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The Effect of Renal Dysfunction on BNP, NT-proBNP, and Their Ratio

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Abstract and Introduction

Abstract

We examined the effect of renal dysfunction on B-natriuretic peptide (BNP), N-terminal (NT)-proBNP, and their molar ratio at varying severities of cardiac function in 94 Thai patients with chest pain (52 men; 32 women), also measuring creatinine and left ventricular ejection fraction (LVEF). Renal function was classified into 5 stages by estimated glomerular filtration rate. The molar NT-proBNP/BNP ratio was calculated. Cardiac status was classified by LVEF (normal, >50%; moderate, 35%–50%; severe, <35%).

BNP, NT-proBNP, and their ratio corresponded to renal disease stage exponential (0.51, 1.05, and 0.54, respectively; correlation coefficients, ≥0.95). BNP and the ratio are affected less than NT-proBNP by renal dysfunction, starting in stage III; NT-proBNP expresses effects starting in stage II. NT-proBNP is more sensitive than BNP to renal disease stage. For log of geometric means vs stage of renal disease, the BNP slopes and correlation coefficients vary considerably (slopes, 0.036–0.531; r^2, 0.017–0.99). The NT-proBNP slopes and regression coefficients vary considerably (slopes, 0.18–0.71; r^2, 0.33–0.99). For the ratio, the slopes show low variation (0.148–0.337), r^2 greater than 0.96, women differing from men (P = .012). The effect of renal disease differs by gender. BNP and NT-proBNP increase by stage III for women but not for men. One must consider renal function, gender, and LVEF when using BNP or NT-proBNP as cardiac biomarkers. The ratio of the 2 peptides is the most consistent marker across LVEFs.

Introduction

B-natriuretic peptide (BNP) and N-terminal (NT)-proBNP are peptides secreted from the cardiac ventricles in response to increasing tension in the ventricular wall.[1] Both peptides are useful in the diagnosis of congestive heart failure (CHF) and as a prognostic tool in predicting mortality for patients with CHF, populations at risk of developing chronic heart failure, recent myocardial infarction, and acute coronary syndromes without myocardial necrosis.[2–4] Many studies proposed the use of these peptides for ruling out noncardiac dyspnea.[5–7] Furthermore, these tests have become tools to assess response to therapeutic interventions in patients with chronic heart failure.[8]

Ventricular stretch causes secretion of BNP (32 aminoacid-long peptide hormone) and NT-proBNP (76 amino-acid-long peptide), which are released in equimolar amounts into the circulation, but comparison of these 2 markers presents difficulties in interpretation because their relationship is nonlinear.[9–11] BNP is eliminated by receptors located in the liver, lung, kidney, and vascular endothelium and through the kidneys.[12,13] Conversely, NT-proBNP clearance occurs only in the kidney. Renal dysfunction affects both peptides, but with a potentially greater effect on NT-proBNP. Increasing BNP and NT-proBNP concentrations are functions of renal and cardiac function and, in addition, receptor function for BNP.

Koch et al[14] found that the ratio of plasma NT-proBNP and BNP decreased with increasing age (from childhood to adolescence). Thus, age-dependent differences in the metabolic clearance of both peptides must be considered.[14]

Cardiovascular disease is the leading cause of death in patients with end-stage renal failure, and the progression of renal disease can be monitored by assessing the decrease in glomerular filtration rate (GFR).[15] Patients in renal failure have a high prevalence of left ventricular disorders, especially structural and functional left ventricular hypertrophy. The intersection of cardiac and renal insufficiency is frequently referred to as the cardiorenal syndrome.[16,17] The cardiac ventricles rapidly release BNP paired with NT-proBNP to increase vasodilation and renal output of sodium and water to counter the increased fluid volume resulting from decreased renal function. Increased concentrations of BNP and NT-proBNP may result from decreasing renal function (progressive kidney disease) because of increased intravascular volume, in addition to impaired cardiac function.[18] Therefore, the proper study of the effect of renal dysfunction on BNP and NT-proBNP concentration must include varying degrees of cardiac function.

In this study, we examined the effect of renal dysfunction on BNP and NT-proBNP concentrations and on their ratios at varying degrees of cardiac function.

Materials and Methods

Study Subjects

The subjects for diagnostic study were from the emergency department, Ramathibodi Hospital (Bangkok, Thailand), examined

during a 6-month period in the 2006–2007 period. Eligible patients had to be at least 30 years old with chest pain lasting more than 20 minutes, suspected to be myocardial in origin, and admitted within 3 to 72 hours of onset of chest pain. We excluded patients who had angina with an established precipitating cause (eg, anemia or tachydysrhythmia). The study included 94 Thai patients with chest pain (52 men and 32 women) who gave informed written consent. The study was approved by the institutional review board committee.

Classification of Chronic Kidney Disease

The renal function status of individual patients was classified by the estimated GFR (eGFR) into 5 stages of renal dysfunction, ranging from I to V: normal, minimally impaired, moderately impaired, severely impaired, and failure. The eGFR was calculated from the serum creatinine concentration (traceable to the isotope dilution mass spectrometry reference method), age, and sex:[19]

$$\text{GFR (mL/min/1.73 m}^2) = 175 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female or } \times 1.210 \text{ if African American})$$

Classification of Patient Functional Capacity

By subjective interpretation, patients were assessed and classified by the New York Heart Association function classification system. Then, patients' heart function was assessed by left ventricular ejection fraction (LVEF), with more than 50% representing normal, less than 35% representing severe cardiac dysfunction, and 35% to 50% representing moderate cardiac dysfunction.

Biochemical Analyses

Blood samples were obtained on arrival at the emergency department and immediately sent to the clinical chemistry laboratory where they were centrifuged (1,500*g* for 15 minutes) within 1 hour of receipt. EDTA plasma samples for the BNP assay and serum samples for NT-proBNP and creatinine assays were used.

Assay of BNP The AxSYM (Abbott Laboratories, Abbott Park, IL) BNP assay uses a microparticle enzyme immunoassay. This assay is a 2-site assay using a monoclonal anti-BNP antibody (mouse) and a fluorescence product; 144 µL of sample react with the reagent (anti–BNP-coated microparticles and anti–BNP-conjugated with alkaline phosphatase) forming an antigen-antibody complex on the microparticles. Addition of substrate, 4-methylumbelliferyl phosphate, yields the fluorescent product (4-methylumbelliferone). This product is measured by the microparticle enzyme immunoassay optical assembly. The assay imprecision claimed by the manufacturer was a coefficient of variation (CV) of less than 12%.

Assay of NT-proBNP NT-proBNP (Roche Diagnostics, Mannheim, Germany) is determined by an electrochemiluminescence immunoassay on the MODULAR ANALYTICS E170 analyzer (Roche Diagnostics). This electrochemiluminescence immunoassay is based on 2 polyclonal antibodies: a biotinylated (capture) antibody and a ruthenium derivative–labeled antibody. The biotinylated antibody recognizes an epitope including the first 20 amino acids of the N-terminal fragment of proBNP (1–76), whereas the ruthenium derivative–labeled antibody recognizes an epitope including the amino acid fragment 40–50 of the same peptide.

The test procedure is as follows: 20 µL of sample reacts with the reagent (biotinylated polyclonal NT-proBNP-specific antibody and polyclonal NT-proBNP-specific antibody labeled with a ruthenium complex) to form a sandwich complex. After addition of streptavidin-labeled microparticles, the complex produced is bound to the solid phase via biotin-streptavidin interaction. The reaction mixtures are measured by inducing chemiluminescent emission, which is measured by a photomultiplier tube. The CVs claimed by the manufacturer were 0.9% (474 pg/mL [55.9 pmol/L]), 1.1% (8,005 pg/mL [945 pmol/L]), and 0.9% (13,682 pg/mL [1,614 pmol/L]) for within-run imprecision and 5.8%, 4.1%, and 3.7%, respectively, for total imprecision.

Assay of Creatinine Serum creatinine was measured on the Dimension Max (Siemens Medical Solution Diagnostics, Tarrytown, NY) by using the Jaffe rate method with a calibrator traceable to the international reference creatinine method (isotope dilution mass spectrometry). The CVs claimed by the manufacturer were 6.7% (0.67 mg/dL [59 µmol/L]), 3.4% (0.85 mg/dL [75 µmol/L]), 1.3% (2.09 mg/dL [185 µmol/L]), and 1.3% (3.93 mg/dL [347 µmol/L]) for within-run imprecision and 7.9%, 5.8%, 1.9%, and 1.5%, respectively, for total imprecision.

Statistical Analyses

Statistical analysis was carried out using SPSS 12.0 software (SPSS, Chicago, IL). Study participants were divided into 5 groups with chronic kidney disease (CKD) stages according to level of eGFR as defined in the clinical practice guidelines of the National Kidney Foundation of the United States through its Kidney Disease Outcomes Quality Initiative.[20] Individual group data for sex are presented as number (percentage) of men, whereas those for age, systolic and diastolic blood pressure, heart rate, LVEF, eGFR, creatinine level, BNP, NT-proBNP, molar ratio of NT-proBNP/BNP (pmol/L/pmol/L), creatine kinase MB activity, and troponin I and troponin T concentrations are reported as the geometric mean and standard error of estimate (SE). Differences among independent groups were analyzed by the analysis of variance model. We applied linear, logarithmic, quadratic, power, and exponential regression models to estimate the relationship between BNP, NT-proBNP, and NT-proBNP/BNP molar ratio with the

CKD stages and LVEF. The exponential model provides the best fit of the data. To transform the exponential to the linear regression model, we used the log transform of the geometric means. Outcomes were considered as statistically significant when the *P* value was less than .05.

Results

Characteristics of the Study Population

Demographic and clinical characteristics of the 94 patients with chest pain are summarized in Table 1. Patients were classified into 5 groups according to baseline stages of eGFR. Group 1 included patients with CKD stage I who had a normal or high eGFR (>90 mL/min/1.73 m^2); group 2 included patients with CKD stage II who had a mildly decreased eGFR (60–89 mL/min/1.73 m^2); group 3 included patients with CKD stage III who had a moderately decreased eGFR (30–59 mL/min/1.73 m^2); group 4 included patients with CKD stage IV who had a severely decreased eGFR (15–29 mL/min/1.73 m^2); group 5 included patients with CKD stage V who had a kidney failure (eGFR <15 mL/min/1.73 m^2).

Table 1. Demographic Characteristics and Biochemical Test Results of Patients Classified According to CKD Classification From eGFR*

	CKD Stage					
	I (n = 6)	II (n = 29)	III (n = 46)	IV (n = 6)	V (n = 7)	*P*
Age (y)	49.7 (3.7)	58.1 (2.3)	67.6 (1.8)	72.8 (3.8)	66.1 (5.1)	.001
No. (%) men	6 (100)	20 (69)	20 (43)	5 (83)	1 (14)	
Blood pressure (mm Hg)						
Systolic	150.5 (15.5)	134.3 (6.5)	134.7 (5.1)	142.8 (12.1)	167.0 (11.5)	.231
Diastolic	83.7 (10.5)	75.7 (3.5)	76.9 (2.4)	81.7 (8.4)	85.8 (5.6)	.593
Heart rate	88.0 (10.2)	76.0 (3.6)	81.3 (2.9)	91.7 (7.6)	80.9 (10.3)	.441
LVEF (%)	42.86 (5.12)	48.24 (3.45)	50.57 (2.12)	33.74 (8.83)	54.88 (4.71)	.430
eGFR (mL/min/1.73 m^2)	98.4 (4.4)	70.2 (1.5)	46.0 (1.1)	24.7 (1.1)	6.3 (1.4)	<.001
Creatinine (mg/dL)	0.82 (0.04)	1.00 (0.03)	1.32 (0.05)	2.35 (0.17)	6.76 (1.10)	<.001
BNP (pg/mL)	276.1 (806.3)	259.7 (161.2)	437.9 (338.5)	1,195.7 (1,356.7)	1,660.7 (553.9)	.056
NT-proBNP (pg/mL)	424.6 (1,249.84)	601.5 (494.1)	1,444.6 (1,143.7)	80,75.8 (5,617.0)	21,658.4 (6,741.6)	<.001
NT-proBNP/BNP ratio	0.629 (0.127)	0.948 (0.114)	1.350 (0.155)	2.763 (0.523)	5.336 (0.556)	<.001
Creatine kinase-MB activity (U/L)	32.3 (19.0)	25.2 (3.1)	25.1 (3.1)	40.7 (144.4)	23.1 (4.0)	.008
Troponin I (ng/mL)	0.022 (3.423)	0.027 (1.629)	0.028 (0.151)	0.343 (0.887)	0.061 (0.064)	.685
Troponin T (ng/mL)	0.038 (0.497)	0.022 (0.219)	0.021 (0.024)	0.162 (0.230)	0.062 (0.046)	.401

BNP, B-natriuretic peptide; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal proBNP.

* Data are given as geometric mean (SE) unless otherwise indicated. The "Materials and Methods" section defines CKD stages I through V. eGFR values were calculated from the Modification of Diet in Renal Disease equation.[19] Creatinine, BNP, and NT-proBNP values are given in conventional units; conversions to Système International units are as follows: creatinine (μmol/L), multiply by 88.4; BNP and NT-proBNP (pmol/L), multiply by 0.289 and 0.118, respectively. NT-proBNP/BNP ratio values are given in the molar ratio of NT-proBNP (pmol/L) to BNP (pmol/L).

Univariable Determinations of BNP, NT-proBNP, and Their Ratio

Notably, systolic BP, diastolic BP, heart rate, LVEF, and troponin I and troponin T levels were not significantly different between CKD stages (all $P > .2$), whereas age, eGFR, creatinine, NT-proBNP, NT-proBNP/BNP ratio, and creatine kinase MB activity differed significantly between groups (all $P < .05$). The mean values for BNP were unaffected by sex; however, the mean values for NT-proBNP and the ratio were Table 2. Neither of the peptides nor the ratio were affected by age. The presence or absence of a final diagnosis of myocardial infarction affected the BNP and the NT-proBNP concentrations but did not affect the ratio. Therefore, analysis of the peptide concentrations as a function of stage of renal disease was separated by sex.

Table 2. Univariable Analyses of BNP, NT-proBNP, and Their Ratio*

	Estimated Mean (SE)					
	BNP (pg/mL)	***P***	**NT-proBNP (pg/mL)**	***P***	**Ratio**	***P***
Sex		.859		.036		.003
Female (n = 42)	1,244.4 (333.2)		9,309.1 (1,694.0)		2.463 (0.232)	
Male (n = 52)	1,162.7 (312.2)		4,345.7 (1,586.8)		1.474 (0.217)	
Age (y)		.657		.690		.566
<50 (n = 17)	841.4 (516.3)		4,181.5 (2,624.4)		1.648 (0.360)	
51–60 (n = 14)	977.1 (549.3)		8,799.6 (2,792.2)		2.336 (0.383)	
61–70 (n = 25)	1,325.6 (405.6)		5,840.7 (2,061.7)		1.782 (0.282)	
71–80 (n = 29)	1,715.1 (376.4)		8,131.2 (1,913.3)		1.757 (0.262)	
>80 (n = 9)	1,158.4 (697.2)		7,184.1 (3,544.3)		2.319 (0.486)	
Myocardial infarction		.040		.004		.161
No (n = 52)	747.0 (304.4)		3,570.8 (1,547.5)		1.753 (0.212)	
Yes (n = 42)	1,660.1 (326.4)		10,084.0 (1,659.4)		2.184 (0.227)	

BNP, B-natriuretic peptide; NT-proBNP, N-terminal proBNP.

* Estimated marginal means (SE) are adjusted for each of the other factors. BNP and NT-proBNP values are given in conventional units; to convert to Système International units (pmol/L), multiply by 0.289 and 0.118, respectively. NT-proBNP/BNP ratio values are given in the molar ratio of NT-proBNP (pmol/L) to BNP (pmol/L).

Association of BNP, NT-proBNP, and the Ratio with CKD Stage

The association between BNP and stage of kidney disease Figure 1 is exponential and is shown in Figure 2 as the log of the geometric mean vs the stage of renal disease. The top row represents women and the bottom row, men. The first column shows an LVEF of more than 50%, the second column an LVEF between 35% and 50% (inconclusive), and the third column an LVEF less than 35%, corresponding to increasing degrees of structural cardiac damage and, thus, heart failure. The slopes for each of the graphs vary considerably, as do the correlation coefficients, with slopes ranging from 0.036 to 0.531 and r^2 ranging from 0.017 to 0.99.

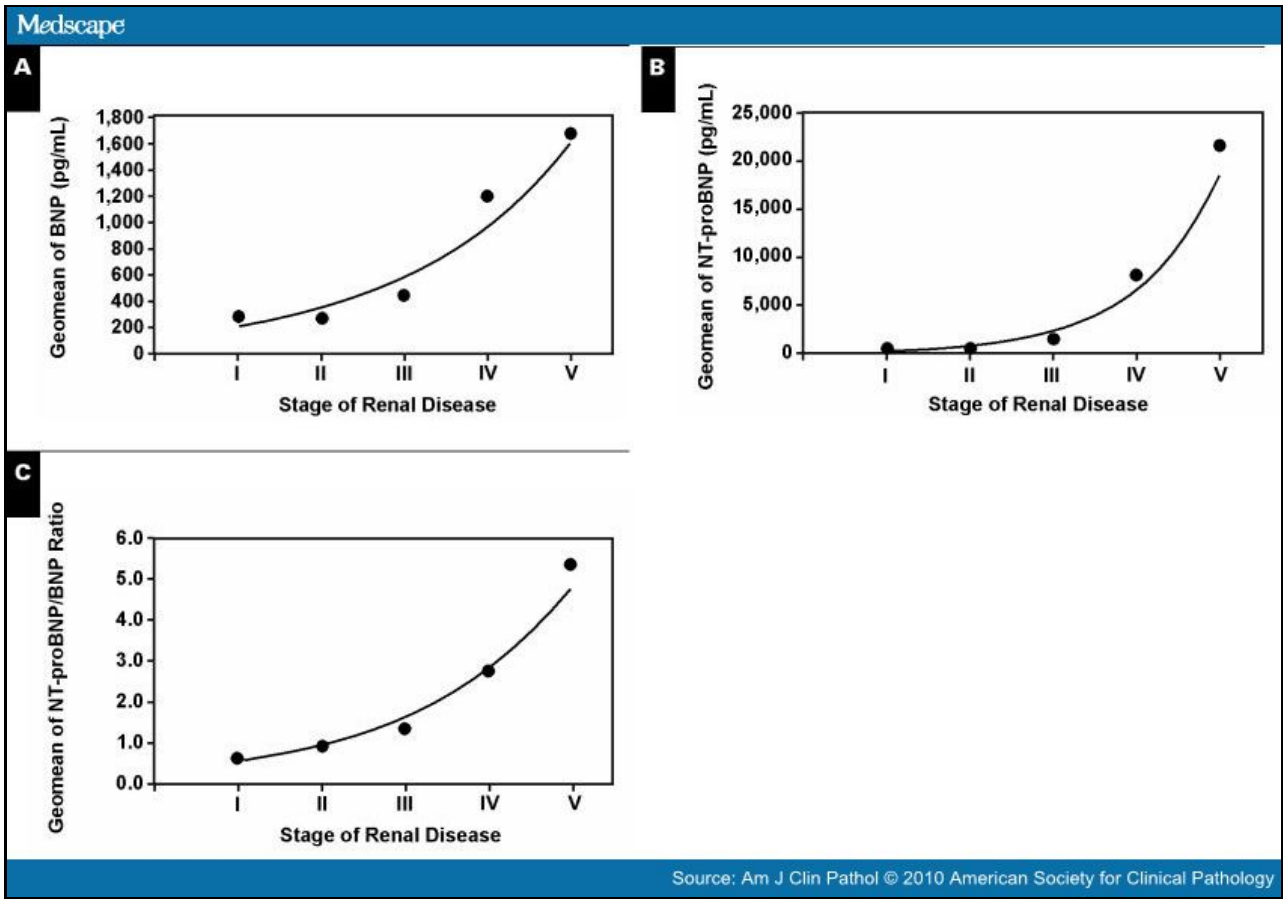

Figure 1. Geometric mean (Geomean) of plasma B-natriuretic peptide (BNP) (**A**) and N-terminal (NT)-proBNP (**B**) concentrations (in pg/mL) and their molar ratio (**C**) in relation to stage of chronic kidney disease. The x-axis is the stage of renal disease classified into 5 groups according to baseline stages of estimated glomerular filtration rate. The details of classification are described in the text. BNP and NT-proBNP values are given in conventional units; to convert to Système International units (pmol/L), multiply by 0.289 and 0.118, respectively. **A**, $y = 123.72e^{0.5116x}$; $r^2 = 0.9008$; **B**, $y = 99.774e^{1.0461x}$; $r^2 = 0.9536$; **C**, $y = 0.3299e^{0.5346x}$; $r^2 = 0.9785$.

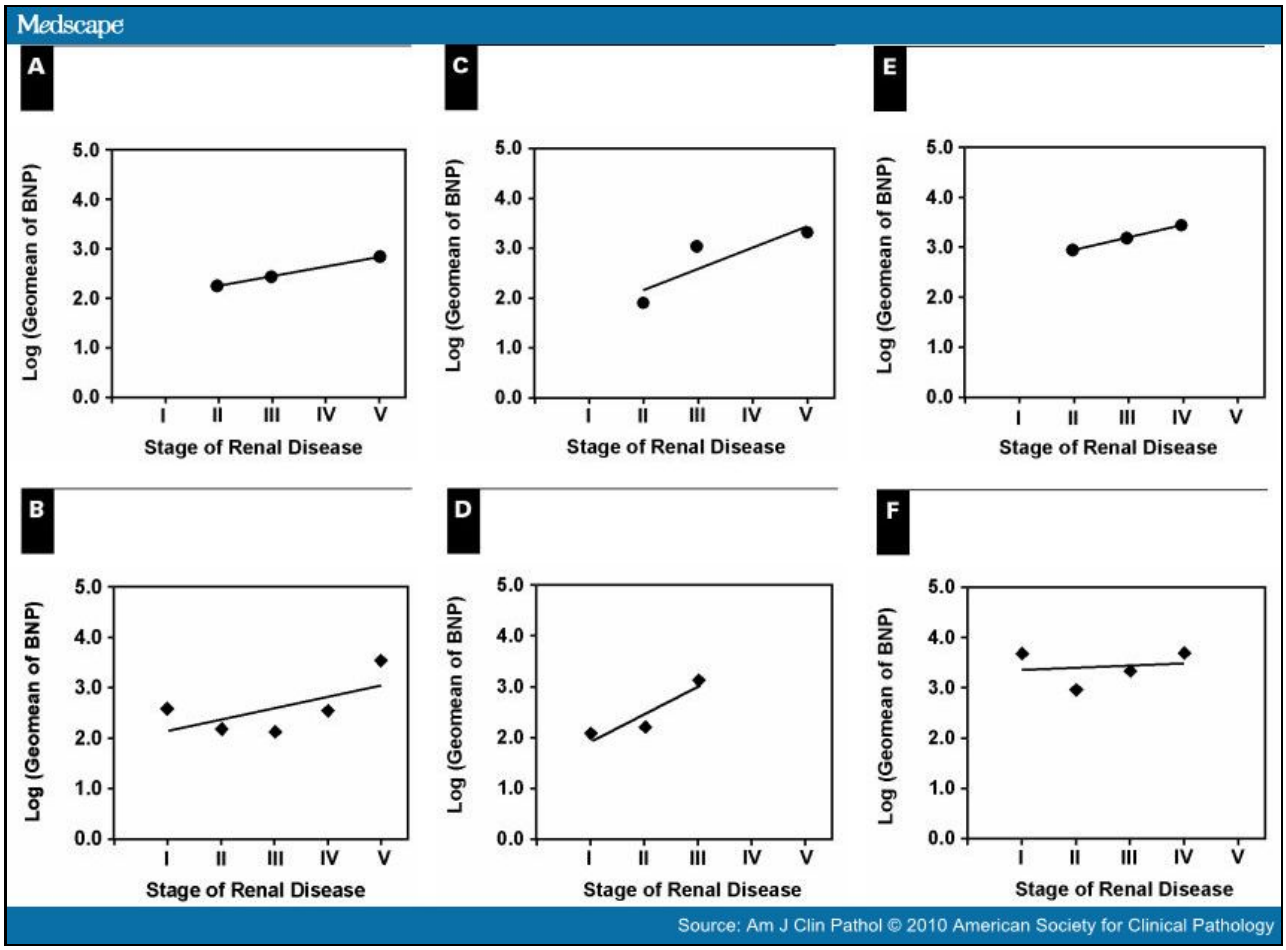

Figure 2. Log of geometric mean (Geomean) of B-natriuretic peptide (BNP) concentration (in pg/mL) in relation to stage of chronic kidney disease separated by sex: female (**A**, **C**, and **E**) and male (**B**, **D**, and **F**), and left ventricular ejection fraction (LVEF): LVEF >50% (**A** and **B**), LVEF 35% to 50% (**C** and **D**), and LVEF <35% (**E** and **F**). The x-axis is the stage of renal disease classified into 5 groups according to baseline stages of estimated glomerular filtration rate. The details of classification are described in the text. BNP values are given in conventional units; to convert to Système International units (pmol/L), multiply by 0.289. **A**, y = 0.195x + 1.862; r^2 = 0.9991; **B**, y = 0.218x + 1.947; r^2 = 0.3828; **C**, y = 0.430x + 1.325; r^2 = 0.7473; **D**, y = 0.531x + 1.42; r^2 = 0.8426; **E**, y = 0.257x + 2.442; r^2 = 0.9959; **F**, y = 0.036x + 3.341; r^2 = 0.0174.

The association between NT-proBNP and stage of kidney disease is shown in Figure 3 as the log of the geometric mean vs the stage of renal disease, with the same arrangement as for Figure 2. Again, the slopes and regression coefficients vary considerably, with the slopes ranging from 0.18 to 0.71 and r^2 from 0.33 to 0.99.

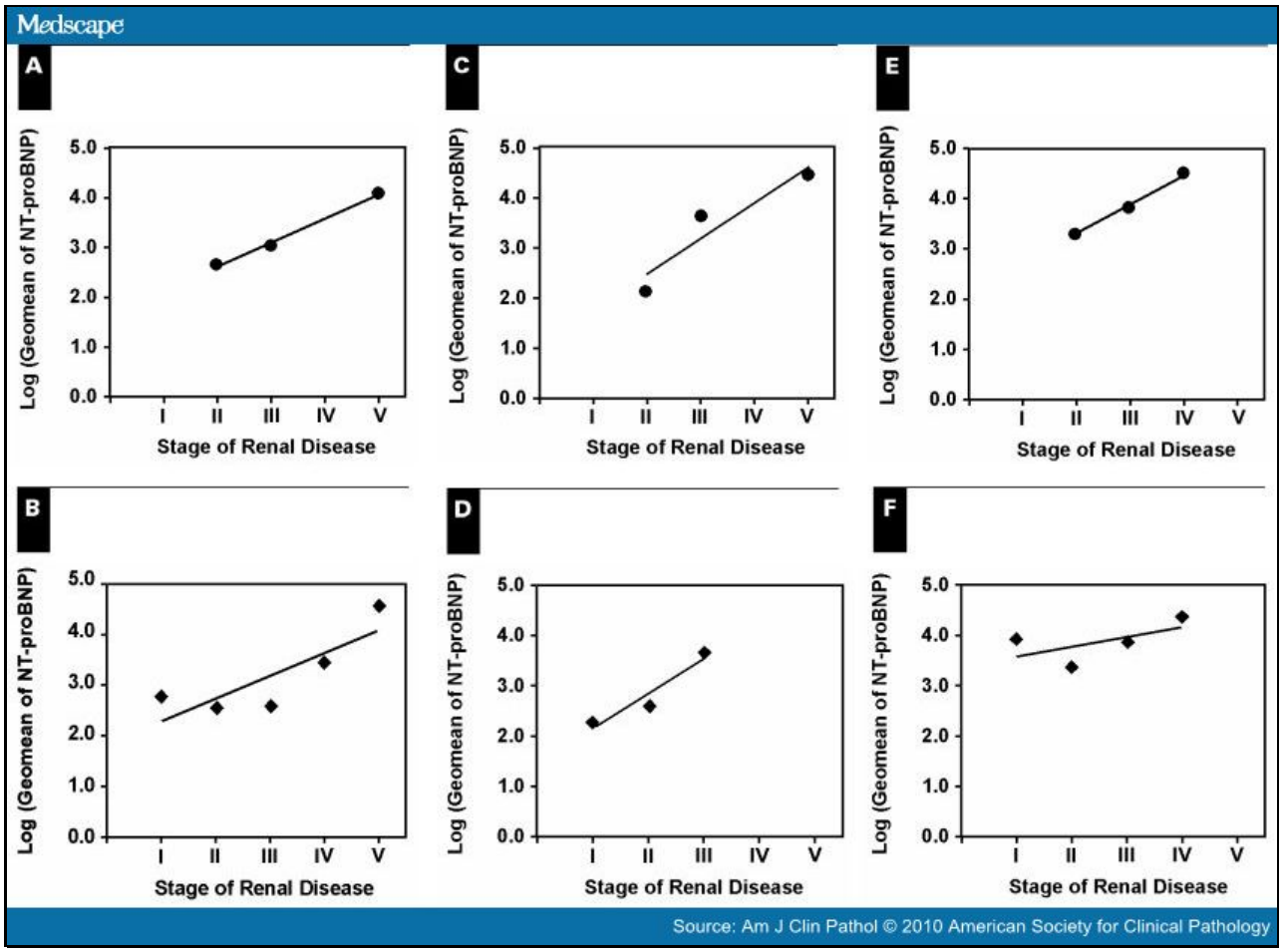

Figure 3. Log of geometric mean (Geomean) of N-terminal (NT)-pro-B-natriuretic peptide (BNP) concentration (in pg/mL) in relation to stage of chronic kidney disease separated by sex: female (**A**, **C**, and **E**) and male (**B**, **D**, and **F**), and left ventricular ejection fraction (LVEF): LVEF >50% (**A** and **B**), LVEF 35% to 50% (**C** and **D**), and LVEF <35% (**E** and **F**). The x-axis is the stage of renal disease classified into 5 groups according to baseline stages of estimated glomerular filtration rate. The details of classification are described in the text. NT-proBNP values are given in conventional units; to convert to Système International units (pmol/L), multiply by 0.118. **A**, y = 0.470x + 1.677; r^2 = 0.9957; **B**, y = 0.440x + 1.851; r^2 = 0.6771; **C**, y = 0.712x + 1.026; r^2 = 0.8698; **D**, y = 0.685x + 1.463; r^2 = 0.909; **E**, y = 0.594x + 2.067; r^2 = 0.9937; **F**, y = 0.184x + 3.393; r^2 = 0.3311.

The association between the molar ratio of NT-proBNP/BNP and stage of kidney disease is shown in Figure 4 as the log of the geometric mean vs the stage of renal disease, with the same arrangement as for Figure 2. Here, the slopes show consistent direction with low variation, ranging from 0.148 to 0.337. All r^2 values are greater than 0.96. The slopes for women differ from those for men (P = .012; unpaired Student t test). The average slope for women was 0.298 with a standard error of the mean (SEM) of 0.096 and for men was 0.172 with an SEM of 0.021. These SEMs represent only 6% and 12% of the mean values for women and men, respectively.

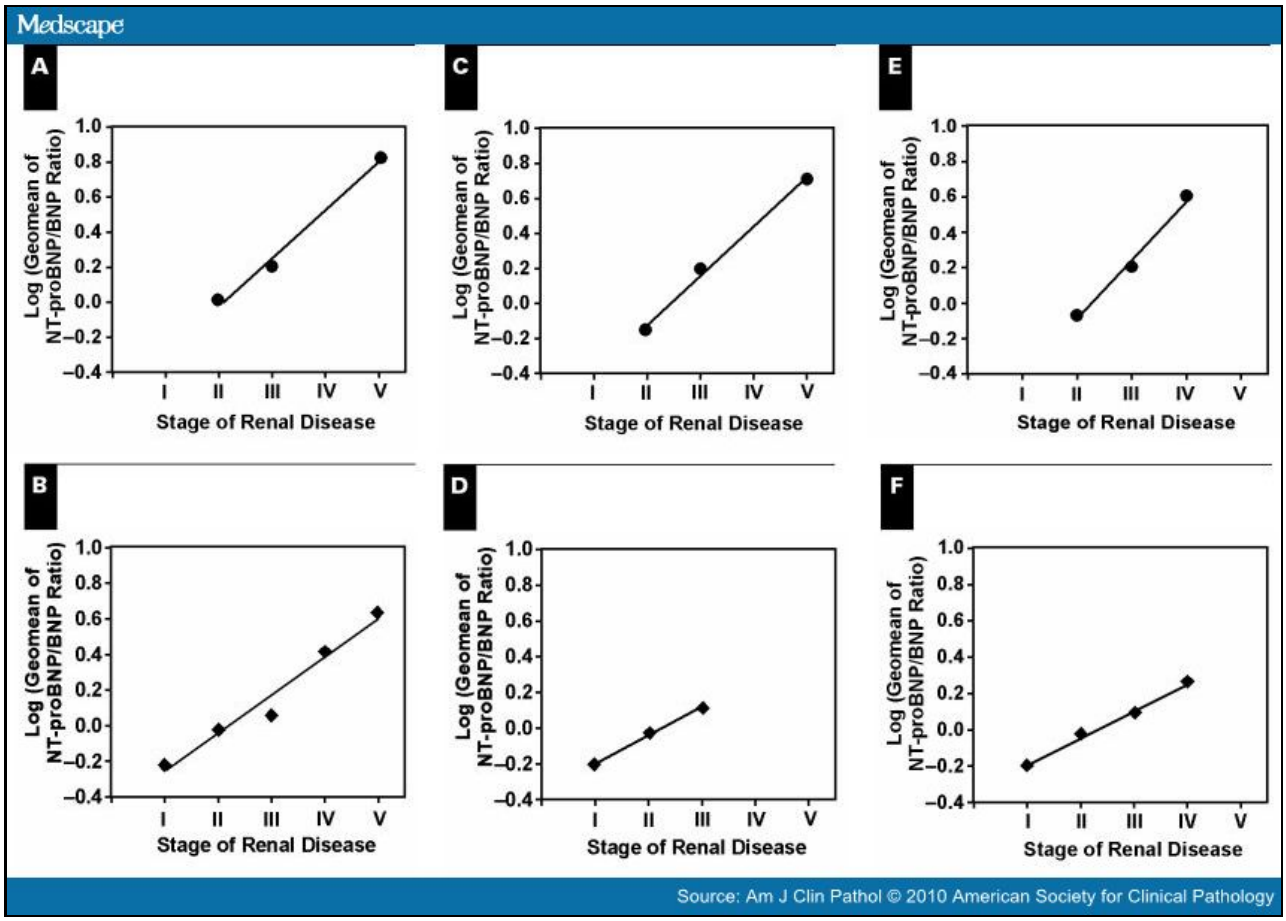

Figure 4. Log of geometric mean (Geomean) of molar ratio of N-terminal (NT)-pro-B-natriuretic peptide (BNP)/BNP in relation to stage of chronic kidney disease separated by sex: female (**A**, **C**, and **E**) and male (**B**, **D**, and **F**), and left ventricular ejection fraction (LVEF): LVEF >50% (**A** and **B**), LVEF 35% to 50% (**C** and **D**), and LVEF <35% (**E** and **F**). The x-axis is the stage of renal disease classified into 5 groups according to baseline stages of estimated glomerular filtration rate. The details of classification are described in the text. **A**, y = 0.275x – 0.573; r^2 = 0.9919; **B**, y = 0.213x – 0.469; r^2 = 0.9621; **C**, y = 0.282x – 0.685; r^2 = 0.9921; **D**, y = 0.154x – 0.345; r^2 = 0.9935; **E**, y = 0.337x – 0.763; r^2 = 0.9872; **F**, y = 0.148x – 0.336; r^2 = 0.9924.

The regression analysis by LVEF as a function of CKD stage is shown in Table 3. The regressions for BNP do not correlate well and for NT-proBNP, only poorly, but the ratio correlates well (P < .01). The regression analysis by CKD stage as a function of LVEF is shown in Table 4. BNP and NT-proBNP showed results to reject the null hypothesis, but the correlation coefficients were low. For the ratio, one would accept the null hypothesis for normal to moderate renal function and marginally accept it for severe failure, indicating that the ratio is fairly independent of the LVEF while more reflective of the renal function.

Table 3. Regression Analyses of Log Geometric Means of BNP, NT-proBNP, and Their Molar Ratio Against the CKD Stage Based on Left Ventricular Ejection Fraction*

Left Ventricular Function (%)	r^2	Standard Error of the Estimate	Coefficient (95% CI)		P
			Slope	Intercept	
BNP					
EF >50	0.342	0.313	0.124 (−0.192 to 0.439)	2.174 (1.128 to 3.229)	.300
35 < EF ≤50	0.867	0.280	0.342 (−0.066 to 0.750)	1.716 (0.443 to 2.989)	.069
EF ≤35	0.002	0.450	0.013 (−0.853 to 0.879)	3.343 (0.971 to 5.715)	.955
NT-proBNP					

EF >50	0.774	0.365	0.370 (0.003 to 0.737)	2.053 (0.835 to 3.271)	.049
35 < EF ≤50	0.957	0.253	0.571 (0.203 to 0.939)	1.625 (0.477 to 2.773)	.004
EF ≤35	0.315	0.453 0.194 (−0.677 to 1.066)	3.352 (0.965 to 5.740)	.439	
NT-proBNP/BNP ratio					
EF >50	0.975	0.073	0.246 (0.173 to 0.320)	−0.510 (−0.753 to −0.267)	.002
35 < EF ≤50	0.978	0.073	0.229 (0.123 to 0.335)	−0.480 (−0.809 to −0.150)	.011
EF ≤35	0.997	0.017	0.191 (0.158 to 0.224)	−0.400 (−0.491to −0.309)	.002

BNP, B-natriuretic peptide; CI, confidence interval; NT-proBNP, N-terminal proBNP.
* BNP and NT-proBNP values are given in conventional units; to convert to Système International units (pmol/L), multiply by 0.289 and 0.118, respectively. NT-proBNP/BNP ratio values are given in the molar ratio of NT-proBNP (pmol/L) to BNP (pmol/L).

Table 4. Regression Analyses of Log Geometric Means of BNP, NT-proBNP, and Their Molar Ratio Against Left Ventricular Ejection Fraction at Different Stages of Renal Function*

Renal Function	r^2	Standard Error of the Estimate	Coefficient (95% CI)		*P*
			Slope	Intercept	
BNP					
Normal to minimal	0.256	2.99	−1.50 (−1.70 to −1.10)	3.35 (3.09 to 3.51)	.002
Moderate	0.173	3.32	−1.82 (−2.04 to −1.35)	3.68 (3.38 to 3.86)	.004
Severe failure	0.308	3.32	−1.87 (−2.16 to −0.385)	3.80 (3.38 to 4.00)	.049
NT-proBNP					
Normal to minimal	0.184	3.39	−1.81 (−2.05 to −1.22)	3.68 (3.34 to 3.87)	.010
Moderate	0.138	3.86	−2.30 (−2.55 to −1.68)	4.19 (3.86 to 4.38)	.011
Severe failure	0.031	4.24	−2.22 (−2.90 to 2.65)	2.50 (−3.10 to 4.81)	.562
NT-proBNP/BNP ratio					
Normal to minimal	0.002	0.489	0.001 (−0.10 to 0.013)	0.974 (0.343 to 1.605)	.815
Moderate	0.004	1.061	−0.005 (−0.027 to 0.017)	1.932 (0.719 to 3.145)	.666
Severe failure	0.238	1.688	0.050 (−0.009 to 0.110)	1.817 (−1.333 to 4.966)	.090

BNP, B-natriuretic peptide; CI, confidence interval; NT-proBNP, N-terminal proBNP.
* BNP and NT-proBNP values are given in conventional units; to convert to Système International units (pmol/L), multiply by 0.289 and 0.118, respectively. NT-proBNP/BNP ratio values are given in the molar ratio of NT-proBNP (pmol/L) to BNP (pmol/L).

Discussion

BNP and NT-proBNP were introduced as biomarkers for heart failure but have also found use as markers for mortality in acute coronary syndromes and myocardial infarction.[2–7] Renal dysfunction or failure represents a variable that complicates the interpretation of these markers.

Both peptide levels correlated well in our study with the severity of heart failure and provided independent predictors of mortality for populations at risk of developing coronary artery disease and for those already diagnosed, in addition to CHF populations,

agreeing with prior studies.[21,22] Several studies have demonstrated that the performance of both peptides provided similar information in daily clinical practice.[23,24]

The American College of Cardiology/American Heart Association recommended the medical treatment even in asymptomatic patients with structural heart disease.[25] In addition, BNP and NT-proBNP now appear to be indicators of asymptomatic cardiac organ damage in patients who eventually develop left ventricular hypertrophy, left arterial dilation, atrial fibrillation, and left ventricular systolic dysfunction.[26]

As with acute heart failure evaluation, knowledge of the cardiac and noncardiac factors that influence BNP and NT-proBNP concentrations is necessary. Natriuretic peptides have a principal effect on the kidney promoting tubular natriuresis and diuresis. Falls in cardiac output, effective blood volume, and renal blood flow are accompanied by activation of the renin-angiotensin-aldosterone system and sympathetic nervous system. BNP action opposes the effects of the renin-angiotensin-aldosterone system, promoting natriuresis and increasing GFR.[27] In simpler terms, increased intravascular volume, resulting from heart failure or renal dysfunction, increases the secretion of BNP; BNP acts through the kidney to reduce intravascular volume, thereby decreasing the stimulus for BNP secretion. Renal dysfunction decreases this effect, requiring more BNP to achieve the same level of activity in the normal kidney. Heart failure decreases the effectiveness of the kidney, simulating renal dysfunction. Thus, heart failure and renal dysfunction act synergistically in their ability to increase the secretion rates of BNP and NT-proBNP. In addition, decreased renal function reduces the clearance of BNP and NT-proBNP. Thus, the proper characterization of the effect of renal dysfunction on BNP and NT-proBNP concentrations requires examination in normal, moderately deficient, and severely deficient LVEF.

Several investigators indicated that elevated BNP and NT-proBNP concentrations can result from renal failure.[28–30] Our results confirmed previous studies that concentrations were progressively higher in patients with progressively more advanced CKD, especially in patients with an eGFR of less than 60 mL/min/1.73 m^2 (CKD stage ≥III), as shown in Figures 2 and 3. Decreased renal clearance raises BNP and NT-proBNP concentrations. Moreover, we found that the influence of renal function on the clearance of NT-proBNP is greater than that on BNP. This finding is consistent with the previous experimental study conducted by Vickery et al[29] that showed that NT-proBNP was affected more than BNP with progression of CKD.

Although plasma BNP and NT-proBNP concentrations were progressively higher in patients with progressively more advanced renal disease, the peptides did not increase in a consistent manner, as shown in Figures 2 and 3, respectively. For men, BNP and NT-proBNP increased monotonically for moderately deficient LVEF but not for normal or severely deficient ejection fractions. For women, this relationship was a bit more monotonic, but the r^2 value for BNP with moderately deficient LVEFs was only 0.75. To use the fitted description of the effect of renal dysfunction, one needs to categorize by sex and LVEF. The increase in the molar ratio was much more monotonic for women and men, with excellent correlation coefficients. Thus, the ratio describes the effect of renal dysfunction better than BNP or NT-proBNP in situations in which one does not know the LVEF.

One must consider renal function along with sex and LVEF when using BNP or NT-proBNP as a cardiac biomarker. Takami et al[30] found that patients with renal impairment had a greater level of serum BNP than patients with hypertension and normal renal function. Failure to consider renal status limits the diagnostic capabilities of BNP and NT-proBNP.[31]

The effect of renal disease differs by sex. In most cases, BNP and NT-proBNP are increased by stage III for women, whereas for men at stage III, the peptide concentrations are still fairly close to stage I, except for men with moderately deficient LVEF (35%–50%).

NT-proBNP and BNP share a common mechanism of clearance through the glomerulus. In patients with normal or mildly decreased GFR (CKD stages I and II), the molar ratio of NT-proBNP and BNP was 1.0 or less (Figure 4). The ratio for the 2 peptides, when it is near 1.0, reflects that they are cleared at about the same rate, suggesting that the 2 peptides have similar half-lives, as previously published (20 minutes for BNP and 25 minutes for NT-proBNP).[32]

In the context of CHF, the presence of renal dysfunction complicates the interpretation of a single concentration of BNP or NT-proBNP. The upper limit of normal is another important consideration of the usefulness of BNP or NT-proBNP in the diagnostic evaluation of patients with acute dyspnea.[33,34] Using manufacturer's recommended cutoffs for BNP (100 pg/mL [28.9 pmol/L]) and NT-proBNP (men, 100 pg/mL [11.83 pmol/L]; women, 150 pg/mL [17.74 pmol/L]) as a "diagnostic test" for heart failure will overdiagnose patients with stage III or IV renal dysfunction. Many investigators suggested that higher cut points for BNP and NT-proBNP should be implied as the CKD stage advances.[33,34] Our results help stratify these cut points based on renal function, LVEF, and sex. In some cases, examining the ratio may provide additional information, especially when the LVEF is not known.

Another factor that affects the interpretation of BNP and NT-proBNP for monitoring patients with heart failure is their intraindividual biologic variation. Because these peptides demonstrate a wide intraindividual biologic variation, ranging from 25% to 30%, serial measurement of these peptides was suggested for prediction of risk in a heart disease population and monitoring therapy for heart failure.[35] To properly evaluate the serial measurements in the light of their intraindividual biologic variation, renal function needs to remain constant or one must be able to predict what the change would be in the presence of altered renal function. The

information in this study potentially can be used in such a manner. When the LVEF is not known, the ratio may provide more reliable slopes than the individual peptides alone.

Conclusion

Renal dysfunction increases the concentrations of BNP and NT-proBNP, but the degree of change is also dependent on the LVEF and sex. The ratio of the peptides is less dependent on the LVEF than the individual peptides. Utilization of the effect of renal dysfunction, as categorized by stage, along with sex and LVEF, may improve interpretation for diagnosis and monitoring, but additional prospective studies are needed.

Sidebar

Upon completion of this activity you will be able to:

- describe the pathophysiologic association between heart failure and renal dysfunction.
- predict the effect of worsening stage of renal disease on B-natriuretic peptide (BNP), N-terminal proBNP (NT-proBNP), and their ratio.
- discriminate among demographic variables and their effect on the natriuretic peptides.
- compute parametric properties associating the natriuretic peptides with heart failure and renal dysfunction.

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Questions appear on p 160. Exam is located at www.ascp.org/ajcpcme.

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