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ORIGINAL ARTICLE
Heart Failure

Renal Clearance of N-Terminal pro-Brain Natriuretic Peptide Is Markedly Decreased in Chronic Kidney Disease

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Background: The ratio of N-terminal pro-brain natriuretic peptide (NT-proBNP) secretion from the heart to peripheral NT-proBNP remains unknown in patients with chronic kidney disease (CKD).

Methods and Results: We measured plasma NT-proBNP in the aortic root (AO; NT-proBNP$_{AO}$) and in the coronary sinus (CS; NT-proBNP$_{CS}$) in 544 patients. Patients were classified into 6 categories based on estimated glomerular filtration rate (eGFR): G1, n=44, eGFR ≥90 mL/min/1.73 m^2; G2, n=221, 60≤eGFR<90 mL/min/1.73 m^2; G3a, n=132, 45≤eGFR<60 mL/min/1.73 m^2; G3b, n=77, 30≤eGFR<45 mL/min/1.73 m^2; G4, n=34, 15≤eGFR<30 mL/min/1.73 m^2; and G5, n=36, eGFR <15 mL/min/1.73 m^2. In non-CKD patients, hemodynamics but not eGFR were independent predictors of log NT-proBNP. In CKD patients, eGFR and hemodynamics were independent predictors of log NT-proBNP. The ratio of NT-proBNP secretion from the heart to NT-proBNP$_{AO}$ significantly decreased with decreasing eGFR in 6 groups (P<0.0001): G1, 67±38%; G2, 50±24%; G3a, 40±21%; G3b, 30±16%; G4, 14.8±7.9%; and G5, 3.5±2.4%, respectively.

Conclusions: eGFR contributes to the value of NT-proBNP for prediction of hemodynamic overload in CKD patients but not in non-CKD patients, and the ratio of NT-proBNP secretion from the heart to peripheral NT-proBNP is markedly decreased in CKD patients, especially those with eGFR <30 mL/min/1.73 m^2.

Key Words: Chronic heart failure; Chronic kidney disease; Estimated glomerular filtration rate; N-terminal pro-brain natriuretic peptide

Plasma brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP), as markers of ventricular wall-stress, are well-established biomarkers of hemodynamic abnormality, diagnosis and prognosis in patients with chronic heart failure (CHF).[1–6] After secretion of BNP and NT-proBNP from the coronary sinus (CS), clearance of BNP occurs via enzymatic breakdown such as by neutral endopeptidase and dipeptidyl peptidase-4, and natriuretic receptor binding, or renal excretion,[7] while NT-proBNP is mainly cleared by the kidneys. Interestingly, urinary NT-proBNP is significantly lower in CHF patients than in control subjects,[8] suggesting that a marked decrease in urinary excretion of NT-proBNP contributes to a high plasma NT-proBNP due to tubular injury in CHF patients with chronic kidney disease (CKD). In addition, the extracardiac mechanism of elevation of plasma NT-proBNP depends on renal clearance and metabolism,[8,9] indicating that the ratio of NT-proBNP secretion from the heart to peripheral NT-proBNP is potentially a marker of renal clearance of NT-proBNP.

NT-proBNP secretion from the heart is regulated by ventricular wall-stress, and peripheral NT-proBNP is mainly influenced by renal clearance and metabolism. Peripheral BNP is significantly decreased by 20% compared with that in the left ventricle.[10] According to preliminary data, there was no difference between plasma NT-proBNP in the aortic root (AO; NT-proBNP$_{AO}$) and that in the peripheral vein, suggesting that NT-proBNP is not cleared in systemic circulation and is mainly cleared by the kidneys. The ratio of NT-proBNP secretion from the heart to peripheral NT-proBNP, however, remains unknown in patients with CKD.

CKD is classified into 6 categories based on estimated glomerular filtration rate (eGFR), and the proportion of deaths from cardiovascular disease increases as eGFR decreases.[11] Importantly, in patients with mild–moderate CKD (stages 3a, 3b), the incidence of cardiovascular mortality is much higher than the incidence of kidney failure.[12,13] Therefore, cut-offs of biomarkers for the diagnosis and prognosis of CHF are important in these patients. Recently, Aimo et al reported that the cut-off of NT-proBNP for predicting hospitalization and death varied widely with CKD stage.[14] We previously reported that NT-proBNP is more influenced by eGFR than is BNP by sampling blood from the AO and CS in CHF patients.[15] The ratio of NT-proBNP secretion to peripheral NT-proBNP,

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Table 1. Characteristics of Patients With Left-Sided Heart Disease (n=544)

Variables		CKD stage (eGFR: mL/min/1.73 m²)						P-value†
		G1 (≥90)	G2 (60–89)	G3a (45–59)	G3b (30–44)	G4 (15–29)	G5 (<15)	
Patients	544	44 (8)	221 (41)	132 (24)	77 (14)	34 (6)	36 (7)	
eGFR (mL/min/1.73 m²)	58±24	102±16	72±8.3	53±4.4	38±3.8	25±4	6.5±3	<0.0001
Age (years)	65±12	54±17	62±11	68±9	69±9.8	72±8.5	65±10	<0.0001
Sex (M/F)	397/150	31/13	163/59	104/28	53/25	20/14	26/10	NS
BMI (kg/m²)	23±3.7	23±5.2	22.8±3.8	23.3±3.5	22.4±3.1	22.8±2.7	22.6±3.2	NS
Heart failure	393 (72)	32 (71)	155 (70)	101 (77)	68 (87)	22 (65)	36 (100)	0.0002
AF	77 (14)	5 (11)	31 (14)	18 (14)	13 (17)	8 (24)	2 (6)	NS
Creatinine (mg/dL)	1.5±2.0	0.6±0.1	0.8±0.1	1.0±0.1	1.3±0.2	2.0±0.5	8.2±3.2	<0.0001
NT-proBNP$_{AO}$ (pg/mL)	669 (293–1,514)	545 (215–868)	437 (224–995)	592 (259–1,261)	800 (461–1,650)	2,552 (1,245–7,081)	10,206 (3,600–24,865)	<0.0001
NT-proBNP$_{CS}$ (pg/mL)	931 (408–504)	808 (376–1,668)	634 (341–1,419)	811 (369–1,736)	979 (621–1,978)	2,752 (1,463–8,454)	10,554 (3,703–25,294)	<0.0001
NT-proBNP$_{CS–AO}$ (pg/mL)	207 (102–459)	268 (128–643)	180 (96–437)	200 (102–399)	173 (110–434)	349 (172–841)	402 (105–496)	0.07
NT-proBNP$_{CS–AO}$/ NT-proBNP$_{AO}$ (%)	41±27	67±38	50±24	40±21	30±16	14.8±7.9	3.5±2.4	<0.0001
MBP (mmHg)	89±16	85±16	89±16	88±15	87±14	90±19	97±17	0.01
LVEF (%)	47±14	47±17	48±14	47±14	47±13	44±15	52±11	NS
LVEDP (mmHg)	13±6.4	14±5.8	12.5±6.2	13.5±6.5	13.4±5.9	14±7.9	12±7.1	NS
Etiology								NS
IHD	317 (58)	20 (42)	135 (61)	80 (61)	42 (54)	20 (59)	20 (56)	NS
DCM	106 (19)	15 (31)	43 (19)	26 (20)	15 (19)	6 (18)	1 (3)	NS
HHD	61 (11)	5 (10)	25 (11)	11 (8)	12 (15)	6 (18)	2 (6)	NS
VHD	68 (12)	6 (13)	23 (10)	20 (15)	10 (13)	6 (18)	3 (8)	NS
HT	271 (50)	16 (33)	102 (46)	70 (53)	44 (56)	10 (29)	29 (81)	NS
HL	258 (47)	17 (35)	116 (52)	67 (51)	35 (45)	7 (21)	16 (44)	NS
DM	184 (34)	11 (23)	63 (28)	49 (37)	26 (33)	10 (29)	25 (69)	NS
Treatment								
ACEI or ARB	399 (73)	32 (67)	159 (72)	109 (83)	62 (80)	19 (56)	18 (50)	NS
Ca blocker	120 (22)	10 (21)	45 (29)	19 (14)	14 (18)	7 (21)	25 (69)	NS
Diuretics	241 (44)	17 (35)	74 (33)	66 (50)	52 (67)	16 (47)	16 (44)	NS
Aldosterone blockers	158 (29)	9 (19)	52 (23)	46 (35)	38 (49)	12 (35)	1 (3)	NS
β-blockers	245 (46)	21 (44)	82 (37)	71 (54)	40 (51)	16 (47)	15 (42)	NS

Data given as n (%), mean±SD or median (IQR). †ANOVA. ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AO, aortic root; ARB, angiotensin receptor blocker; BMI, body mass index; CKD, chronic kidney disease; CS, coronary sinus; DCM, dilated cardiomyopathy; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HHD, hypertensive heart disease; HL, hyperlipidemia; HR, heart rate; HT, hypertension; IHD, ischemic heart disease; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; MBP, mean blood pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; VHD, valvular heart disease.

however, remains unknown in patients with CKD, especially in severe and end-stage CKD patients. In addition, obesity is associated with the development of CKD and is a risk for CHF. Body mass index (BMI) is a marker of obesity, characterized by low NT-proBNP, but whether this NT-proBNP secretion is from the heart remains unclear.

Methods

Patients

The subjects consisted of 544 consecutive heart disease patients who underwent cardiac catheterization for clinical indications. Patients with acute coronary syndrome, aortic valve stenosis, mitral valve stenosis, hypertrophic cardiomyopathy, pericarditis, primary pulmonary hypertension, or lung disease were excluded. Patients on dialysis were not excluded. Patients with right-side heart disease were excluded and patients with mean pulmonary arterial pressure ≥25 mmHg and pulmonary capillary wedge pressure <15 mmHg were excluded because most patients had left-sided heart disease at the present institution. CHF was defined as symptomatic heart failure at sampling or hospitalization for heart failure in the previous 12 months. eGFR was used as an indicator of renal function based on the abbreviated Modification of Diet in Renal Disease study formula.[16] Patients were classified into 6 categories based on eGFR:[17] G1, n=44, eGFR ≥90 mL/min/1.73 m²; G2, n=221, 60≤eGFR<90 mL/min/1.73 m²; G3a, n=132, 45≤eGFR<60 mL/min/1.73 m²; G3b, n=77, 30≤eGFR<45 mL/min/1.73 m²; G4, n=34, 15≤eGFR<30 mL/min/1.73 m²; and G5, n=36, eGFR <15 mL/min/1.73 m². Informed consent was obtained from all patients for participation in the study, according to a protocol approved by the institution Committee on Human Investigation.

Study Protocol

All patients were pre-medicated with an oral dose of diazepam (5 mg) and rested in bed in a supine position

Table 2. Indicators of Transcardiac Increase in Log NT-proBNP$_{CS-AO}$ (n=544)

Variables	Univariate correlation coefficient	P-value	Multivariable β-coefficient (SE)	P-value
Age (years)	−0.089	0.038		
Sex (male=1)	0.057	0.187		
AF (AF=1)	0.007	0.87		
BMI (kg/m^2)	−0.131	0.0022	−0.017 (0.005)	0.0002
LVEDP (mmHg)	0.285	<0.0001	0.017 (0.005)	<0.0001
LVEF (%)	−0.330	<0.0001	−0.09 (0.001)	<0.0001
eGFR (mL/min/1.73 m^2)	−0.028	0.508		

Abbreviations as in Table 1.

Table 3. Indicators of Log NT-proBNP$_{AO}$ in 264 Non-CKD Patients

Variables	Univariate correlation coefficient	P-value	Multivariable β-coefficient (SE)	P-value
Age (years)	−0.015	0.814		
Sex (male=1)	0.143	0.025		
AF (AF=1)	0.006	0.923		
BMI (kg/m^2)	−0.171	0.0053	−0.025 (0.006)	<0.0001
LVEDP (mmHg)	0.278	<0.0001	0.021 (0.004)	<0.0001
LVEF (%)	−0.233	<0.0001	−0.08 (0.002)	<0.0001
eGFR (mL/min/1.73 m^2)	0.001	0.991		

Abbreviations as in Table 1.

Table 4. Indicators of Log NT-proBNP$_{AO}$ in 280 CKD Patients

Variables	Univariate correlation coefficient	P-value	Multivariable β-coefficient (SE)	P-value
Age (years)	−0.027	0.648		
Sex (male=1)	0.105	0.080		
AF (AF=1)	0.020	0.737		
BMI (kg/m^2)	−0.227	0.0001	−0.027 (0.008)	0.0005
LVEDP (mmHg)	0.238	<0.0001	0.020 (0.004)	<0.0001
LVEF (%)	−0.223	0.0002	−0.10 (0.002)	<0.0001
eGFR (mL/min/1.73 m^2)	−0.645	<0.0001	−0.25 (0.002)	<0.0001

Abbreviations as in Table 1.

for at least 20 min. Right-sided and left-sided cardiac catheterization was performed and blood pressure was measured. Blood samples for measuring plasma NT-proBNP were collected simultaneously from the AO and CS (NT-proBNP$_{AO}$ and NT-proBNP$_{CS}$). A 6-Fr catheter for blood sampling was positioned in the CS, and the position of the catheter was confirmed as previously reported.[18]

Measurement of NT-proBNP

Plasma NT-proBNP concentration was measured using the Elecsys proBNP sandwich immunoassay (Roche Diagnostics, Elecsys proBNP II), as previously reported.[15]

Statistical Analysis

All results are expressed as mean±SD or median (IQR). The chi-squared test or 1-way analysis of variance was used to determine differences between the 6 groups, and the differences were tested using Scheffe's F-test. Univariate analysis was examined using Student's t-test. Because NT-proBNP was not normally distributed, differences in mean NT-proBNP between the groups were detected on Wilcoxon rank-sum test with 2-tailed P<0.05, and log NT-proBNP was used in correlations and regression models. To evaluate the contribution of the transcardiac increase in NT-proBNP (i.e., log NT-proBNP$_{CS-AO}$), and log NT-proBNP$_{AO}$, univariate and stepwise multivariate analyses were used to compare 7 variables including hemodynamic parameters and eGFR. Linear regression analysis was used to determine the relationships between continuous variables. The difference in the intercept of the linear regression line between 2 groups was analyzed using ANCOVA. P<0.05 was regarded as significant.

Results

Patient Characteristics

Table 1 summarizes the patient characteristics according to CKD stage based on eGFR. There were no differences in NT-proBNP$_{CS-AO}$, left ventricular ejection fraction (LVEF), or left ventricular end-diastolic pressure (LVEDP) in

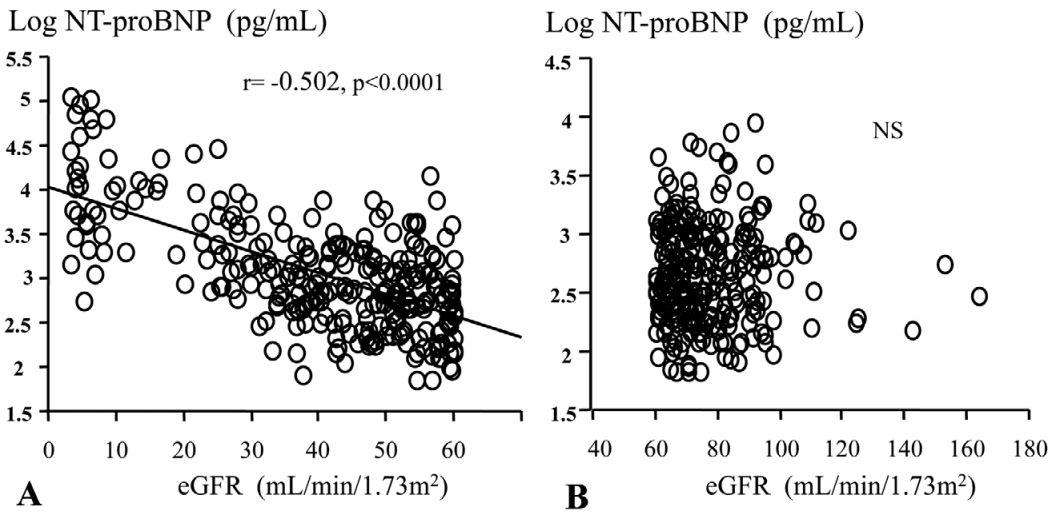

Figure 1. Relationship between estimated glomerular filtration rate (eGFR) and plasma log N-terminal pro-brain natriuretic peptide (NT-proBNP) in (**A**) patients with chronic kidney disease (CKD) and (**B**) patients with non-CKD.

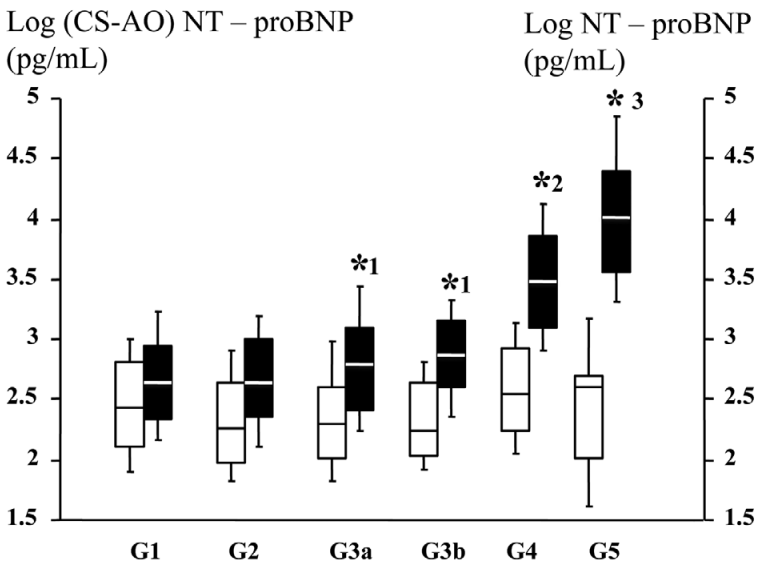

Figure 2. (□) Log N-terminal pro-brain natriuretic peptide (coronary sinus–aortic root; NT-proBNP$_{CS-AO}$) and (■) log NT-proBNP$_{AO}$ vs. chronic kidney disease (CKD) stage. Crossbars, median; box, IQR. CKD stages: G1, estimated glomerular filtration rate (eGFR) ≥90 mL/min/1.73 m^2; G2, 60≤eGFR<90 mL/min/1.73m^2; G3a, 45≤eGFR<60mL/min/1.73m^2; G3b, 30≤eGFR<45 mL/min/1.73 m^2; G4, 15≤eGFR<30mL/min/1.73 m^2; G5, eGFR <15 mL/min/1.73 m^2. *^{1}P<0.001 vs. G2, *^{2}P<0.001 vs. G3a and G3b, *^{3}P<0.001 vs. G4 with ANOVA regarding with log NT-proBNP in the AO.

left-sided heart disease patients.

Predictors of Plasma NT-proBNP in Left-Sided Heart Disease

On stepwise multivariate analysis, LVEDP, LVEF, and BMI were independent predictors of logNT-proBNP$_{CS-AO}$, and eGFR was not an independent predictor (**Table 2**). In non-CKD patients (n=264), LVEDP, LVEF, and BMI were independent predictors of log NT-proBNP$_{AO}$, and eGFR was not an independent predictor (**Table 3**). In patients with CKD (n=280), LVEDP, LVEF and BMI, and eGFR were independent predictors of log NT-proBNP$_{AO}$ (**Table 4**). In non-CKD patients, there was no relationship between eGFR and log NT-proBNP$_{AO}$. In patients with CKD there was a significant negative correlation between eGFR and log NT-proBNP$_{AO}$ (**Figure 1**).

Log NT-proBNP$_{CS-AO}$ and Log NT-proBNP$_{AO}$ vs. CKD Stage

Between the 6 groups, there were no significant differences in NT-proBNP$_{CS-AO}$ (**Table 1**). NT-proBNP$_{AO}$ was significantly increased with increasing CKD stage (**Table 1**; **Figure 2**). The NT-proBNP$_{CS-AO}$/NT-proBNP$_{AO}$ ratio significantly decreased with decreasing eGFR in the 6 groups (P<0.0001; G1, 67±38%; G2, 50±24%; G3a, 40±21%; G3b, 30±16%; G4, 14.8±7.9%; and G5, 3.5±2.4%, respectively; **Figure 3**). There were no differences in LVEF, LVEDP, or the transcardiac gradient of NT-proBNP, but plasma NT-proBNP$_{AO}$ in the CKD stage 3 patients was

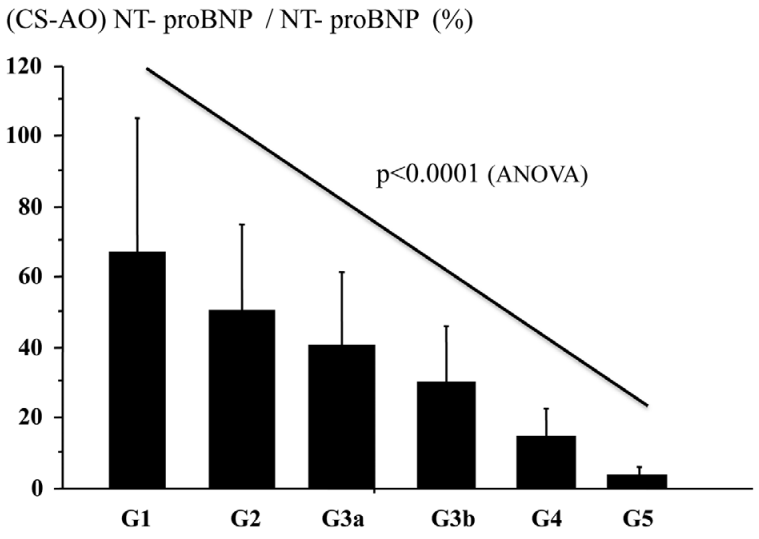

Figure 3. N-terminal pro-brain natriuretic peptide (coronary sinus–aortic root; NT-proBNP$_{CS-AO}$)/NT-proBNP$_{AO}$ ratio vs. chronic kidney disease (CKD) stage. G1, estimated glomerular filtration rate (eGFR) ≥90 mL/min/1.73 m^2; G2, 60≤eGFR<90 mL/min/1.73 m^2; G3a, 45≤eGFR<60 mL/min/1.73 m^2; G3b, 30≤eGFR<45 mL/min/1.73 m^2; G4, 15≤eGFR<30 mL/min/1.73 m^2; G5, eGFR <15 mL/min/1.73 m^2.

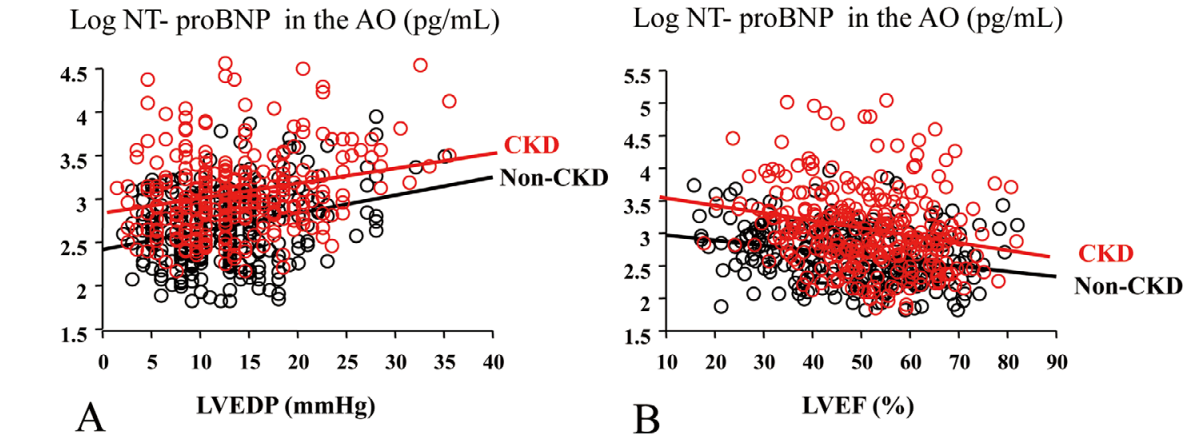

Figure 4. Log N-terminal pro-brain natriuretic peptide in the aortic root (log NT-proBNP$_{AO}$) vs. (**A**) left ventricular end-diastolic pressure (LVEDP) and (**B**) left ventricular ejection fraction (LVEF) in (black circles) non-chronic kidney disease (non-CKD) patients and (red circles) patients with CKD.

approximately double that of the non-CKD patients; and approximately 5-fold in the CKD stage 4, and approximately 10-fold in the CKD stage 5 patients compared with the non-CKD patients (**Table 1**).

Hemodynamics and NT-proBNP: Impact of Renal Function

There were significant correlations between LVEDP, LVEF and the transcardiac increase in log NT-proBNP in non-CKD and CKD patients in both groups with the same regression line (data not shown). The regression line between LVEDP, LVEF and log NT-proBNP$_{AO}$ in CKD patients had a significant upward shift compared with that in non-CKD patients (P<0.001, **Figure 4**).

Discussion

Plasma NT-proBNP is a useful biomarker for mortality including cardiovascular death, not only in CHF patients but also in the general population.[1,6,14,18] Given that NT-proBNP ranges widely in patients with CKD,[14,19,20] the percentage of peripheral NT-proBNP of cardiac origin remains unknown in these patients. To address the problem, we measured the plasma NT-proBNP level in the AO and CS in 544 consecutive patients with left-sided heart disease and compared hemodynamic parameters in CKD patients. The present study suggests that (1) if we evaluate the severity of hemodynamic overload by plasma NT-proBNP, we should not account of eGFR in non-CKD patients; (2) in CKD patients (stages 3, 4, and 5), we should take eGFR into account in the evaluation of hemodynamic overload by plasma NT-proBNP (the NT-proBNP$_{CS-AO}$/NT-proBNP$_{AO}$ ratio was significantly decreased [G1, 67±38%; G2, 50±24%; G3a, 40±21%; G3b, 30±16%; G4, 14.8±7.9%; and G5, 3.5±2.4%, respectively], especially in

those with eGFR <30 mL/min/1.73 m^2); and (3) BMI, a marker of obesity, is an independent factor of NT-proBNP secretion from the heart.

We are in the midst of a chronic epidemic of CHF and CKD worldwide. Obesity is associated with the development of CKD and progression to kidney failure. Additionally, obesity is predictive of cardiovascular disease and mortality in patients with CKD. BMI is a clinical marker of obesity. Many studies have reported that plasma NT-proBNP and BNP are low in obesity with or without CHF. The mechanism of low NT-proBNP and BNP, however, remains unknown. After BNP and NT-proBNP secretion from the CS, clearance of BNP via enzymatic breakdown and receptor binding may explain the low BNP in obesity,[7] due to the upregulation of clearance receptor and neutral endopeptidase activity.[21,22] NT-proBNP, however, is mainly cleared by the kidneys. The present study has shown that the low NT-proBNP secretion from the heart directly contributes to the low NT-proBNP in obesity.

After angiotensin receptor–neprilysin inhibitor (ARNI) treatment, cardiovascular death decreased by 20% compared with enalapril, with increased BNP and decreased NT-proBNP,[23,24] suggesting that NT-proBNP may be recommended as a biomarker of CHF after ARNI treatment.[24] In the present study, the cut-offs of BNP and NT-proBNP for cardiac events may be influenced by eGFR, especially in NT-proBNP.[14] The cut-off of NT-proBNP for predicting hospitalization and death ranges widely across the CKD stages,[14] and urinary NT-proBNP is significantly lower in CHF patients than in control subjects,[8] suggesting that a marked decrease in urinary excretion of NT-proBNP contributes to a high plasma NT-proBNP by tubular injury in CHF patients with CKD.[8,9]

Because NT-proBNP has a long half-life and is cleared only by the kidneys, the NT-proBNP$_{CS-AO}$/NT-proBNP$_{AO}$ ratio may be an indicator of renal clearance and metabolism of NT-proBNP in patients in stable conditions. The extracardiac mechanism of elevation of plasma NT-proBNP levels depends on the renal clearance and metabolism,[8,9] indicating that both decreased renal blood flow and renal tubular injury may influence NT-proBNP, especially in stages 4 and 5.

In patients with eGFR-based CKD stage 4 and 5, renal clearance of NT-proBNP is approximately 15% and 3.5%, respectively (**Table 1**), indicating that approximately 85% and 95%, respectively, of NT-proBNP in the plasma is due to the decrease in renal clearance. If physicians evaluate hemodynamics according to the level of NT-proBNP, they should take into account eGFR in CKD patients, especially those with eGFR <30 mL/min/1.73 m^2. There was no significant difference in the ratio of NT-proBNP$_{CS-AO}$/NT-proBNP$_{AO}$ between CKD stage 5 patients with and without dialysis (data not shown). These results are consistent with previous reports noting a very high NT-proBNP in end-stage CKD patients with or without CHF.[25,26] NT-proBNP is often O-glycosylated in cardiac myocytes,[27] which may result in underestimation of total NT-proBNP level, which includes both glycosylated and non-glycosylated NT-proBNP, by the NT-proBNP assay system used in the present study.[15] The NT-proBNP$_{CS-AO}$/NT-proBNP$_{AO}$ ratio, however, may not be influenced by O-glycosylation.

Study Limitations

BMI in a general Japanese population is lower than in Western countries.[28] The difference in BMI between the present patients and Western patients may influence the relationships between BMI and NT-proBNP. In the present study, we used creatinine to calculate eGFR. Cystatin C may be better than creatinine, and further studies are needed. The small numbers of patients with eGFR-based stages 4 and 5 was a further limitation. Finally, in the present study we did not measure renal blood flow, urinary NT-proBNP excretion, or the markers of renal tubular injury. Further studies are needed to clarify the relationship between the ratio of NT-proBNP secretion from the heart to peripheral NT-proBNP, the renal clearance of NT-proBNP in CKD and the mechanism of low NT-proBNP secretion in obesity.

Conclusions

eGFR influences the level of NT-proBNP for prediction of hemodynamic overload in CKD patients but not in non-CKD patients, and the ratio of NT-proBNP secretion from the heart to peripheral NT-proBNP is markedly decreased in CKD patients, especially those with eGFR <30 mL/min/1.73 m^2. In addition, BMI, a marker of obesity, is an independent factor of NT-proBNP secretion from the heart.

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Disclosures

The authors declare no conflicts of interest.

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