Plasma Concentrations of Atrial Natriuretic Peptide in Cardioembolic Stroke with Atrial Fibrillation

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Summary: The aim of the present study was to determine whether the level of plasma atrial natriuretic peptide (ANP), an indicator of atrial stretching, correlates with the formation of a thrombus in the left atrium during cardioembolic stroke with atrial fibrillation. Plasma concentrations of immunoreactive ANP and thrombin-antithrombin III complex (TAT) were measured in five age-matched groups including: 16 patients with acute cardioembolic stroke and atrial fibrillation (group 1), 26 patients with chronic cardioembolic stroke and atrial fibrillation (group 2), 27 patients with atrial fibrillation without previous stroke (group 3), 21 patients with acute lacunar stroke (group 4), and 27 healthy controls. The plasma ANP levels were higher in group 1, regardless of the stage, than those estimated at chronic stage in group 4 and in healthy controls. There were no stage-related differences between groups 1, 2 and 3. Plasma levels of ANP in group 2, a high risk group of cardioembolic stroke, were higher than in group 3, a low risk group. There was no correlation between plasma levels of ANP and mean blood pressure, pulse rate or plasma levels of TAT in any group. These results indicate that the determination of plasma ANP concentration is useful to distinguish a high risk patient from a low risk patient and also a cardioembolic stroke patient from a lacunar stroke patient. They also underscore the difficulties in recognizing left atrial thrombus formation by determining the plasma ANP concentration in cardioembolic stroke.

Key words: cardioembolic stroke — lacunar stroke — atrial fibrillation — atrial natriuretic peptide — thrombin-antithrombin III complex

Introduction

It is generally accepted that atrial fibrillation is associated with an increased risk of stroke. The risk among patients with non-rheumatic atrial fibrillation is estimated to be five times greater than that for comparable patients in sinus rhythm (Wolf et al. 1978; Kannel et al. 1982). Low-intensity anticoagulation with warfarin is effective in preventing thromboembolic episodes (Boston Area...
Anticoagulation Trial for Atrial Fibrillation Investigators, 1990; Ezekowitz et al. 1992). Because prothrombin activation is significantly suppressed in vivo by warfarin in patients with atrial fibrillation (Kistler et al. 1993; Sato et al. 1993), the beneficial effect of warfarin must depend on a decrease in embolization subsequent to clot formation in the cardiac atria.

On the other hand, atrial natriuretic peptide (ANP) is released from the atria in response to an elevation of pressure (Lang et al. 1985) and the concentration tends to be high in paroxysmal atrial fibrillation. As the left atrial enlargement by echocardiography conveys an additional stroke risk in patients with atrial fibrillation (Caplan et al. 1986), plasma concentrations of ANP and thrombin-antithrombin III complex (TAT), a sensitive indicator of a hypercoagulable state, were determined in patients with cardioembolic stroke and chronic atrial fibrillation.

As controls, 27 patients with chronic atrial fibrillation without previous stroke (age, 76±10 years) and 21 patients with acute lacunar stroke (age, 71±10 years) were included in the study. Brain computed tomography (CT) was performed to confirm the presence of an embolic stroke (Cerebral Embolism Task Force, 1986). Lacunar stroke was diagnosed by the presence of a typical neurological syndrome and CT findings. Cases with liver or renal dysfunction and apparent clinical symptoms of congestive heart failure were not included in this study. In 20 of 26 patients with chronic cardioembolic stroke and 6 of 27 patients with atrial fibrillation without stroke, the International Normalized Ratio (INR) (Poller, 1986) was kept between 1.5 and 2.7 by the anticoagulant, warfarin.

Twenty-seven healthy men (age, 76±10 years) were used as age-matched controls.

Methods

In patients with acute cardioembolic or lacunar stroke, blood samples were obtained within 24hs after the onset of symptoms but prior to therapy (acute stage), on the 14th (subacute stage) and on the 28th (chronic stage) day of hospitalization. In patients with chronic cardioembolic stroke, with atrial fibrillation without stroke and in the healthy controls, blood was drawn once for the basal state. Blood pressure and pulse rate were determined at the time of blood sampling.

The plasma was separated by centrifugation at 3000 rpm for 10min at 4°C and stored at −30°C until use. The plasma ANP assay was performed radioim-
munologically using commercially available kits (CIS diagnostic Co., Japan). The plasma concentrations of TAT were measured using an enzyme-linked immunosorbent assay kit (Behring Werke AG Marburg, Federal Republic of Germany).

The values are expressed as mean± standard deviation. A Student's t test was used to compare data. Correlations between the various parameters were performed by linear regression. A p value less than 0.05 was considered to be statistically significant.

**Results**

The concentrations of plasma ANP (mean±SD) for the various stages of both acute cardioembolic and lacunar stroke are listed in Table 1. During the acute stage of stroke, the plasma ANP level was significantly higher in patients with cardioembolic and lacunar stroke than in controls (p<0.01, 0.05); but during the subacute and chronic stages, it remained significantly higher only in patients with cardioembolic stroke. Comparisons of each stage of cardioembolic and lacunar stroke demonstrated that the plasma ANP level was significantly higher only at the chronic stage of cardioembolic stroke.

Serial determinations during each stage revealed no significant stage-related differences of the plasma ANP levels with cardioembolic stroke. However, the level during the acute stage of lacunar stroke was significantly higher than that at the chronic stage.

Table 2 shows the plasma ANP levels for chronic cardioembolic stroke and atrial fibrillation without stroke. In both groups, the plasma ANP levels were significantly higher than the controls; while for chronic cardioembolic stroke, it was significantly higher than for atrial fibrillation without previous stroke and for the acute stage of lacunar stroke.

There was no apparent correlation between the plasma ANP level and pulse

<table>
<thead>
<tr>
<th>TABLE 1.</th>
<th>Concentrations of plasma atrial natriuretic peptide in acute cardioembolic and lacunar stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cardioembolic stroke (n)</td>
</tr>
<tr>
<td>Acute stage (pg/ml)</td>
<td>92.4±32.5*</td>
</tr>
<tr>
<td>Subacute stage (pg/ml)</td>
<td>73.4±38.8*</td>
</tr>
<tr>
<td>Chronic stage (pg/ml)</td>
<td>81.5±35.2***</td>
</tr>
</tbody>
</table>

*p<0.01 compared with control; **p<0.05 compared with control; #p<0.01 compared with chronic stage; ##p<0.01 compared with chronic stage of lacunar stroke
TABLE 2.
Concentrations of plasma atrial natriuretic peptide (ANP) in patients with chronic cardioembolic stroke or atrial fibrillation without previous stroke

<table>
<thead>
<tr>
<th></th>
<th>Cardioembolic stroke (n)</th>
<th>Atrial fibrillation (n)</th>
<th>Control (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma ANP level (pg/ml)</td>
<td>117.6±71.3*#</td>
<td>83.2±47.4*</td>
<td>48.4±17.4</td>
</tr>
</tbody>
</table>

*p<0.01 compared with control; *p<0.05 compared with atrial fibrillation

TABLE 3.
Correlation between the plasma concentration of atrial natriuretic peptide and pulse rate, mean blood pressure or plasma concentration of thrombin-antithrombin III complex (TAT) in each group

<table>
<thead>
<tr>
<th></th>
<th>Pulse rate (r)</th>
<th>Mean blood pressure (r)</th>
<th>TAT (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute cardioembolic stroke</td>
<td>0.08</td>
<td>0.05</td>
<td>0.11</td>
</tr>
<tr>
<td>Chronic cardioembolic stroke</td>
<td>0.06</td>
<td>0.13</td>
<td>-0.11</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>-0.28</td>
<td>0.11</td>
<td>-0.07</td>
</tr>
<tr>
<td>Acute lacunar stroke</td>
<td>-0.11</td>
<td>0.04</td>
<td>0.07</td>
</tr>
</tbody>
</table>

TABLE 4.
Plasma concentrations of atrial natriuretic peptide (ANP) and thrombin-antithrombin III complex (TAT) in patients with chronic cardioembolic stroke or atrial fibrillation that were treated or not treated with warfarin

<table>
<thead>
<tr>
<th></th>
<th>Warfarin-treated group</th>
<th>Warfarin-untreated group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>ANP (pg/ml)</td>
</tr>
<tr>
<td>Chronic cardioembolic stroke</td>
<td>20</td>
<td>106±68</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>6</td>
<td>80±35</td>
</tr>
</tbody>
</table>

*: Not significant

rate, mean blood pressure or plasma TAT level (Table 3). Table 4 shows the plasma concentrations of ANP and TAT in patients with chronic cardioembolic stroke and atrial fibrillation with or without warfarin-treatment. There was no significant difference in the TAT levels of the two subgroups, although
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the levels tended to be elevated in the warfarin group.

Discussion

A precise knowledge of the haemostatic system has made it possible to measure specific intermediate products, i.e., the haemostatic molecular markers, generated by fibrin formation and fibrinolysis. These molecular markers are important parameters of thrombin and plasmin generation for detecting activated coagulation and fibrinolysis. It has been reported that both coagulation and fibrinolysis are activated in stroke, especially in cardioembolic stroke (Tohgi et al. 1990; Tanaka et al. 1992; Yamazaki et al. 1993). A previous study (Sato et al. 1993) demonstrated that plasma TAT, which is a sensitive molecular marker of a hypercoagulable state, was elevated not only during an acute cardioembolic stroke but also during atrial fibrillation without stroke.

The formation of intracardiac thrombi during an acute cardioembolic stroke can often be detected by serial two-dimensional echocardiography (Yasaka et al. 1990a) and the thrombi, located mainly in the left atrium, can be eliminated by treatment with an anticoagulant (Yasaka et al. 1990b).

Three peptides have recently been isolated from human atrial myocytes (alpha, beta and gamma human atrial natriuretic peptides: ANP), all of which have natriuretic, diuretic and hypotensive activities. Of these three peptides, alpha-human ANP appears to be the predominant peptide in plasma. Experimental studies indicate that ANP is released from the atria in response to increased atrial pressure (Lang et al. 1985; Schuetten et al. 1987).

The aims of this study were (1) to determine if left atrial thrombus formation is associated with elevated plasma ANP levels and if the alterations are correlated with plasma TAT levels in acute cardioembolic stroke, (2) to examine whether the elevation of plasma ANP in acute cardioembolic stroke occurs in atrial fibrillation without stroke, chronic cardioembolic stroke and acute lacunar stroke.

The concentrations of plasma ANP in patients with acute cardioembolic stroke were significantly higher at every stage than in controls, although the differences were not age-related. At a chronic stage of acute brain infarction, the plasma ANP level was significantly higher in patients with cardioembolic stroke than in patients with lacunar stroke. This indicates that the plasma ANP concentration varies with the type of stroke at the chronic stage of brain infarction. Caplan et al. (1986) divided patients with atrial fibrillation into high and low risk groups depending on the presence or absence of a previous ischemic stroke. In the present study, the plasma ANP level was higher in the high-risk subgroup with chronic cardioembolic stroke than in the low-risk subgroup with atrial fibrillation and no previous stroke. Also, the plasma ANP levels were significantly higher in both high and low-risk subgroups than in controls. It has been demonstrated that patients with atrial fibrillation have high plasma ANP levels (Petersen et al. 1988). An important aspect in the prevention of cardioembolic stroke in patients with
atrial fibrillation is that the plasma ANP level of the high-risk subgroup is significantly higher than that of the low-risk subgroup.

The reason that the plasma ANP level tends to be elevated in both high- and low-risk subgroups in the absence of warfarin-treatment is still unclear. To clarify, the relationship of embolic stroke to the use of warfarin, further detailed studies on a large scale are needed in patients with atrial fibrillation. Since the plasma ANP concentration remained at the same level in every stage of acute cardioembolic stroke and in high or low risk subgroups; the plasma ANP concentration must be constantly high in patients with acute cardioembolic stroke, before and after the onset. It has been demonstrated that plasma ANP increases in association with an elevation of atrial pressure under certain conditions such as congestive cardiac failure, hypertension, paroxysmal supraventricular tachycardia and atrial fibrillation and decreases with dehydration (Schiffrin et al. 1985; Paillard et al. 1987; Petersen et al. 1988). In the present study, however, no apparent correlation was observed between the plasma ANP level and the mean blood pressure or pulse rate. In addition, the plasma ANP concentration does not seem to be correlated with a hypercoagulability during atrial fibrillation, as there was no correlation between plasma ANP and TAT levels. Berglund et al. (1990) indicated that increased plasma concentrations of ANP are independent of left atrial dimensions, as demonstrated by echocardiography in patients with chronic atrial fibrillation. This was attributed to ANP being a sensitive indicator of changes in hemodynamic function, such as atrial compliance and transmural pressure during atrial fibrillation. Resetting some of the atrial receptors or decreasing the sensitivity with chronic dilatation may also have influenced these results. The investigation of the determinant factors for plasma ANP in patients with atrial fibrillation is an important aspect in the prevention of embolic stroke.

The present study provides new clinical data showing that the determination of the plasma ANP concentration is useful to separate patients with atrial fibrillation into a high risk group or a low risk group, and to separate the patients with acute cardioembolic stroke from those with lacunar stroke.

References


