INCREASED SECRETION OF ATRIAL NATRIURETIC POLYPEPTIDE IN RESPONSE TO CARDIAC PACING

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Effects of cardiac pacing on secretion of atrial natriuretic polypeptide (ANP) were examined in 20 patients during cardiac catheterization under control conditions. The plasma ANP concentration in the coronary sinus (900 ± 115 pg/ml) was significantly higher than those in the aorta (147 ± 19 pg/ml) and the femoral vein (105 ± 15 pg/ml) (p < 0.001). The plasma ANP concentration was also significantly higher in the aorta than in the femoral vein (p < 0.001). Its concentration at all three sites significantly increased during cardiac pacing (from 900 ± 115 to 1461 ± 218, from 147 ± 19 to 250 ± 36, and from 105 ± 15 to 150 ± 24 pg/ml, respectively). However, mean right atrial pressure and mean pulmonary capillary wedge pressure showed no significant changes between control conditions and during pacing (5 ± 1 vs 6 ± 1, and 8 ± 1 vs 8 ± 1 mmHg). Furthermore, there was no significant correlation between ANP secretion and the pressure in both atria. Thus, cardiac pacing can release ANP from the heart without increasing atrial pressure.

It is now established that mammalian atria secrete a potent natriuretic, diuretic, vasorelaxant and aldosterone inhibiting factor. This factor has been identified as a 28-amino acid peptide, and its structure has been determined in humans as well as in other mammals and designated as atrial natriuretic polypeptide (ANP). The radioimmunoassay methods for ANP have been developed and there is now increasing evidence that ANP plays an important role in the regulation of body fluids and blood pressure. Several reports indicate that plasma ANP levels are increased during heart failure, hypertension and atrial tachycardias, and these reports suggest that an increase in atrial pressure is a strong stimulus for ANP secretion. However, the precise mechanism(s) by which ANP secretion is regulated remains to be elucidated. We have previously reported that ANP is secreted into the general circulation by way of the coronary sinus blood flow, and that ANP's plasma level in the coronary sinus increases in response to atrial pacing. In the present study we further examined the mechanism of ANP secretion in response to atrial pacing by simultaneously measuring coronary sinus blood flow, right atrial pressure and pulmonary capillary wedge pressure using a more sensitive method to assay plasma ANP.

**MATERIALS AND METHODS**

**Patients:** Twenty patients (15 men and 5 women, their ages ranging from 21 to 69, with a mean age of 52) were the subjects of this study.

Key words:
- Atrial natriuretic polypeptide (ANP)
- Cardiac pacing
- Atrial pressure
- Coronary sinus blood flow
TABLE 1 PLASMA ANP CONCENTRATION BEFORE AND DURING CARDIAC PACING

<table>
<thead>
<tr>
<th></th>
<th>Before pacing</th>
<th>During pacing</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANP (pg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS</td>
<td>900 ± 115</td>
<td>1461 ± 218</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Ao</td>
<td>147 ± 19</td>
<td>250 ± 36</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FV</td>
<td>105 ± 15</td>
<td>150 ± 24</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

ANP = atrial natriuretic polypeptide; CS = coronary sinus; Ao = aorta; FV = femoral vein; * = p < 0.001

Fig.1. Plasma ANP concentration in the coronary sinus (CS), the aorta (Ao), and the femoral vein (FV) under control conditions.

They included 7 patients with atypical chest pain who had normal coronary arteriograms, 5 patients who previously had a myocardial infarction, 3 patients with cardiomyopathy, 3 patients with angina pectoris, and 2 patients with valvular heart disease. All medications were stopped for more than 24 hours before the study began. The patients were studied in the nonsedated state after the procedure had been explained and written informed consent obtained from each patient.

**Study protocol:** In the catheterization laboratory a Swan-Ganz catheter was inserted from the right femoral vein into the pulmonary artery, a Webster’s thermodilution catheter was inserted from the right brachial vein into the coronary sinus, and a Sones catheter was inserted from the brachial artery into the root of the aorta. Control measurements of cardiac output, pulmonary capillary wedge pressure, right atrial pressure, and coronary sinus blood flow were performed, and blood samples for plasma ANP measurement were taken simultaneously from the coronary sinus, the root of the aorta and the femoral vein.

Right atrial pacing was then performed, initially at a rate of 130 beats/min, and then increased stepwise by 10 beats/min up to 150 beats/min. If second-degree atrioventricular block of the Wenckebach type occurred, the pacing rate was decreased by 10 beats/min and continued at the same rate for 7 min. The above parameters were
TABLE II  HEMODYNAMIC DATA BEFORE AND DURING PACING

<table>
<thead>
<tr>
<th></th>
<th>Before pacing</th>
<th>During pacing</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RAP (mmHg)</strong></td>
<td>5 ± 1</td>
<td>6 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td><strong>PCWP (mmHg)</strong></td>
<td>8 ± 1</td>
<td>8 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td><strong>CSBF (ml/min)</strong></td>
<td>101 ± 9</td>
<td>136 ± 13</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td><strong>Index of ANP secretion rate (ng/ml)</strong></td>
<td>43 ± 7</td>
<td>97 ± 17</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

**RAP** = mean right atrial pressure; **PCWP** = mean pulmonary capillary wedge pressure; **CSBF** = coronary sinus blood flow; **NS** = not significant

![Graph](image1)

**Fig.3.** Right atrial pressure (a) and pulmonary capillary wedge pressure (b) before and during cardiac pacing. Before = before pacing, During = during pacing, NS = not significant

![Graph](image2)

**Fig.4.** The coronary sinus blood flow before and during cardiac pacing. Before = before pacing, During = during pacing

...again measured and blood samples for plasma ANP taken again at the end of the atrial pacing.

Coronary sinus blood flow was measured by the thermodilution technique using Webster's catheter. The position of the catheter in the coronary sinus was kept constant by checking it against images of the vertebrae and ribs. Because ANP is secreted into the general circulation mainly by way of the coronary sinus, as we previously reported, we calculated the following parameter as an index of ANP's secretion rate: Index for ANP secretion rate (pg/min) = (plasma ANP concentration in the coronary sinus–plasma ANP concentration in the aorta (pg/ml)) × the coronary sinus blood flow (ml/min) × (1–Hematocrit(%)/100).

**Measurement of plasma ANP concentration:** Blood samples were promptly centrifuged at 4°C, and aliquots of plasma were immediately frozen at -20°C until assay. Plasma ANP concentrations were measured by a specific radioimmunoassay (RIA) for alpha ANP as described previously.** This RIA recognizes a carboxy-terminal fragment of ANP, the minimum detectable quantity of alpha-human ANP being 1 pg/tube. Extraction of ANP from plasma was performed using a Sep-Pak cartridge (Waters Associates Inc., Milford, Massachusetts) as previ-

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ously described\cite{11}

Statistical analysis: Comparisons were made between values obtained under control conditions and those obtained during atrial pacing, using paired Student's t test. Correlation coefficients and significance values denote results of least square analysis. Regression lines were obtained by linear regression analysis. All values were expressed as means ± SEM. A p value less than 0.05 was considered statistically significant.

RESULTS

Second-degree atrioventricular block appeared in 10 patients at a rate of 140 beats/min and in 8 patients at a rate of 150 beats/min. Thus, atrial pacing was carried out at a rate of 130 beats/min, 140 beats/min and 150 beats/min in 10, 8 and 2 patients, respectively.

Plasma concentrations of ANP under control conditions and during pacing are presented in Table I and in Fig. 1 and 2. Plasma concentrations of ANP in the coronary sinus, the aorta, and the femoral vein were 900 ± 115 pg/ml, 147 ± 19 pg/ml, and 105 ± 15 pg/ml, respectively under control conditions, and were thus significantly higher in the coronary sinus than in the

\[ r = 0.19 \]
\[ p = \text{NS} \]

\[ r = 0.22 \]
\[ p = \text{NS} \]

Fig. 6. Relationship between index for ANP secretion rate and right atrial pressure (a) and that between index for ANP secretion rate and pulmonary capillary wedge pressure (b). NS = not significant
aorta or the femoral vein (p < 0.001, respectively). The plasma ANP concentration was also significantly higher in the aorta than in the femoral vein (p < 0.001). During pacing there was a significant increase in plasma ANP concentrations in the coronary sinus (from 900 ± 115 pg/ml under control conditions to 1461 ± 218 pg/ml during pacing, p < 0.01), in the aorta (from 147 ± 19 pg/ml under control conditions to 250 ± 36 pg/ml during pacing, p < 0.001), and in the femoral vein (from 105 ± 15 pg/ml under control conditions to 150 ± 24 pg/ml during pacing, p < 0.01).

The hemodynamic data and secretion rate for ANP are presented in Table II and in Fig. 3 and 5. The right atrial pressure was 5 ± 1 mmHg under control conditions and 6 ± 1 mmHg during pacing. The pulmonary capillary wedge pressure was 8 ± 1 mmHg under control conditions and 8 ± 1 mmHg during pacing. Thus, there was no significant difference in either right atrial or pulmonary capillary wedge pressures between control and pacing conditions. Coronary sinus blood flow significantly increased from 101 ± 9 ml/min under control conditions to 136 ± 13 ml/min during pacing (p < 0.01). The index for the ANP secretion rate significantly increased from 45 ± 7 ng/min under control conditions to 97 ± 17 ng/min during pacing (p < 0.01), indicating that there was no significant correlation between the ANP secretion rate and right atrial or pulmonary capillary wedge pressures before and during pacing (Fig. 6).

DISCUSSION

It is now known that the plasma level of ANP is increased in various disease states, including congestive heart failure, hypertension, and paroxysmal tachycardias. However, the precise mechanism(s) by which ANP is secreted into the general circulation is not known. We have previously reported that ANP is secreted into the general circulation mainly by way of the coronary sinus because ANP's plasma concentration is much higher in the coronary sinus than in any other part of the circulation. The present study confirms our previous results by showing that ANP's plasma concentration is approximately 8 times higher than that in the aorta or the femoral vein. We also previously reported that the plasma ANP concentration in the coronary sinus increases in response to atrial pacing, and we postulated that ANP secretion might increase in response to atrial pacing. However, the secretion rate depends not only on plasma concentration but also flow rate, and so in the present study we simultaneously measured both coronary sinus blood flow and plasma ANP concentration in the coronary sinus in order to calculate an index for ANP secretion rate. The results show that ANP's secretion rate increased in response to atrial pacing.

Several previous reports indicate that there is a roughly linear correlation between plasma ANP level and right atrial pressure and/or pulmonary capillary wedge pressure, an indicator of left atrial pressure. It has thus been proposed that the right and/or left atrial pressure play a central role in the regulation of ANP secretion. Haufl et al. reported that both release of ANP and right atrial pressure increased at atrial pacing rates above 140 beats/min, and that no changes in ANP release or right atrial pressure were observed at a pacing rate of 110 beats/min. They concluded that release of ANP was caused by an increase in right atrial pressure, and that acceleration of heart rate alone had no effect on ANP secretion. However, the number of patients in their study was small (n = 6), and at pacing rates above 140 beats/min most of the patients might have developed second-degree atrioventricular block, resulting in an increase in right atrial pressure. Furthermore, a pacing rate of 110 beats/min may not be strong enough to stimulate ANP secretion. In the present study second-degree atrioventricular block occurred at a pacing rate of 140 beats/min in 10, and at 150 beats/min in 8 patients. Thus, cardiac pacing was performed at a rate of 130 beats/min, 140 beats/min and 150 beats/min in 10, 8 and 2 patients, respectively. Neither right atrial pressure nor pulmonary capillary wedge pressure changed significantly in response to the atrial pacing, and there was no significant correlation between ANP secretion rate and right atrial pressure or pulmonary capillary wedge pressure. Thus, the increase in ANP secretion rate in response to atrial pacing is not necessarily due to an increase in atrial pressures but mainly due to atrial pacing per se. Nishimura and his coworkers also recently reported that in dogs with complete atrioventricular block plasma ANP level increases in response to atrial pacing in the presence of constant right atrial pressure. Stretching of the atria caused by atrial pacing or depolarization is probably a strong stimulus for ANP secretion. In the previous study we were able to demon-
strate a significant increase in plasma ANP level during atrial pacing only in the coronary sinus. In the present study the plasma ANP level significantly increased in both the aorta and the femoral vein as well as in the coronary sinus in response to atrial pacing. This difference is probably due to the fact that in the present study we used a more sensitive method to assay the plasma ANP level. It may also be due to the fact that the number of patients examined was greater in the present than in the previous study. Thus, if the sensitive plasma ANP assay method is used plasma ANP levels in the aorta or femoral vein may be used indicators of ANP secretion rate during tachycardia.

In the present study coronary sinus flow was measured for evaluation of coronary blood flow. Because coronary sinus flow measures mainly the flow from the area of the heart perfused by the left coronary artery, it underestimates the true coronary blood flow. Thus, the index for ANP secretion rate calculated in the present study underestimates the true secretion rate. Nevertheless, the present study's calculated ANP secretion rate index is useful for studying the mechanism(s) involved in the secretion of ANP.

In the present study right atrial and pulmonary capillary wedge pressures did not change significantly during atrial pacing at 130, 140 or 150 beats/min from control levels. In attacks of paroxysmal supraventricular tachycardia, however, heart rate is usually more than 160 beats/min and an increased plasma ANP level in this condition may not necessarily be explicable on the basis of increased heart rate alone because atrial pressures may also increase under conditions of greatly increased heart rate.

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