Diagnostic Value of Plasma Levels of Brain Natriuretic Peptide in Arrhythmogenic Right Ventricular Dysplasia

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Background—Arrhythmogenic right ventricular dysplasia (ARVD) is characterized by local or diffuse wall motion abnormalities in the right ventricle (RV), associated with recurrent ventricular tachycardia (VT) of VT origin. Brain natriuretic peptide (BNP) was first isolated from a porcine brain extract. In humans, BNP is expressed predominantly in the ventricles of failing hearts, and its expression has been observed primarily in myocytes in the interstitial fibrous area in dilated cardiomyopathy. We hypothesized that BNP is increasingly secreted from the residual myocytes within the atrophic tissue in patients with ARVD.

Methods and Results—Plasma BNP levels were measured in 17 patients with ARVD, 12 patients with idiopathic RV outflow tract tachycardia (RVOT), and 120 control subjects. We performed cardiac catheterization, RV endomyocardial biopsy, electron-beam CT, and biventricular endomyocardial mapping in the ARVD patients. There was a significant increase in plasma BNP levels in the ARVD patients compared with the RVOT patients and control subjects (61.4 ± 59.6 pg/mL versus 8.3 ± 5.5 pg/mL and 9.3 ± 5.8 pg/mL; P < 0.0001, respectively). The plasma BNP levels had no correlation with any of the hemodynamic data, but they had a significant correlation with the RV ejection fraction (r = -0.588, P = 0.025) and with the fractionated-area scores (r = 0.705, P = 0.005). Light microscopic immunohistochemistry showed strong BNP immunoreactivity in residual myocytes with fibrofatty replacement.

Conclusions—These results suggest that plasma BNP levels were not increased in RVOT patients but were increased in ARVD patients, and that the increased BNP levels indicate the severity of both the RV dysfunction and the arrhythmogenic substrate. (Circulation. 1998;98:2433-2440.)

Key Words: tachyarrhythmias ▪ cardiomyopathy ▪ brain natriuretic peptide ▪ electrophysiology
TABLE 1. Clinical Characteristics of the 17 ARVD Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y/sex</th>
<th>FH</th>
<th>Twelve-Lead ECG</th>
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<tr>
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<td></td>
<td>QRS Width, ms</td>
<td>Sinus Rhythm</td>
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<td></td>
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<tr>
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<tr>
<td>17</td>
<td>57/M</td>
<td></td>
<td>220</td>
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</table>

Late potential was present, as shown by signal-averaged ECG, in all patients. Fractionated electrograms in all patients through electrophysiological study. FH indicates family history of premature sudden death (<35 y) due to suspected right ventricular dysplasia; Clinical VT, clinically recorded ventricular tachycardia; BBB; bundle-branch block; LB, left bundle-branch block; Inf, inferior; Sup, superior; S, sustained, NS, nonsustained; Echo, echocardiogram; EBCT, electron-beam CT; MG, mild global dilatation; LA, localized aneurysms; SS, severe global dilatation; LA, LA, SS, MG, 2 2 2; RB, regional hypokineses; ND, not done; Int Fib, interstitial fibrosis; Fat Rep, fatty replacement; 0, none; 1, mild; 2, moderate; and 3, severe.

ARVD and RVOT patients underwent several tests including a physical examination, laboratory tests, chest X-ray, 12-lead ECG, signal-averaged ECG, echocardiography, electron-beam CT, MRI, and an electrophysiological study including catheter mapping. Cardiac catheterization including RV endomyocardial biopsy was performed in all 17 ARVD patients and 2 RVOT patients. In all patients and control subjects, before blood sampling, the heart rate and blood pressure were measured in the morning (8 to 9 AM) after they had fasted overnight and rested supine for 30 minutes. The blood was immediately transferred into a chilled glass tube containing aprotinin (500 U/mL) for the measurement of plasma BNP.

**ARVD Group**
This group consisted of 15 men and 2 women with ARVD (mean age, 47±11 years; range, 18 to 59 years). All 17 ARVD patients were class I according to the New York Heart Association functional classification. The diagnosis of ARVD was established on the basis of the criteria proposed by the ARVD task force of the European Society of Cardiology. According to the criteria, 7 patients (patients 2, 4, 7, 8, 9, 11, and 17) met 2 major criteria, 8 patients (patients 1, 5, 6, 12, 13, 14, 15, and 16) met one major plus 2 minor criteria, and the remaining 2 patients (patients 3 and 10) met 4 minor criteria. The characteristics of the patients with ARVD are shown in Table 1. Among these patients, 6 had been taking β-blockers alone (n=2), or in combination with class I antiarrhythmic agents (n=4). Three patients were taking both class I and III antiarrhythmic agents, and one was receiving both diuretic and an angiotensin-converting enzyme inhibitor. The remaining 7 patients had not been taking any drugs. No drugs were administered on the morning the blood sampling was performed.

**RVOT Group**
This group consisted of 6 men and 6 women (mean age, 35±13 years; range, 19 to 54 years) who had monomorphic VT with a left bundle-branch block configuration and inferior axis. The 12 RVOT patients were not consecutive cases, but they were all patients who underwent blood sampling as an RVOT patient between January 1996 and December 1997. All of their VTs originated from the RV outflow tract and the VTs were sustained or nonsustained. The findings of all diagnostic tests including 12-lead ECG, signal-averaged ECG, echocardiography, and electron-beam CT were normal; no fractionated electrograms were recorded. One of the 6 RVOT patients who underwent an MRI study had mild segmental dilatation of the RV outflow tract. The β-blockers being taken by 3 of the RVOT patients were not administered in the morning before the blood sampling. The other patients were not taking any medications.

**Control Group**
This group consisted of 120 healthy volunteers, 80 men and 40 women (mean age±SD, 49±11 years; range, 21 to 71 years). There was no history of VT in this group. None of the control subjects were taking any medications.

**Assays of Plasma BNP**
The plasma BNP levels were measured with a highly sensitive immunoradiometric assay (Shiono RIA BNP assay kit, Shionogi Co), as previously reported. This assay system uses 2 monoclonal...
antibodies against human BNP-32, one recognizing a carboxy-terminal sequence and the other the ring structure of human BNP; the assay measures human BNP by sandwiching it between the 2 antibodies without the extraction of plasma. The minimal detectable quantity of human BNP in the assay is 2 pg/mL. Coefficients of variation of the intra-assay, interassay, and repeated measurements were 5.3%, 5.9%, and 5.2%, respectively. The recovery rate of 10 to 300 pg/mL of human BNP added to plasma was 103.7±5.4%. The correlation between the plasma level of human BNP measured by this method and that by the extraction method was highly significant, in the range of 0 to 1500 pg/mL (r=0.98; P<0.001).

Cardiac Catheterization

With the use of a Swan-Ganz catheter inserted into the femoral vein, hemodynamic measurements including pulmonary arterial pressure, pulmonary capillary wedge pressure, RV pressure, right atrial pressure, and cardiac output were measured. Cardiac output was determined by the thermodilution technique. A pigtail catheter was inserted into the femoral artery and advanced to the left ventricle (LV) to measure the LV pressure.

Electron-Beam CT

Electron-beam CT was performed in all of the ARVD patients with a C-100 scanner (Imatron), as described previously. Volume-mode scanning (scanning time, 100 ms for 512 matrix images) was performed in all of the patients after the administration of nonionic contrast medium (Iopamidol 370, Nippon Schering). Eight levels (covering 8 cm) near the short-axis cine-mode scans (10 contiguous images per level) were obtained to examine the function of both the RV and LV. We used a modified version of Simpson’s method to obtain these multisection cine-mode scans; we then calculated the biventricular end-diastolic and end-systolic volume indexes and the biventricular ejection fraction.

Electrophysiological Study

A 6F or 7F quadripolar diagnostic pacing and sensing catheter (EP Technologies) was introduced through the femoral vein and artery and advanced into the RV and LV under fluoroscopic guidance to record the local electrograms. The 12 sites of each ventricle were the segmental areas assessed.

Electrophysiological Study

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Histological Evaluation

RV endomyocardial biopsy specimens were obtained from the RV septum in 15 ARVD patients and 2 RVOT patients at cardiac catheterization. The specimens were fixed in 10% formalin and embedded in paraffin for hematoxylin-eosin staining. The severity of the histopathological findings was classified into 4 grades; none=0, mild=1, moderate=2, and severe=3, as previously described. The findings of interstitial fibrosis and fatty replacement were divided by the point-counting method in which 375 (25×15) points in 2 or 3 fields were observed at a magnification of ×200. The gradings of interstitial fibrosis were then determined as follows: none, <10%; mild, <10% to 30%; moderate, <30% to 50%; and severe, >50%, and those of fatty replacement as follows: none, <2%; mild, <2% to 10%; moderate, <10% to 30%; and severe, >30%.

Light Microscopic Immunohistochemistry

The 2 monoclonal antibodies against human BNP-32 which constitute the radiimmunounassay system used in this study were prepared. These monoclonal antibodies belong to the IgG1 subclass. Immunohistochemical reactions using an indirect immunoperoxidase method were obtained as described previously. Serial 4-μm-thick sections of paraffin-embedded specimens were dewaxed and immunostained with the streptavidin-biotin method using a DAKO LSAB, according to the manufacturer’s instruction, as reported previously. Briefly, the first step involved the inhibition of intrinsic peroxidase activity by the addition of 0.3% hydrogen peroxidase in phosphate-buffered saline. Nonspecific binding was blocked with normal goat serum. As a primary antibody, the monoclonal antibody described above was incubated with the sections for 48 hours at 4°C. Diaminobenzidine (Sigma Chemical Co) was used as the chromogen. The presence of immunoreactive BNP was assessed by light microscopy.

Statistical Analysis

Data are expressed as the mean±SD. Comparisons between groups were performed by 1-way ANOVA. The significance of differences

Figure 1. Schema of mapping sites in both ventricles. The 12 sites of each ventricle were the segmental areas assessed.

Figure 2. Recordings from a patient with ARVD. From the top are surface ECG leads I, aVF, and V3 and intracardiac recordings from the RV areas 7 (RV 7) and 10 (RV 10). The electrogram at RV 7 is markedly fractionated.
between the mean values in the control group, RVOT group, and ARVD group was tested with Fisher’s multiple comparison test. The correlation coefficients between plasma BNP levels and hemodynamic and volumetric data were calculated by linear regression analysis. Spearman’s rank correlation test was used to evaluate the correlation coefficients between the plasma BNP levels and the fractionated-area scores. A P value <0.05 was regarded as significant.

Results

Plasma BNP Levels in ARVD and RVOT Patients and Control Subjects

There were no significant differences in the plasma BNP levels between the RVOT patients (8.3±5.5 pg/mL; range, 4 to 19 pg/mL) and control subjects (9.3±5.8 pg/mL; range, 2 to 28 pg/mL), whereas there was a significant increase in plasma BNP levels in the ARVD patients (61.4±59.6 pg/mL; range, 15 to 200 pg/mL) (Figure 3). The plasma BNP levels of all but 3 of the 17 ARVD patients were ≥20 pg/mL, whereas those of all 12 RVOT patients were <20 pg/mL. In addition, the plasma BNP levels of 12 of the 17 ARVD patients were ≥25 pg/mL (71% sensitivity), whereas those of all but one of the 120 control subjects were <25 pg/mL (99% specificity).

Hemodynamic Parameters and Plasma BNP Levels in ARVD

Hemodynamic data of the 17 ARVD patients were obtained from cardiac catheterization. Table 2 shows the correlations between the hemodynamic parameters and the plasma BNP levels. The mean values of the pressure data were all normal. The mean value of the cardiac index was also normal. The plasma BNP levels had no correlation with any of the hemodynamic parameters.

Volumetric Parameters and Plasma BNP Levels in ARVD

Volumetric data of the 17 ARVD patients were obtained by electron-beam CT. Table 3 shows the correlations between the volumetric parameters and the plasma BNP levels. The mean values of the LV end-diastolic and end-systolic volume indexes and the LV ejection fraction were normal. The plasma BNP levels had no significant correlation with the LV volumetric parameters. In contrast, the mean RV values (RV end-diastolic and end-systolic volume indexes) and the RV ejection fraction were abnormal. An increased RV end-diastolic volume index (≥90 mL/m²) and an increased end-systolic volume index (≥40 mL/m²) were recognized in 13 and all 17 ARVD patients, respectively, and a decreased RV ejection fraction (≤45%) was found in 16 ARVD patients. The plasma BNP levels had no significant correlation with the RV end-diastolic or end-systolic volume indexes. However, there was a significant negative correlation between the plasma BNP levels and the RV ejection fraction (Figure 4).

Fractionated-Area Scores and Plasma BNP Levels in ARVD

The fractionated-area scores of the 17 ARVD patients were obtained by sinus mapping (range, 1 to 5 areas; mean±SD, 2.8±1.2). All of the ARVD patients had fractionated electrograms in the RV. In 2 of the ARVD patients (patients 8 and 10), fractionated electrograms were also obtained from the LV. The most frequently affected site was the inferior wall of the RV inflow tract (RV area 6); in 12 of the 17 patients, fractionated electrograms were also obtained from the LV. The most frequently affected site was the inferior wall of the

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**Figure 3.** Plasma BNP levels in the 120 control subjects, 12 patients with RVOT, and 17 patients with ARVD.

**Table 2.** Correlations Between Hemodynamic Parameters and Plasma BNP Levels in Patients With ARVD

<table>
<thead>
<tr>
<th>Hemodynamic parameter</th>
<th>Mean±SD</th>
<th>r</th>
<th>P</th>
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</thead>
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<tr>
<td>Mean PCWP, mm Hg</td>
<td>6.7±3.0</td>
<td>−0.029</td>
<td>0.923</td>
</tr>
<tr>
<td>Mean RAP, mm Hg</td>
<td>4.4±2.9</td>
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<tr>
<td>Mean PAP, mm Hg</td>
<td>13.0±3.1</td>
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</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>10.5±4.8</td>
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<td>0.939</td>
</tr>
<tr>
<td>RVEDP, mm Hg</td>
<td>7.5±4.4</td>
<td>0.070</td>
<td>0.817</td>
</tr>
<tr>
<td>Cardiac Index, L·min⁻¹·m⁻²</td>
<td>2.9±0.6</td>
<td>−0.428</td>
<td>0.129</td>
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</table>

PCWP indicates pulmonary capillary wedge pressure; RAP, right atrial pressure; PAP, pulmonary artery pressure; LVEDP, left ventricular end-diastolic pressure; and RVEDP, right ventricular end-diastolic pressure.

**Table 3.** Correlations Between the Volumetric Parameters and Plasma BNP Levels in Patients With ARVD

<table>
<thead>
<tr>
<th>Volumetric parameter</th>
<th>Mean±SD</th>
<th>r</th>
<th>P</th>
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<tr>
<td>LVEDVI, mL/m²</td>
<td>68.4±14.1</td>
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<td>LVESVI, mL/m²</td>
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<td>LVEF, %</td>
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<td>RVEF, %</td>
<td>28.5±10.5</td>
<td>−0.588</td>
<td>0.025</td>
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</table>

LVEDVI indicates left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; RVEDVI, right ventricular end-diastolic volume index; RVESVI, right ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; and RVEF, right ventricular ejection fraction.
RV outflow tract (RV area 12) including the anterior infundibulum. Only one had such an electrogram at the RV apex (RV area 8). The plasma BNP levels had a significant positive correlation with the fractionated-area scores in the patients with ARVD (Figure 5).

Light Microscopic Examination and Immunohistochemical Expression of BNP

In the light microscopic examination, varying degrees of interstitial fibrosis and fatty replacement were found in 13 of the 15 ARVD patients on whom this study was performed (Table 1). However, no abnormal findings were observed in the 2 RVOT patients who underwent RV biopsy. No obvious inflammatory infiltration was detected in any specimens.

In the immunohistochemical study of the endomyocardial biopsy specimens, none of the control specimens obtained from the RVOT patients showed BNP immunoreactivity (Figure 6A and 6B). In contrast, BNP immunoreactivity was found in all of the ARVD patients, showing a fine granular pattern in residual myocytes with fibrofatty replacement. The immunoreactivity was similar between the 2 monoclonal antibodies. No immunopositive products were seen in the endocardium or in any of the connective or adipose tissues. In the 2 ARVD patients whose biopsy specimens showed no apparent fibrofatty replacement, BNP immunoreactivity was relatively weak (Figure 6C and 6D), whereas strong BNP immunoreactivity was found in the other ARVD patients whose biopsy specimens showed fibrofatty replacement (Figure 6E and 6F).

Discussion

Diagnostic Tools in the Discrimination Between ARVD and RVOT

The electrocardiographic diagnosis of ARVD is difficult in the initial stage of the disease.4 During sinus rhythm, 5 of 17 the present ARVD patients had almost normal findings in a 12-lead ECG. Although echocardiography is considered the most convenient noninvasive tool for detecting diffuse or localized abnormalities of the RV, it has several limitations.17 MRI is useful for the diagnosis of ARVD.18 However, mild wall motion and structural abnormalities have been detected by MRI even in patients with RVOT.19 A signal-averaged ECG has demonstrated high sensitivity and specificity in previous studies.17,20 In the present study, a late potential was found in all 17 of the ARVD patients but not in any of the 12 RVOT patients. However, the relation between signal-averaged ECG variables and RV function has not been established. The plasma BNP levels were found to be a specific and sensitive indicator for the distinction of patients with ARVD from those with RVOT. Compared with these conventional diagnostic methods, the measurement of the plasma BNP level is also useful as a simple, noninvasive, and reliable tool for the discrimination between ARVD and RVOT. In addition, the plasma BNP levels had a significant correlation with the RV ejection fraction and the fractionated-area scores.

Clinical Significance of Plasma BNP Levels in ARVD

In previous clinical studies, the plasma BNP levels demonstrated a significant correlation with the LV end-diastolic pressure, cardiac index, and end-diastolic and end-systolic volume indexes of the LV in patients with dilated or hypertrophic cardiomyopathy.7,15 In the present study, the plasma BNP levels had no significant relationship with those parameters related to the RV as well as the LV. These results may be responsible for the absence of biventricular heart failure in the present ARVD patients. However, the plasma BNP levels were particularly increased in proportion to the deterioration of the RV ejection fraction. Nagaya et al21 recently reported that the plasma BNP levels were significantly correlated with the RV ejection fraction but not with the RV end-diastolic volume index in patients with primary or thromboembolic pulmonary hypertension or atrial septal defects, which is consistent with the present results.
Figure 6. Light microscopic findings in hematoxylin-eosin staining (A, C, E) and light microscopic BNP immunoreactivity (B, D, F), using a monoclonal antibody which recognizes a ring structure of human BNP-32 in the RV endomyocardial biopsy specimen. A and B, C and D, and E and F are consecutive sections obtained from an RVOT patient (A, B) and patients 1 (C, D) and 4 (E, F) with ARVD. Note that the finely granular dark brown immunoreaction products indicating BNP (arrows) are scattered in the cytoplasm (D, F). In the RVOT patient whose plasma BNP level was 8.0 pg/mL, no fibrofatty replacement is seen (A) and no immunoreactivity of BNP is found (B). In patient 1, whose plasma BNP level was 16.0 pg/mL, no fibrofatty replacement is found (C), and the immunoreactivity of BNP is relatively weak (D). In patient 4, whose plasma BNP level was 63.0 pg/mL, moderate fibrofatty replacement is found (E), and strong BNP immunoreactivity can be seen (F). Original magnification ×66. Scale bar=50 μm.
during sinus rhythm are considered a substrate of reentrant VT in patients with organic heart disease. Tada et al recently reported that the endocardial fat-infiltrated areas detected by electron-beam CT tended to encompass the fractionated areas demonstrated by the endocardial mapping in patients with ARVD. In the present study, we found several grades of electrophysiologically abnormal areas in which fractionated abnormal electrograms were recorded. Thus, plasma BNP levels might be increased in proportion to the expansion of electrophysiological disorder based on the histopathological abnormalities. The plasma BNP levels in the ARVD patients showed values in a significantly wide range (from 15 to 200 pg/mL), suggesting that the present study included ARVD patients at several stages of the disease; ie, from the early clinically concealed phase to overt electrical heart disorder with severe RV dysfunction.

**Ventricular Expression of BNP in ARVD**

The specimens of endomyocardial biopsy are usually obtained from the right or left side of the interventricular septum, which is unlikely to be an affected region in ARVD. Therefore, an endomyocardial biopsy specimen may be unlikely to demonstrate evidence of the synthesis of BNP. However, the positive finding of fibrofatty replacement of myocytes on biopsy can be a valuable diagnostic indicator. Strong BNP immunoreactivity was found in the present RV endomyocardial biopsy specimens showing fibrofatty replacement, whereas its immunoreactivity was relatively weak in the tissue not indicating fibrofatty replacement. In addition, the present finding that BNP-positive myocytes were always present in the specimens obtained from the interventricular septum of ARVD patients suggests that BNP may be produced from the relatively wide region including atrophic area in the RV. The exact relationship between BNP secretion and the grading of atrophy in the most affected site of the RV free wall remains unclear. It was also reported that BNP-positive myocytes are noted in the chronic myocarditis. In addition, inflammation is thought to be one of the main pathological findings in ARVD. In the present ARVD patients, although obvious inflammatory infiltrates could not be found, it may be responsible for our endomyocardial biopsy specimens obtained from the right side of the interventricular septum which is rarely involved in ARVD. Further histopathological investigations, eg, using surgically resected specimens and necropsy specimens is needed to identify the genesis of BNP in patients with ARVD.

**Mechanisms of the Synthesis and Secretion of BNP in ARVD**

Although the etiology and pathogenesis of ARVD are still obscure, two possible mechanisms are considered for the synthesis and secretion of BNP in ARVD. One is local wall stress on myocytes around the atrophic area. Because the fibrofatty area may be relatively resistant to contraction, residual myocytes around this area may undergo more stretching. Such regional mechanical stress may stimulate the synthesis and secretion of BNP. However, the mean values of plasma BNP in the present patients with ARVD (mean values, 61.4 pg/mL) are much less than those in patients with RV hypertrophy due to pulmonary artery hypertension (mean values, 250 pg/mL). The differences of plasma BNP levels between the two groups may be due to the grading of wall stress; ie, regional wall stress in ARVD versus generalized wall stress in pulmonary artery hypertension. The other possible explanation concerns the effect of the vasoactive substances and growth factors which are synthesized and secreted by the fibroblasts, adipocytes, and vascular endothelial cells. The synthesis and secretion of BNP are also stimulated by endothelin-I and angiotensin II in vivo and in vitro. Under these circumstances, BNP may be secreted increasingly from the residual myocytes in the atrophic tissue with fibrofatty replacement.

**Study Limitations**

ARVD is often familial (about 30%), with an autosomal dominant inheritance. Rampazzo et al recently reported that a gene defect was localized on chromosome 14q23-q24. Because we could not perform a linkage analysis, the diagnosis for ARVD was defined according to the diagnostic criteria by the ARVD task force of the European Society of Cardiology. Further studies using genetic diagnosis with ARVD patient series that are more homogenous are needed to determine the true diagnostic value of the plasma BNP level in ARVD.

The medical treatments differed among the 3 groups. Although all medications were stopped on the day of the blood sampling, their influences cannot be completely excluded. Because the effects of drugs, including antiarrhythmic agents, on BNP in humans have not been reported, further studies are necessary.

**Acknowledgments**

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