Plasma B-type natriuretic peptide levels reflect the presence and severity of stable coronary artery disease in chronic haemodialysis patients

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Abstract

Background. Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality in haemodialysis (HD) patients. Although the plasma B-type natriuretic peptide (BNP) levels may be a strong marker of long-term mortality in HD patients, what plasma BNP levels reflect is not well known in this setting. Therefore, we examined the relationship between plasma BNP levels and the presence and severity of stable CAD based on coronary angiography (CAG) in chronic HD patients.

Methods. Plasma BNP levels were measured in 179 consecutive HD patients who were referred for CAG due to symptoms or objective signs of stable CAD. Left ventricular end-diastolic wall stress (LV EDWS) was also calculated as a crucial haemodynamic determinant of plasma BNP.

Results. Plasma BNP levels were significantly higher in patients with CAD than in those with non-CAD. The area under the receiver operating characteristic curve for BNP to predict CAD was 0.837. Plasma BNP levels increased progressively with the extent of CAD [1-vessel disease (VD), 496 ± 49 pg/ml; 2-VD, 932 ± 119 pg/ml; 3-VD, 2073 ± 317 pg/ml; P < 0.01]. LV EDWS was well correlated with plasma BNP levels (r = 0.61, P < 0.01), and a multivariable regression analysis that took into account EDWS demonstrated a significant association between the extent of CAD and BNP (P < 0.01).

Conclusions. These results suggest that the presence and severity of stable CAD determine plasma BNP levels in chronic HD patients. Plasma BNP levels may be a useful marker in the management of HD patients.

Keywords: BNP; coronary artery disease; haemodialysis; left ventricular diastolic wall stress

Introduction

The high mortality rate in end-stage renal disease (ESRD), particularly in patients on dialysis, has been well documented by several investigators [1,2]. Cardiovascular diseases account for >50% of ESRD deaths, and the cardiovascular death rates in patients who are receiving dialysis are substantially higher than those in the general population [3]. Coronary artery disease (CAD) is one of the leading causes of death among cardiovascular diseases [4,5]. Therefore, the screening or early diagnosis and aggressive management of CAD are required in long-term dialysis patients.

B-type natriuretic peptide (BNP) is synthesized in the ventricular myocardium in response to ventricular stretching and wall stress (WS) [6,7]. BNP as well as NT-proBNP is widely used as a marker for various cardiovascular diseases. In heart failure, they are used for diagnosis, risk stratification or prognosis and treatment monitoring. In the setting of acute coronary syndrome (ACS), BNP/NT-proBNP has also been reported to be an extremely powerful prognostic indicator [8]. Hypoxia, independent of stretching, might also stimulate peptide release [9,10]. Recently, BNP/NT-proBNP has also been shown to be useful in stable CAD patients. Bibbins-Domingo et al. reported that elevated plasma BNP levels are independently associated with inducible ischaemia in patients with stable CAD [11] and that they predict cardiovascular morbidity and mortality, independent of other prognostic markers, in the same population [12]. Weber et al. demonstrated that NT-proBNP is closely correlated with disease severity in patients with stable CAD [13]. However, their utility and validity in patients with ESRD is not yet established, since their levels are recognized to be strikingly elevated and variable even in most asymptomatic patients with ESRD [14,15]. Recently, the prognostic potential of plasma BNP levels has been investigated in several studies on patients with chronic kidney disease (CKD), haemodialysis (HD) and peritoneal dialysis [16–18]. However, in this setting, it is not yet.
clear what plasma BNP levels reflect and whether previous observations in patients without CKD could be applied to ESRD patients.

Accordingly, we tested the hypothesis that plasma BNP levels might reflect the presence and severity of stable CAD in chronic HD patients. We also examined left ventricular end-diastolic wall stress (LV EDWS), which we previously found is a crucial hemodynamic determinant of plasma BNP levels [7], to clarify the contribution of hemodynamic factors in the regulation of plasma BNP in this setting.

Subjects and methods

Study patients

One hundred seventy-nine chronic HD patients who had been referred for CAG due to symptoms of angina pectoris, or with objective evidence of ischemia (positive exercise electrocardiogram or nuclear test), were enrolled in the present study. Patients with ACS including unstable angina and acute myocardial infarction were excluded from this study. All patients underwent regular 4-h sessions of HD using polysulfone membrane filters three times weekly. After dialysis, they were shown to have a condition that entailed no clinical signs of hypervolemia such as oedema, dyspnea or an excessive increase in arterial blood pressure, which was established under the supervision of experienced nephrologists.

Plasma BNP levels, haemoglobin, serum albumin, serum C-reactive protein (CRP) and serum creatinine were determined in blood samples withdrawn immediately before coronary angiography (CAG). Echocardiographic examination was performed after an HD session on the day before CAG.

CAG and lesion morphology

CAG was performed following a standard technique. Two experienced cardiologists who were blinded to plasma BNP levels assessed the coronary angiograms. If they disagreed, a third expert examined the angiogram to determine the characteristics of the lesions. Diameter stenosis of ≥70% by quantitative angiography was accepted as significant. Extension of CAD was classified as 1-, 2- or 3-vessel disease (VD) by the standard method. We also estimated the degree of CAD using the Gensini score and the CAD prognostic index. The former is a measure of the extent and severity of CAD using the Gensini score and the CAD prognostic index. The latter considers the number of diseased vessels, the presence of left anterior descending or left main coronary disease, which have been validated in an overlapping heart failure population [20,21]. Left ventricular pressure was recorded with a 5-F pigtail catheter connected to a fluid-filled transducer. Left ventricular volume and ejection fraction (EF) were determined by left ventriculography with a contrast medium using Kennedy’s formula.

Echocardiography

Echocardiographic examinations were performed in all patients with a Sonos 5500 machine equipped with a 2.5 MHz probe. M-mode images were obtained to measure left atrial and ventricular dimensions [22]. The left ventricular mass index (LVMI) was estimated using the formula of Devereux et al. In patients with sinus rhythm, the pulsed Doppler mitral valve flow velocity was recorded to measure the ratio of peak mitral E-wave velocity to peak mitral A-wave velocity (E/A ratio) and the deceleration time of the mitral E-wave velocity. Based on hemodynamic and echocardiographic data, end-diastolic and systolic meridional WS were calculated as follows: \( WS = 0.334 \times \frac{P(LVID)}{WT(1 + WT/LVID)} \), where \( P = LV \) pressure (i.e. peak systolic pressure or end-diastolic pressure (EDP), which was obtained during cardiac catheterization), \( LVID = \) left ventricular internal dimension and \( WT = \) wall thickness [7].

Statistical analysis

Groups were compared using a chi-square analysis for proportions and unpaired Student \( t \) tests for continuous variables. Cut-off levels of BNP and the sensitivities and specificities of the cut-off levels were calculated using a receiver operating characteristics (ROC) curve analysis. The linearity of a relationship between two variables was assessed by linear regression analysis. Further multivariable analysis was performed to evaluate the independent relationship between severity of CAD (VD, Gensini score or CAD prognostic index) and plasma BNP levels in concert with demographic variables, hemodynamic indexes and laboratory data using JMP version 5.0. Variables included in the analysis were sex, age, BMI (body mass index), NYHA (New York Heart Association) class, HT (hypertension), DM (diabetes mellitus), HLP (hyperlipidaemia), AF (atrial fibrillation), HD etiology and duration, medications, hemodynamic and echocardiographic indexes and laboratory data (creatinine, CRP, albumin and haemoglobin); \( P < 0.05 \) was considered significant. Results were expressed as mean ± SEM.

Results

Patient characteristics

The baseline clinical characteristics in chronic HD patients according to the presence and extent of CAD are shown in Tables 1 and 2, respectively. In all of the studied patients, the mean age was 67.6 ± 0.7 years and 13% of the patients were female. Patients with CAD were more likely to have a history of DM and HLP. There were no significant differences in other past history, duration of HD, etiology, medications or haemoglobin and creatinine levels between CAD and non-CAD or among the three CAD-extension groups. Patients with CAD showed a higher CRP level than those with non-CAD, but there was no difference among the three CAD-extension groups. Patients with 1-VD had a higher serum albumin level than with 2-VD or 3-VD. Patients who showed NYHA functional class ≥2 were more prevalent in those with multivessel disease or CAD.
Geometric and functional parameters obtained by echocardiography or cardiac catheterization are shown in Table 3. In all of the studied patients, mean EF was 45.5 ± 1.1% and mean LVI, LV end-diastolic volume index (LVEDVI) and LV EDWS were 163.5 ± 4.3 g/m², 84.4 ± 3.0 ml/m² and 35.5 ± 2.0 kdynes/cm², respectively.

### Table 3. Echocardiographic and haemodynamic parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Non-CAD</th>
<th>1-VD</th>
<th>2-VD</th>
<th>3-VD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD (mm)</td>
<td>48.9 ± 1.0</td>
<td>51.6 ± 1.2</td>
<td>52.7 ± 1.3</td>
<td>54.6 ± 1.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PWT (mm)</td>
<td>11.3 ± 0.3</td>
<td>10.3 ± 0.3</td>
<td>11.2 ± 0.3</td>
<td>10.3 ± 0.3</td>
<td>0.01</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>42.3 ± 0.8</td>
<td>43.8 ± 1.0</td>
<td>43.0 ± 1.6</td>
<td>42.7 ± 1.1</td>
<td>0.79</td>
</tr>
<tr>
<td>E/A</td>
<td>0.80 ± 0.05</td>
<td>0.98 ± 0.12</td>
<td>0.83 ± 0.07</td>
<td>0.93 ± 0.09</td>
<td>0.44</td>
</tr>
<tr>
<td>DCT (msec)</td>
<td>249 ± 9</td>
<td>219 ± 11</td>
<td>226 ± 12</td>
<td>203 ± 10</td>
<td>0.03</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>152 ± 10</td>
<td>157 ± 6</td>
<td>183 ± 10</td>
<td>167 ± 7</td>
<td>0.02</td>
</tr>
<tr>
<td>EF (%)</td>
<td>52.7 ± 1.6</td>
<td>45.8 ± 2.2</td>
<td>44.0 ± 2.6</td>
<td>40.1 ± 1.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVEDVI (ml/m²)</td>
<td>73.5 ± 4.1</td>
<td>88.0 ± 5.8</td>
<td>85.0 ± 7.4</td>
<td>90.8 ± 6.5</td>
<td>0.18</td>
</tr>
<tr>
<td>LVSP (mmHg)</td>
<td>147 ± 3</td>
<td>145 ± 4</td>
<td>146 ± 4</td>
<td>140 ± 4</td>
<td>0.52</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>12.4 ± 0.6</td>
<td>13.7 ± 1.0</td>
<td>14.7 ± 1.1</td>
<td>18.4 ± 0.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>EDWS (kdynes/cm²)</td>
<td>23.8 ± 1.6</td>
<td>34.0 ± 5.1</td>
<td>32.5 ± 3.1</td>
<td>48.7 ± 3.8</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

DCT = deceleration time of early diastolic filling; EDWS = end-diastolic wall stress; EF = ejection fraction; E/A = ratio of peak mitral E-wave velocity to peak mitral A-wave velocity; LAD = left atrial dimension; LVEDD = left ventricular end-diastolic dimension; LVEDP = left ventricular end-diastolic pressure; LVEDVI = left ventricular end-diastolic volume index; LVMI = left ventricular mass index; LVSP = left ventricular peak systolic pressure; PWT = posterior wall thickness.

Values are mean ± SEM.

### Cut-off level for detecting CAD

Fifty-one patients who underwent CAG had no significant coronary stenotic lesions. Plasma BNP levels were significantly higher in patients with CAD than in those with non-

### Table 2. Patient characteristics [2]

<table>
<thead>
<tr>
<th>Category</th>
<th>Non-CAD</th>
<th>1-VD</th>
<th>2-VD</th>
<th>3-VD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>44</td>
<td>33</td>
<td>51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>67.7 ± 1.2</td>
<td>68.1 ± 1.8</td>
<td>68.4 ± 1.2</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>2 (5%)</td>
<td>5 (15%)</td>
<td>8 (15%)</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.0 ± 0.4</td>
<td>21.3 ± 0.5</td>
<td>22.6 ± 0.10</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>HT</td>
<td>39 (89%)</td>
<td>33 (100%)</td>
<td>48 (96%)</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>20 (46%)</td>
<td>18 (56%)</td>
<td>34 (68%)</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>HLP</td>
<td>17 (39%)</td>
<td>16 (49%)</td>
<td>27 (53%)</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>AF</td>
<td>4 (9%)</td>
<td>2 (6%)</td>
<td>5 (10%)</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>OMI</td>
<td>12 (27%)</td>
<td>9 (27%)</td>
<td>17 (33%)</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>NYHA class ≥ 2</td>
<td>7 (16%)</td>
<td>2 (6%)</td>
<td>11 (22%)</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>HD duration (yrs)</td>
<td>9.9 ± 0.4</td>
<td>7.6 ± 1.4</td>
<td>6.2 ± 0.8</td>
<td>0.10</td>
<td></td>
</tr>
</tbody>
</table>
| Echocardiographic parameters

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BMI = body mass index; CABG = coronary artery bypass grafting; CGN = chronic glomerulonephritis; Cr = serum creatinine; CRP = C-reactive protein; DM = diabetes mellitus; HD = haemodialysis; HLP = hyperlipidaemia; HT = hypertension; NYHA = New York Heart Association; OMI = old myocardial infarction; PCKD = polycystic kidney disease. Values are mean ± SEM or number (%).

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CGN = chronic glomerulonephritis; Cr = serum creatinine; CRP = C-reactive protein; DM = diabetes mellitus; HD = haemodialysis; HLP = hyperlipidaemia; HT = hypertension; NYHA = New York Heart Association; OMI = old myocardial infarction; PCKD = polycystic kidney disease. Values are mean ± SEM or number (%).
Fig. 1. Receiver operating characteristic (ROC) curve for plasma BNP as a predictor of relevant coronary artery disease. AUC = area under the ROC curve.

Fig. 2. (A) Plasma BNP levels in relation to the number of coronary arteries with >70% diameter stenosis. The box defines the interquartile range with the median indicated by the crossbar. The error bars indicate the 10th and 90th percentiles. (B) Correlation between log plasma BNP level and log Gensini score.

CAD (1237 ± 144 and 285 ± 30 pg/ml, respectively; P < 0.01). The ROC curve for BNP as an indicator of the presence of CAD is shown in Figure 1. The area under the ROC curve was 0.837 (95% confidence interval 0.778–0.895).

The optimal value of BNP as an indicator of CAD was 366 pg/ml, with a sensitivity of 79%, a specificity of 73%, an accuracy of 77%, a positive predictive value of 88% and a negative predictive value of 58%.

**CAD extension and plasma BNP levels**

Of the 128 patients in the CAD groups, 44, 33 and 51 patients had 1-VD, 2-VD and 3-VD, respectively. As shown in Figure 2, plasma BNP levels increased progressively with the extent of CAD (1-VD, 496 ± 49 pg/ml; 2-VD, 932 ± 119 pg/ml; 3-VD, 2073 ± 317 pg/ml; P < 0.01). Furthermore, they correlated well with the Gensini score (r = 0.65, P < 0.01) or the CAD prognostic index (r = 0.60, P < 0.01). Thus, plasma BNP levels were directly correlated to the extent of CAD, and the difference between each category was highly significant.

**Haemodynamic parameters and plasma BNP levels**

In comparisons among the CAD groups, there were no significant differences in L VMI (P = 0.08), LV volume (P = 0.83) or EF (P = 0.15). However, higher LV EDWS and EDP were observed in the 3-VD group (P < 0.01), as shown in Table 3. Also, the non-CAD group showed lower LV volume and EDWS and higher EF than CAD group.

As demonstrated in Figure 3, LV EDWS and EF were well correlated with plasma BNP levels (r = 0.61 and 0.53, P < 0.01, respectively) and LVMI was significantly, but poorly, correlated (r = 0.27, P = 0.009). Furthermore, a multivariable regression analysis that took into account EDWS demonstrated a significant positive association between the Gensini score, the extent of CAD (the number of diseased vessels), or the CAD prognostic index and plasma BNP levels. In addition, EF was independently associated with plasma BNP level, whereas LVMI and NYHA ≥ 2 were unrelated to plasma BNP once the effects of the EDWS, Gensini score and EF were accounted for (Table 4). The fit (R-square) of the model including these variables was 0.53.

**Discussion**

CAD is one of the leading causes of morbidity and mortality in chronic HD patients. However, since most patients remain asymptomatic because of deconditioning, limited activity levels and the effects of long-standing DM, the early detection of CAD is difficult. Recently, Charytan et al. studied 67 asymptomatic HD patients who volunteered for CAG with a median follow-up of 2.7 years [23]. They showed that 41.7% of the patients had CAD and that the proximal CAD, multivessel disease or the CAD prognostic index >48 was associated with higher mortality. CAG is a definitive diagnostic tool, but it is invasive. It is essential to diagnose the presence and severity of CAD by non-invasive tests as early as possible in HD patients. In the present study, although the area under the ROC curve was <0.85, which makes a BNP test of limited clinical value for detecting CAD, the present result seems to be superior to other reports on patients with no CKD [13] or on those with CKD not requiring dialysis [24]. Also, the diagnostic utility
Table 4. Predictors for BNP levels in regression analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>β-coefficient</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA ≥ 2</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>LVMI</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>EF</td>
<td>-0.018</td>
<td>0.009</td>
</tr>
<tr>
<td>Log EDWS</td>
<td>0.694</td>
<td></td>
</tr>
<tr>
<td>Log Gensini score</td>
<td>0.012</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

NYHA = New York Heart Association; LVMI = left ventricular mass index; EF = ejection fraction; EDWS = end-diastolic wall stress.

Significant univariable predictors were included into the multivariable regression model as continuous and NYHA ≥ 2 as a binary variable.

of other non-invasive tests, including exercise ECG, dobutamine stress echocardiography and scintigraphy for patients with CKD, is reported to be less than that observed in those with no CKD [25]. Thus, the measurement of plasma BNP levels in combination with other non-invasive inves-tigations might help in assessing CAD involvement and aggressive management in this high-risk population.

Several recent studies have suggested that plasma BNP levels may have prognostic potential in chronic HD patients. Zoccali et al. demonstrated that BNP was an independent predictor of overall and cardiovascular mortality in HD patients [17]. Cataliotti et al. reported that BNP was significantly higher in dialysis patients who died of cardio-

vascular causes than in survivors [26]. Although LV mass and function have been considered to be important associated factors, ischaemia was not sufficiently considered in these reports. There have been few studies on the association between plasma BNP level and ischaemia itself in chronic HD patients. Although both Osajima et al. and Nishikimi et al. reported elevated plasma BNP levels in HD patients with CAD [27,28], the diagnostic evaluation of CAD does not seem to be sufficient and the sample number was relatively small. In the present study, we used CAG in all patients for a thorough evaluation of disease severity. The number of diseased coronary arteries, the Gensini score or the CAD prognostic index well correlated with the plasma BNP levels in our study population. Plasma BNP levels may achieve prognostic potential, at least in part, by reflecting the presence and severity of CAD in chronic HD patients. Recently, BNP/NT-proBNP has also been shown to be useful in stable CAD patients with normal renal function. Plasma BNP levels could predict the extent of angio-

graphic coronary artery stenosis and prognosis in patients with stable angina pectoris [13,29] as well as in those with ACS [30]. McClure et al. reported that, in patients with coronary ischaemia, removal of coronary stenosis by percu-
taneous coronary revascularization resulted in decrease of plasma NT-proBNP [31]. Although the pathophysiological mechanism behind the relation between CAD and elevated BNP levels is not well defined, Goetze et al. reported that tissue hypoxia alone could trigger release of BNP in the absence of LV dysfunction [10]. We recently demonstrated that LV EDWS is a crucial haemodynamic determinant of plasma BNP levels in patients with chronic heart failure [7]. Therefore, we measured LV EDWS and tried to clarify the independent role of chronic ischaemia on plasma BNP from haemodynamic load in the setting of CAD in HD pa-
tients. As a result, LV EDWS was associated with plasma BNP levels, but to a lesser extent than in patients with heart failure [7,32]. The extent of CAD (including the Gensini score or the CAD prognostic index) was correlated with plasma BNP levels independent of the haemodynamic load according to a multivariable analysis. Chronic ischaemia itself might contribute to the elevated BNP levels in the present setting.

Several limitations should be considered in interpreting our results. First, the study population was relatively small, especially in the non-CAD group. Any negative findings could thus be caused by a low statistical power. Second, only plasma BNP levels were considered in our study. Re-
cently, the measurement of NT-proBNP was increasingly used clinically because of its longer half-life and larger size. NT-proBNP might be more dependent on renal clearance than BNP [33]. However, most studies have demonstrated that both are equally useful, even in CKD and HD patients [34,35]. Third, echocardiography was typically performed...
the day before cardiac catheterization. This time lag could have influenced the results. Last, in the present study, a cohort of HD patients consisted of those who had been referred for CAG due to symptoms or objective evidence of ischaemia, and asymptomatic patients with lack of objective evidence of ischaemia were not included. Therefore, the applicability of our results to the screening for CAD in all HD patients might be limited.

The present study clearly showed that plasma BNP levels were closely correlated with disease severity as assessed by the number of stenotic coronary arteries, the Gensini score and CAD prognostic index in chronic HD patients with CAD. In addition, they had significantly higher plasma BNP levels than those with non-CAD. We also analyzed EDWS and showed that chronic ischaemia itself might contribute to the increased BNP levels in addition to the EDWS in this setting. Therefore, our data suggest that plasma BNP levels may be a useful marker in the diagnosis and follow-up of stable CAD in patients with chronic HD by reflecting both the haemodynamic load and the presence and severity of ischaemia.

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