those in MRAP or HR.

Discussion

The present study obviously showed that tachycardia induced by atrial pacing stimulated ANP release associated with a rise in MRAP and PPRA, but did not influence M-Enk and AVP releases, except for a slight suppression of the latter at the rate of 200 beats/min.

Crozier et al. (1986) reported that atrial pacing at a rate above 140 beats/min brought about a rise in ANP release in human. Moreover, Rankin et al. (1986) recently showed that atrial tachycardia induced by atrial pacing brought about a rise in atrial pressure in rabbits and resulted in increased ANP release. Indeed, there are several reports that an increase in RAP and left atrial pressure (LAP) is associated with a rise in plasma ANP (Katsube et al. 1985; Ogawa et al. 1986). Ogawa et al. (1986) reported that plasma ANP in patients with congestive heart failure was correlated with pulmonary capillary wedge pressure. This finding suggests that a rise in LAP may play a dominant role in ANP release. In contrast, Katsube et al. (1985) showed that a rise in RAP rather than LAP played a major role in ANP release in rats.

Since LAP was not measured in the present study, it remains unclear which, RAP or LAP, plays a dominant role in the regulation of ANP release during atrial pacing. However, it is possible that changes in RAP have a certain effect on ANP release during the pacing, since plasma ANP correlated well with the changes in RAP.

Basal plasma ANP in this study was about three times higher than that observed in peripheral venous blood (Kimura et al. 1986). This difference may be due to a high level of plasma ANP in right ventricular blood. In fact, Bürgisser et al. (1985) and Sugawara et al. (1985) reported that plasma ANP is higher in right atrial or coronary sinus blood than in peripheral venous blood. It is unlikely that the rise in plasma ANP observed during the rapid pacing rate of 200 beats/min is due to a decreased metabolic clearance rate for ANP, since MAP, the decrease of which would reduce the metabolic clearance rate, did not change throughout the study and the other two simultaneously determined hormones did not show any rise.

Canepa-Anson et al. (1984) showed that plasma AVP and urinary AVP excretion were decreased in a patient with atrioventricular nodal tachycardia accompanied by polyuria. Indeed, it has been documented that increased LAP during atrial pacing (Boykin et al. 1975; Canepa-Anson et al. 1984) attenuates AVP release via the atrial stretch receptor (Share 1965).

In the present study, therefore, the exact mechanisms by which AVP release was not obviously suppressed during atrial pacing are unknown, but it is probable that the duration of atrial pacing (4 to 5 min) is too short to induce an ample rise in atrial pressure with a resultant inhibition of AVP release. Indeed, Wood (1963) reported that a heart rate of more than 110 beats/min should be maintained for over 20 min in order to induce diuresis in patients with atrial tachycardia. Goetz & Bond (1973), however, reported that plasma AVP did not change significantly during atrial pacing in dogs.

Lang et al. (1983) showed that enkephalins were present in the cardiac sympathetic neuron and that the content in the atrium was much higher than in the ventricle. Moreover, opioid analgesics have been documented to enhance the positive chronotropic effect owing to nerve stimulation (Kosterlitz & Taylor 1959; Montel & Starke 1973). Therefore, it would be reasonable to assume that atrial pacing may stimulate the release of M-Enk as well as of ANP. However, this is not the case, since plasma M-Enk did not vary in the present study despite increased ANP release during atrial pacing. Thus, atrial pacing per se may not directly influence the activity of the sympathetic nervous system and adrenal gland resulting in M-Enk release.
It is concluded from these results that atrial pacing stimulates ANP release associated with a rise in RAP, but does not significantly influence M-Enk and AVP releases.

References


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