Atrial Natriuretic Factor During Atrial Fibrillation and Supraventricular Tachycardia

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Plasma immunoreactive atrial natriuretic factor was measured in 10 patients with chronic atrial fibrillation before and after cardioversion to sinus rhythm, and in 14 patients during electrophysiologic evaluation of paroxysmal supraventricular tachycardia. The mean plasma concentration of atrial natriuretic factor in atrial fibrillation was 138 ± 48 pg/ml and decreased to 116 ± 45 pg/ml 1 hour after cardioversion to sinus rhythm (p < 0.005). The mean plasma concentration of atrial natriuretic factor increased from 117 ± 53 pg/ml in sinus rhythm to 251 ± 137 pg/ml during laboratory-induced supraventricular tachycardia (p < 0.005). Right atrial pressures were recorded in 12 patients; the baseline atrial pressure was 4.3 ± 1.9 mm Hg and increased to 7.4 ± 3.6 mm Hg during supraventricular tachycardia (p < 0.005). A modest but significant linear relation was noted between the changes in plasma atrial natriuretic factor and right atrial pressure measurements during induced supraventricular tachycardia (r = 0.60, p < 0.05).

In conclusion, changes in atrial rhythm and pressure may be an important factor modulating the release of atrial natriuretic factor in the circulation and raised levels of this hormone may be a contributing factor for the polyuria and the hypotension associated with paroxysmal supraventricular tachyarrhythmias.

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Peptides with potent vasodilator and diuretic activities have been purified from animal and human atrial extracts (1–8). Recently, a direct radioimmunoassay was developed for measuring atrial natriuretic factor in human plasma (9). Several reports (10–14) have shown that the release of atrial natriuretic factor is stimulated by volume sodium loading and that high concentrations of this hormone are found in patients with congestive heart failure. However, the stimuli that induce the release of atrial natriuretic factor remain to be characterized (15). Furthermore, the role of this hormone in certain pathophysiologic states is not well understood and, more specifically, little of the previous work in this field has been conducted in patients with supraventricular tachyarrhythmias (12,16–19).

The purpose of this study was to measure changes in plasma immunoreactive atrial natriuretic factor in two groups: 1) patients undergoing cardioversion of chronic atrial fibrillation, and 2) patients undergoing electrophysiologic testing for the assessment of paroxysmal supraventricular tachycardia. In addition, because the changes in plasma atrial natriuretic factor activity that occur with these arrhythmias might result from variations in atrial hemodynamics, we measured the right atrial pressure during laboratory-induced supraventricular tachycardia.

Methods

Study patients. Atrial fibrillation (Table 1). Ten patients (six men, four women), 48 to 73 years old (mean 60 ± 8), undergoing elective cardioversion for atrial fibrillation were studied. Three patients had pure mitral stenosis, one had both mitral regurgitation and stenosis and one had mitral valve prolapse. Three patients had mild hypertension with a diastolic pressure of 90 mm Hg or less while receiving diuretic agents. The remaining two patients had no evidence of cardiovascular disease by history, physical examination or M-mode and two-dimensional echocardiography. All patients were studied on a stable regimen of digitalis and oral anticoagulants.

Recurrent supraventricular tachycardia (Table 2). This group consisted of 14 patients (five women, nine men) referred for electrophysiologic evaluation of recurrent par-
oxysmal supraventricular tachycardia. Their ages ranged from 15 to 64 years (mean 39 ± 18). One patient had idiopathic cardiomyopathy and one patient had coronary artery disease. Twelve patients were without clinical evidence of heart disease.

Of the 24 patients studied, none had congestive heart failure or renal failure. The blood urea nitrogen, serum creatinine and serum electrolytes were normal in all patients.

**Procedures.** *Cardioversion.* The subjects with atrial fibrillation underwent direct current cardioversion while in the fasting state after receiving a short-acting barbiturate. Synchronized shocks of 150 to 300 J successfully terminated the arrhythmias in all instances. All pre- and postcardioversion blood samples for atrial natriuretic factor measurement were drawn from a forearm vein with the subject in the supine rest position for 15 to 30 minutes.

**Electrophysiological evaluation.** The 14 patients with a history of recurrent supraventricular tachycardia were evaluated for clinical purposes in the cardiac electrophysiology laboratory while in the postabsorptive state and while receiving no medication for at least 72 hours. Each patient gave written informed consent. Four quadripolar catheters (for sensing and pacing) were inserted percutaneously using lidocaine local anesthesia through the femoral veins or left basilic vein and placed in the right atrium, right ventricle, coronary sinus and across the tricuspid valve for His bundle recording. A USCI 5520 No. 6 catheter with the tip in the right atrium was used for measurement of the right

### Table 1. Characteristics of the 10 Patients Undergoing Cardioversion For Atrial Fibrillation

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr) &amp; Sex</th>
<th>Heart Disease</th>
<th>AF Duration (weeks)</th>
<th>LA (mm)</th>
<th>Heart Rate (beats/min)</th>
<th>AF</th>
<th>SR</th>
<th>ANF (pg/ml)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>48M MS</td>
<td></td>
<td>10</td>
<td>55</td>
<td>100 75</td>
<td>192.2</td>
<td>167.9</td>
<td>—</td>
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<tr>
<td>2</td>
<td>61M SH</td>
<td></td>
<td>&gt;15</td>
<td>50</td>
<td>90 70</td>
<td>48.3</td>
<td>32.1</td>
<td>50.9</td>
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<tr>
<td>3</td>
<td>59F MS</td>
<td></td>
<td>&gt;10</td>
<td>42</td>
<td>92 72</td>
<td>125.9</td>
<td>123.9</td>
<td>100.6</td>
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<tr>
<td>4</td>
<td>72M SH</td>
<td></td>
<td>&gt;12</td>
<td>47</td>
<td>140 74</td>
<td>206.8</td>
<td>151.4</td>
<td>148.1</td>
</tr>
<tr>
<td>5</td>
<td>61M SH, MVP</td>
<td></td>
<td>&gt;15</td>
<td>35</td>
<td>100 68</td>
<td>167.6</td>
<td>121.8</td>
<td>94.2</td>
</tr>
<tr>
<td>6</td>
<td>73F SH</td>
<td></td>
<td>2</td>
<td>36</td>
<td>70 68</td>
<td>126.1</td>
<td>89.3</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>55M None</td>
<td></td>
<td>&gt;15</td>
<td>39</td>
<td>90 72</td>
<td>82.3</td>
<td>61.6</td>
<td>48.9</td>
</tr>
<tr>
<td>8</td>
<td>51M MS</td>
<td></td>
<td>&gt;18</td>
<td>52</td>
<td>75 70</td>
<td>157.8</td>
<td>160.7</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>55F None</td>
<td></td>
<td>&gt;18</td>
<td>40</td>
<td>70 70</td>
<td>136.5</td>
<td>111.4</td>
<td>131.3</td>
</tr>
<tr>
<td>10</td>
<td>70F MS + MR</td>
<td></td>
<td>12</td>
<td>47</td>
<td>90 75</td>
<td>150.7</td>
<td>144.2</td>
<td>136.5</td>
</tr>
</tbody>
</table>

**AF = atrial fibrillation; ANF = atrial natriuretic factor; F = female; LA = left atrial size by echocardiography; M = male; MR = mitral regurgitation; MS = mitral stenosis; MVP = mitral valve prolapse; SH = systemic hypertension; SR = sinus rhythm; — = data not available.**

### Table 2. Characteristics of the 14 Patients With Supraventricular Tachycardia

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr) &amp; Sex</th>
<th>Heart Disease</th>
<th>Right Atrial Pressure (mm Hg)</th>
<th>ANF (pg/ml)</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>SR</td>
<td>SVT</td>
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<tr>
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<td>20M None</td>
<td>AP</td>
<td>70</td>
<td>220</td>
</tr>
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<td>AP</td>
<td>65</td>
<td>150</td>
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<tr>
<td>3</td>
<td>63F None</td>
<td>AP</td>
<td>70</td>
<td>160</td>
</tr>
<tr>
<td>4</td>
<td>33M None</td>
<td>AP</td>
<td>72</td>
<td>205</td>
</tr>
<tr>
<td>5</td>
<td>25F None</td>
<td>AP</td>
<td>60</td>
<td>200</td>
</tr>
<tr>
<td>6</td>
<td>24F None</td>
<td>AVN</td>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td>7</td>
<td>17F None</td>
<td>AP</td>
<td>60</td>
<td>155</td>
</tr>
<tr>
<td>8</td>
<td>35M None</td>
<td>AP</td>
<td>75</td>
<td>185</td>
</tr>
<tr>
<td>9</td>
<td>64M CAD</td>
<td>AVN</td>
<td>55</td>
<td>160</td>
</tr>
<tr>
<td>10</td>
<td>15M None</td>
<td>AP</td>
<td>60</td>
<td>160</td>
</tr>
<tr>
<td>11</td>
<td>63M None</td>
<td>AVN</td>
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<td>AP</td>
<td>75</td>
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<tr>
<td>13</td>
<td>58M None</td>
<td>AP</td>
<td>70</td>
<td>195</td>
</tr>
<tr>
<td>14</td>
<td>54F None</td>
<td>AP</td>
<td>60</td>
<td>160</td>
</tr>
</tbody>
</table>

**AP = accessory pathway; AVN = atrioventricular nodal reentry; CAD = coronary artery disease; CM = cardiomyopathy; SVT = supraventricular tachycardia; other abbreviations as in Table 1.**
atrial pressure. The intracardiac electrograms were filtered at 30 to 500 Hz and simultaneously displayed with three surface electrocardiographic leads (I, aVF, V1) on a multichannel oscilloscope (Electronics for Medicine VR 12). In addition, all data were recorded with an ink-jet recorder (Elema Mingograph) at paper speeds of 25 to 250 mm/s and stored on magnetic tape. The atrial pressure was processed through a Bentley 800 transducer and model V2206A amplifier in the Electronics for Medicine recorder.

In each patient, baseline electrophysiologic intervals, arterial blood pressure, right atrial pressure and right atrial blood samples for atrial natriuretic factor were obtained during sinus rhythm. Supraventricular tachycardia was then induced with a programmable stimulator using a stimulation protocol that included atrial and ventricular incremental pacing at cycle lengths of 500 to 250 ms for 10 to 30 seconds and extrastimulus testing during two paced cycle lengths (600 and 400 ms). The measurements obtained at baseline were repeated 5 minutes after the first induced stable supraventricular tachycardia and subsequently repeated at the end of the electrophysiologic procedure. Blood samples for atrial natriuretic factor were also drawn 24 hours later from a forearm vein with the subject in the supine position and experiencing sinus rhythm.

**Measurements of atrial natriuretic factor.** Blood samples for atrial natriuretic factor were taken into cold tubes containing ethylenediaminetetraacetic acid and (per 1 ml blood) pepstatin, 10 μl (500 μM), and PMSF, 10 μl (10⁻⁴ M). Blood was centrifuged at 4,000 rpm for 20 minutes at 4°C. Plasma was stored at −70°C for 2 to 4 days and retrieved for assay. The sensitivity of the method is 1.9 pg/ml.

**Statistical analysis.** The data were assessed by Student’s t test for paired and unpaired data. The strength of association between the changes in plasma concentration of immunoactive atrial natriuretic factor and right atrial pressure was assessed by linear regression analysis using the plasma atrial natriuretic factor ratio (plasma level during tachycardia divided by baseline plasma level during sinus rhythm) and the right atrial pressure ratio (right atrial pressure during tachycardia divided by baseline right atrial pressure during sinus rhythm); the coefficient of regression was calculated by the method of least squares.

All values are expressed as mean ± 1 SD. A probability value of <0.05 was considered indicative of a significant difference.

**Results**

**Atrial fibrillation (Fig. 1).** The mean plasma concentration of atrial natriuretic factor in the 10 patients with chronic atrial fibrillation decreased from 138 ± 48 pg/ml before cardioversion to 116 ± 45 pg/ml 1 hour after conversion to sinus rhythm (p < 0.005). The change was small and nonsignificant between the 1 hour (107 ± 44 pg/ml) and the 24 hour measurements (102 ± 40 pg/ml). There was no significant correlation between the heart rate and the plasma atrial natriuretic factor concentration either during atrial fibrillation (r = 0.51) or during sinus rhythm (r = 0.55). There was no significant difference in systolic and diastolic arterial pressures before and after cardioversion (121 ± 14/77 ± 11 versus 119 ± 13/77 ± 5 mm Hg).

**Supraventricular tachycardia (Fig. 2 to 4).** The mean plasma concentration of atrial natriuretic factor increased from 117 ± 53 pg/ml at rest to 251 ± 137 pg/ml during supraventricular tachycardia (p < 0.005) and decreased to 125 ± 69 pg/ml 24 hours after the study (p < 0.0005). The mean right atrial pressure (Fig. 3) was 4.3 ± 1.9 mm Hg during sinus rhythm and increased during supraventricular tachycardia to 7.4 ± 3.6 mm Hg (p < 0.005). Within 15 minutes after terminating the tachycardia, right atrial pressure decreased to 4 ± 2.5 mm Hg (p < 0.0005). Only one patient demonstrated a decrease in right atrial pressure during tachycardia that was associated with a slight increase in atrial natriuretic factor production (Fig. 4). In all other instances, the plasma atrial natriuretic factor levels and right atrial pressures increased during the tachycardia.
When the plasma atrial natriuretic factor ratio was compared with the right atrial pressure ratio, a modest but significant (p < 0.05) linear regression was noted (regression coefficient r = 0.60).

The mean heart rate during supraventricular tachycardia was 179 ± 24 beats/min (range 155 to 220). There was no significant correlation between the heart rate and the atrial natriuretic factor concentration either during sinus rhythm (r = 0.43) or during supraventricular tachycardia (r = 0.11). The mean systolic/diastolic arterial pressures were 124 ± 16/79 ± 5 mm Hg during sinus rhythm and 118 ± 16/79 ± 15 during the tachycardia; the decrease was not significant.

Discussion

There are three main findings in this study. First, the plasma concentrations of atrial natriuretic factor in patients with chronic atrial fibrillation decrease after restoration to sinus rhythm. Second, plasma concentrations of atrial natriuretic factor increase markedly and rapidly during laboratory-induced supraventricular tachycardia. Third, the increase in right atrial pressure during supraventricular tachycardia may be a contributing factor for the release of atrial natriuretic factor. Taken together, these findings suggest that the release of atrial natriuretic factor in the circulation is rapid and is modulated by changes in atrial rhythm and pressure.

Mechanism of secretion of atrial natriuretic factor during supraventricular tachyarrhythmias. The exact mechanism underlying the secretion of atrial natriuretic factor has not yet been defined. Immunocytochemical studies indicate that both atria contain atrial natriuretic factor although more in the cardiocytes of the right than the left atrium (20). Our results of parallel increase in right atrial
pressure and plasma atrial natriuretic factor during supraventricular tachycardia are consistent with the view expressed by others that acute atrial distension elicits the release of this substance (10,12,15,17,21). We did not measure atrial pressure during atrial fibrillation. However, previous studies have shown that the mean atrial pressure increases with the onset of atrial fibrillation and decreases after cardioversion to sinus rhythm (22,23). These findings may indicate that chronic atrial stretch contributed to the high plasma atrial natriuretic factor levels during atrial fibrillation.

Effects of release of atrial natriuretic factor during supraventricular tachyarrhythmias. Our results may be used to gain insights into some of the pathophysiologic phenomena associated with paroxysmal atrial fibrillation and supraventricular tachycardia. Wood first spoke about the polyuria associated with paroxysmal supraventricular tachyarrhythmias in 1961. His observations were reported in 1963 by Campbell (24) and later confirmed by others (25–27). Infusion of atrial peptides produces potent diuretic and natriuretic effects in rats (2–4,6) and humans (12,13). Plasma atrial natriuretic factor levels were measured during paroxysmal supraventricular tachyarrhythmias in five preliminary studies with a total of 16 patients (12,16–19). The rapidity and the magnitude of increase in plasma atrial natriuretic factor observed with supraventricular tachycardia in these studies is in agreement with our findings and may explain the polyuria and natriuresis associated with paroxysmal supraventricular tachycardia. However, our data suggest that elevated immunoreactive atrial natriuretic factor levels are not necessarily related to this phenomenon because high atrial natriuretic factor levels were also recorded in patients with chronic atrial fibrillation, which is not associated with polyuria. It may be that chronically elevated levels of atrial natriuretic factor lead to a resetting of the specific renal receptors.

The atrial natriuretic peptides also relax vascular smooth muscle, oppose the vasoconstrictive effects of angiotensin and reduce renin and aldosterone secretion (5,15,28–34). It has been shown that systolic and diastolic blood pressures decrease significantly in some patients during a paroxysm of atrial fibrillation or supraventricular tachycardia and that these arrhythmias may produce dizziness and syncope in patients who are otherwise in good health and without organic heart disease (24,35). A contributing factor for the disabling symptoms in these patients may be due to the hypotensive effects of a marked increase in plasma atrial natriuretic factor activity.

Conclusions. Changes in atrial pressure and rhythm are probably involved in inhibiting and inducing cardiac secretion of atrial natriuretic factor. This hormone may play a role in the polyuria and hypotension sometimes associated with paroxysmal supraventricular tachyarrhythmias. Finally, the laboratory induction of reentrant supraventricular tachycardia provides an experimental model to further study the physiologic effects of endogenous atrial natriuretic factor in humans.

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References


