N-Terminal Pro-Brain Natriuretic Peptide: An Independent Risk Predictor of Cardiovascular Congestion, Mortality, and Adverse Cardiovascular Outcomes in Chronic Peritoneal Dialysis Patients

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This study was performed to determine whether the N-terminal pro-brain natriuretic peptide (NT-pro-BNP) is a useful biomarker in predicting cardiovascular congestion, mortality, and cardiovascular death and event in chronic peritoneal dialysis (PD) patients. A prospective cohort study was conducted in 230 chronic PD patients in a dialysis unit of a university teaching hospital. Serum NT-pro-BNP was measured at baseline together with echocardiography and dialysis indices. Each patient was followed for 3 yr from the day of enrollment or until death. Time to develop first episode of cardiovascular congestion and other cardiovascular event and time to mortality and cardiovascular death were studied in relation to NT-pro-BNP. NT-pro-BNP showed the strongest correlation with residual GFR, followed by left ventricular ejection fraction and left ventricular mass index. In the univariate Cox regression model, NT-pro-BNP was a significant predictor of cardiovascular congestion, mortality, and cardiovascular death and event. In the fully adjusted multivariable Cox regression analysis that included residual GFR, left ventricular ejection fraction, and left ventricular mass index, the hazard ratios for cardiovascular congestion, mortality, composite end point of mortality and cardiovascular congestion, and cardiovascular death and event for patients of the fourth quartile were 4.25 (95% confidence interval [CI] 1.56 to 11.62; \( P = 0.005 \)), 4.97 (95% CI 1.35 to 18.28; \( P = 0.016 \)), 5.03 (95% CI 2.07 to 12.26; \( P < 0.001 \)), 7.50 (95% CI 1.36 to 41.39; \( P = 0.021 \)), and 9.10 (95% CI 2.46 to 33.67; \( P = 0.001 \)), respectively, compared with the first quartile. These data showed that NT-pro-BNP is an important risk predictor of cardiovascular congestion, mortality, and adverse cardiovascular outcomes in chronic PD patients and adds important prognostic information beyond that contributed by left ventricular hypertrophy, systolic dysfunction, and other conventional risk factors.


Brain (B-type) natriuretic peptide (BNP) is a peptide hormone that is released primarily by the ventricular myocytes in response to myocyte stretch such as increased cardiac filling pressure (1). It is synthesized as an inactive prohormone and is cleaved into the biologically active fragment (c-BNP) and the N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), and both are measurable in plasma or serum (2–4). Compared with BNP, NT-pro-BNP has the advantage of having a longer plasma half-life and lower biologic variation (3). Numerous studies have demonstrated the potential value of BNP measurement in predicting abnormal ventricular function in the general population (5–7). In addition, elevated BNP and NT-pro-BNP may result directly from cardiac ischemia (8). There is ample evidence that BNP and NT-pro-BNP are useful in diagnosing heart failure (9–12) and predict prognosis in heart failure (13–16). BNP guidance in treating heart failure also has been shown to reduce subsequent cardiovascular events in hospitalized heart failure patients (17). Furthermore, in patients who were treated for acutely decompensated heart failure, BNP concentration decreased in parallel with fall in pulmonary capillary wedge pressure during a period of 24 h (18), suggesting that BNP may be able to mirror changes in fluid status and monitor therapeutic responses in heart failure.

These findings are of particular relevance to patients who have ESRD and receive long-term peritoneal dialysis (PD) treatment, because they are frequently complicated with volume overload and hypertension (19,20), which contribute to a high incidence of ventricular hypertrophy and dysfunction, heart failure, and cardiovascular mortality (21–24). Indeed, natri-
uremic peptides are elevated almost universally in patients with ESRD as a result of the high prevalence of left ventricular hypertrophy (LVH) and ventricular dysfunction and markedly diminished renal clearance (25). Cardiac natriuretic peptides, especially BNP, are useful in identifying dialysis patients with LVH, excluding systolic dysfunction (26), and predict mortality independent of LV mass (LVM) and LV ejection fraction (LVEF) (27). Given this important background, we hypothesized that NT-pro-BNP is a useful serum biomarker that predicts cardiovascular congestion, mortality, and cardiovascular death and event in chronic PD patients.

Materials and Methods

Patients

The Clinical Research Ethics Committee of the Chinese University of Hong Kong approved the study. Patients were considered eligible for study inclusion when they had been on continuous ambulatory peritoneal dialysis (CAPD) treatment for 3 mo or more and not in obvious volume overload. Exclusion criteria included patients with underlying malignancy, chronic liver disease, chronic obstructive airways disease, systemic lupus erythematosus, chronic rheumatic heart disease, or congenital heart disease; patients who were receiving automated PD; and patients who refused to give study consent. Altogether, 230 patients who had ESRD (117 men and 113 women) and were receiving CAPD treatment were recruited from a single dialysis center of a university teaching hospital in Hong Kong, and they represented 86% of the total PD population in the center. The remaining 14% were excluded on basis of exclusion criteria. All patients were dialyzed using conventional lactate-buffered glucose-based PD solutions. Informed consent was obtained from all patients who participated in the study. The study enrollment was started in September 1999 and completed in December 2000.

Study Design

This is a prospective cohort study with 3 yr of longitudinal follow-up. At study entry, all eligible patients underwent measurement of NT-pro-BNP and other biochemical parameters. At the same time, echocardiography was performed and residual renal function and dialysis indices were measured. In patients who developed acute coronary syndrome, acute cardiovascular congestion, peritonitis, exit-site infections, other infective complications, or any other complications that required hospitalization, all of the above assessments were deferred for at least 1 mo after complete resolution of the complication. In all patients, a thorough medical history was taken at study entry. Clinical and demographic data including presence of diabetes, smoking status, details of any previous history of angina, myocardial infarction with or without percutaneous coronary intervention or coronary artery bypass grafting, previous history of cardiovascular congestion, previous stroke or transient ischemic attacks, intermittent claudication or other symptoms suggestive of peripheral vascular disease with or without history of amputation or revascularization, and use of different antihypertensive medications were recorded.

Biochemical Analysis

Clotted blood samples were collected for measurement of NT-pro-BNP, high-sensitivity C-reactive protein (CRP), albumin, and hemoglobin on study enrollment. Serum NT-pro-BNP was quantified by electrochemiluminescence immunoassay on the Elecsys 2010 analyser (Roche Diagnostics Corp., Indianapolis, IN) with an interassay coefficient of variation (CV) of 2.6% at 1068 pg/ml and a measuring range from 5 to 35,000 pg/ml. For samples with NT-pro-BNP concentrations above the measuring range, the final concentrations would be taken as 35,000 pg/ml. CRP and albumin in heparin plasma were measured, respectively, using the Tina-quant CRP latex ultrasensitive assay (detection limit of 0.01 mg/L and CV of 1.6% at 2.0 mg/L) and the bromcresol purple method (CV of 2.8% at 45 g/L) on the Roche modular analyzer (Roche Diagnostics). Serum fetuin-A was determined using a human fetuin-A ELISA assay kit (Epitope Diagnostics, San Diego, CA). The assay used the two-site “sandwich” technique with two selected polyclonal antibodies that bind to different epitopes of human fetuin-A. Intra-assay precision is 4.8 to 5.5%, and interassay precision is 5.7 to 6.8%.

Echocardiography

Two-dimensional echocardiography was performed with patients lying in the left decubitus position using a GE-VingMed System 5 echocardiographic machine (GE-VingMed Sound AB, Horten, Norway) with a 3.3-MHz multiphase array probe by a single experienced cardiologist who was blinded to all clinical details of patients. All echocardiographic data were recorded according to the guidelines of the American Society of Echocardiography (28). Mitral inflow velocities, diastolic filling, and the different pattern of diastolic dysfunction were assessed by Doppler echocardiography as described previously (29). LVM was indexed by height rather than body surface area to minimize potential distortion by extracellular volume expansion. LVH was defined as LVM index (LVMi) of >47 g/m2.7 in women and >50 g/m2.7 in men. The LVEF was obtained using a modified biplane Simpson’s method from apical two- and four-chamber views (30).

BP Measurements

The systolic and diastolic BP were measured on every follow-up visit at 8-wk intervals for 1 yr before the study entry. Each set of values was averaged to give the final systolic or diastolic BP in each patient.

Assessment of Residual Renal Function and Dialysis Indices

Residual GFR was estimated at the time of echocardiography as the average of 24-h urine urea and creatinine clearances (31). Adequacy of dialysis was estimated by the measurement of total weekly urea and creatinine clearances using standard methods (32). Creatinine concentration in dialysate was corrected for interference by glucose according to the reference formula determined in our laboratory (33). Contribution of PD and renal component to the total urea clearance was estimated separately. Total body water was derived using the Watson formula (34). A standard peritoneal equilibration test was performed to determine the peritoneal transport characteristics.

Follow-Up and Outcome Measures

All patients were followed up prospectively for 3 yr from the day of the baseline assessments at study enrollment or until death. No patient was lost to follow-up. The outcome measures included the first episode of cardiovascular congestion, mortality, composite end point of mortality and cardiovascular congestion, cardiovascular death, and first episode of fatal or nonfatal cardiovascular event. All outcomes were defined a priori, and the cohort was assembled purposely to examine these outcomes.

Cardiovascular congestion was defined as such to include only episodes that were documented clearly to require hospitalization. Essentially, the diagnosis of cardiovascular congestion was made clinically by the attending physician on the basis of the presence of the following three criteria with no preceding knowledge of the NT-pro-BNP results: (1) Presence of symptoms and signs of heart failure including dyspnea,
was not censored because the early mortality was considered to reflect
sored at the time of transfer to alternative renal replacement therapy.
plantation or were transferred permanently to hemodialysis were cen-
was adjusted by the Bonferroni correction. Linear regression analysis
patients with and without cardiovascular congestion were performed
by the attending physician, and this information was retrieved from the
hypertonic peritoneal dialysis exchanges. This information was re-
and (3) resolution of symptoms, signs, and radiographic changes with
York Venous pressure, and basal crepitations; (2) radiographic
evidence of pulmonary venous congestion or interstitial edema (35); and
and radiographic changes with hypertensive peritoneal dialysis exchanges. This information was re-
from the computerized Clinical Management System of the Hong Kong Hospital Authority and the Renal Registry Database, de-
holds detailed record of all hospitalization episodes. The diagnosis of cardiovascular congestion was confirmed further by the study in-
vestigators who reviewed all of the hospitalization records of study
on a regular basis and checked that all three diagnostic criteria
for cardiovascular congestion indeed were fulfilled in each episode of
cardiovascular congestion that required hospitalization. In patients
who presented to the outpatient clinic with milder symptoms of car-
diovascular congestion, including ankle edema or facial puffiness, that
did not require hospitalization, the episode would not be counted as
cardiovascular congestion. For patients who developed multiple epi-
sodes of cardiovascular congestion, survival analysis was limited to the
first episode.

All deaths were recorded accurately, with the exact cause of death
provided by the attending physician. In case of death out of hospital,
family members were interviewed by telephone to ascertain the cir-
cumstances surrounding death. Cardiovascular mortality included
death that was associated with a definite myocardial ischemic event,
cardiovascular congestion, cerebrovascular event (hemorrhagic or
thromboembolic stroke), arrhythmia, and peripheral vascular disease,
all of which were defined according to standard clinical criteria, and
sudden death, which was defined as unexpected natural death within
1 h from the symptom onset and without any previous condition that
would seem fatal (36,37).

Fatal or nonfatal cardiovascular event included angina with electro-
cardiographically documented changes of myocardial ischemia, myo-
cardial infarction, electrocardiographically documented arrhythmia,
transient ischemic attack, thromboembolic or hemorrhagic stroke, pe-
ipheral vascular disease, or sudden cardiac death as defined previ-
ously. The nature of cardiovascular event was established by the at-
tending physician, and this information was retrieved from the
computerized Clinical Management System of the Hong Kong Hospital
Authority and the Renal Registry Database. For patients who devel-
oped multiple cardiovascular events, survival analysis was limited to the
first episode.

Statistical Analyses
Continuous data were tested for normality by the Kolmogorov-
Smirnov test. Data were expressed as mean ± SD or median (inter-
quartile range), depending on the distribution. Comparisons between
patients with and without cardiovascular congestion were performed
by the t test or Mann-Whitney U test, as appropriate. Comparisons of
NT-pro-BNP levels among patients with different episodes of cardio-
vascular congestion were performed by Kruskal-Wallis test. The α level
was adjusted by the Bonferroni correction. Linear regression analysis
was performed to evaluate the correlations of different parameters with
NT-pro-BNP. NT-pro-BNP was log-transformed before entering the
linear regression model in view of its skewed distribution.

Patients were stratified into quartiles according to the NT-pro-BNP
concentrations. Survival curve was generated by means of the Kaplan-
Meier estimates, and differences in survival were compared by the
log-rank test. In this analysis, patients who underwent kidney trans-
plantation or were transferred permanently to hemodialysis were cen-
sored at the time of transfer to alternative renal replacement therapy.
When a patient died within 3 mo of transfer to hemodialysis, he or she
was not censored because the early mortality was considered to reflect
health status during the period of failing CAPD treatment. In the
analysis for cardiovascular congestion, patients who died also were
censored at the time of death. For evaluation of the effect of NT-pro-
BNP in predicting the time to develop first episode of cardiovascular
congestion, mortality, composite end point of mortality and cardiovas-
cular congestion, cardiovascular death, and first episode of fatal or
nonfatal cardiovascular event, relative risks and 95% confidence inter-
vals (CI) were calculated as hazard ratios (HR) derived from the Cox
proportional hazards regression model. Multivariable Cox regression
models were fitted using covariates with P < 0.25 in the univariate
analysis. For adequate control for confounders, covariates including
age, gender, diabetes, duration of dialysis, hemoglobin, CRP, residual
GFR, previous history of cardiovascular congestion, LVMI, and LVEF
were retained in the models regardless of their statistical significance.
Other covariates that were highly nonsignificant and whose absence
from the model did not result in a substantial change in the risk
estimates of the other covariates were dropped from the model. The
underlying assumptions of the proportional hazards model were tested
and found valid. All P values were two tailed. P < 0.05 was considered
to be statistically significant. Statistical analysis was performed using
SPSS version 11.0 (SPSS, Chicago, IL).

Results
Tables 1 through 3 summarize the baseline demographic, clinical,
biochemical, dialysis, and echocardiographic parameters. The median serum NT-pro-BNP concentration of our study popula-
tion was 5698 pg/ml (interquartile range 1944 to 16711 pg/ml) and
was elevated >10-fold the upper limit of normal, which was
155 and 222 pg/ml in women aged <50 and between 50 to 65 yr, re-
spectively, and 84 and 194 pg/ml in men aged <50 and between
50 to 65 yr, respectively. Eighty-seven (37.8%) of 230 patients
developed cardiovascular congestion; 49 had one single episode,
20 had two episodes, nine had three to five episodes, seven had six
to nine episodes, and two had 10 episodes or more. Sixty-six
patients had died, 25 patients had kidney transplantation, and 22
patients were transferred permanently to long-term hemodialysis.
Forty-three of the 66 deaths were of cardiovascular causes (includ-
ing ischemic heart disease in six patients, cerebrovascular event in
12 patients, cardiovascular congestion in two patients, sudden
death in 18 patients, peripheral vascular disease in four patients,
and arrhythmia in one patient). Twenty-three deaths were of
noncardiovascular causes (including peritonitis in nine patients,
other infections in 10 patients, malignancy in one patient, and
termination of dialysis in three patients). During follow-up, 78
patients had one or more cardiovascular events. The first fatal or
nonfatal cardiovascular event was ischemic heart disease in 23
patients, cerebrovascular event in 25 patients, peripheral vascular
disease in 6 patients, arrhythmia in 10 patients, and sudden death
in 14 patients.

In the fully adjusted multivariate analysis, log-transformed NT-
pro-BNP showed the strongest correlation with residual GFR
(standardized coefficient, β = −0.314, P < 0.001), followed by
LVEF (β = −0.221, P < 0.001), LVMI by height² (β = 0.213, P <
0.001), systolic BP (β = 0.169, P < 0.001), serum fetuin-A (β =
−0.168, P = 0.001), hemoglobin (β = −0.146, P = 0.003), diabetes
(β = −0.080, P = 0.010), valvular calcification (β = 0.109, P =
0.020), previous history of cardiovascular congestion (β = 0.108,
P = 0.034), serum albumin (β = −0.093, P = 0.045), and athero-
sclerotic vascular disease (β = 0.095, P = 0.047).
Kaplan-Meier estimates of the composite end point of all fatal or nonfatal cardiovascular event-free survival (including cardiovascular congestion) in relation to quartiles of NT-pro-BNP are shown in Figure 1. Table 4 shows the unadjusted and fully adjusted HR (95% CI) of quartiles of NT-pro-BNP in relation to all-cause mortality and the different cardiovascular outcomes. NT-pro-BNP remained a significant predictor of all-cause mortality, cardiovascular congestion, composite end point of mortality and cardiovascular congestion, cardiovascular death, and fatal and nonfatal cardiovascular events in both the univariate and the fully adjusted multivariable Cox regression models. The fully adjusted HR (95% CI) of LVMI by height^2.7 in relation to all-cause mortality, cardiovascular congestion, composite end point of all-cause mortality and cardiovascular congestion, cardiovascular death, and fatal and nonfatal cardiovascular events were 1.00 (1.00 to 1.01), 1.003 (0.996 to 1.010), 1.004 (0.998 to 1.009), 0.997 (0.987 to 1.006), and 1.003 (0.997 to 1.010), respectively. The fully adjusted HR (95% CI) of LVEF in relation to all-cause mortality, cardiovascular congestion, composite end point of all-cause mortality and cardiovascular congestion, cardiovascular death, and fatal and nonfatal cardiovascular events were 0.99 (0.96 to 1.02), 0.99 (0.96 to 1.02), 0.99 (0.96 to 1.01), 1.01 (0.97 to 1.05), and 1.00 (0.97 to 1.03), respectively. No significant interaction was observed between hemoglobin and NT-pro-BNP in relation to cardiovascular congestion (P = 0.15). The use of cardioprotective medications including angiotensin-converting enzyme inhibitor and angiotensin receptor blocker and β blocker had no significant relations with the risk for development of cardiovascular congestion.

Further subgroup analysis of NT-pro-BNP concentrations in patients stratified by LVMI and cardiovascular congestion is shown in Figure 2A. Irrespective of whether the LVMI at study entry is less than or equal to median or more than the median, patients who had subsequent cardiovascular congestion showed higher NT-pro-BNP at study entry than those who were not. Subgroup analysis of NT-pro-BNP concentrations in patients stratified by LVEF and cardiovascular congestion is shown in Figure 2B. Irrespective of whether the LVEF at study entry is ≤50% or >50%, patients who had subsequent cardiovascular congestion showed higher NT-pro-BNP at study entry than those who did not.

Further subgroup analysis showed that among patients with no previous history of cardiovascular congestion (n = 141), 34 developed cardiovascular congestion. Controlling for age, male gender, duration of dialysis, background atherosclerotic vascular disease, diabetes, and duration of dialysis, patients who developed cardiovascular congestion showed higher NT-pro-BNP concentrations than those who did not. No significant difference was observed in the use of cardioactive medications including angiotensin-converting enzyme inhibitor and angiotensin receptor blocker and β blocker.

Table 1. Baseline demographic and clinical characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 230)</th>
<th>No Cardiovascular Congestion (n = 143)</th>
<th>With Cardiovascular Congestion (n = 87)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>56 ± 11</td>
<td>55 ± 12</td>
<td>57 ± 11</td>
<td>0.26</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>51</td>
<td>50</td>
<td>53</td>
<td>0.64</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>30</td>
<td>23</td>
<td>41</td>
<td>0.003</td>
</tr>
<tr>
<td>Positive smoking history (%)</td>
<td>37</td>
<td>34</td>
<td>44</td>
<td>0.12</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.1 ± 3.4</td>
<td>23.0 ± 3.3</td>
<td>23.3 ± 3.5</td>
<td>0.53</td>
</tr>
<tr>
<td>Duration of dialysis (mo)^b</td>
<td>26 (14.8 to 50.3)</td>
<td>28 (16 to 55)</td>
<td>25 (13 to 49)</td>
<td>0.13</td>
</tr>
<tr>
<td>Renal diagnosis (%)</td>
<td>chronic glomerulonephritis</td>
<td>32</td>
<td>35</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>diabetic nephropathy</td>
<td>24</td>
<td>18</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>hypertensive nephrosclerosis</td>
<td>14</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>others</td>
<td>30</td>
<td>34</td>
<td>25</td>
</tr>
<tr>
<td>Background atherosclerotic vascular disease (%)</td>
<td>23</td>
<td>17</td>
<td>32</td>
<td>0.007</td>
</tr>
<tr>
<td>Background coronary artery disease (%)</td>
<td>19</td>
<td>14</td>
<td>28</td>
<td>0.011</td>
</tr>
<tr>
<td>Background history of cardiovascular congestion (%)</td>
<td>39</td>
<td>25</td>
<td>61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Use of erythropoietin (%)</td>
<td>40</td>
<td>38</td>
<td>43</td>
<td>0.47</td>
</tr>
<tr>
<td>Use of aspirin (%)</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>0.96</td>
</tr>
<tr>
<td>Use of HMG-CoA reductase inhibitors (%)</td>
<td>14</td>
<td>13</td>
<td>15</td>
<td>0.61</td>
</tr>
<tr>
<td>Total no. of antihypertensives</td>
<td>1.5 ± 1.0</td>
<td>1.5 ± 0.9</td>
<td>1.6 ± 1.0</td>
<td>0.20</td>
</tr>
<tr>
<td>Use of antihypertensive medication (%)</td>
<td>β blockers</td>
<td>52</td>
<td>51</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>calcium channel blockers</td>
<td>62</td>
<td>63</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>ACEI or ARB</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>147 ± 17</td>
<td>144 ± 16</td>
<td>152 ± 17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>83 ± 10</td>
<td>82 ± 10</td>
<td>83 ± 11</td>
<td>0.87</td>
</tr>
</tbody>
</table>

*Unless specified otherwise, data are means ± SD. Percentages may not add up to 100 due to rounding off of decimal places. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DBP, diastolic BP; HMG, hepatic hydroxymethyl glutaryl; SBP, systolic BP.

^bMedian (interquartile range).
Table 2. Baseline biochemical parameters and dialysis indices

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total (n = 230)</th>
<th>No Cardiovascular Congestion (n = 143)</th>
<th>With Cardiovascular Congestion (n = 87)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-pro-BNP (pg/ml)b</td>
<td>5698 (1944 to 16,711)</td>
<td>3568 (1498 to 11,439)</td>
<td>11250 (3575 to 35,000)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Log-transformed NT-pro-BNP</td>
<td>8.61 ± 1.38</td>
<td>8.26 ± 1.33</td>
<td>9.18 ± 1.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Distribution of patients (%) in NT-pro-BNP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>first quartile (≤1927 pg/ml)</td>
<td>24.8</td>
<td>32.2</td>
<td>12.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>second quartile (1928 to 5667 pg/ml)</td>
<td>25.2</td>
<td>29.4</td>
<td>18.4</td>
<td>0.190</td>
</tr>
<tr>
<td>third quartile (5668 to 17,533 pg/ml)</td>
<td>25.7</td>
<td>25.2</td>
<td>26.4</td>
<td>0.754</td>
</tr>
<tr>
<td>fourth quartile (≥17,534 pg/ml)</td>
<td>24.3</td>
<td>13.3</td>
<td>42.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>9.2 ± 1.7</td>
<td>9.5 ± 1.6</td>
<td>8.6 ± 1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>28.6 ± 5.1</td>
<td>29.2 ± 4.9</td>
<td>27.6 ± 5.4</td>
<td>0.019</td>
</tr>
<tr>
<td>Calcium × phosphorus (mmol²/L²)</td>
<td>4.30 ± 1.33</td>
<td>4.28 ± 1.34</td>
<td>4.34 ± 1.31</td>
<td>0.754</td>
</tr>
<tr>
<td>Parathyroid hormone (pmol/L)b</td>
<td>41 (18 to 74)</td>
<td>44 (17 to 81)</td>
<td>36 (19 to 63)</td>
<td>0.595</td>
</tr>
<tr>
<td>CRP (mg/L)b</td>
<td>2.66 (0.92 to 8.04)</td>
<td>2.07 (0.8 to 9.11)</td>
<td>3.15 (1.27 to 6.37)</td>
<td>0.281</td>
</tr>
<tr>
<td>Serum fetuin-A (g/L)</td>
<td>0.309 ± 0.066</td>
<td>0.316 ± 0.069</td>
<td>0.297 ± 0.059</td>
<td>0.035</td>
</tr>
<tr>
<td>Daily PD exchanges (L)</td>
<td>6.5 ± 1.1</td>
<td>6.5 ± 1.0</td>
<td>6.6 ± 1.2</td>
<td>0.276</td>
</tr>
<tr>
<td>Total weekly Kt/V</td>
<td>1.81 ± 0.43</td>
<td>1.83 ± 0.43</td>
<td>1.79 ± 0.44</td>
<td>0.625</td>
</tr>
<tr>
<td>Total weekly CCR (L/wk per 1.73 m²)</td>
<td>56 ± 21</td>
<td>57 ± 22</td>
<td>55 ± 20</td>
<td>0.545</td>
</tr>
<tr>
<td>PD Kt/V</td>
<td>1.52 ± 0.36</td>
<td>1.53 ± 0.38</td>
<td>1.50 ± 0.34</td>
<td>0.490</td>
</tr>
<tr>
<td>Dialysate to plasma creatinine ratio</td>
<td>0.70 ± 0.10</td>
<td>0.70 ± 0.10</td>
<td>0.72 ± 0.12</td>
<td>0.235</td>
</tr>
<tr>
<td>High or high average transporter by PET (%)</td>
<td>16</td>
<td>13</td>
<td>21</td>
<td>0.110</td>
</tr>
<tr>
<td>Residual GFR (ml/min per 1.73 m²)</td>
<td>0.61 (0 to 1.94)</td>
<td>0.66 (0 to 2.08)</td>
<td>0.53 (0 to 1.83)</td>
<td>0.561</td>
</tr>
<tr>
<td>Daily net PD ultrafiltration volume (L)</td>
<td>0.96 ± 0.96</td>
<td>1.04 ± 0.98</td>
<td>0.84 ± 0.91</td>
<td>0.130</td>
</tr>
<tr>
<td>Daily urine volume (L)</td>
<td>0.40 ± 0.54</td>
<td>0.41 ± 0.56</td>
<td>0.39 ± 0.51</td>
<td>0.830</td>
</tr>
<tr>
<td>Total daily net PD + urine ultrafiltration volume (L)</td>
<td>1.34 ± 0.97</td>
<td>1.42 ± 0.98</td>
<td>1.22 ± 0.93</td>
<td>0.130</td>
</tr>
</tbody>
</table>

*Unless specified otherwise, data are means ± SD. CCr, creatinine clearance; CRP, C-reactive protein; NT-pro-BNP, N-terminal-pro-brain natriuretic peptide; PD, peritoneal dialysis; PET, peritoneal equilibration test.

**Median (interquartile range).**

CRP, residual GFR, LVMI, and LVEF, the adjusted HR of cardiovascular congestion were 4.16 (95% CI 1.18 to 14.57; P = 0.026), 3.06 (95% CI 0.85 to 11.02; P = 0.088), and 1.37 (95% CI 0.50 to 3.75; P = 0.54), respectively, for patients of the fourth, third, and second quartiles of NT-pro-BNP compared with those in the first quartile. Among patients with previous history of cardiovascular congestion (n = 89), 53 developed cardiovascular congestion. Controlling for the same covariates as previously, the adjusted HR of cardiovascular congestion was 2.64 (95% CI 0.97 to 7.15; P = 0.056), 1.43 (95% CI 0.48 to 4.24; P = 0.52), and 1.36 (95% CI 0.53 to 3.50; P = 0.53), respectively, for patients of the fourth, third, and second quartiles compared with the first quartile.

In the subgroup analysis of patients with LVEF ≥50% (n = 157), 49 developed cardiovascular congestion. Controlling for age, male gender, diabetes, duration of dialysis, background atherosclerotic vascular disease, CRP, residual GFR, and LVMI, the adjusted HR for cardiovascular congestion for patients of the fourth, third, and second quartiles were 3.74 (95% CI 1.28 to 10.94; P = 0.016), 1.87 (95% CI 0.65 to 5.40; P = 0.25), and 1.88 (95% CI 0.67 to 5.26; P = 0.23), respectively, compared with patients of the first quartile. Among patients with LVEF ≤50% (n = 73), 38 developed cardiovascular congestion. Controlling for the same covariates, the adjusted HR of cardiovascular congestion for patients of the fourth, third, and second quartiles were 4.51 (95% CI 1.56 to 13.03; P = 0.005), 1.88 (95% CI 0.67 to 5.25; P = 0.23), and 1.92 (95% CI 0.68 to 5.38; P = 0.22), respectively, compared with the first quartile.

**Discussion**

The importance of cardiovascular congestion in predicting mortality has been demonstrated clearly in chronic PD patients (38). However, it is not known whether serum markers can predict this complication, thus allowing earlier and more aggressive intervention to improve fluid control in these patients. In this study, we demonstrated that NT-pro-BNP predicts cardiovascular congestion, mortality, and cardiovascular death and event in chronic PD patients. Most important of all, its predictive power for cardiovascular congestion, mortality, and cardiovascular death seems stronger than that of measurements of LVM and systolic function. This observation confirms our hypothesis and extends the current available information about the value of NT-pro-BNP as a diagnostic marker of heart failure in the general population (9–13) to the chronic PD population, which is at a heightened risk for cardiovascular congestion and cardiovascular mortality.

There is strong evidence that BNP or NT-pro-BNP is useful in establishing or excluding the diagnosis of heart failure in the general population (9–13) to the chronic PD population, which is at a heightened risk for cardiovascular congestion and cardiovascular mortality.
Table 3. Baseline echocardiographic measurements

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total (n = 230)</th>
<th>No Cardiovascular Congestion (n = 143)</th>
<th>With Cardiovascular Congestion (n = 87)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVMI (g/m²²)</td>
<td>104 ± 40</td>
<td>95 ± 36</td>
<td>117 ± 43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Valvular calcification (n [%])</td>
<td>58 (25.2)</td>
<td>33 (23.1)</td>
<td>25 (28.7)</td>
<td>0.34</td>
</tr>
<tr>
<td>LVEDD (cm)</td>
<td>5.01 ± 0.82</td>
<td>4.87 ± 0.78</td>
<td>5.25 ± 0.84</td>
<td>0.001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>53.7 ± 9</td>
<td>55 ± 8</td>
<td>51 ± 10</td>
<td>0.001</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>33.4 ± 8.5</td>
<td>34.3 ± 7.7</td>
<td>31.0 ± 9.4</td>
<td>0.024</td>
</tr>
<tr>
<td>% of patients with LVEF ≤ 50%</td>
<td>31.7</td>
<td>24.5</td>
<td>43.7</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Left ventricular diastolic function pattern (%)

| Normal                            | 22.5           | 22.5                                  | 22.4                                  | 0.68    |
| Abnormal relaxation pattern       | 68.7           | 70.4                                  | 65.9                                  |         |
| Restrictive filling pattern       | 7.9            | 6.3                                   | 10.6                                  |         |
| Pseudonormal                      | 0.9            | 0.7                                   | 1.2                                   |         |
| E (m/s)                           | 0.79 ± 0.27    | 0.77 ± 0.26                           | 0.82 ± 0.27                           | 0.12    |
| A (m/s)                           | 0.92 ± 0.24    | 0.91 ± 0.23                           | 0.94 ± 0.26                           | 0.30    |
| E/A                               | 0.92 ± 0.47    | 0.89 ± 0.42                           | 0.97 ± 0.55                           | 0.26    |
| DT (s)                            | 0.25 ± 0.10    | 0.26 ± 0.11                           | 0.23 ± 0.08                           | 0.090   |

*Continuous data are means ± SD. Percentages may not add up to 100 due to rounding off of decimal places. A, late diastolic transmural flow velocity; DT, deceleration time; E, early diastolic transmural flow velocity; E/A, ratio of early to late transmural flow velocity; LADs, left atrial diameter at end-systole; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVMI, left ventricular mass index.

Figure 1. Kaplan-Meier estimates of patients stratified by quartiles of N-terminal pro-brain natriuretic peptide (NT-pro-BNP) in relation to the composite end point of all fatal and nonfatal cardiovascular events including cardiovascular congestion. Log-rank test showed significant difference in the cumulative fatal and nonfatal cardiovascular event-free survival between the first and second quartiles (P = 0.022), first and third quartiles (P < 0.0001), first and fourth quartiles (P < 0.0001), second and third quartiles (P = 0.002), second and fourth quartiles (P < 0.0001), and third and fourth quartiles (P = 0.001).

In the general population, with a sensitivity and specificity well above 85%, and improves the diagnostic accuracy of heart failure from 73 to 84% (9,39,40). In this study, the predictive power of NT-pro-BNP for cardiovascular congestion, mortality, and cardiovascular death and event is well beyond that contributed by its associations with cardiac hypertrophy and systolic dysfunction and may be explained in part by its relation with extracellular volume expansion. In addition, the interassay CV of NT-pro-BNP was low in contrast to echocardiographic measurements of LVM and LV function, which have larger CV of 10% or more. It is likely that NT-pro-BNP may reflect residual variance that is not captured by LVM and LV function.

BNP is widely known to be affected by LVM and LV function. In the general population, BNP is useful in predicting LVH and ruling out systolic dysfunction (5–7,41). In addition, a recent study showed a correlation between BNP and LV filling pressure, a marker of LV volume status (42). In patients who were treated for acutely decompensated heart failure, BNP concentration decreased in parallel with a fall in pulmonary capillary wedge pressure during a 24-h period (18). All of this is evidence that BNP may be a marker of extracellular volume expansion apart from reflecting cardiac morphology and function. In keeping with these observations in the general population, a study in hemodialysis patients demonstrated the usefulness of BNP in identifying LVH and excluding systolic dysfunction (26). BNP predicted mortality in dialysis patients without heart failure, and the prognostic value of BNP was independent of LVM and LVEF (27). Furthermore, changes in BNP levels with hemodialysis correlated with extracellular fluid retention and volume change independent of LV function (43–46). However, there are as yet no data on this aspect in PD patients. Our study so far is the first to demonstrate the important prognostic value of NT-pro-BNP for cardiovascular congestion, mortality, and cardiovascular death and event in chronic PD patients. A recent study in predialysis patients with chronic kidney disease (CKD) showed an association between...
BNP and LV volume that is independent of the degree of renal dysfunction (47). Putting these together with our observation, this suggests the degree of NT-pro-BNP elevation in chronic PD patients partly may reflect extracellular volume expansion other than being a biomarker of LVH and systolic dysfunction and inversely correlated with residual renal function. The additional finding of significantly higher baseline NT-pro-BNP among patients who subsequently were complicated with cardiovascular congestion irrespective of whether LVMI was less than or equal to 50 or >50% adds favor for this concept. There also is some suggestion that the PD patients who developed cardiovascular congestion during the 3-yr follow-up probably had poor fluid management all along in view of the higher incidence of previous history of cardiovascular congestion, more severe baseline LVH, dilation, and systolic dysfunction as well as a much higher baseline NT-pro-BNP. It is worth noting that the NT-pro-BNP concentrations of our patients were much higher compared with the patients with CKD reported in the literature (48,49). One possibility is that our patients had more advanced stage of CKD. The other possibility is that our patients were already having subclinical volume overload at baseline, thus explaining the more severe cardiac hypertrophy and ventricular dysfunction at baseline and resulting higher NT-pro-BNP. Our analysis showed that cardiovascular congestion in chronic PD patients is largely related to preexisting background cardiovascular disease, cardiac hypertrophy and dysfunction, hypertension, duration of dialysis, and extracellular volume expansion. Although it remains inconclusive whether PD or hemodialysis is associated with better volume and BP control (50–52), our data suggest a high incidence of cardiovascular congestion in PD patients. Nearly half of them developed further recurrences. This is in keeping with another series that showed that the prevalence of heart failure was 31% on initiation of dialysis; 56% of these patients had further recurrences (37). In the retrospective review by Tzamaloukas et al. (53), pulmonary congestion was present in 80% of PD patients with volume overload. This calls for a more proactive approach in managing fluid status in PD patients. Although the NT-pro-BNP testing may not obviate the need for echocardiography, our data suggest that NT-pro-BNP testing may have a role in allowing us to target more detailed echocardiographic workup and aggressive fluid management on patients who run an increased risk for cardiac hypertrophy and dysfunction as well as extracellular volume expansion. Contrary to the previous notion that cardiac natriuretic peptides may have limited role in assessing the volume status of patients with ESRD as a result of the confounding influence by cardiac mass and function (54), our data suggest that NT-pro-BNP may serve as a useful composite biomarker of LVH and LV dysfunction, residual renal function, and extracellular volume expansion in chronic PD patients. In fact, cardiovascular congestion can be difficult to determine clinically in patients with ESRD. As shown by our data, BNP monitoring may be useful in filling in this gap and identifying patients who have ESRD and are at risk for cardiovascular congestion. Further prospective study is needed to evaluate whether serial changes in NT-pro-BNP may be more powerful than a single measurement of NT-pro-BNP in early identification of chronic PD patients with cardiac dysfunction and those who are at risk for cardiovascular congestion. Study also is needed to evaluate whether there exists a cutoff that discriminates preexisting cardiac dysfunction and hypertrophy from concurrent extracellular volume overload. On the basis of our results, there also may be a case for further randomized study to compare management of patients on the basis of NT-pro-BNP levels versus conventional care without NT-pro-BNP measurement.

One surprising observation was that CRP had no predictive value for cardiovascular congestion in our PD patients. This is

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>NT-pro-BNP (pg/ml)</th>
<th>Fourth versus First Quartile HR (95% CI)</th>
<th>P</th>
<th>Third versus First Quartile HR (95% CI)</th>
<th>P</th>
<th>Second versus First Quartile HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality (n = 66)</td>
<td>Unadjusted</td>
<td>13.42 (4.73 to 38.07)</td>
<td>&lt;0.001</td>
<td>5.63 (1.91 to 16.55)</td>
<td>0.002</td>
<td>3.19 (1.02 to 10.02)</td>
<td>0.047</td>
</tr>
<tr>
<td></td>
<td>Adjustedd,e</td>
<td>4.97 (1.35 to 18.28)</td>
<td>0.016</td>
<td>2.52 (0.78 to 8.16)</td>
<td>0.12</td>
<td>2.09 (0.63 to 6.93)</td>
<td>0.23</td>
</tr>
<tr>
<td>Cardiovascular congestion (n = 87)</td>
<td>Unadjusted</td>
<td>8.20 (4.14 to 16.24)</td>
<td>0.001</td>
<td>2.94 (1.38 to 5.83)</td>
<td>0.005</td>
<td>1.66 (0.77 to 3.59)</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td>Adjustedd,e</td>
<td>4.25 (1.56 to 11.62)</td>
<td>0.005</td>
<td>1.29 (0.51 to 3.21)</td>
<td>0.59</td>
<td>1.49 (0.63 to 3.55)</td>
<td>0.37</td>
</tr>
<tr>
<td>Composite end point of mortality and cardiovascular congestion (n = 117)</td>
<td>Unadjusted</td>
<td>5.71 (5.22 to 18.07)</td>
<td>0.001</td>
<td>3.55 (1.87 to 6.75)</td>
<td>0.001</td>
<td>2.06 (1.04 to 4.06)</td>
<td>0.038</td>
</tr>
<tr>
<td></td>
<td>Adjustedd,e</td>
<td>5.03 (2.07 to 12.26)</td>
<td>0.001</td>
<td>1.80 (0.81 to 4.01)</td>
<td>0.15</td>
<td>1.84 (0.86 to 3.96)</td>
<td>0.12</td>
</tr>
<tr>
<td>Cardiovascular mortality (n = 43)</td>
<td>Unadjusted</td>
<td>18.10 (4.24 to 77.24)</td>
<td>0.001</td>
<td>8.30 (1.89 to 36.56)</td>
<td>0.005</td>
<td>2.90 (0.56 to 14.95)</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>Adjustedd,e</td>
<td>7.50 (1.36 to 41.39)</td>
<td>0.021</td>
<td>3.63 (0.72 to 18.30)</td>
<td>0.12</td>
<td>1.76 (0.32 to 9.81)</td>
<td>0.52</td>
</tr>
<tr>
<td>Fatal and nonfatal cardiovascular event (n = 78)</td>
<td>Unadjusted</td>
<td>14.79 (5.20 to 42.10)</td>
<td>0.001</td>
<td>11.20 (3.95 to 31.77)</td>
<td>0.001</td>
<td>3.46 (1.12 to 10.73)</td>
<td>0.032</td>
</tr>
<tr>
<td></td>
<td>Adjustedd,e</td>
<td>9.10 (2.46 to 33.67)</td>
<td>0.001</td>
<td>7.98 (2.46 to 25.82)</td>
<td>0.001</td>
<td>3.05 (0.92 to 10.08)</td>
<td>0.068</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio; NT-pro-BNP, N-terminal-pro-brain natriuretic peptide.

*Additional covariates adjusted were serum fetuin-A and valvular calcification.

*Additional covariates adjusted were serum fetuin-A and valvular calcification.
somewhat contrary to our belief that volume overload is a process that involves immune activation (55). The exact reason for this discrepancy is not clear. It may suggest that inflammation, despite being highly prevalent and frequently associated with cardiovascular disease in dialysis patients, is unlikely to be the triggering factor for cardiovascular congestion. The other possibility is that only a single CRP was determined at baseline and may not reflect time-averaged exposure.

Several limitations of this study should be considered. First, this is a prognostic rather than an etiologic study. All of the parameters were measured on a single occasion at baseline and did not take into account changes over time. This may explain in part why some of the conventional risk factors such as residual renal function and peritoneal transport characteristics did not retain their significance in the final model. The use of a single NT-pro-BNP measurement likely understates the predictive power of NT-pro-BNP. However, it also reproduces the typical situation of everyday clinical practice. For the phenomenon of regression to the mean, one would expect the prediction power of NT-pro-BNP with the different outcomes being stronger than what emerged in our study. Further study with serial measurements of NT-pro-BNP and other important time-dependent covariates is needed to determine whether ongoing levels have stronger prognostic value for cardiovascular congestion and other outcomes. Second, peritoneal sodium removal was not estimated at baseline. Third, fluid status was not assessed at the time of enrollment. This would have enabled us to evaluate whether patients with higher NT-pro-BNP were in incipient volume overload. Fourth, only episodes of cardiovascular congestion that required hospitalization were considered as events. In patients who developed subclinical volume overload that did not require hospitalization, the episode was not counted as an event, and this may have resulted in an underestimation of this problem in our patients. Last, it is important to caution that the observed HR with NT-pro-BNP as well as some of the other factors were very high. This may be related to the relatively high numbers of independent predictors that were considered in the multivariable Cox regression models without a large number of events. It also may reflect a very selective racial population. Our results will need further confirmation in other prospective studies to become generally accepted.

Conclusion

NT-pro-BNP is not only a biomarker of LVH and LV dysfunction but also an important predictor of cardiovascular congestion that is associated with cardiac dysfunction. In addition, NT-pro-BNP predicts all-cause mortality and cardiovascular death and events in chronic PD patients. Our data suggest that NT-pro-BNP adds important prognostic value beyond that contributed by LVH and LV dysfunction, and NT-pro-BNP testing is a valuable adjunct to echocardiography. It should be incorporated as part of the regular cardiovascular assessment in chronic PD patients to identify those who have cardiac dysfunction and are at increased risk for cardiovascular congestion and adverse cardiovascular outcomes for earlier active intervention.

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Disclosures

None.

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