Plasma brain natriuretic peptide level after radiofrequency catheter ablation of paroxysmal, persistent, and permanent atrial fibrillation

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Received 26 May 2007; accepted after revision 5 July 2007; online publish-ahead-of-print 1 August 2007

Introduction

It is known that during atrial fibrillation (AF), an inappropriately rapid ventricular response, loss of the atrial contribution to the cardiac output, and atrial overloading lead to the activation of the neurohormonal system.1 It was demonstrated that successful elimination of paroxysmal AF (PAF) normalized the plasma brain natriuretic peptide (BNP) level after pulmonary vein isolation (PVI).2,3 However, the change in the BNP level after PVI in patients with persistent (Pers-AF) and permanent AF (Perm-AF) remains unknown. The purpose of this study was to investigate this in Pers-AF and Perm-AF patients without any structural heart disease compared with PAF patients.

Methods

Patient characteristics

The study population consisted of 96 consecutive patients (80 men, 59 ± 10 years) with symptomatic AF (PAF = 65, Pers-AF = 17, and Perm-AF = 14) refractory to 3 ± 1 class I or class III anti-arrhythmic drugs. The AF patients who were administered class II or class IV anti-arrhythmic drugs before and after PVI were not enrolled in this study because of the potential of those drugs that modify the results of the study by affecting the autonomic nervous system directly or indirectly. The mean duration of the AF was 4 ± 3 years (range 1–18). The mean echocardiographic dimension of the left atrium (LA) was 35 ± 5 mm (25–45) and mean left ventricular (LV) ejection fraction 67 ± 8% (55–90). For the Doppler echocardiographic parameters, the mean E/A wave ratio was 0.9 ± 0.3 (0.4–1.7) and mean deceleration time 198 ± 35 ms (160–235). No patient had any structural heart disease, LV diastolic function for their age, or renal dysfunction. Owing to hypertension, angiotensin-converting enzyme-inhibitors were administered in four patients and angiotensin II type 1 receptor blockers in nine patients. The Institutional Review Board approved the study protocol, and all patients provided their written informed consent. All anti-arrhythmic drugs were discontinued for at least five half-lives prior to the study.

Electrophysiological study and pulmonary vein isolation procedure

Catheterization into the LA was performed with a one puncture and two-sheath technique. Intravenous heparin was administered to maintain an activated clotting time > 250 s after the atrial
transseptal procedure. In all cases, circumferential PVI targeting the PV antrum potentials of three to four PVs was performed using a 31 mm multielectrode basket catheter (MBC) (Constellation™, EP Technologies, Boston Scientific Corporation, San Jose, CA, USA) as previously reported. Radiofrequency energy was delivered with a target temperature of 55°C and a maximum power output of 40 W for 60 s (EPT-1000TC generator, EP Technologies), using an 8 mm tip catheter (Blazer II 5770T, EP Technologies). Successful PVI was defined as either the abolition or dissociation of the distal PV potentials. Left atrial ablation was never added after the PVI.

**Blood sampling and hormone assay**
Before and 3 months after the successful PVI, blood samples to measure the BNP level were obtained from the antecubital vein in the supine position after a resting period of 30 min just before echocardiographic examination. If the latest PAF attack persisted for > 8 h, blood samples were obtained at least 3 h after the PAF terminated. The BNP level was determined using a chemi-luminescent enzyme immunoassay.

**Definition of the atrial fibrillation type and classification of the patients**
Paroxysmal, persistent, and permanent AF were defined as follows according to the international consensus. Paroxysmal atrial fibrillation was defined as AF usually self-terminating within 48 h and, by definition, in < 7 days, Pers-AF as AF lasting (7 days and requiring pharmacological therapy or electrical cardioversion to terminate, and Perm-AF as AF which fails to terminate using cardioversion or is terminated but relapses within 24 h.

**Assessment of the atrial fibrillation attacks**
All the patients were contacted and asked if they had had any attacks of their rhythm problem before and 3 months after the ablation procedure. A 24 h Holter monitoring was also performed at least twice before the ablation procedure to evaluate the reliability of the patients’ answers.

**Follow-up**
During the follow-up period, no anti-arrhythmic drugs were administered in any of the patients. Clinical follow-up was performed at 2 weeks, 1 month, and every month thereafter, using 24 h Holter recordings and 12-lead electrocardiograms in all patients. All patients who reported symptoms were given an event monitor to document the cause of the symptoms. No patients were lost to the follow-up.

**Statistical analysis**
The continuous variables are expressed as the group mean ± 1 SD. Comparisons between groups were performed with either the Student’s t-test or ANOVA. Categorical variables expressed as numbers and percentages were compared with a χ² test. Statistical significance was selected as a value of P < 0.05.

**Results**

**Clinical characteristics**
The clinical characteristics of each type of AF are shown in *Table 1*. There were no significant differences in the age, male gender, AF duration, LV ejection fraction, Doppler echocardiographic parameters, or administration of angiotensin-converting enzyme-inhibitors or angiotensin II type 1 receptor blockers among the PAF, Pers-AF, and Perm-AF patients. The LA dimension was significantly greater in the Pers-AF and Perm-AF patients than in the PAF patients (38 ± 4 and 39 ± 4 vs. 35 ± 5 mm, P < 0.05).

**Pulmonary vein isolation and follow-up**
The isolation of three PVs was performed in six patients (two PAF, two Pers-AF, and two Perm-AF) because of right or left PVs with a common ostium in four patients and small right inferior PVs in two, and the isolation of all four PVs was performed in the remaining patients. A successful isolation of the targeted PVs could be achieved in all patients. At more than 3 months of follow-up after the first PVI, AF recurred without any anti-arrhythmic drugs in 14 (22%) PAF, 12 (71%) Pers-AF, and 11 (79%) Perm-AF patients. Atrial fibrillation did not recur in the patients undergoing isolation of three PVs alone because of small right inferior PVs. No asymptomatic AF recurrences were observed. Nineteen (PAF = 5, Pers-AF = 8, and Perm-AF = 6) of those patients with recurrent AF after the first PVI underwent a second session. Because the electrophysiological study revealed the recurrence of electrical connections between

<table>
<thead>
<tr>
<th>Table 1 Clinical characteristics</th>
<th>Paroxysmal (n = 65)</th>
<th>Persistent (n = 17)</th>
<th>Permanent (n = 14)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61 ± 10</td>
<td>56 ± 7</td>
<td>56 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>53/12</td>
<td>13/4</td>
<td>14/0</td>
<td>NS</td>
</tr>
<tr>
<td>AF duration (years)</td>
<td>4 ± 4</td>
<td>5 ± 4</td>
<td>6 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>Echocardiographic parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA dimension</td>
<td>35 ± 5</td>
<td>38 ± 4</td>
<td>39 ± 4</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>LVEF</td>
<td>67 ± 9</td>
<td>65 ± 12</td>
<td>65 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE-I [n (%)]</td>
<td>2 (3)</td>
<td>2 (12)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>ARB [n (%)]</td>
<td>4 (6)</td>
<td>4 (23)</td>
<td>1 (7)</td>
<td>NS</td>
</tr>
<tr>
<td>Catheter ablation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrically isolated PVs [n/cases]</td>
<td>4.0 ± 0.2</td>
<td>3.9 ± 0.3</td>
<td>3.9 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Number of procedures</td>
<td>1.2 ± 0.4</td>
<td>1.6 ± 0.5</td>
<td>1.5 ± 0.5</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Cavo-tricuspid isthmus ablation [n (%)]</td>
<td>12 (18)</td>
<td>4 (24)</td>
<td>2 (14)</td>
<td>NS</td>
</tr>
<tr>
<td>AF recurrence [n (%)]</td>
<td>12 (18)</td>
<td>7 (41)</td>
<td>8 (57)</td>
<td>P &lt; 0.01</td>
</tr>
</tbody>
</table>

ACE-I, angiotensin-converting enzyme-inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; LA, left atrial; LVEF, left ventricular ejection fraction; PV, pulmonary vein.
the LA and one to two PVs previously ablated in all of those patients, the PVI was repeated using the same technique as in the first session. In 13 of those patients, focal ablation targeting non-PV AF foci and/or a cavo-tricuspid isthmus ablation was also performed. Ten patients (PAF = 2, Pers-AF = 5, and Perm-AF = 3) were free of symptomatic AF without any anti-arrhythmic drugs after the second procedure. In seven of the nine patients with recurrent AF after multiple procedures, the AF converted from a persistent or permanent to a paroxysmal form in five, and from a permanent to a persistent form in two. Though the remaining 27 patients had recurrent AF even after the multiple procedures, 14 (PAF = 9, Pers-AF = 3, and Perm-AF = 2) of those patients became free of symptomatic AF after the administration of one anti-arrhythmic drug that failed to control the AF before the procedure. Eight (PAF = 4, Pers-AF = 3, and Perm-AF = 1) of the 13 patients who still had recurrent AF after multiple procedures continued to be followed up because both the frequency and duration of the AF attacks had decreased and consequently the symptoms remarkably improved. The remaining five patients with recurrent Perm-AF continued to be followed up, with medication aiming at a rate control. The results of the catheter ablation are summarized in Table 1. There were no significant differences in the number of electrically isolated PVs or in the proportion of cavo-tricuspid isthmus ablations. The number of procedures and the AF recurrence rate after multiple procedures were significantly greater in the Pers-AF and Perm-AF patients than in the PAF patients (1.6 ± 0.5 and 1.5 ± 0.5 vs. 1.2 ± 0.4, P < 0.0001, and 41 and 57 vs. 18%, P < 0.01, respectively).

**Plasma brain natriuretic peptide level**

At baseline, the BNP level was elevated in all patients with AF and it was significantly greater in the Pers-AF and Perm-AF patients than in the PAF patients (68.9 ± 39.0 vs. 52.7 ± 36.1, P < 0.05) (Figure 1). In the Pers-AF and Perm-AF patients, there were no significant differences in the BNP level at baseline between those patients with and without AF recurrence after the multiple procedures. After the multiple procedures, the BNP level significantly decreased in the PAF and Pers-AF patients (52.7 ± 36.1 vs. 19.7 ± 15.7 pg/mL, P < 0.0001, and 59.8 ± 28.7 vs. 26.6 ± 25.4 pg/mL, P = 0.005) but not in the Perm-AF patients (79.9 ± 47.6 vs. 58.4 ± 70.7 pg/mL, NS) (Figure 1). The BNP level after multiple procedures was significantly greater in the Perm-AF patients than in the PAF or Pers-AF patients (58.4 ± 70.7 vs. 19.7 ± 15.7 or 26.6 ± 25.4 pg/mL, P < 0.0005). In 31 Pers-AF and Perm-AF patients, the elevated BNP level at baseline decreased to within-normal limits in 16 (52%) patients without any AF recurrence after multiple procedures (Figure 2). In the remaining Pers-AF and Perm-AF patients, no significant differences in the BNP level were observed between at baseline and after the multiple procedures, however, in all 7 of 31 (23%) patients, whose AF type improved after the multiple procedures, the BNP level decreased (Figure 2).

**The relationship between the clinical parameters and atrial fibrillation recurrence in the persistent atrial fibrillation and permanent atrial fibrillation patients**

In the Pers-AF and Perm-AF patients, there were no significant differences in the age, male gender, AF duration, LV ejection fraction, or administration of angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers between those patients with and without AF recurrence after the multiple procedures. The LA dimension was significantly greater in the patients with AF recurrences

![Figure 1](https://example.com/figure1.png)  
**Figure 1** The plasma brain natriuretic peptide (BNP) level before and after multiple procedures in paroxysmal, persistent, and permanent atrial fibrillation patients. The dotted line indicates the normal limit of the plasma brain natriuretic peptide level. AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation.

![Figure 2](https://example.com/figure2.png)  
**Figure 2** The change in the plasma brain natriuretic peptide level after multiple procedures in persistent and permanent atrial fibrillation patients. The effective group consisted of seven patients with recurrent atrial fibrillation after multiple procedures in whom the atrial fibrillation was converted from a persistent or permanent to a paroxysmal form in five and from a persistent form in two. The non-effective group consisted of eight patients with recurrent atrial fibrillation after multiple procedures in whom the atrial fibrillation type did not convert. The circles indicate the persistent atrial fibrillation patients, and triangles the permanent atrial fibrillation patients.
than in the patients without AF recurrences (38 ± 4 vs. 35 ± 5 mm, P < 0.05).

Discussion

An attempt to cure Pers-AF and Perm-AF by PVI may be more challenging than PAF. However, this study demonstrated that the elevated BNP level decreased after the PVI procedures independent of any AF recurrence in Pers-AF patients as well as PAF patients. That might be because PVI may relieve the cardiac load by reducing the AF burden (converting a persistent to paroxysmal form) in the cases with AF recurrence and even remove it completely by eliminating the PAF in the cases without AF recurrence. Therefore, in consideration of the neurohormonal system, PVI may be recommended to treat lone AF in Pers-AF patients as well as PAF patients. On the other hand, in Perm-AF patients, PVI may be challenging for decreasing the BNP level probably because in a large part of Perm-AF patients, the elimination of AF or even the conversion from a persistent to a persistent or paroxysmal form cannot be achieved by PVI.

This study also demonstrated that the BNP level normalized in the Pers-AF and Perm-AF patients without any AF recurrence after the PVI procedures. Furthermore, the LA diameter was demonstrated to be a predictor of the AF recurrence in those patients after PVI. Brain natriuretic peptide is a neurohormone secreted during a ventricular volume and pressure overload. Some reports have suggested that in Perm-AF cases, one of the causes for an increased LA volume might be a sustained increase in the LV filling pressure owing to the haemodynamic alteration and disappearance of the atrial contraction. Accordingly, it is suggested that an increased BNP secretion from the ventricular wall in response to the increased LV filling pressure might be associated with an increased LA volume. The increased atrial dimension in patients with AF (anatomical remodelling) is attributable to the recurrence and maintenance of AF with atrial electrophysiological remodelling. Anatomical remodelling of the atra may reduce the cure rate of AF by PVI because it provides the arrhythmogenic substrate for AF in the atria. In Pers-AF and Perm-AF patients with a lesser LA enlargement in this study, AF could be eliminated by PVI because the atrial anatomic remodelling was limited. In those patients, the BNP level might have normalized after the AF burden was removed by the PVI because the atrial anatomic remodelling was trivial or reversible.

It has been demonstrated that the BNP level can be a useful marker for evaluating the efficacy of PVI in each PAF patient. This study demonstrated that in Pers-AF and Perm-AF patients, the BNP level decreased with an improvement in the AF type even if AF recurred after the PVI. Therefore, the BNP level also may be a useful marker for evaluating the efficacy of PVI in each Pers-AF and Perm-AF patient.

Study limitations

In this study, the number of Pers-AF and Perm-AF patients was lower than that of the PAF patients. Therefore, the conclusions about PAF might be more consistent than those about Pers-AF and Perm-AF.

Recent reports using transtelephonic and long-term Holter monitoring have revealed that asymptomatic AF recurrences after an AF ablation occur more often than we would expect, and thus freedom from AF after PVI may be overestimated. In this study, asymptomatic AF recurrences might have been missed and the cure rate might have been a little overestimated because intermittent Holter recordings alone were performed for the clinical follow-up. Further studies using a continuous 7 day Holter monitoring as used in the previous reports will be needed to investigate whether the BNP is useful for evaluating asymptomatic AF recurrences after PVI.

Conclusions

The reduction in the BNP level after the PVI seemed to be a marker for a good outcome in AF post-ablation patients.

Conflict of interest: There was no financial support for this study.

References
