Natriuretic Peptides in Chronic Kidney Disease

Rajat Tagore,* Lieng H. Ling,† Hong Yang,† Hla-Yee Daw,† Yiong-Huak Chan,‡ and Sunil K. Sethi§

Division of Nephrology, Department of Medicine, National University Hospital, Singapore, and the Departments of Medicine, †Biostatistics Unit, and §Pathology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Background and objectives: B-type natriuretic peptide (BNP) and amino-terminal pro-B-type natriuretic peptide (NT-proBNP) are biomarkers of cardiovascular disease that is common in patients with chronic kidney disease (CKD). Conflicting data on the influence of glomerular filtration rate (GFR) on BNP and NT-proBNP levels in CKD may stem from failure to account fully for the effects of coexistent cardiac disease, dysfunction, and volume overload.

Design, setting, participants, & measurements: Prospective head-to-head comparison of plasma BNP and NT-proBNP in ambulatory euvolemic CKD patients with normal LV ejection fraction and no manifest cardiac or vascular disease. GFR was estimated by the Modification of Diet in Renal Disease formula, BNP and NT-proBNP measured using Abbott AxSYM and Roche Elecsys assays, respectively, and cardiac morphology and function assessed by transthoracic echocardiography.

Results: In 142 patients (42% female) of mean age 60 ± 11 yr, mean left ventricular ejection fraction was 71% ± 6%, GFR 38 ± 14 ml/min per 1.73 m², and median BNP and NT-proBNP level 59 and 311 pg/ml, respectively. Multivariate predictors of NT-proBNP level were GFR, β-blocker usage, LV mass index, and hemoglobin level. Plasma BNP was independently predicted by LV mass index and β-blocker usage but not GFR. In the 74 patients without diastolic dysfunction, there was a significant rise in NT-proBNP but not BNP as GFR declined.

Conclusions: Unlike NT-proBNP, plasma BNP level is relatively independent of GFR. BNP may therefore be the more appropriate biomarker to screen for cardiac dysfunction in CKD.


Patients with chronic kidney disease (CKD) are at increased risk of cardiovascular disease. Natriuretic peptides (NPs), biomarkers of myocardial dysfunction (1), offer the potential for early detection and risk stratification of cardiac disease, as evident in emergency department (2) and community (3,4) settings. This screening utility could be extended to CKD patients asymptomatic of cardiovascular disease.

However, the precise influence of CKD on circulating levels of B-type natriuretic peptide (BNP) and amino-terminal pro-B-type natriuretic peptide (NT-proBNP), the two commonly used NPs in clinical practice, continues to be debated. Dependence of plasma BNP on glomerular filtration rate (GFR) has been reported among patients with and without heart failure (HF) (5,6), but this relationship may not be independent of cardiac or volume-related factors (7,8). The data on NT-proBNP in renal dysfunction are more concordant but were derived from populations that included patients with myocardial infarction, reduced left ventricular (LV) ejection fraction (LVEF), or HF (9,10). Indeed, most studies examining the impact of renal dysfunction on NPs uniformly included such patients (5,6,8–10). Recent Doppler myocardial imaging studies have shown that even HF patients with normal LVEF have reduced LV contractility compared with controls (11,12).

To limit confounding by cardiac dysfunction or volume overload, we prospectively constituted a clinically euvolemic CKD cohort without symptoms or history of cardiac disease and normal LVEF and regional function. We measured circulating levels of both NPs, hypothesizing that, in these patients, BNP can be shown to be relatively independent of GFR compared with NT-proBNP if cardiac and loading factors can be comprehensively accounted for.

Materials and Methods

Study Subjects

Adult Asian outpatients aged 19 to 75 yr attending a CKD clinic at National University Hospital, Singapore, from November 2004 through October 2005 were prospectively recruited. All patients with stable stages III and IV CKD with estimated GFR of 15 to 60 ml/min per 1.73 m² body surface area (BSA) were invited to have an echocardiogram followed immediately by a blood draw. Exclusion criteria were 1) renal replacement therapy (dialysis or transplantation), 2) history of coronary artery disease, i.e., angina pectoris, previous myocardial infarction, and coronary artery intervention, 3) LVEF ≤50% or regional wall motion deficit assessed by any modality, 4) congenital or organic valvular heart disease, 5) cardiac arrhythmias including atrial fibrillation, 6) history of cerebrovascular disease, 7) peripheral vascular disease, i.e., a revascularization procedure or limb amputation, 8) hemoglobin <9 g/dl, 9) liver dysfunction, and 10) acute intercurrent illness. The study was

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Correspondence: Dr. Rajat Tagore, Department of Medicine, Level 3 Main Building, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074. Phone: (65) 67724339; Fax: (65) 67794361; E-mail: Rajat_Tagore@nuhs.edu.sg

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Information on age, gender, body mass index (BMI, calculated as weight divided by square of height), clinic blood pressure, regular medications, and associated comorbidities was recorded. Hypertension and diabetes mellitus were defined as documentation of the diagnosis or use of medications. GFR was estimated using the four-variable Modification of Diet in Renal Disease (MDRD) formula (13) and expressed in ml/min per 1.73 m² BSA.

Biochemical Analysis

Biochemical assays were performed at the College of American Pathologists-accredited Department of Laboratory Medicine at National University Hospital, Singapore. Anticoagulant free venous blood samples were assayed for NT-proBNP by electrochemiluminescence immunoassay on the Elecsys 2010 Immunoanalyzer (Roche Diagnostics, Indianapolis, IN). BNP levels were measured in plasma samples stored in ethylene diamine tetra acetic acid-coated tubes, using Microparticle Enzyme Immunoassay on the Abbott AxSYM analyzer (Abbott Laboratories Diagnostic Division, Abbott Park, IL). Exact values of these NPs were used in data analysis.

Echocardiography

All patients had a comprehensive M-mode, two-dimensional, and Doppler echocardiogram performed by a single experienced sonographer (H.Y.) using Vivid 7 Dimension ultrasound equipment (General Electric, Milwaukee, WI) and reported by an echocardiographer (L.H.L.) blinded to clinical and biochemical data. Studies were performed and quantitated in accordance with guidelines of the American Society of Echocardiography (14,15).

LV end-diastolic volume (LVEDV) and end-systolic volume (LVESV) were calculated using the Teichholz correction of the cube formula (16). LVEF was calculated as $100 \times \left( \frac{LVEDV - LVESV}{LVEDV} \right)$, LVEDV and LVESV were derived using the modified cube formula $1.04 \times (LVIDd + IVSd + LVPWd)^3 - LVIDd^3 \times 0.8 + 0.6$ (17). LA volume was calculated as $\pi/6 (A1 \times A2 \times A3)$, where A1 is the M-mode LA dimension and A2 and A3 are measurements of short- and long-axis LA dimensions, respectively, in the apical four-chamber view (18). LV mass (LVM), LVEDV, and LA volume were indexed for BSA and expressed as LVM/BSA, LVEDV/BSA, and LA volume/BSA, respectively. Maximum inferior vena cava (IVC) diameter was measured at end-expiration about 2 cm from the right atrial-IVC junction, just proximal to the hepatic veins.

Standard diastolic filling indices were measured from pulsed Doppler inflow, including early (E) and late (A) diastolic velocities and their ratio and pulmonary venous flow velocity curves. Early diastolic velocity of the mitral annulus (E′) was measured at the septal corner in the apical four-chamber view and the ratio of E to E′ velocity (E/E′) computed as a surrogate of LV filling pressure (19). By integrating these indices, global LV diastolic function was categorized as normal (grade 0), prolonged relaxation (grade 1), pseudonormal (grade 2), or restrictive (grades 3 and 4) (20).

Statistics

Data analysis was performed using SPSS 15.0 software (SPSS Inc, Chicago, IL). Continuous data were checked for normality using the Kolmogorov-Smirnov test and expressed as mean ± SD or median (range) as appropriate, and categorical data as percentages. Differences between groups were tested using one-way analysis of variance or a nonparametric alternative (Mann-Whitney or Kruskal-Wallis test) as appropriate. The Spearman rank sum test was used to correlate NP levels with a priori selected clinical and echocardiographic variables of LV remodeling, systolic function, relaxation, and preload. Linear regression vis-à-vis quartiles of NP levels was performed on variables that correlated at a threshold $P \leq 0.15$ with either NP in univariate analysis. Preliminary analyses were conducted to ensure no important violation of the assumptions of linearity, multicollinearity, and homoscedasticity. Multicollinearity was assessed by first examining the pairwise relationships between variables (excluding if rho > 0.70) and in the multivariate model, the tolerance of the variable (significant collinearity if $>0.10$). Multiple regression was done in two stages, first using a backward removal algorithm of candidate clinical (including GFR) and echocardiographic variables to identify the best predictors in either block, followed by hierarchical multiple regression, controlling for clinical covariates. The analysis was repeated after excluding statistically redundant variables. Models were separately constructed for BNP and NT-proBNP. Statistical significance was set at $P < 0.05$.

Based on reported correlations (in the range of $-0.2$ to $-0.3$) between BNP and GFR for patients with and without HF (5), a sample size of 140 to 150 patients was considered sufficient to achieve statistical significance with 85% power and allowable 2-sided error of 0.05.

Results

A total of 149 patients consented to participate. Of these, 6 were excluded on the basis of echocardiographic abnormalities, i.e., LVEF <50% (3 patients), regional wall motion abnormality (3 patients), and moderate mitral regurgitation (one patient). One patient was later excluded after magnetic resonance imaging showed evidence of remote ischemic stroke. The study cohort therefore comprised 142 patients of Chinese (90 subjects), Malay (41), and Indian (11) ethnicity whose clinical and echocardiographic characteristics are detailed in Table 1. Excluding one patient with uninterpretable diastolic function, diastolic dysfunction grade was 0, 1, and 2 in 74 (52%), 45 (32%), and 22 (15%) patients, respectively. No patient had frank restrictive LV filling.

CKD was attributed to diabetic nephropathy in 57 patients (39%), hypertensive nephrosclerosis in 14 (10%), small endogenic kidneys in 43 (30%), IgA nephropathy in 10 (7%) and miscellaneous causes in 19 patients (14%), including focal segmental glomerular sclerosis, autosomal dominant polycystic kidney disease, membranoproliferative and membranous glomerulonephritis, renal calculus disease, systemic lupus erythematosus, and chronic sclerosing glomerulonephritis. Medications used included angiotensin-converting enzyme inhibitors (89 patients, 62%), angiotensin receptor blockers (79, 55%), ß-blockers (79, 55%) diuretics (76, 53%), and statins (106, 74%).

Figure 1 shows scatter plots of GFR against both NPs. With increasing severity of renal dysfunction, there was an increasing trend and scatter of circulating NT-proBNP levels that was apparent with BNP. Table 2 shows BNP, NT-proBNP, and LVEF values stratified by GFR groups; differences across groups were significant only for NT-proBNP.

Univariate correlations of clinical and echocardiographic variables with NP levels are shown in Table 3. GFR showed a moderate, highly significant correlation with NT-proBNP and a weak, borderline significant correlation with BNP. There were
also moderate correlations between hemoglobin level and NT-proBNP and between LV mass/BSA and LA volume/BSA and both NPs.

Table 4 shows the final multiple regression models for each NP. Independent predictors of BNP level were LVM/BSA ($P < 0.0016$) and β-blocker usage ($P < 0.0071$), each variable accounting for approximately 7% of total variance. For NT-proBNP, multivariate predictors were GFR ($P < 0.00001$), β-blocker usage ($P = 0.0010$), LV mass/BSA ($P = 0.011$), and hemoglobin level ($P = 0.023$). The clinical model alone explained 33% of the total variance with GFR accounting for just over half of this. After incorporation of LV mass/BSA, the model explained 36% of NT-proBNP variance ($R^2$ change, 3%). There was no significant multicollinearity in any of the analyses.

Figure 2 shows three-dimensional plots trending median NP levels by GFR and diastolic dysfunction grade. These illustrate the general trend, especially among patients with GFR < 30 ml/min per 1.73 m$^2$ that NP levels increase with progressive diastolic dysfunction. In the 74 patients with grade 0 diastolic dysfunction, median NT-proBNP level increased significantly with each lower GFR strata (test for trend, $P = 0.001$). This was not observed with plasma BNP ($P = 0.58$).

**Discussion**

NPs are increasingly used in clinical practice to diagnose myocardial dysfunction. Their growing importance as reflected in a recent consensus statement on HF (21) mandates a clear characterization of the dependence of NP levels on renal dysfunction, a common comorbidity among HF patients. The ideal NP to diagnose or monitor cardiac dysfunction in the setting of CKD remains debated. Clearance of plasma BNP, the biologically active fragment of proBNP, occurs via endocytosis and lysosomal degradation after binding to NP clearance receptor type C and secondarily via proteolysis by neutral endopeptidase 24.11 (22). Peripheral receptors for NT-proBNP are not known and its clearance less well established, but renal excretion may play a role (23). Nevertheless, few data convincingly support the presumption that NT-proBNP is more prone than BNP to be influenced by renal dysfunction (10,24). In this head-to-head study, we demonstrate an independent inverse correlation between GFR and NT-proBNP but not BNP in asymptomatic stage III and IV CKD outpatients in whom cardiac risk stratification is of particular importance.

The large Breathing Not Properly Multinational Study (5) established a weak but statistically significant relationship between GFR and BNP in patients presenting emergently with acute dyspnea, 35% of whom had a history of HF and 25%
myocardial infarction. In this setting, the impact of renal dysfunction on NP levels is difficult to ascertain given additional and variable contributions of LV and right ventricular systolic and diastolic dysfunction, myocardial ischemia, volume overload, and mitral regurgitation (25). Thus, in the study of Tsuchimoto et al. (6), HF patients with estimated GFR <40 ml/min and the highest BNP levels did indeed have higher median LV end-diastolic pressure compared with those with better preserved GFR. Such patients with presumed “cardiorenal syndrome” (26) may also have higher NP levels arising from advanced heart disease, greater preload, and multiple other comorbidities (27,28). Falsely low estimated GFR caused by poor renal perfusion or diuretic use in acute HF further complicate the relationship with NPs (5). To minimize some of these confounders, Takami et al. (8) excluded patients with LVEF <40%, regional wall motion abnormality, and valvular disease in their study of 103 Japanese predialysis inpatients with more severe volume or pressure overload than our cohort, as evidenced by larger IVC diameter and LV mass index. Consistent with our study, they found that BNP level in CKD patients was independent of GFR but dependent on echocardiographic surrogates of LV volume overload and LV end-diastolic pressure.

To date, few studies have compared NPs head-to-head in patients with CKD (10,11). Vickery et al. (9) showed increases in NP concentrations with declining GFR, which was greater for NT-proBNP. Although median LVEF was normal for all CKD

Table 2. Distribution of plasma natriuretic peptide levels, left ventricular (LV) ejection fraction, and frequency of diastolic dysfunction in relation to glomerular filtration rate (GFR), expressed in ml/min per 1.73 m²

<table>
<thead>
<tr>
<th>GFR Group A, 15–30 (n = 51)</th>
<th>GFR Group B, 31–45 (n = 40)</th>
<th>GFR Group C, 46–60 (n = 51)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR</td>
<td>24 (19–29)</td>
<td>37 (34–41)</td>
<td>54 (51–58)</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>64 (27–136)</td>
<td>82 (23–153)</td>
<td>40 (5–134)</td>
</tr>
<tr>
<td>NT-proBNP (pg/ml)</td>
<td>270 (100–404)</td>
<td>150 (76–327)</td>
<td>77 (33–130)</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>72 (67–75)</td>
<td>71 (67–76)</td>
<td>71 (66–74)</td>
</tr>
</tbody>
</table>

Data are median (range). GFR, glomerular filtration rate; BNP, B-type natriuretic peptide; NT-proBNP, amino-terminal pro-B-type natriuretic peptide.

Table 3. Association of selected clinical and echocardiographic variables with B-type natriuretic peptide (BNP) and amino-terminal pro-B-type natriuretic peptide (NT-proBNP)

<table>
<thead>
<tr>
<th>BNP</th>
<th>NT-proBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.23</td>
</tr>
<tr>
<td>Female gender</td>
<td>-0.02</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.24</td>
</tr>
<tr>
<td>ACEI or ARB usage</td>
<td>-0.02</td>
</tr>
<tr>
<td>β-blocker usage</td>
<td>0.26</td>
</tr>
<tr>
<td>Diuretic usage</td>
<td>0.09</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.04</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>-0.13</td>
</tr>
<tr>
<td>GFR</td>
<td>-0.17</td>
</tr>
<tr>
<td>LV end-diastolic volume</td>
<td>0.18</td>
</tr>
<tr>
<td>LV end-systolic volume</td>
<td>0.11</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>0.06</td>
</tr>
<tr>
<td>LV mass/BSA</td>
<td>0.32</td>
</tr>
<tr>
<td>LA volume/BSA</td>
<td>0.34</td>
</tr>
<tr>
<td>Maximum IVC diameter</td>
<td>0.18</td>
</tr>
<tr>
<td>Mitral E/A ratio</td>
<td>0.05</td>
</tr>
<tr>
<td>Mitral deceleration time</td>
<td>0.06</td>
</tr>
<tr>
<td>IVRT</td>
<td>-0.01</td>
</tr>
<tr>
<td>Septal E’ velocity</td>
<td>-0.16</td>
</tr>
<tr>
<td>Septal E/E’ ratio</td>
<td>0.19</td>
</tr>
</tbody>
</table>

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; GFR, glomerular filtration rate; LV, left ventricular; BSA, body surface area; E/A, ratio of early and late diastolic velocities; IVRT, isovolumic relaxation time.

aNot considered in multiple regression of echocardiographic variables.
strata, 6% of patients had prevalent HF and 35% had known cardiovascular disease. Because detailed evaluation of cardiac function was not performed, the observed rise in BNP may not relate solely to GFR, but there is consensus with the present study on the greater GFR dependence of NT-proBNP. In contrast, Luchner et al. (10) showed, among survivors of myocardial infarction, virtually equal (2-fold) increases in median values of both NPs in those with renal dysfunction. Because the assigned creatinine clearance partition value for renal dysfunction was 85 ml/m² with mean clearance being 71 ml/min in the renally impaired patients and because both groups with and without renal dysfunction had identically reduced LVEF (mean, 50%) and self-reported HF symptoms (1 of 5 cases), their findings could reflect preponderant cardiac dysfunction in the face of relatively mild renal impairment.

Our study attempts to account for the confounding influence of systolic and, in a more limited fashion, diastolic dysfunction on NP levels. The degree of diastolic dysfunction was not severe in our cohort, consistent with the asymptomatic population. In patients without diastolic dysfunction or raised LV filling pressure, there was again a clear inverse relationship of NT-proBNP level with GFR that was not observed with BNP.

Apart from GFR, the observed associations of NP levels with β-blocker treatment (29–32), LVM/BSA (33,34), and hemoglobin concentration (35,36) have previously been highlighted in isolation. Similar to previous studies (34), LVM/BSA better predicted NP levels than any echocardiographic variable assessed and, in particular, was superior to both blood and tissue Doppler indices of diastolic dysfunction. Such may not be the case for less homogeneous populations. Additionally, the predictor model for BNP explained only 13% of total variance, suggesting that multiple, more complex factors modulate plasma BNP. NT-proBNP level was more readily predicted by candidate variables, most notably GFR, which explained more than one third of the variance.

A correlation of NP levels with age, especially NT-proBNP, has been reported in both Western (39,40) and Asian populations (41). In our patients, age correlated with plasma NP levels in univariate analysis but lacked independent predictive value. This is not unexpected in a CKD cohort where LV hypertrophy, a variable highly correlated with age, is frequently encountered.

Table 4. Multivariate predictors of plasma B-type natriuretic peptide (BNP) and amino-terminal pro-B-type natriuretic peptide (NT-proBNP)

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>SE</th>
<th>95% CI</th>
<th>β</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV mass/BSA</td>
<td>0.012</td>
<td>0.004</td>
<td>0.005 to 0.019</td>
<td>0.258</td>
<td>0.0016</td>
</tr>
<tr>
<td>β-blocker usage</td>
<td>0.489</td>
<td>0.179</td>
<td>0.135 to 0.843</td>
<td>0.219</td>
<td>0.0071</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR</td>
<td>−0.035</td>
<td>0.006</td>
<td>−0.046 to −0.023</td>
<td>−0.426</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>β-blocker usage</td>
<td>0.527</td>
<td>0.157</td>
<td>0.217 to 0.837</td>
<td>0.235</td>
<td>0.0010</td>
</tr>
<tr>
<td>LV mass/BSA</td>
<td>0.008</td>
<td>0.003</td>
<td>0.002 to 0.015</td>
<td>0.179</td>
<td>0.011</td>
</tr>
<tr>
<td>hemoglobin</td>
<td>−0.086</td>
<td>0.038</td>
<td>−0.161 to −0.012</td>
<td>−0.165</td>
<td>0.023</td>
</tr>
</tbody>
</table>

B, unstandardized regression coefficient; β, standardized regression coefficient; CI, confidence intervals; SE, standard error of the estimate; LV, left ventricular; BSA, body surface area; GFR, glomerular filtration rate.

Figure 2. Three-dimensional bar graphs of median levels of B-type natriuretic peptide (BNP, left panel) and N-terminal pro-B-type natriuretic peptide (NT-proBNP, right panel) versus glomerular filtration rate (GFR, expressed in ml/min per 1.73 m²) and diastolic dysfunction grade.
Limitations

Despite careful patient selection, occult myocardial ischemia, which may raise circulating NP levels (42), cannot be ruled out in some of our CKD patients. Intensive screening for coronary artery disease was not systematically performed as all patients were free of symptoms or signs of cardiovascular disease.

LVEF was assessed using volumes derived from the M-mode rather than Simpson’s method. The former technique provides excellent temporal resolution of endocardial motion, is highly reproducible and appropriate for use in our patients with symmetric LV morphology, and validated by a wealth of clinical data (43). Despite known limitations, LVEF was used as the index of systolic function in our study to permit comparison across studies.

Use of the MDRD formula to estimate GFR is controversial, especially in Asians (44,45). Compared with other formulas, however, MDRD provides the most precise estimate of true renal function, especially in the lower GFR ranges, and is hence the most reliable in clinical practice (46). Indeed, a good correlation in patients with GFR <60 ml/min has been recently reported in a large, diverse population (47).

Conclusion

CKD and consequent end-stage renal failure are threatening to reach epidemic proportions worldwide over the next decade (48). Thus, an increasing number of CKD patients will require early institution of retardation strategies and screening for co-morbidity, in particular, cardiac BNP appears not to be significantly influenced by renal dysfunction and may therefore be the biomarker of choice for detection and surveillance of myocardial dysfunction in CKD patients. This recommendation is predicated on the demonstrated equivalence of BNP and NT-proBNP in detection of LV systolic and diastolic dysfunction among predominantly non-CKD patients (40,49). However, further studies should be done to verify the performance characteristics of both NPs in prospective detection of cardiac dysfunction in the CKD population.

Acknowledgments

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Disclosures

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References

24. Hall C: NT-ProBNP: the mechanism behind the marker.


