Brain Natriuretic Peptide Predicts Chronic Atrial Fibrillation After Ventricular Pacing in Patients With Sick Sinus Syndrome

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Chronic atrial fibrillation (AF) is one of the main complications of sick sinus syndrome (SSS). As previously reported, plasma brain natriuretic peptide (BNP), reflects hemodynamic changes in different pacing modes, as does plasma atrial natriuretic peptide (ANP), so the present study investigated whether plasma BNP or ANP can predict chronic AF after single-chamber ventricular (VVI) pacemaker implantation in patients with SSS. Plasma ANP and BNP levels were measured before and 1–3 months after implantation in 99 SSS patients. Long-term follow-up was conducted with chronic AF as an endpoint. Chronic AF occurred in 19 patients during a mean follow-up of 5.1 years. Plasma ANP and BNP were significantly higher in the patients who developed chronic AF after implantation than in those who did not, despite similar ANP and BNP levels between the 2 groups before implantation. Post-implant high BNP and a history of paroxysmal AF were independent predictors of chronic AF by a multivariate Cox proportional hazards analysis. Plasma BNP can predict the development of chronic AF after VVI pacemaker implantation in patients with SSS because increased levels may reflect latent hemodynamic abnormalities, which may contribute to the development of AF after VVI pacemaker implantation. (Jpn Circ J 2000; 64: 965–970)

Key Words: Atrial fibrillation; Pacemaker; Plasma natriuretic peptide

Chronic atrial fibrillation (AF), which may lead to stroke, is one of the main complications of sick sinus syndrome (SSS). In subjects with SSS, permanent pacemakers have been implanted to prevent bradycardia and bradycardia-related symptoms. Compared with single-chamber ventricular pacing (non-physiological pacing), dual-chamber pacing (physiological pacing), which can preserve atrioventricular (AV) synchrony, has both hemodynamic and survival benefits1,2 and reduces the risk of chronic AF and stroke4,4. However, dual-chamber pacemakers are used less than expected; because they are considered to be more expensive and more difficult to implant and monitor than single-chamber ventricular pacemakers; that is, the choice of pacemaker is often based not on the results of clinical trials, but rather on the physician's biases. Therefore, it is very important among those patients with SSS to identify who is more likely to develop chronic AF after single-chamber ventricular pacemaker implantation.

Cardiac natriuretic peptide systems such as atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are thought to play an important role in the regulation of cardiovascular homeostasis and fluid volume6.10 ANP is mainly synthesized in and secreted from the atria, whereas BNP is mainly synthesized in and secreted from the ventricles. Previous studies have shown that plasma ANP and BNP levels increased in patients with chronic heart failure11,12. Plasma BNP is more sensitive than ANP for predicting hemodynamic abnormalities such as left ventricular dysfunction13.15 We previously reported that plasma BNP and ANP levels reflect hemodynamic changes in cardiac rhythm elicited by different cardiac pacing modes, and are significantly higher during non-physiological pacing (VVI pacing) than during physiological pacing (AAI or DDD pacing)16. We also demonstrated that plasma BNP is a sensitive biochemical marker for evaluating hemodynamics in patients with permanent pacemakers.

Therefore, we hypothesized that if the adverse hemodynamic effects associated with non-physiological pacing contributed to chronic AF, plasma ANP and BNP levels may predict the development of chronic AF. Moreover, we also hypothesized that they could be sensitive markers for identifying patients, particularly those with SSS, who were more likely to develop chronic AF after VVI pacemaker implantation.

Methods

Study Population

One-hundred-eighty-nine patients who had been implanted with VVI pacemakers because of SSS were prospectively analyzed. SSS was defined by the presence of inappropriate, persistent sinus bradycardia (less than 50 beats/min), sinus pauses longer than 3 s accompanied by symptoms, or sinoatrial block17. Patients who had established AF, advanced AV block, or a concomitant cardiac disease (prior myocardial infarction (n=19), moderate or severe valvular heart disease (n=9) or cardiomyopathy (n=14)) as assessed by ECG, cardiac catheterization, angiogram or echocardiography, were excluded from the study. Patients...
with apparent cardiac dysfunction and who have increased levels of plasma natriuretic peptides, are known to be at risk for the development of chronic AF. It should therefore be easy to predict which patients would develop chronic AF after VVI pacemaker implantation among the SSS patients with concomitant cardiac disease, so the study was designed to enroll a homogenous group of patients without concomitant cardiac disease to assess whether plasma BNP or ANP could predict the development of chronic AF in patients without concomitant cardiac disease. Patients with spontaneous ventricular beats might fail to alter the plasma BNP or ANP levels after permanent pacemaker implantation, so we recorded 2 Holter strips during the study period and excluded those who showed at least one spontaneous ventricular beat. Thus, 99 patients were included in the study. Baseline variables, including a history of pre-implant paroxysmal AF (PAF), pre-implant medication with class I antiarrhythmic agents and retrograde ventriculo-atrial (VA) conduction before pacemaker implantation, were analyzed. PAF was defined as recurrent self-terminating episodes lasting <7 days and alternating with periods of sinus rhythm evaluated at least 6 months before pacemaker implantation. Medications that were given with the intention to treat were allowed. Other cardioactive agents (β-blockers and angiotensin-converting enzyme inhibitors (ACEI)) were also administered at the discretion of the physician.

**Implantation and Programming**

The implanted VVI pacemaker was either a Miniti 8340, Legend 8416 (Medtronic, Inc., Minneapolis, MN, USA), or a Quantum 253-19 (Intermedics, Inc, Freeport, TX, USA). Each pacemaker was programmed at a rate of 60 or 70 beats/min. The selection of rate adaptive function was not randomized, but rather based on the discretion of the physician.

**Study Protocol**

All of the patients gave their informed consent. Blood samples were taken in all 99 patients from the femoral or antecubital vein before pacemaker implantation to measure plasma ANP and BNP. Blood samples were also collected in all of the patients 1–3 months (mean, 1.7 months) after pacemaker implantation, which was considered to reflect stable levels of ANP and BNP after implantation. Patients were allowed to rest for at least 45 min in a supine position before blood sampling. Echocardiograms and chest X-ray were also taken before and 1–3 months after pacemaker implantation, and left atrial dimensions (LAD), left ventricular dimensions, such as left ventricular diastolic and systolic dimensions (LVDD, LVDs), left ventricular ejection fraction (LVEF), and the cardiothoracic ratio (CTR), were measured.

**Measurement of Plasma ANP and BNP Concentrations**

Samples for the assay of plasma ANP and BNP concentrations were transferred to chilled disposable tubes containing aprotinin (500 kilokrein inactivator units/ml). The blood samples were immediately placed on ice and centrifuged at 4°C as previously reported. Plasma ANP concentrations were measured with a specific immunoradiometric assay for α-human ANP using a commercial kit (Shionoria, Japan) as previously reported. Briefly, this assay uses 2 monoclonal antibodies against α-human ANP (one that recognizes a carboxyterminal sequence and another that recognizes the ring structure of ANP) and measures α-human ANP by sandwiching it between the 2 antibodies without plasma extraction. The minimal detectable quantity of α-human ANP using this method is 5 pg/ml. The intra-assay and inter-assay coefficients of variation were 5.1% and 5.8%, respectively. This assay system did not cross-react with angiotensin I or II, vasopressin, or human BNP. The cross-reactivity with human BNP was <0.001% on a molar basis.

Plasma BNP concentrations were measured with a specific immunoradiometric assay for human BNP using a commercial kit (Shionoria, Japan) as previously reported. Briefly, this assay uses 2 monoclonal antibodies against human BNP (one that recognizes a carboxyterminal sequence and another that recognizes the ring structure of BNP) and measures BNP by sandwiching it between the 2 antibodies without plasma extraction. The minimal detectable quantity of human BNP using this method is 2 pg/ml. The intra-assay and inter-assay coefficients of variation were 5.2% and 6.1%, respectively. This assay system did not cross-react with angiotensin I or II, vasopressin, or human ANP. The cross-reactivity with human ANP was <0.001% on a molar basis.

**Long-Term Follow-up**

Long-term follow-up was conducted every month at a hospital visit with chronic AF as an endpoint. Chronic AF was defined as AF in 2 Holter strips obtained in a period of 2 months, with no subsequent sinus rhythm. Long-term follow-up was based on a systematic review of all of the hospital and outpatient charts to assess the development of chronic AF during the follow-up period.

**Statistical Analysis**

The results are expressed as the mean ± standard error (SEM). Statistical analyses were performed with Student’s t test for continuous variables and the chi square test for categorical variables, with a p value less than 0.05 considered significant. Differences in AF-free survival between the groups were evaluated by the Kaplan-Meier method. Comparisons were made using the log-rank test. For clinical and neurohumoral variables, a multivariate analysis was performed using the Cox proportional hazards model, run in a stepwise manner, to assess the association with the development of chronic AF.

**Results**

**Baseline Characteristics**

The average age of the study patients was 65.8 years (range, 49–76 years), and 53 patients (53%) were male. Off the 99 patients, 26% had hypertension, and 16% had a history of PAF.

**Development of Chronic AF**

We were able to follow-up all of the patients. During the mean follow-up period of 5.1±2.6 years, 19 patients (19%) developed chronic AF. The actuarial incidence of chronic AF was 10.1% at 1 year and 19% at 5 years (Fig 1).

**Comparison of Patients Who Developed Chronic AF and Those Who Maintained Sinus Rhythm**

Table 1 shows the clinical characteristics of the patients divided into those who developed chronic AF during the follow-up period (chronic AF group) and those who maintained sinus rhythm (sinus rhythm group). There were no significant differences between the 2 groups with respect to

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**Author Information**

age at implant, CTR, left atrial and ventricular dimensions before and after implantation, male gender, hypertension, percentage of patients with rate adaptives, \(\beta\)-blockers or ACEI. However, the percentages of patients with a history of PAF and antiarrhythmic agents were significantly greater in the chronic AF group than in the sinus rhythm group (\(<0.0001\), \(<0.0001\), respectively). Plasma ANP and BNP before pacemaker implantation were similar in both groups, but a few months after implantation were significantly higher in the chronic AF group than in the sinus rhythm group (ANP: 145.2±8.80 vs 58.1±3.17 pg/ml, \(<0.0001\); BNP: 221.8±6.65 vs 97.9±4.18 pg/ml, \(<0.0001\)). Of the 99 study patients, 34 showed retrograde VA conduction, and 65 showed AV dissociation. Nine patients (26%) with retrograde VA conduction and 10 (15%) without retrograde VA conduction developed chronic AF. The percentage of patients who developed chronic AF was greater in those with retrograde VA conduction compared with those without, but this difference was not significant.

Changes in plasma ANP and BNP and other echocardiographic parameters before and after pacemaker implantation were also analyzed (Table 2). Actual changes in plasma ANP and BNP were significantly greater in the chronic AF group than in the sinus rhythm group. However, there were no significant changes in echocardiographic parameters between the groups before and a few months after pacemaker implantation.

**Natriuretic Peptides and the Development of Chronic AF**

Fig 2 shows the 5-year Kaplan–Meier actuarial chronic AF-free survival curves for post-implant ANP and BNP. Patients with high levels (greater than the median values of 66.0 and 99.0, respectively) had a significantly higher incidence of chronic AF.

**Factors Associated With the Development of Chronic AF During Follow-up**

Cox proportional hazards analysis was performed to determine which factors were associated with the development of chronic AF during the follow-up period. The following were considered independent variables: age, gender, hypertension, history of PAF, pre-implant high ANP (greater

![Graph showing Kaplan–Meier actuarial survival curves for chronic AF](image)

**Table 1** Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Chronic AF group (n=19)</th>
<th>Sinus rhythm group (n=80)</th>
<th>(p) value</th>
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</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>68.4±1.56</td>
<td>65.2±1.47</td>
<td>NS</td>
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<tr>
<td><strong>Male (%)</strong></td>
<td>9 (47)</td>
<td>44 (55)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Hypertension (%)</strong></td>
<td>6 (31)</td>
<td>20 (25)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>History of PAF (%)</strong></td>
<td>15 (79)</td>
<td>11 (13)</td>
<td>&lt;0.0001</td>
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<tr>
<td><strong>Medications</strong></td>
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<tr>
<td>(\beta)-blockers (%)</td>
<td>3 (16)</td>
<td>15 (19)</td>
<td>NS</td>
</tr>
<tr>
<td>ACEI (%)</td>
<td>3 (16)</td>
<td>22 (27)</td>
<td>NS</td>
</tr>
<tr>
<td>Class I antiarrhythmic agents (%)</td>
<td>7 (37)</td>
<td>3 (4)</td>
<td>&lt;0.0001</td>
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<tr>
<td><strong>Retrograde VA conduction (%)</strong></td>
<td>9 (47)</td>
<td>25 (31)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Rate adaptives</strong></td>
<td>14 (74)</td>
<td>55 (69)</td>
<td>NS</td>
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<tr>
<td><strong>CTR (%)</strong></td>
<td>53.5±1.75</td>
<td>51.9±0.74</td>
<td>NS</td>
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<td><strong>Echocardiographic findings</strong></td>
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<td>Before implantation</td>
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<tr>
<td>LAD (mm)</td>
<td>36.3±2.59</td>
<td>33.0±1.73</td>
<td>NS</td>
</tr>
<tr>
<td>LVd (mm)</td>
<td>47.1±5.61</td>
<td>46.4±2.79</td>
<td>NS</td>
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<tr>
<td>LVF (%)</td>
<td>29.8±3.51</td>
<td>28.7±1.80</td>
<td>NS</td>
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<tr>
<td>After implantation</td>
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<tr>
<td>LAD (mm)</td>
<td>36.3±3.72</td>
<td>33.3±1.72</td>
<td>NS</td>
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<tr>
<td>LVd (mm)</td>
<td>48.2±4.34</td>
<td>45.6±2.83</td>
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<tr>
<td>LVF (%)</td>
<td>31.4±3.89</td>
<td>28.4±1.76</td>
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<td>Natriuretic peptides</td>
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<td>Before implantation</td>
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<tr>
<td>ANP (pg/ml)</td>
<td>48.8±5.02</td>
<td>40.5±2.43</td>
<td>NS</td>
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<tr>
<td>BNP (pg/ml)</td>
<td>58.7±4.99</td>
<td>52.0±3.29</td>
<td>NS</td>
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<tr>
<td>After implantation</td>
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<tr>
<td>ANP (pg/ml)</td>
<td>145.2±8.80</td>
<td>58.1±3.17</td>
<td>&lt;0.0001</td>
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<tr>
<td>BNP (pg/ml)</td>
<td>221.8±6.65</td>
<td>97.9±4.18</td>
<td>&lt;0.0001</td>
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</table>

Means±SEM. PAF, paroxysmal atrial fibrillation; ACEI, angiotensin-converting enzyme inhibitor; VA, ventriculo-atrial; CTR, cardio-thoracic ratio; LVF, left ventricular ejection fraction; LAD, left atrial dimension; LVd, left ventricular end-diastolic dimension; LVFs, left ventricular end-systolic dimension.

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![Graph showing Kaplan–Meier actuarial survival curves for chronic AF](image)
Table 2 Changes in Parameters Before and After Pacemaker Implantation

<table>
<thead>
<tr>
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<th>Chronic AF group (n=19)</th>
<th>Sinus rhythm group (n=80)</th>
<th>p value</th>
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<tr>
<td><strong>Changes in echocardiographic findings</strong></td>
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<tr>
<td>Before and after implantation</td>
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<tr>
<td>ΔLAD (mm)</td>
<td>0.24±0.40</td>
<td>0.23±0.49</td>
<td>NS</td>
</tr>
<tr>
<td>ΔLVdL (mm)</td>
<td>1.06±2.33</td>
<td>-0.80±0.92</td>
<td>NS</td>
</tr>
<tr>
<td>ΔLVd (% )</td>
<td>1.62±1.98</td>
<td>-0.30±0.73</td>
<td>NS</td>
</tr>
<tr>
<td>ΔLVEF (%)</td>
<td>-2.51±2.86</td>
<td>-0.53±1.49</td>
<td>NS</td>
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<tr>
<td><strong>Changes in natriuretic peptides</strong></td>
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<tr>
<td>Before and after implantation</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ΔANP (pg/ml)</td>
<td>96.4±28.59</td>
<td>17.6±23.61</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ΔBNP (pg/ml)</td>
<td>163.1±73.30</td>
<td>45.8±23.99</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Mean±SEM. LAD, left atrial dimension; LVdL, left ventricular end-diastolic dimension; LVd, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction.

Fig.2. (Upper) The Kaplan–Meier actuarial AF-free curves comparing patients with high ANP (ANP>66.0) and low ANP (ANP<66.0) a few months after pacemaker implantation. (Lower) The Kaplan–Meier actuarial AF-free curves comparing patients with high BNP (BNP>99.0) and low BNP (BNP<99.0) a few months after pacemaker implantation. Patients with high ANP or BNP had a significantly worse prognosis during the follow-up period (p<0.0001, p<0.0001, respectively).

than the median value of 36.0 pg/ml and high BNP (greater than the median value of 53.0 pg/ml), post-implant high ANP (ANP>66.0 pg/ml) and high BNP (BNP>99.0 pg/ml), pre- and post-implant LAD, LVdL, LVd, LVEF, and CTR, class I antiarrhythmic agents, retrograde VA conduction, and rate adaptives. As a result, post-implant high BNP and a history of PAF were significantly associated with the development of chronic AF (p=0.0006; hazard ratio 24.477 and p=0.0247; hazard ratio 2.824).

Discussion

The major findings in this study are that (1) BNP and ANP, measured a few months after implantation, predicted the development of chronic AF after VVI pacemaker implantation in patients with SSS, and (2) post-implant high BNP and a history of PAF were independent predictors of chronic AF.

In previous studies, it has been difficult to predict whether patients without any concomitant cardiac disease, such as old myocardial infarction, valvular heart disease or cardiomyopathy, will develop chronic AF after VVI pacemaker implantation. This is the first report that plasma BNP may be an independent predictor of chronic AF after VVI pacemaker implantation.

Chronic AF

Although chronic AF is part of the natural history of SSS, several studies have suggested that ventricular pacing may increase the risk of developing AF. Furthermore, it has also been shown that left atrial dimension and left ventricular function before pacemaker implantation are risk factors among clinical variables. Accordingly, patients with impaired left ventricular function, so-called sick heart, would be expected to develop chronic AF. On the other hand, it may become more difficult to identify patients who may develop chronic AF among patients without either impaired left ventricular function or left atrial enlargement.

In the present study, univariate analysis showed that left atrial dimension, left ventricular dimension, and left ventricular function before and a few months after pacemaker implantation were similar in both the patients who developed chronic AF and those who maintained sinus rhythm. However, univariate analysis also demonstrated that post-implant levels of plasma ANP and BNP were significantly higher in patients who developed chronic AF than in those with sinus rhythm, despite the pre-implant levels of plasma ANP and BNP being similar in the 2 groups. It has been suggested that the loss of atrioventricular synchrony, which is observed in non-physiologically (VVI) paced patients, leads to progressive increases in left atrial and left ventricular end-diastolic pressure, and consequently to chronic AF. Our study enrolled a homogeneous group of patients with almost normal plasma ANP and BNP levels at baseline, but
ventricular pacing might disclose latent hemodynamic abnormalities and impaired left ventricular diastolic function in the patients with increased plasma ANP and BNP after VVI pacing even though they may have had a normal hemodynamic status at baseline. Previous reports have shown that plasma ANP reflects pulmonary capillary wedge pressure (PCWP), whereas plasma BNP reflects left ventricular end-diastolic pressure (LVEDP). Non-physiological pacing might lead to progressive increases in left atrial and left ventricular end-diastolic pressure, reflected as increases in plasma ANP and BNP levels, and consequently lead to greater susceptibility to chronic AF.

Multivariate analysis demonstrated that BNP was superior to ANP and other clinical variables for predicting the development of chronic AF. ANP is thought to be stored in secretory granules, and its secretion is predominantly regulated by stretching of the atria, whereas it is thought that mRNA releases BNP just after synthesis. An age-related process and continuous stretching of the atria caused by hemodynamic dysfunction or loss of AV synchrony by VVI pacing may lead to functional in the atrium and sinus node, which might impair the release of ANP. Plasma levels of BNP have been reported to be a sensitive marker for left ventricular dysfunction and one of the best prognostic factors in heart failure. Therefore, BNP was considered to be partially related to the development of chronic AF.

In our multivariate analyses, we found that a history of PAF was another independent predictor of chronic AF. The percentage of patients with a history of PAF was significantly greater among those who developed chronic AF than in those with sinus rhythm. A previous study reported that a history of PAF was an independent predictor of chronic AF. Although the exact mechanism of the development of chronic AF is still not known, micro- and macro-reentry have been proposed as possibilities. Patients with PAF have had micro- and macro-reentry, and the heterogeneous pattern of depolarization and repolarization of the atrium during non-physiological ventricular pacing might facilitate chronic AF.

In conclusion, BNP and ANP can predict the development of chronic AF after VVI pacemaker implantation in patients with chronic AF. The plasma BNP level a few months after implantation and a history of PAF were independent predictors of chronic AF.

Study Limitations

Our study has several limitations. First, we planned to enroll a homogenous group of patients who all had pacing in order to evaluate the changes in plasma ANP and BNP influenced only by ventricular pacing. We recorded 2 Holter strips to exclude the patients with spontaneous ventricular beats, but we could not rule out the chance of missing all pacing throughout the study.

Second, the pacing mode was selected at the discretion of the physician, so the subjects were not consecutive patients. Although it is not important to enroll consecutive patients to eliminate selection bias, this was not possible because of several previous reports on the hemodynamic and survival benefits of physiological pacemakers. Single-chamber ventricular pacemakers are mostly reserved for relatively high-risk subjects, such as elderly patients, or patients with a higher prevalence of PAF. Therefore, the incidence of chronic AF was relatively higher in our study population, compared with other clinical studies.

Third, we did not randomize the class I antiarrhythmic agents. Several studies have reported that these have beneficial effects on arrhythmia. On the other hand, the percentage of patients with class I antiarrhythmic agents was significantly greater among patients who developed chronic AF than in those who were free from chronic AF in our study population. These paradoxical results might suggest that patients with severe or prolonged PAF receive such medications. However, these medications were not risk factors for chronic AF in multivariate analysis. Therefore, medications do not appear to play an important role in preventing the onset of chronic AF.

Fourth, it was difficult to define PAF in patients without any symptoms. Although we examined the Holter ambulatory ECG in every patient before pacemaker implantation, the chance of detecting PAF is quite low. Patients were considered to have a history of PAF if they had symptomatic PAF at least 6 months before implantation, or if they had Holter-documented PAF. Therefore, PAF may have been underdiagnosed in our study population, and many of our study patients with PAF had a long prior history of PAF. A previous study reported that subjects with a long prior history of PAF had a significantly higher incidence of chronic AF than those with a short history of PAF. Further examination of the definition of PAF might give different results.

Finally, the diagnosis of chronic AF may be delayed, and the eventual unrecovered return to sinus rhythm after prolonged episodes of PAF may lead to an overdiagnosis of chronic AF. In addition, performing multiple statistical comparisons there is a risk that some parameters were significant by chance alone. Therefore, these results require confirmation by other studies.

Clinical Implications

SSS patients who are older or who have PAF are likely to be treated less aggressively in permanent pacemaker implantation. Single-chamber ventricular pacemakers are usually selected in such patients, but these patients are at high risk for subsequent chronic AF, which may lead to increased morbidity and mortality.

Hama et al reported that in rats with acute myocardial infarction (AMI) induced by coronary artery ligation, BNP concentration increased at as early as 12 h and BNP mRNA expression was augmented as early as 4 h post infarction. If these animal experimental results apply to humans, and temporary ventricular pacing may increase the BNP level to that similar to AMI, high plasma BNP measured a few days after temporary ventricular pacemaking, which is thought to be sufficient time for plasma BNP levels to stabilize, may be able to detect patients with latent hemodynamic abnormalities, and may be helpful for identifying patients who are more likely to develop chronic AF prior to permanent pacemaker implantation.

Acknowledgments

We thank Ms Ikuko Sakaguchi for her excellent technical assistance.

References

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