Plasma Natriuretic Peptide Levels and Daily Physical Activity in Patients with Pacemaker Implantation

Xiaoyi Wu, MD, Yoshihiko Seino, MD, Hiromichi Ogura, MD, Nagaharu Fukuma, MD, Takao Katoh, MD, and Teruo Takano, MD

SUMMARY

To determine whether plasma ANP and/or BNP levels can be used to detect limitations in daily physical activity after pacemaker implantation, we measured plasma ANP and BNP levels at a pacemaker follow-up clinic in 56 patients (62±15 yrs, 2AAI, 9VVI, 34DDD, 7VDD and 4 rate-responsive modes). Daily physical activity evaluated by a specific activity scale questionnaire (METs) and VO2 max obtained by expired gas analysis during ergometer exercise. A very close correlation \( r=0.89, p<0.05 \) was observed between ANP in patients with daily physical activity class III (2-4 METs, \( n=21 \)) was significantly higher than class II (5-6 METs, \( n=23, p<0.01 \)) and class I (>7 METs, \( n=8, p<0.01 \)), while BNP in class III patients was significantly higher than in class II (\( p<0.0001 \)) and class I (\( p<0.0001 \)) patients. Significant correlations between daily physical activity and BNP \( r=-0.64, p<0.0001 \) and ANP \( r=-0.43, p<0.001 \) were observed. Physiological pacing mode did not necessarily offer a better profile for BNP levels compared with non-physiological pacing modes. Patients with ventricular pacing (wide QRS: VDD, RR-VVI and VVI) showed significantly high ANP (\( p<0.01 \)) and BNP (\( p<0.01 \)) levels compared with those in patients with atrial pacing (narrow QRS: AAI and RR-AAI). During exercise, plasma catecholamines and ANP levels were significantly elevated, however, BNP levels, which were already elevated at rest, did not change significantly, and reflected a limitation of daily physical activity. The present study revealed that 37.5% of the patients displayed an elevation in BNP and this was judged to be a limitation of physical activity class III being equivalent to NYHA II or more. Elevated resting BNP levels reflected a limitation in daily physical activity in these patients. These findings suggested a third condition for physiological pacing - synchronization of ventricular contraction (narrow QRS pacing) - in addition to the two conventional conditions of atrioventricular synchrony and rate-responsiveness. (Jpn Heart J 2001; 42: 471-482)

Key words: Physiological pacing, Brain natriuretic peptide, Congestive heart failure, Physical activity, Dyssynchronization

We have reported that the electrophysiological consequences of the heart following pacemaker implantation are closely related to the cardiodynamic and neu-
rohormonal conditions in patients with pacemaker implantation.\textsuperscript{1,2}) Currently physiological pacing is defined in terms of satisfying as to satisfy atrioventricular synchrony and rate-responsiveness. previous reports\textsuperscript{3}) has discussed the displayed beneficial effects of atrial pacing in comparison with ventricular pacing on the overall survival rate and survival from cardiovascular death in a long-term follow-up study. In contrast,a more recent report\textsuperscript{4}) described that physiological pacing provided little benefit over ventricular pacing for the prevention of stroke or death due to cardiovascular causes. The limitation of pacemaker therapy might be related to dyssynchronization by right ventricular pacing, even in terms of physiological pacing, which produces a wide QRS complex (left bundle branch block pattern). Recently, it has been shown that simultaneous pacing of both ventricles elicited a significant improvement in cardiac performance\textsuperscript{5}) and neurohormonal circumstances in patients with advanced heart failure, which shortens prolonged QRS duration, reducing cardiac morbidity, improving functional capacity and cardiac performance, and further increasing survival rate.\textsuperscript{6-9)}

In the present study, we prospectively investigated the following three issues: 1) Does physiological pacing really contribute to an improvement in daily physiological activity? 2) Does plasma atrial or brain natriuretic peptide levels reflect daily physical activity after pacemaker implantation? and 3) To further understand the electrophysiological-neurohormonal axis in patients with pacemaker implantation.

\section*{Patients and Methods}

\textbf{Study patients: } The study included 56 patients (average age 62±15 years old; 23 males and 33 females) with implanted pacemakers for complete AV block ($n=33$, 62±12 years) or sick sinus syndrome ($n=23$, 65±15 years). The permanent pacemakers had been implanted for at least 6 months and up to 14 years. Patients with dilated cardiomyopathy, hypertrophic cardiomyopathy, previous myocardial infarction, valvular heart disease or atrial fibrillation were excluded from this study. Patients taking anti-arrhythmia drugs, including $\beta$-blockers, were also excluded. PACing modes were AAI in 2 patients, DDD in 34 patients, VDD in 7 patients, rate-responsive AAI (RR-AAI) in 2 patients as the physiological modes, and VVI in 9 patients and rate-responsive VVI (RR-VVI) in 2 patients as the non-physiological modes.

The plasma concentrations of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and catecholamines were measured and correlated with daily physical activity in all patients. Daily physical activity was evaluated by a specific activity scale questionnaire which was derived from the metabolic cost of individual physical activity.\textsuperscript{10,11}) Exercise tolerance and maximum oxygen con-
sumption (VO\textsubscript{2}\text{max}) were measured by expired gas analysis during the ergometer exercise test. Specific activity scale and VO\textsubscript{2}\text{max} were transformed to the metabolic equivalent unit (MET: 1 MET is equal to an oxygen consumption of 3.5 ml/kg/min).\textsuperscript{12}

**Measurements of plasma concentrations of ANP, BNP and catecholamines:** We measured plasma ANP and BNP levels and catecholamine concentrations in a pacemaker follow-up clinic. Peripheral blood was obtained from the antecubital vein. Samples for ANP and BNP measurements were drawn into tubes containing EDTA, chilled, centrifuged and the plasma separated and stored at 4°C before analysis.\textsuperscript{13,14} Plasma ANP and BNP concentrations were measured with specific immunoradiometric assays for human ANP and BNP, respectively, using commercial kits (Shionoria, Japan).\textsuperscript{14,15} The plasma concentrations of noradrenaline and adrenaline were quantified using radioimmunoassay methods, as previously reported.\textsuperscript{1,2,16}

At the same time as blood sampling, we evaluated daily physical activity by the specific activity scale questionnaire. Specific activity was only evaluated in 52 patients since 4 patients did not cooperate in the evaluation. Table I shows the

<table>
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<tr>
<th>Table I. Specific Activity Scale Questionnaire (originally for evaluation of severity of CHF)</th>
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<tbody>
<tr>
<td>1. Have a good sleep in evening (less 1 MET)</td>
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<tr>
<td>2. Feel better when lay down on a bed (less 1 MET)</td>
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<tr>
<td>3. Eat and wash face by yourself (1.6 METs)</td>
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<tr>
<td>4. Can go to toilet by yourself (2 METs)</td>
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<tr>
<td>5. Can dress and undress by yourself (2 METs)</td>
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<tr>
<td>6. Can prepare food and clean room (2-3 METs)</td>
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<tr>
<td>7. Can make the bed by yourself (2-3 METs)</td>
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<tr>
<td>8. Can clean the floor (3-4 METs)</td>
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<tr>
<td>9. Can take shower by yourself (3-4 METs)</td>
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<tr>
<td>10. Can finish radio exercise (3-4 METs)</td>
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<tr>
<td>11. Can walk 100-200 m (3-4 METs)</td>
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<tr>
<td>12. Can cut the grass in the garden (4 METs)</td>
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<tr>
<td>13. Can take a bath by yourself (4-5 METs)</td>
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<td>14. Can climb stairs (5-6 METs)</td>
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<tr>
<td>15. Can do some light farm work (5-7 METs)</td>
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<td>16. Can walk fast (6-7 METs)</td>
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<td>17. Can shovel snow (6-7 METs)</td>
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<td>18. Can play tennis (6-7 METs)</td>
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<td>19. Can jog (8 km/hour) 300-400 m (7-8 METs)</td>
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<td>20. Can swim (7-8 METs)</td>
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<td>21. Can skip rope (8 METs)</td>
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MET=metabolic equivalent unit; CHF=congestive heart failure.
specific activity scale questionnaire, which was originally developed for evaluation of the severity of chronic heart failure.\textsuperscript{10-11} The classifications (from I to IV) of the specific activity scale were determined according to the MET evaluated from answers to the 21 listed questions. Daily physical activity equal to or greater than 7 METs was defined as class I, between 5-6 METs as class II, 2-4 METs as class III, and equal or less than 1 MET as class IV.

**Exercise testing with expired gas analysis:** Exercise testing with expired gas analysis was performed in 6 patients (age 66±13 years old, 2 males, 4 females) with a DDD pacemaker. Exercise testing was performed on an upright electronically braked bicycle ergometer. During exercise, the 12-lead electrocardiogram was monitored continuously and blood pressure was recorded at 3 minute intervals. Before exercise, blood samples for measurement of ANP, BNP and catecholamines were obtained. The patients wore a mask in order to analyze expired gas. The patients were encouraged to exercise for as long as possible. Blood samples for ANP, BNP and catecholamine measurements were taken at peak exercise or when the heart rate reached 120/min, and after 30 minute of recovery. Continuous on-line measurement of expired gas exchange was performed. Peak oxygen consumption (peak VO\textsubscript{2}) was defined as the highest VO\textsubscript{2} value averaged over 15 seconds during the final minute of exercise.\textsuperscript{17-20}

**Statistics:** All data are were expressed as the mean±standard deviation (SD). A value of \(p<0.05\) was considered statistically significant. One-way analysis of variance was used to compare values between groups. METs were correlated with the specific activity scale, ANP, BNP and peak VO\textsubscript{2} for each subject in each group using Pearson's rank correlation test. Changes in ANP, BNP and catecholamines during ergometer exercise were analyzed using Student's \(t\)-test for paired data.

**RESULTS**

**Relationship between plasma ANP and BNP levels and patient background:** In the present study, significant correlations between age and ANP levels (\(r=0.36, p<0.01\)) and age and BNP (\(r=0.35, p<0.01\)) levels were observed. Furthermore, it was observed that ANP levels significantly correlated (\(r=0.51, p<0.01\)) with the post implantation period (2 months -10 years), namely, the longer the period after pacemaker implantation, the higher the ANP levels. However, BNP did not show any significant relationship to them.

Regarding the underlying arrhythmias, no significant differences in ANP or BNP levels between patients with complete AV block and those with sick sinus syndrome (ANP: 35.5±20.5 vs 32.2±30.2 pg/ml, NS, BNP: 57.5±49.9 vs 57.25±55.5 pg/ml, NS,) were observed.
When ANP and BNP levels were correlated with the cardiothoracic ratio (CTR), BNP levels in patients with CTR greater than 50% were significantly higher than that in those with a CTR less than 50% (80.6±54.6 pg/ml vs 33.6±33.8 pg/ml, p<0.001). Patients with non-physiological pacing modes, except for one case, were classified in the larger CTR group. However, ANP levels showed no significant difference between the two groups (39.3±20.6 vs 29.0±20.9 pg/ml, NS.)

**Evaluation of daily physical activity using the specific activity scale questionnaire:** We correlated a specific activity scale with VO$_2$max obtained by the analysis of expired gas during ergometer exercise and observed a close correlation ($n=6$, $r=0.89$, $p<0.05$) between them. In the present study, we assumed we would be able to evaluate daily physical activity using the specific activity scale questionnaire instead of performing the exercise test.

**Correlation of daily physical activity with ANP and BNP levels:** Figure 1 shows the correlation between the specific activity scale (METs) and plasma ANP and BNP levels. A significant correlation was found between the specific activity scale and ANP ($r=-0.43$, $p<0.001$) and BNP ($r=-0.63$, $p<0.0001$) levels. When ANP and BNP levels were compared between the physical activity classes, BNP ($p<0.0001$) levels in the class III group were significantly higher than those in class I and II (Figure 2). ANP levels in class III were significantly higher than those in class I and class II ($p<0.01$). The difference was more remarkable for BNP than ANP.

![Figure 1. Correlation of daily physiological activity (METs) and plasma ANP and BNP levels. ○: non-physiological pacing; ●: Physiological pacing. ANP=atrial natriuretic peptide; BNP=brain natriuretic peptide; MET=metabolic equivalent unit.](image-url)
Comparison of daily physical activity and plasma ANP and BNP levels between physiological and non-physiological pacing modes: Comparison of the specific activity scale between physiological and non-physiological pacing modes, revealed no significant difference between the two groups (4.8±1.2 vs 4.8±1.8 METs, NS.). Also, we could not find any significant difference in ANP (39.9±25.3 vs 48.3±34.4 pg/ml, NS.) or BNP (66.7±63.0 vs 86.2±55.3 pg/ml, NS.) levels between the two groups (Figure 3).

Comparison of daily physical activity and plasma ANP and BNP levels between atrial (narrow QRS) and ventricular (wide QRS) pacing modes: Daily physical activity and plasma ANP and BNP levels were compared between atrial pacing (narrow QRS: AAI and RR-AAI), both atrial and ventricular pacing (DDD), and ventricular pacing (wide QRS: VDD, RR-VVI and VVI) modes (Figure 4). We found no significant difference in daily physical activity among the three groups. Patients with ventricular pacing modes showed significantly higher ANP (20.0±8.7 vs 43.8±30.1 pg/ml, p<0.01) and BNP (28.5±17.3 vs 83.5±60.5 pg/ml, p<0.01) levels compared with those in patients with atrial pacing modes. Patients with both atrial or ventricular pacing mode (DDD) showed intermediate levels of ANP (31.3±19.1 pg/ml) and BNP (44.7±40.0 pg/ml) between them.
Changes in ANP, BNP and catecholamine levels during exercise: Table II and Figure 5 display the changes in plasma concentrations of ANP, BNP and catecholamines during ergometer exercise testing. Noradrenaline, adrenaline and ANP levels were significantly elevated during exercise, however, BNP levels, which were already elevated at rest, did not change significantly following exercise.
DISCUSSION

Evaluation of daily physical activity in patients with pacemaker implantation: In the present study, we correlated MET levels judged by a specific activity scale questionnaire with those obtained by expired gas analysis during exercise testing, and found a very close correlation. Therefore, we assumed we were able to evaluate daily physical activity by the specific activity scale questionnaire instead of performing an exercise test. Furthermore, we found significant correlations between the specific activity scale and plasma ANP and BNP levels. The measurement of plasma BNP levels is widely used to detect left ventricular systolic dysfunction and assess the severity of left ventricular failure. When ANP and
BNP levels were correlated with daily physical activity classes, BNP levels in the class III group were significantly higher than those in the class I and II groups. The difference in BNP levels between daily physical activity classes was more remarkable than the difference in ANP levels. The results of the present study indicate that plasma ANP and BNP levels, especially BNP levels, reflect the limitation of daily physical activity in patients with pacemaker implantation.

A specific activity scale was originally used to evaluate the severity of chronic heart failure. It is well known that the plasma levels of ANP and BNP increase with the severity of congestive heart failure. In patients with congestive heart failure, Yoshimura, et al reported that the plasma levels of ANP in patients with New York Heart Association (NYHA) class II were about 100 pg/ml, and BNP levels about 50 pg/ml; both about 200 pg/ml in NYHA class III, and about 300 pg/ml and 450 pg/ml in NYHA class IV. In the present study, ANP levels in patients with specific activity scale class II, III and IV were all lower than those in the respective NYHA classes. On the other hand, the BNP levels for each specific activity scale were almost equivalent to the respective NYHA classes. An important finding in the present study is that 78% of the patients were judged to be specific activity scale class II or more, and 37.5% of the patients were evaluated as class III, which was considered to be equivalent to NYHA class II or more in congestive heart failure.

**Comparison of physiological and non-physiological pacing modes, atrial and ventricular pacing modes:** The present study shows that physiological pacing mode did not necessarily result in superior physical activity. No significant differences in the specific activity scale or plasma levels of ANP and BNP were observed between patients with the physiological mode and those with the non-physiological mode. Dual-chamber pacemakers are thought to be more physiological than ventricular pacemakers. Lukl, et al performed a quality-of-life analysis using a questionnaire with regard to cardiovascular symptoms, physical activity, psychosocial and emotional functioning, and self-perceived health, and found that DDD pacing offered a better quality-of-life than RR-VVI pacing. However, Lamas, et al reported no significant difference between VVI and DDD modes in either the quality of life or prespecified clinical outcomes, including cardiovascular events or death.

The data on the order of ANP levels for each pacing mode suggest that ANP levels reflect whether atrioventricular synchrony and rate responsiveness, conventional conditions for physiologic pacing, are fulfilled or not. In contrast, plasma levels of BNP in patients with physiological pacing mode were not necessarily lower. The present data on BNP levels suggest that dyssynchrony of ventricular contraction following right ventricular pacing with a wide QRS complex, seems to relate to these elevated levels of BNP. The BNP levels reflect whether
the third condition for physiological pacing, that of synchrony of ventricular contraction, as well as the previous two conditions are satisfied or not.

The pacemaker therapy is based on right ventricular pacing even in DDD mode, which represents a wide QRS complex. The wide QRS complex (left bundle branch block pattern) has pronounced effects on cardiodynamics because of the dyssynchrony of ventricular contraction. Biventricular pacing has been recently proposed for the treatment of patients with refractory heart failure with a wide QRS complex. The purpose of biventricular pacing is to restore ventricular contraction and relaxation sequences as homogeneously as possible. Biventricular pacing which restores the electrical and mechanical synchronization would produce faster activation and better systolic and diastolic function than applying conventional right ventricular pacing. Restoration of ventricular synchrony, expressed by paced QRS narrowing, may account for the additional benefit of dual-site vs single-site pacing in enhancing contractility in patients with pacemaker implantation. The present study suggests the importance of correction of electrical and mechanical dyssynchronization as the third condition for physiological pacing.

**Changes in neurohormonal factors during exercise:** We have already reported a difference in cardiodynamic and neurohormonal responses between patients with RR-AAI and those with RR-VVI modes. With an increasing pacing rate during exercise, the RR-AAI mode had significant increases in cardiac index and ejection fraction; however, the RR-VVI mode had a significant decrease in ejection fraction. At rest, the mean plasma concentration of ANP was significantly higher in the RR-VVI group than that in the RR-AAI group and normal subjects. Thus, plasma ANP levels are believed to reflect whether the two conventional conditions for physiological pacing, namely, atrioventricular synchrony and rate-responsiveness, are fulfilled or not. Oldroyd, et al demonstrated that resting plasma concentrations of ANP were restored to normal by DDD pacing but not by VVI pacing.

The present study which measured BNP levels has revealed the third condition for physiological pacing, synchronization of ventricular contraction, namely paced QRS narrowing. Pacing modes presenting a wide QRS complex (VDD, RR-VVI, VVI), even in DDD mode, showed elevated BNP levels compared with other narrow QRS modes (RR-AAI and AAI). Plasma BNP levels were already elevated before exercise, and did not change significantly during exercise in the present study. Elevated resting BNP levels already reflected the limitations of physical activity and dyssynchronization of ventricular contraction. **Clinical implications and limitations of the present study:** The present study did not analyze the rate of contribution of paced heart beats in daily activity because of the difficulty with its evaluation. The rate of paced heart beats in daily activity
would significantly influence the levels of plasma neurohormonal factors. The present study did not analyze cardiac function, however patients with underlying organic heart diseases such as dilated cardiomyopathy, hypertrophic cardiomyopathy, previous myocardial infarction, valvular heart disease or atrial fibrillation were excluded to minimize the influence on plasma natriuretic levels. In spite of these limitations, the evaluation of plasma concentrations of ANP, BNP and catecholamines significantly reflected daily physical activity.

We believe that pacemaker therapy should satisfy not only cardiodynamic conditions but also neurohormonal conditions such as adequate levels of plasma ANP and BNP concentrations, which suggest the third condition for physiological pacing; synchronization of ventricular contraction, as well as the two previous conditions for physiological pacing; atrioventricular synchrony and rate-responsiveness.

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