Renal Dysfunction Is a Confounder for Plasma Natriuretic Peptides in Detecting Heart Dysfunction in Uremic and Idiopathic Dilated Cardiomyopathies

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Background: The diagnostic value of natriuretic peptides in uremic cardiomyopathy has not been defined, nor has the effect of a hemodialysis (HD) session on peptides.

Methods: We performed an observational study of 100 white adult outpatients in New York Heart Association class I–II, with neither diabetes nor ischemic heart disease, 50 of whom had idiopathic dilated cardiomyopathy (DCM) and 50 of whom had uremic cardiomyopathy and were undergoing HD. We measured plasma N-terminal proB-type natriuretic peptide (NT-proBNP), BNP, and atrial natriuretic peptide (ANP) both before and after a dialysis session. Doppler echocardiograms were evaluated. We performed multiple regression analysis on the logarithm of peptide concentrations using clinical, laboratory, and echocardiographic data as explanatory variables.

Results: Mean peptide concentrations were higher in the HD group, with an HD:DCM ratio of 25 for NT-proBNP and 5 for BNP and ANP. Peptides were correlated with each other (r > 0.85). After HD, NT-proBNP significantly increased by 14%, BNP decreased by 17%, and ANP decreased by 56%. Predialysis concentrations correlated with postdialysis values (r > 0.85). A multiple regression equation significantly fitted the observed peptide concentrations, both pre- and postdialysis, using the same set of 4 variables: disease group (DCM or HD), diastolic pattern, left atrial volume, and body mass index.

Conclusions: Renal dysfunction was a confounder for natriuretic peptides, which were present in higher concentrations in the uremic patients with milder cardiac dysfunction than in those with idiopathic DCM without renal dysfunction. Left diastolic function pattern and atrial volume were cardiac determinants of peptide concentrations in DCM and HD.

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The cardiac natriuretic peptides of clinical relevance include atrial natriuretic peptide (ANP),4 B-type natriuretic peptide (BNP), and the N-terminal fragment of proBNP (NT-proBNP). Circulating natriuretic peptide concentrations are greatly increased in patients with either acute or chronic heart failure, acute myocardial infarction, and renal failure (1, 2). Several articles have reported increased peptide concentrations in hemodialysis (HD) patients, possibly due to cardiac dysfunction, fluid overload, and decreased renal clearance of peptides (2, 3). The function and structure of atrial and ventricular chambers in uremic cardiomyopathy are sensitive to volume and pressure overload through a remodeling process characterized by an increase in myocardial fibrosis (4–7). Both myocyte disarray and fibrosis in uremic patients are...
similar to those observed in patients with idiopathic dilated cardiomyopathy (DCM) (8, 9).

In this study, we compared uremic HD patients with idiopathic DCM patients who showed more severe heart involvement and normal or slightly decreased renal function. We hypothesized that if natriuretic peptide concentrations depended on the severity of heart failure regardless of renal function, higher peptide concentrations should be found in the DCM group; moreover, we hypothesized that DCM patients with lower vs higher glomerular filtration rates (GFRs) have similar peptide concentrations.

**Materials and Methods**

This cross-sectional observational study enrolled 100 white, adult cardiomyopathy patients, made up of 2 groups of 50 individuals each: a dialysis group with uremic cardiomyopathy (36 men, 14 women) and a non-dialysis group with idiopathic DCM (31 men, 19 women). In accordance with the Declaration of Helsinki, the protocol was approved by the ethics committee of our institution, and written informed consent was obtained from all of the participants. Uremic outpatients undergoing thrice-weekly, standard bicarbonate dialysis with low-flux dialyzers for 6 months or longer, with uremic cardiomyopathy (defined as an abnormality of echocardiographic parameters with systolic or diastolic dysfunction in the absence of other cardiomyopathies) were considered. All patients were anuric. Compensated outpatients with idiopathic DCM with a current left ventricular ejection fraction <50%, an end-diastolic volume index >70 mL/m², and normal or slightly decreased renal function (chronic kidney disease class I–II) made up the control group. The DCM group was divided into 2 subgroups with GFR values below and above the median rates [85 mL·min⁻¹·(1.73 m²)⁻¹]. Diagnosis of idiopathic DCM had been previously made according to the current WHO definition (10). Inclusion criteria for both groups were age 25–80 years, body mass index (BMI) 17–35, and normal body hydration as assessed by the bioelectrical impedance (11). Exclusion criteria for both groups were atrial fibrillation, pacemakers, previous surgical heart procedures, valvular and congenital heart disorders, myocardial ischemic events, pericardial effusion, edema, diabetes, pulmonary disorders, liver disorders, alcohol abuse (>90 g/day longer than 5 years), cancer, and treatment with cytotoxic drugs.

Protocol measurements were carried out on the same day and included height, body weight, BMI (weight in kg/squared height in m²), systolic and diastolic blood pressure, mean blood pressure, heart rate, echocardiogram, echocardio-Doppler, whole body bioelectrical impedance (resistance and reactance components at 50 kHz frequency, BIA-101 analyzer, RJL Systems) (11), and routine clinical laboratory tests (plasma Na, K, Ca, urea, hemoglobin). An alkaline picrate method was used for creatinine measurement (calibration traceable to isotope dilution mass spectrometry, Roche Diagnostics). C-reactive protein (CRP) was measured in lithium-heparin plasma using a high-sensitivity assay (Cardiophase hsCRP), with total CVs ranging from 2.1% to 5.7% at 0.5 to 56.0 mg/L. NT-proBNP was assayed on lithium-heparin plasma (PBNP, Dade Behring), with a total CV of 3.1% to 5.7% at 159 to 3734 ng/L and decision threshold of 125 or 450 ng/L for participants younger than or older than 75 years, respectively. BNP was assayed on plasma K3-EDTA (BNP, Bayer Diagnostics) with total CVs of 2.8% to 5.4% at 42 to 1615 ng/L, and a decision threshold of 100 ng/L. ANP was assayed on plasma K3-EDTA (Shionogi) with total CVs of 5.7% to 6.0% at 20 to 563 ng/L without an established decision threshold.

Doppler echocardiography was performed following recommendations of the American Society of Echocardiography (13). Complete M-mode, 2-dimensional, and Doppler echocardiograms were performed with a Hewlett-Packard 5500 Sonos system by use of a 2.5-MHz combined imaging and Doppler transducer. The left ventricular mass was calculated with the Devereux formula (14) and was indexed by body surface area (g/m²). An end-diastolic volume index >70 mL/m² was considered a ventricle dilation. A left ventricular ejection fraction <50% was defined as systolic dysfunction. Left ventricular diastolic function was classified into 4 patterns (15, 16): normal, E/A >1, DT <220 ms, IRT <100 ms; abnormal relaxation, E/A <1 in individuals <55 years or E/A <0.8 in individuals >55 years, DT >220 ms, IRT >100 ms; pseudonormal: 1 < E/A < 2, 150 ms < DT < 200 ms, IRT <100 ms; restrictive filling, E/A >2, DT <150 ms, IRT <60 ms, where E is the peak E-wave velocity and A is the peak A-wave velocity of the mitral inflow, DT is the deceleration time of the E wave, and IRT is the left ventricular isovolumic relaxation time (13). The index of myocardial performance (Tei index) was calculated as the ratio isovolumic contraction time plus isovolumic relaxation time/ejection time, which reflects the global myocardial performance (reference value <0.4) and combines systolic and diastolic elements (17).

In DCM patients, GFR was estimated according to kidney/Dialysis Outcomes Quality Initiative recommendations using the simplified Modification of Diet in Renal Disease equation (18) not applicable to anuric HD patients. In the dialysis patients, body weight, blood pressure, bioelectrical impedance, routine laboratory tests, and natriuretic peptides were recorded before and after a midweek dialysis session.

Statistical calculations were performed with SPSS statistical software (SPSS, version 14). After the natural logarithmic (Ln) transformation of the natriuretic peptides and CRP values (distributions skewed to the right), we obtained log-normal distributions (Kolmogorov–Smir-
Demographic and metabolic characteristics of patients (predialysis in HD patients) are shown in Table 1. The DCM group was divided into 2 subgroups with median GFRs of 85–126 mL·min⁻¹·(1.73 m²)⁻¹ and 52–84 mL·min⁻¹·(1.73 m²)⁻¹. Patients in both disease groups and in both GFR subgroups belonged to the same NYHA class (I and II), age, and BMI range, and were free from diabetes and heart ischemic events.

BNP, ANP, and NT-proBNP were highly correlated to one another within groups (0.81 < r < 0.97, P < 0.001) and also in the pooled groups (0.86 < r < 0.90, P > 0.001). The correlation between Ln NT-proBNP and Ln BNP is depicted in the scattergram in Fig. 1. Mean peptide concentrations were higher in the HD group, with an HD:DCM ratio of 24.7 for NT-proBNP (1584–274 995 ng/L in HD vs 10–9162 ng/L in DCM), 4.7 for BNP (28–7625 ng/L in HD vs 2–1387 ng/L in DCM), and 4.8 for ANP (24–904 ng/L in HD vs 3–413 ng/L in DCM) (Table 1). None of the 50 HD patients and 24% of the 50 DCM patients [17% with GFR > 85 mL·min⁻¹·(1.73 m²)⁻¹] had normal NT-proBNP concentrations. All the HD patients and 76% of the DCM patients [61% with GFR > 85 mL·min⁻¹·(1.73 m²)⁻¹] had abnormal NT-proBNP concentrations. Normal BNP concentrations were found in 14% of the HD patients and in 60% of the DCM patients [30% with GFR > 85 mL·min⁻¹·(1.73 m²)⁻¹]. Abnormal BNP concentrations were found in 86% of the HD patients and 40% of the DCM patients [80% with GFR > 85 mL·min⁻¹·(1.73 m²)⁻¹].

Results

Table 1. Demographic and metabolic characteristics of patients by GFR in the DCM group and by disease group.¹

<table>
<thead>
<tr>
<th></th>
<th>DCM GFR &lt;85 mL·min⁻¹·(1.73 m²)⁻¹</th>
<th>DCM GFR &gt;85 mL·min⁻¹·(1.73 m²)⁻¹</th>
<th>P</th>
<th>DCM</th>
<th>HD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>57.3 (2.7)</td>
<td>49.9 (2.6)</td>
<td>NS</td>
<td>53.7 (1.9)</td>
<td>62.8 (2.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.2 (0.7)</td>
<td>25.6 (0.8)</td>
<td>NS</td>
<td>24.9 (0.5)</td>
<td>24.8 (0.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>123.2 (2.7)</td>
<td>133.0 (3.3)</td>
<td>0.03</td>
<td>128.1 (2.2)</td>
<td>142.4 (3.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>79.4 (1.8)</td>
<td>78.4 (1.9)</td>
<td>NS</td>
<td>78.9 (1.3)</td>
<td>78.3 (1.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean blood pressure, mmHg</td>
<td>93.9 (1.9)</td>
<td>96.7 (2.2)</td>
<td>NS</td>
<td>95.3 (1.4)</td>
<td>99.7 (2.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Urea, mmol/L</td>
<td>6.1 (0.2)</td>
<td>8.6 (0.5)</td>
<td>&lt;0.001</td>
<td>7.3 (0.3)</td>
<td>22.3 (0.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>72.0 (2.2)</td>
<td>99.8 (3.2)</td>
<td>&lt;0.001</td>
<td>88.9 (2.8)</td>
<td>796.4 (22.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>137.0 (2.3)</td>
<td>138.7 (3.1)</td>
<td>NS</td>
<td>138.9 (1.9)</td>
<td>112.7 (1.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>1.2 (1.2)</td>
<td>1.7 (1.2)</td>
<td>NS</td>
<td>1.4 (1.2)</td>
<td>4.8 (1.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resistance/height, Ohm/m</td>
<td>297.9 (12.8)</td>
<td>295.2 (10.9)</td>
<td>NS</td>
<td>296.5 (8.3)</td>
<td>307.0 (6.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Reactance/height, Ohm/m</td>
<td>30.3 (1.1)</td>
<td>31.4 (1.1)</td>
<td>NS</td>
<td>30.8 (0.8)</td>
<td>26.8 (0.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>NT-proBNP, ng/L</td>
<td>785 (1.3)</td>
<td>191 (1.3)</td>
<td>0.001</td>
<td>387 (1.3)</td>
<td>9509 (1.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BNP, ng/L</td>
<td>135 (1.3)</td>
<td>40 (1.3)</td>
<td>0.004</td>
<td>74 (1.2)</td>
<td>348 (1.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ANP, ng/L</td>
<td>56 (1.3)</td>
<td>23 (1.3)</td>
<td>0.006</td>
<td>36 (1.2)</td>
<td>174 (1.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

¹ Data are mean (SE); geometric mean of CRP, NT-proBNP, BNP, and ANP. The 95% CI of the geometric mean is the antilog of Ln(M) ± 2 Ln(SE). SD = 2.24 SE for all variables. Resistance and Reactance are the bioimpedance vector components.
m²⁻¹]. Mean individual peptide concentrations by sex and NYHA class were comparable within the HD and DCM groups (2-way ANOVA: sex P = 0.55–0.97, NYHA P = 0.29–0.94).

Most echocardiographic findings were significantly different in the disease groups (Table 2). In the HD group, the relative wall thickness and the left atrial volume index were greater than those in the DCM group. The heart was more severely affected in the DCM patients in whom the ejection fraction was decreased (ejection fraction <50% in 100% of DCM vs 10% of HD group), the diastolic volume was increased (dilation in 100% of DCM vs 36% of HD), the index of myocardial performance was worse (0.7 in DCM vs 0.4 in HD), and the left ventricular mass index was increased (172 g/m² in DCM vs 151 g/m² in HD, marginally significant, P = 0.05). The frequency distribution of diastolic patterns was comparable in the disease groups (Fisher exact test) [borderline normal with abnormal relaxation patterns in one category (N-AR) vs pseudonormal with restrictive patterns in another category (Pn-R)]. The 3 natriuretic peptides were significantly increased in patients with a Pn-R vs N-AR pattern in both disease groups, but this difference was obscured by the greater increase in peptide concentrations found in the HD patients compared to the DCM patients with the same diastolic pattern (Fig. 2). For instance, a BNP value of 150 ng/L (5 in the Ln scale in Fig. 2) can be found in an HD patient with a N-AR diastolic pattern as well as in a DCM patient with a Pn-R pattern.

The influence of extreme GFR values on natriuretic peptides was stronger than the degree of heart involvement. As a consequence, we obtained misleading ROC curve patterns of natriuretic peptides in detecting systolic dysfunction (ejection fraction <50%). The areas under the ROC curve for all 100 participants were small, ranging from 0.10 to 0.26 for the 3 peptides. The areas under the ROC curves modestly increased to the values of 0.23 to 0.40 for the 3 peptides in detecting an ejection fraction <40%. In the DCM group, all patients had an ejection fraction <50% by inclusion criteria, whereas 54% had an ejection fraction <40%. The area under the ROC curve increased to 0.64 for NT-proBNP [not significant (NS)], 0.66 for BNP (NS), and 0.70 for ANP (P = 0.02) in detecting an ejection fraction <40%.

In DCM patients, the concentration of the 3 natriuretic peptides linearly increased with decreasing GFR irrespective of the severity of heart involvement [significant inverse correlation, P < 0.001, between GFR and Ln NT-

![Fig. 2. Means with SE of Ln(NT-proBNP), Ln(BNP), and Ln(ANP) by disease group and by Doppler diastolic pattern (normal or abnormal relaxation, N-AR, vs pseudonormal or restrictive, Pn-R). The influence of dialysis is indicated by a line connecting the peptide concentrations in the HD and DCM groups with the same diastolic pattern.](image)

### Table 2. Mean values of Doppler echocardiography variables by GFR in the DCM group and by disease group. a

<table>
<thead>
<tr>
<th>Variable</th>
<th>DCM GFR &lt;85</th>
<th>DCM GFR &gt;85</th>
<th>P</th>
<th>DCM</th>
<th>HD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior wall thickness, mm</td>
<td>11.0 (0.3)</td>
<td>10.1 (0.3)</td>
<td>NS</td>
<td>10.6 (0.2)</td>
<td>13.6 (0.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Interventricular wall thickness, mm</td>
<td>10.2 (0.3)</td>
<td>9.7 (0.3)</td>
<td>NS</td>
<td>9.9 (0.2)</td>
<td>12.5 (0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ventricular diameter, mm</td>
<td>68.1 (2.4)</td>
<td>65.2 (2.2)</td>
<td>NS</td>
<td>66.6 (1.6)</td>
<td>50.1 (1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.3 (0.01)</td>
<td>0.3 (0.01)</td>
<td>NS</td>
<td>0.3 (0.01)</td>
<td>0.5 (0.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>End-diastolic volume, mL/m²</td>
<td>123.9 (9.4)</td>
<td>98.3 (5.3)</td>
<td>0.02</td>
<td>111.1 (5.6)</td>
<td>62.4 (2.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>End-systolic volume, mL/m²</td>
<td>82.9 (8.3)</td>
<td>60.4 (4.2)</td>
<td>0.02</td>
<td>71.6 (4.9)</td>
<td>24.7 (1.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>35.4 (2.2)</td>
<td>39.7 (1.3)</td>
<td>NS</td>
<td>37.6 (1.3)</td>
<td>60.7 (1.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ventricular mass, g/m²</td>
<td>188.3 (11.9)</td>
<td>154.8 (9.3)</td>
<td>0.03</td>
<td>171.6 (7.9)</td>
<td>150.5 (7.3)</td>
<td>0.05</td>
</tr>
<tr>
<td>Left atrial volume, mL/m²</td>
<td>41.1 (3.3)</td>
<td>39.1 (2.7)</td>
<td>NS</td>
<td>40.1 (2.1)</td>
<td>54.3 (2.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak E wave/peak A wave</td>
<td>1.4 (0.2)</td>
<td>1.2 (0.1)</td>
<td>NS</td>
<td>1.3 (0.1)</td>
<td>1.0 (0.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Deceleration time E wave, ms</td>
<td>215.4 (16.2)</td>
<td>227.9 (14.6)</td>
<td>NS</td>
<td>221.6 (10.8)</td>
<td>173.3 (8.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Myocardial performance index</td>
<td>0.7 (0.1)</td>
<td>0.7 (0.1)</td>
<td>NS</td>
<td>0.7 (0.04)</td>
<td>0.4 (0.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary systolic wave, ms</td>
<td>51.1 (3.6)</td>
<td>55.3 (4.4)</td>
<td>NS</td>
<td>52.9 (2.8)</td>
<td>51.7 (2.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary diastolic wave, ms</td>
<td>47.4 (3.0)</td>
<td>48.5 (3.6)</td>
<td>NS</td>
<td>47.9 (2.3)</td>
<td>50.7 (1.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary diastolic/systolic</td>
<td>0.9 (0.1)</td>
<td>0.9 (0.1)</td>
<td>NS</td>
<td>0.9 (0.04)</td>
<td>1.1 (0.1)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Data are mean (SE); SD can be calculated as 2.24 SE.
proBNP, \( r = -0.54 \) (Fig. 3A); Ln BNP, \( r = -0.50 \) (Fig. 3B); and Ln ANP, \( r = -0.49 \). As a consequence, mean natriuretic peptide concentrations were higher in patients with GFR below the median [52 to 84 mL·min\(^{-1}\)·(1.73 m\(^2\))\(^{-1}\)] compared to those above it (85 to mL·min\(^{-1}\)·(1.73 m\(^2\))\(^{-1}\)), with a ratio of 4.1 for NT-proBNP, 3.4 for BNP, and 2.4 for ANP, although most echo-Doppler variables were comparable in the 2 GFR groups (Tables 1 and 2).

Natriuretic peptides were linearly correlated with several continuous protocol variables in both groups (0.20 \( r < 0.54, P = 0.04 \) to \( P < 0.001 \)). The highest correlations were found between natriuretic peptides and the left atrial volume index in both disease groups (\( r = 0.54, P <0.001 \)). Most correlation coefficients were of the same order due to the high mutual correlation between peptides. Multiple regression analysis was used to identify among the correlated variables those with an independent influence on natriuretic peptide concentrations both before and after a dialysis session. The prediction of NT-proBNP concentration achieved the highest R value both before (\( R = 0.85, P <0.001 \)) and after (\( R = 0.83, P <0.001 \)) the dialysis session, followed by Ln BNP (\( R = 0.65 \) and \( 0.62, P <0.001 \)) and Ln ANP (\( R = 0.53 \) and \( 0.59, P <0.001 \)). Standardized partial regression coefficients (\( \beta \)) indicated that uremic status was the most important variable, both before and after dialysis, followed in decreasing order by diastolic pattern, atrial volume index, and BMI. The following regression equations significantly fitted natriuretic peptide concentration before dialysis (disease encoded 0 if DCM, 1 if HD; D pattern encoded 0 if N-AR, 1 if Pn-R):

\[
\text{Ln(NT-proBNP)} = 7.48 + 3.05 \text{ Disease} + 1.29 \text{ D Pattern} + 0.02 \text{ Atrial volume} - 0.11 \text{ BMI}
\]

\[
\text{Ln(BNP)} = 5.94 + 1.42 \text{ Disease} + 1.37 \text{ D Pattern} + 0.02 \text{ Atrial volume} - 0.12 \text{ BMI}
\]

\[
\text{Ln(ANP)} = 4.49 + 1.44 \text{ Disease} + 0.80 \text{ D Pattern} + 0.02 \text{ Atrial volume} - 0.08 \text{ BMI}
\]

The diastolic pattern, atrial volume, and BMI significantly fitted the peptide distribution also within each disease group [Ln NT-proBNP, \( R = 0.60 \) and 0.62 (\( P <0.001 \)); Ln BNP, \( R = 0.65 \) and 0.62 (\( P <0.001 \)); Ln ANP, \( R = 0.53 \) and 0.59 (\( P <0.001 \)), in the DCM and HD groups, respectively]. In the DCM group, GFR did not significantly correlate with left ventricular mass and volumes (\( -0.31 < r < -0.20 \)). Although mean values of left ventricular mass and diastolic and systolic volumes were significantly increased in the lower GFR group (\( P = 0.03, \) Table 2), GFR was the only significant explanatory variable for natriuretic peptides in a multiple regression equation that included GFR and left ventricular mass and volumes (\( 0.52 < R < 0.57, P <0.001 \)).

After HD sessions (low-flux dialyzer), an average of 2900 mL fluid was removed by ultrafiltration, systolic and diastolic blood pressure decreased by 13 mmHg (\( P <0.01 \)) and 5 mmHg (\( P <0.01 \)), respectively, and heart rate increased by 2 bpm (\( P = 0.03 \)). The peptides reacted differently to a dialysis session. NT-proBNP increased by 14% (from 9509 to 9711 ng/L, \( P = 0.03 \)), BNP decreased by 17% (from 348 to 271 ng/L, \( P <0.01 \)), and ANP decreased by 56% (from 174 to 70 ng/L, \( P <0.01 \)). The correlation between pre- and postdialysis measurements of any peptide was very high (\( P <0.001, r = 0.94 \) for NT-proBNP, 0.94 for BNP, and 0.85 for ANP), and the same set of significant variables entered both pre- and post-HD multiple regression equations.
Discussion

We compared the concentrations of natriuretic peptides in uremic patients with abolished renal function with those in cardiac patients with normal or slightly decreased renal function to establish whether uremic status or cardiomyopathy affects plasma concentrations of the peptides in HD patients. Although patients in the HD and DCM groups belonged to the same NYHA class and both cardiomyopathies were likely characterized by a similar myocyte disarray and intermyocyte fibrosis (17), the groups differed in their extreme values of renal function and Doppler-echocardiographic parameters. Heart involvement was more severe in the DCM patients. If heart function had been the determinant for plasma peptide concentrations, increased concentrations of the peptides should have been found in the DCM group owing to increased wall stress (9). Peptide concentrations instead were increased 5- to 25-fold in the HD patients, indicating that uremic status and not heart involvement was the major determinant of the peptide increase. Peptides were also increased 2- to 4-fold in the DCM patients with early renal dysfunction compared to those with preserved GFR, reflecting the inverse linear relation with GFR. If heart function had been the determinant for plasma peptide concentrations in DCM patients, no difference should have been found in the patients with lower vs higher GFR values because measures of heart involvement were similar in the 2 groups.

Increased concentrations of NT-proBNP, BNP, and ANP have been reported in dialysis patients compared to patients with mild and moderate renal dysfunction (2,17,19). We extended the investigation to cardiac patients with preserved renal function. However, the hydration status of both groups, as assessed by bioelectrical impedance vector analysis (20), was normal and comparable.

We suggest 4 explanatory variables that significantly fitted the 3 different natriuretic peptide concentrations in the DCM and HD groups: uremic status, diastolic pattern, left atrial volume, and BMI. Abolished GFR had the greatest influence on the increased peptide concentrations. Although higher peptide concentrations are associated with a worse prognosis, there is agreement in the literature that current decision thresholds for BNP without adjustment for kidney function should not be applied (18,21–24). Empirical thresholds have been suggested in mild-to-moderate renal dysfunction, e.g., BNP 300 ng/L instead of 100 ng/L for GFR of 18–60 mL/min (22) and 390 ng/L in HD patients (21). We found that even in cardiac patients with normal GFR, the relationship between peptides and GFR was continuous and linear (Fig. 3), therefore preventing the identification of any fixed decision threshold. Peptide concentration expression corrected for GFR is impractical and cannot be used at all in uremic patients with abolished GFR.

Diagnostic testing is useful for identifying a decision threshold with high sensitivity and specificity that should be independent of other clinical conditions. We provide evidence that natriuretic peptide concentrations depend more on GFR than on cardiac involvement, both in the extreme reduction of GFR and in the initial renal dysfunction. The confounding effect of renal dysfunction explains why natriuretic peptides are unable to detect systolic dysfunction. Therefore, although the validity of decision thresholds should probably be restricted to GFR >100 mL·min⁻¹·(1.73 m²)⁻¹ (Fig. 3), changes in peptide concentrations over time may be meaningful in the same patient with stable renal function. For instance, our equation predicts that a 3.5-fold increase in the NT-proBNP value from 2640 to 9500 ng/L in an HD patient would correspond to the increase from 125 to 450 ng/L in a DCM patient with comparable diastolic pattern, atrial volume, and BMI. Specific outcome studies are needed to test our preliminary hypothesis and to establish whether our equations can be used for a correction procedure in uremic patients in a larger study group.

After an HD session, a variable decrease in circulating peptides has been reported, especially with high-flux dialyzers (2,3). The effects of our dialysis session with low-flux dialyzers differed among the peptides. We have no clear explanation for the different behaviors of the peptides, which can reflect different half-lives combined with the different molecular sizes. However, the cross-correlation between peptides, the high correlation between pre- and postdialysis measurements of any peptide, and the same set of significant variables in the multiple regression equations indicate that the predialysis ranking of individual values is preserved after dialysis, meaning that long- rather than short-term regulation is stronger.

Several reports support a regulatory role of left ventricular diastolic pattern and left atrial volume on circulating peptide concentrations (5,8,25–29). The meaning of the inverse relationship between natriuretic peptide concentration and BMI is not clear in the literature (30–32). In our study, ANP, BNP, and NT-proBNP decreased with the increase of BMI in the 17 to 35 kg/m² range. In the absence of other data, we consider BMI as a scale factor for peptide metabolism in different body compartments.

Other potential explanatory variables reported in the literature, such as blood pressure (33,34), C-reactive protein (35), ventricular wall thickness and mass (33,36), and ejection fraction (36), although correlated with peptides, were not able to enter the regression equation with a significant contribution in our study. The strict selection criteria of patients in our protocol rules out confounding factors such as ischemia, pulmonary disorders, diabetes, obesity, abnormal body hydration, or differences in the NYHA class (2,5–7).

A limitation of the present study is the lack of a follow-up period evaluating the association between peptide concentrations and outcomes in the 2 cardiomyopa-
In conclusion, abolished renal function rather than cardiomyopathy was the cause of increased peptides in HD, the long-term regulation of which was stronger than 1 HD session. Natriuretic peptide concentrations were dependent on GFR even at the onset of renal dysfunction.

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References


