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Original Paper

Elevated Levels of N-Terminal Pro-Brain Natriuretic Peptide in Patients with Chronic Dyspnea and Moderate Renal Dysfunction: Decreased Clearance or Increased Cardiac Stress?

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Key Words
Cardiac stress · Heart disease · Natriuretic peptides · Renal dysfunction

Abstract
Background/Aims: Serum levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) are often increased in patients with impaired renal function. The objective of this study was to investigate whether the increase in NT-proBNP is predominantly due to a reduced renal clearance or an increased cardiac secretion. ***Methods:*** A series of 697 outpatients (age: 57.5 ± 16.4 years) referred for evaluation of dyspnea were assigned to 4 groups according to their estimated glomerular filtration rate [eGFR (ml/min per 1.73 m^2)]: group 1, eGFR <60 (n = 77); group 2, eGFR ≥60 to <75 (n = 139); group 3, eGFR ≥75 to <90 (n = 191), and group 4, eGFR ≥90 (n = 289). The patients were also grouped into 2 categories based on the presence (n = 176) or absence (n = 521) of heart disease. ***Results:*** In patients with heart disease, the adjusted values for NT-proBNP were higher in eGFR group 1 than in eGFR groups 2–4 ($p \leq 0.01$). In patients without heart disease, eGFR group 1 membership had no effect on NT-proBNP. ***Conclusion:*** A reduced renal clearance does not explain increased NT-proBNP levels in patients with moderate renal impairment and dyspnea. Our data suggest that a moderate reduction in renal function places additional stress on the heart in patients with established cardiac disease.

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Introduction

The inverse relationship between the estimated glomerular filtration rate (eGFR) and cardiovascular risk has been well characterized across a wide range of renal function [1]. According to the results of the Hoorn study, a small decrement in eGFR, from 90 to 60 ml/min per 1.73 m^2, is associated with a fourfold increased risk of cardiovascular death [2]. In a study of >1 million adults, the subjects with an eGFR of 45–59 ml/min per 1.73 m^2 had a 40% higher adjusted risk of cardiovascular events than those with an eGFR ≥60 ml/min per 1.73 m^2 over a median follow-up period of 2.84 years [3]. A higher prevalence of the conventional risk factors cannot fully explain the elevated cardiovascular risk in patients with renal impairment. Chronic kidney disease is often associated with increased oxidative stress and systemic inflammation. These factors promote atherosclerosis, induce cardiac stress, and sensitize the vascular endothelium, and thus may contribute to the link between renal function and cardiovascular risk [4]. The serum level of N-terminal pro-brain natriuretic peptide (NT-proBNP) provides prognostic information and has gained acceptance as a marker of cardiac stress [5]. Because the kidney is involved in the clearance of NT-proBNP, there has been much debate over its diagnostic value in the presence of renal impairment [6–8]. Our study examined the question of whether the increased serum levels of NT-proBNP often seen in patients with renal impairment are due to reduced renal clearance of the peptide, an increased prevalence of cardiac pathology, or a kidney-mediated excess stress burden on the heart.

Patients and Methods

Patients

This prospective single-center study included 697 consecutive outpatients referred to the pulmonology services of an academic teaching hospital during a 2-year period (January 2005 to January 2007) to evaluate dyspnea, which had lasted at least 2 weeks, as previously described [9]. Excluded from the study were patients with dialysis-dependent renal failure and data concerning previously measured NT-proBNP levels. Assessing the effect of renal function on NT-proBNP levels was among the predefined aims of this study. The study was approved by the ethics committee of the Baden-Württemberg State Chamber of Physicians.

Diagnostic Procedures and Patient Classification

The patients underwent an examination for heart and lung disease that included chest X-ray, pulmonary function tests, resting electrocardiogram (ECG), exercise treadmill ECG, and Doppler echocardiography. Further studies were performed when clinically indicated. Existing lung disease was classified as asthma, chronic obstructive pulmonary disease (COPD), or as other diseases. The degree of airway obstruction was divided into 3 levels of severity using the lower limits of normal for lung volume and the forced expiratory volume in 1 s (FEV_1)/maximum vital capacity ratio: mild to moderate (FEV_1 ≥60% of predicted), moderately severe (FEV_1 from 50 to <60% of predicted), and severe to very severe (FEV_1 <50% of predicted) [10]. The COPD patients were also categorized according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages.

The patients were classified into two groups based on the presence or absence of heart disease. Heart disease was diagnosed in the presence of at least one of the following criteria and was categorized according to the following 6 cardiac characteristic groups: (1) left ventricular hypertrophy (an end-diastolic septal wall thickness ≥12 mm or a positive Sokolow index in the presence of arterial hypertension); (2) exercise-induced myocardial ischemia due to angiographically proven coronary disease; (3) at least mild aortic stenosis (mean transvalvular pressure gradient ≥20 mm Hg), at least moderate aortic regurgitation, at least moderate mitral regurgitation, severe tricuspid regurgitation, atrial septal defect or pericardial effusion; (4) pulmonary hypertension (peak systolic gradient across the tricuspid valve measured with continuous-wave Doppler ≥35 mm Hg); (5) atrial fibrillation or left bundle branch block, and (6) im-

paired left ventricular systolic function. All of these cardiac characteristic groups are associated with elevated NT-proBNP levels in the above rank order [9]. The presence of arterial hypertension and minor echocardiographic findings were also recorded. Minor echocardiographic findings included mild aortic regurgitation, mild mitral regurgitation, and a borderline systolic pressure gradient of 30–34 mm Hg across the tricuspid valve. Blood samples were assayed for NT-proBNP using an ELISA test (Roche Diagnostics, Mannheim, Germany). The lower limit of detection of C-reactive protein (CRP) was 0.71 mg/l. A value of 0.35 mg/l was assigned to the 92 patients with undetectable CRP levels. Serum creatinine values were used to calculate the eGFR using an estimation equation from the Modification of Diet in Renal Disease Study [11].

Data Analysis

The CRP, NT-proBNP, and eGFR values did not have normal distributions and are presented as medians. The NT-proBNP values were transformed to their natural logarithm [ln(NT-proBNP)] to achieve normality. The eGFR values were divided into 4 prospectively defined groups: (1) eGFR <60 ml/min per 1.73 m^2; (2) eGFR ≥60 to <75 ml/min per 1.73 m^2; (3) eGFR ≥75 to <90 ml/min per 1.73 m^2, and (4) eGFR ≥90 ml/min per 1.73 m^2. Dummy variables were used to code eGFR group membership. Using eGFR group 1 as a reference group, the effect of an eGFR group membership on ln(NT-proBNP) was analyzed by a multiple linear regression model. The continuous covariates considered were age, body mass index (BMI), CRP level, and hemoglobin level. The categorical variables included the following: sex, severity of airway obstruction, and minor echocardiographic findings, as well as the presence of arterial hypertension, asthma, COPD, hypercapnic respiratory failure, other lung disease, or malignant disease. To further examine whether the increased NT-proBNP values in eGFR group 1 were the result of reduced renal clearance, we performed a subgroup analysis of the patients without heart disease who exhibited NT-proBNP values in the highest quartile. In the group of patients with heart disease, the model was additionally adjusted for the above-mentioned 6 cardiac characteristic groups, which were treated as independent and equally weighted covariates. The relationship between eGFR and the crude values for ln(NT-proBNP) as continuous variables was analyzed by calculating Pearson's correlation coefficient for each group and depicted using scatter plots and linear regression lines. Given the exploratory nature of the study, the test results should not be interpreted as confirmatory, and no adjustment for multiple testing was performed. A p value <0.05 was considered significant. Analyses were performed using SAS, version 9.2 (SAS Institute, Chicago, Ill., USA).

Results

The baseline characteristics of the study group and the distribution of cardiac and pulmonary disorders as defined by the eGFR group membership are presented in table 1. Age decreased continuously from eGFR group 1 to eGFR group 4. The trends for the presence of all types of lung disease, malignant disease, arterial hypertension, and diabetes across the eGFR groups were no longer significant after adjusting for age; however, the trend for the presence of heart disease ($p < 0.01$) persisted after adjusting for age. After adjusting for age, BMI, sex, and the presence of arterial hypertension and diabetes, the patients in eGFR group 1 had a higher odds ratio (OR) of heart disease than those in eGFR group 3 (OR 2.60; 95% confidence interval, CI, 1.37–4.93, $p < 0.01$) and eGFR group 4 (OR 2.19; 95% CI 1.14–4.22; $p = 0.02$). The contrast between the odds of having heart disease in patients in eGFR groups 1 and 2 was not significant (OR 1.41; 95% CI 0.75–2.63; $p = 0.29$). The patients in eGFR group 1 had a higher prevalence of significant systemic inflammation defined as a CRP value >5 mg/l than those in eGFR group 4 (OR 2.11; 95% CI 1.11–4.02, $p = 0.02$) after adjusting for age ($p = 0.58$), sex ($p = 0.19$), and BMI ($p < 0.01$), as well as the presence of heart disease ($p = 0.02$), asthma ($p = 0.94$), COPD ($p = 0.95$), other lung disease ($p = 0.05$), at least moderately severe airway obstruction ($p < 0.01$), hypercapnic respiratory failure ($p = 0.04$), and malignant disease ($p < 0.01$). The differences in the prevalence of a CRP level >5 mg/l between eGFR groups 1 and 2 ($p = 0.23$) and between eGFR groups 1 and 3 ($p = 0.29$) were not significant.

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Table 1. Patient characteristics and values for NT-proBNP according to the groups of eGFR (ml/min per 1.73 m^2)

	All patients (n = 697)	eGFR				Comparison of eGFR groups p value	p value adjusted for age
		group 1 eGFR <60 (n = 77)	group 2 eGFR ≥60 – <75 (n = 139)	group 3 eGFR ≥75 – <90 (n = 191)	group 4 eGFR ≥90 (n = 289)		
Median eGFR	85.8	51.7	69.3	82.7	105.4		
Range	71.5–103.3	43.4–56.2	64.8–72.0	78.7–86.3	96.9–115.5		
Age, years	57.5 ± 16.4	71.4 ± 9.6	65.2 ± 11.1	58.6 ± 14.9	49.4 ± 16.5	<0.01[a]	
CRP, mg/l	2.40 [1.01–5.80]	4.98 [1.65–12.60]	2.56 [1.05–5.80]	2.48 [1.00–6.00]	1.88 [0.90–4.08]	<0.01[a]	0.09[a]
BMI	27.6 ± 5.2	29.6 ± 6.2	28.1 ± 4.5	27.3 ± 4.6	27.0 ± 5.5	<0.01[a]	0.30[a]
Females, %	47.6	54.6	48.2	53.4	41.5	0.03[b]	<0.01[e]
Arterial hypertension, %	43.6	76.6	56.1	41.9	30.1	<0.01[b]	0.08[e]
Diabetes, %	8.8	19.5	9.4	6.3	7.3	<0.01[b]	0.18[e]
Serum creatinine, mg/100 ml	0.85 [0.73–1.01]	1.30 [1.07–1.57]	1.05 [0.87–1.14]	0.84 [0.76–0.98]	0.73 [0.65–0.83]	<0.01[d]	<0.01[d]
National Kidney Foundation Stage 1, 2, 3, 4, 5	289, 330, 74, 3, 0	0, 0, 74, 3, 0	0, 139, 0, 0, 0	0, 191, 0, 0, 0	289, 0, 0, 0, 0		
Hemoglobin, g/dl	14.4 ± 1.4	13.8 ± 1.9	14.5 ± 1.4	14.3 ± 1.3	14.5 ± 1.4	<0.01[a]	<0.01[a]
Malignant disease, %	6.0	10.4	5.8	8.9	3.1	0.02[b]	0.26[e]
Minor echocardiographic findings, %	17.4	28.6	23.0	18.3	11.1	<0.01[b]	0.90[e]
Heart disease, %	25.3	57.1	38.1	19.9	14.2	<0.01[b]	<0.01[a]
Impaired left ventricular function, n	30 (4.3%)	11 (14.3%)	12 (8.6%)	5 (2.6%)	2 (0.7%)	<0.01[b]	<0.01[a]
AF and/or LBB, n	50 (7.2%)	11 (14.3%)	17 (12.2%)	10 (5.2%)	12 (4.2%)	<0.01[b]	0.47[a]
Pulmonary hypertension, n	61 (8.7%)	21 (27.3%)	16 (11.5%)	14 (7.3%)	10 (3.5%)	<0.01[b]	0.04[e]
Valvular or pericardial disease or ASD, n	26 (3.7%)	5 (6.5%)	7 (5.0%)	6 (3.1%)	8 (2.8%)	0.09[b]	0.94[e]
Exercise-induced myocardial ischemia, n	12 (1.7%)	3 (3.9%)	4 (2.9%)	3 (1.6%)	2 (0.7%)	0.02[b]	0.89[e]
Left ventricular hypertrophy, n	66 (9.5%)	16 (20.8%)	20 (14.4%)	13 (6.8%)	17 (5.9%)	<0.01[b]	0.43[e]
Lung disease, %	78.6	85.7	79.1	75.9	78.6	0.29[b]	0.45[e]
COPD, n	124 (17.8%)	25 (32.5%)	29 (20.9%)	31 (16.2%)	39 (13.5%)	<0.01[b]	0.62[e]
GOLD I, II, III, IV	5, 49, 36, 34	1, 10, 4, 10	2, 11, 10, 6	2, 11, 10, 8	0, 17, 12, 10		
Asthma, n	356 (51.1%)	30 (39.0%)	67 (48.2%)	97 (50.8%)	162 (56.1%)	<0.01[b]	0.86[e]
Hypercapnic respiratory failure, n	20 (2.9%)	5 (6.5%)	3 (2.2%)	4 (2.1%)	8 (2.8%)	0.28[b]	0.45[e]
Other, n	68 (9.8%)	11 (14.3%)	14 (10.1%)	17 (8.9%)	26 (9.0%)	0.23[b]	0.86[e]
Neither heart disease nor lung disease, n	108 (15.5%)	4 (5.2%)	17 (12.2%)	36 (18.8%)	50 (17.3%)	<0.01[b]	0.17[e]
No heart disease, n	521 (74.7%)	33 (42.9%)	86 (61.9%)	153 (80.1%)	248 (85.8%)	<0.01[b]	<0.01[e]
NT-proBNP, pg/ml							
All patients	72 [33– 182]	276 [97–1,871]	105 [44–296]	91 [38–181]	43 [23–90]	<0.01[c]	<0.01[c]
Without heart disease (n = 521)	55 [27– 105]	97 [58–236]	66 [29–121]	63 [31–127]	40 [22–77]	<0.01[c]	0.04[c]
With heart disease (n = 176)	291 [118– 1,464]	1,486 [207–3,627]	296 [129–834]	368 [194–1,218]	127 [63–360]	<0.01[c]	<0.01[c]

Means ± SD, median values [interquartile ranges] and numbers of patients (%) are shown unless indicated otherwise. AF and/or LBB: 1 of the patients had both atrial fibrillation and left bundle branch block; ASD = atrial septal defect; Other = the group included patients with fibrosing alveolitis, sarcoidosis, silicosis, allergic alveolitis, chronic fibrotic tuberculosis, cryptogenic organizing pneumonia, cystic fibrosis and lymphomatoid granulomatosis.

[a] Linear regression model, used with estimate statement; [b] Cochrane armitage test for trend; [c] linear regression model, used with estimate statement for ln-transformed values of NT-proBNP, [d] linear regression model, used with estimate statement for ln-transformed values of serum creatinine; [e] logistic regression model.

In the 521 patients without heart disease, adjustment for age attenuated the trend for ln(NT-proBNP) across the eGFR groups, leaving little association (p = 0.04) between eGFR group membership and ln(NT-proBNP) (table 1). Multiple regression analysis with adjustment for the covariates listed above showed that the values for ln(NT-proBNP) did not differ between eGFR group 1 and eGFR group 2 (p = 0.59), eGFR group 3 (p = 0.58) and eGFR group 4 (p = 0.46) in the entire cohort. Likewise, eGFR group 1 membership had no effect on the adjusted values for ln(NT-proBNP) in the subgroup of patients with NT-proBNP levels in the highest quartile (p = 0.29). The median values for NT-proBNP in the subgroup of patients with NT-proBNP values in the highest quartile were 236 pg/ml in eGFR group 1, 179 pg/ml in eGFR group 2, 168 pg/ml in eGFR group 3, and 186 pg/ml in eGFR group 4. In contrast, in the 176 patients with heart disease, the adjusted values for ln(NT-proBNP) were higher in eGFR group 1 than in eGFR group 2 ($p < 0.01$), eGFR group 3 (p = 0.01) and eGFR group 4 ($p < 0.01$; fig. 1). The correlations between the values for ln(NT-proBNP) and eGFR as continuous variables are shown in figure 2.

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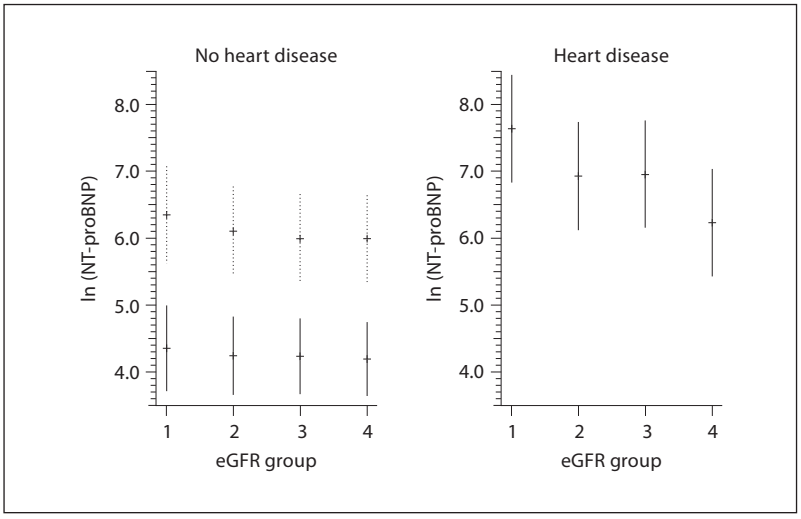

Fig. 1. Relationship between eGFR group membership and the values for ln(NT-proBNP) after adjustment for various covariates in patients with and without heart disease. The bars represent the 95% CIs. The results of the subgroup analysis of patients without heart disease who exhibited NT-proBNP values in the highest quartile are also shown (dotted lines). In patients without heart disease, the adjusted values for ln(NT-proBNP) were not different between eGFR group 1 and eGFR groups 2, 3, and 4 both in the entire cohort and in the subgroup of patients with NT-proBNP levels in the highest quartile. In patients with heart disease, the adjusted values for ln(NT-proBNP) were higher in eGFR group 1 than in eGFR group 2, eGFR group 3 and eGFR group 4 (group 1: eGFR <60 ml/min per 1.73 m^2; group 2: eGFR ≥60 to <75 ml/min per 1.73 m^2; group 3: eGFR ≥75 to <90 ml/min per 1.73 m^2, and group 4: eGFR ≥90 ml/min per 1.73 m^2).

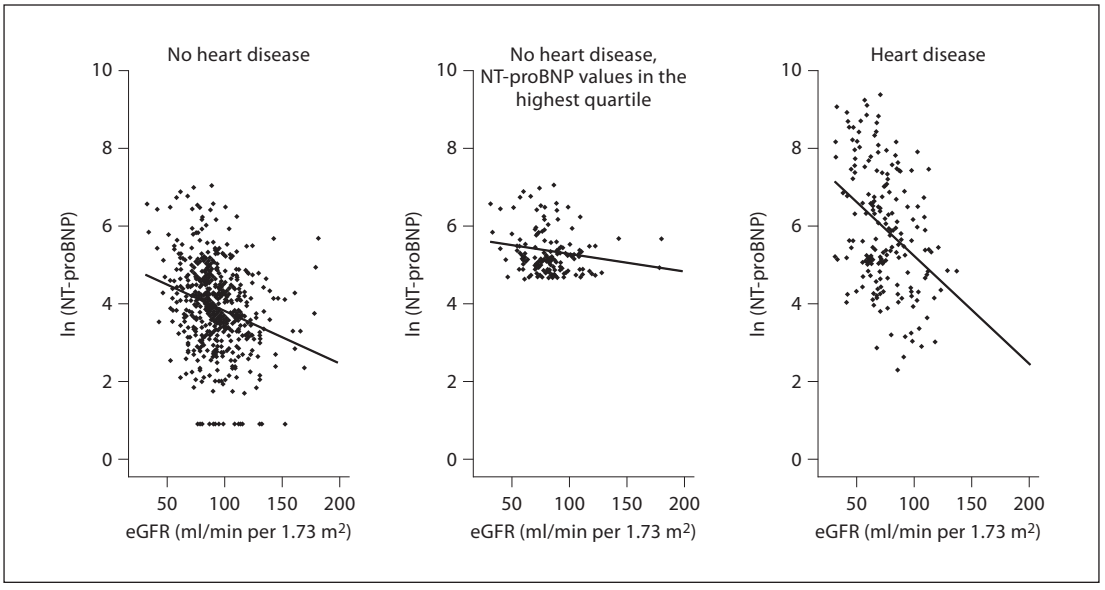

Fig. 2. Relationships between the crude values for ln(NT-proBNP) and eGFR as continuous variables. The x-axis value range was limited to 30–200 ml/min per 1.73 m^2, because only 5 values for eGFR fell outside this range. The values for ln(NT-proBNP) were inversely correlated with eGFR in all groups ($p < 0.05$).

Discussion

The results of this study show that among patients with heart disease, ln(NT-proBNP) values were higher in eGFR group 1 than in eGFR groups 2–4 after adjusting for extracardiac confounders and the 6 cardiac characteristic groups. In contrast, no effect of renal function on the values for ln(NT-proBNP) was seen in the patients without heart disease, both in the whole group and in the subgroup of patients with NT-proBNP values in the highest quartile. In the case of accumulation because of impaired glomerular filtration, an increase in the values for ln(NT-proBNP) would also be anticipated for the patients without heart disease assigned to eGFR group 1. These findings do not suggest that a reduced glomerular filtration plays a major role in determining the serum levels of NT-proBNP across the range of eGFR observed in this study. Rather, our data are consistent with the hypothesis that tubular secretion or metabolism is the major renal clearance mechanism for circulating NT-proBNP. There is some evidence in the literature that renal NT-proBNP clearance by tubular mechanisms is upregulated rather than reduced with decreasing eGFR [12]. Our data also support the notion that the disproportionate increase in the ln(NT-proBNP) values seen in the group of patients with heart disease and at least moderate renal impairment is the result of increased cardiac secretion. Myocardial wall stress is thought to be the principal trigger of proBNP release from cardiac myocytes [13]. Therefore, our data suggest that a moderately reduced eGFR is associated with additional cardiac stress in patients with established heart disease. This assumption is in agreement with the negative prognostic impact of a reduced eGFR following acute myocardial infarction and in chronic heart failure patients [14–16]. The mechanisms underlying the proposed interaction between renal function and cardiac stress cannot be determined from our study.

The kidney-mediated excess stress burden on the heart is not trivial. To illustrate the magnitude of stress, it is useful to compare the impact of eGFR group 1 versus eGFR group 2–4 membership on ln(NT-proBNP) in regard to the other covariates. In patients with heart disease, moving from the combined eGFR group (2–4) to eGFR group 1 increases ln(NT-proBNP) 0.5 times as much as the presence of an impaired left ventricular function and to the same extent as the presence of pulmonary hypertension. Furthermore, eGFR group 1 membership has approximately the same effect on ln(NT-proBNP) as the presence of significant systemic inflammation as indicated by a CRP value >5 mg/l. Previous studies have shown an inverse correlation between exercise capacity and the serum levels of NT-proBNP, such that NT-proBNP has been proposed as an indicator of the exercise cardiac reserve [17]. Patients with advanced kidney disease often have a reduced exercise tolerance [18–20]. Systemic inflammation and the effects of metabolic acidosis on the heart and skeletal muscles have been proposed to account for the decreased exercise tolerance. Inducing additional cardiac stress might be another mechanism by which impaired renal function reduces exercise tolerance in patients with coexistent heart disease. Our cohort consisted primarily of patients with lung disease. Systemic inflammation is common among patients with advanced lung disease [21, 22]. It is noteworthy that eGFR group 1 membership was shown to be a predictor for the presence of systemic inflammation and heart disease, even in this population with a significant 'background noise' of lung-related systemic inflammation and with a low prevalence of moderate renal impairment and heart disease. This finding indicates how important the interaction between renal function, heart disease and systemic inflammation is, even in patients with only moderately reduced renal function.

The eGFR groups were not equally balanced with respect to the number of covariates that influenced the serum level of NT-proBNP (table 1). Determinants that increase NT-proBNP and were adjusted for include the following: higher age, higher CRP level, female sex, lower hemoglobin level, lower BMI, and minor echocardiographic findings. Table 1 also

shows a steady decrease in the prevalence of heart disease from eGFR group 1 to group 4. Accordingly, the median values for NT-proBNP decreased by approximately 90% from eGFR group 1 to group 4 in patients with heart disease. Failure to adjust the NT-proBNP values would result in an overestimation of the effect of eGFR on the NT-proBNP values (fig. 2). We controlled for the effect of heart disease on NT-proBNP by putting the cardiological findings into 6 characteristic groups and adjusting the ln(NT-proBNP) values for the type of heart disease. However, it can be assumed that not all cardiac disorders were diagnosed with the noninvasive methods used in this study.

The following limitations also warrant mentioning. First, data to analyze diastolic function were not available. Impairment in diastolic function may occur early in patients with kidney disease, even in the absence of left ventricular hypertrophy, and is associated with increased NT-proBNP levels [23]. Second, compared with eGFR group 1, eGFR groups 3 and 4 exhibited substantially lower prevalence rates for impaired left ventricular systolic function, atrial fibrillation or left bundle branch block, and pulmonary hypertension (table 1). These covariates are key determinants of the NT-proBNP values. Therefore, the validity of our regression models may have been weakened by these large differences in the prevalence of major heart disease between the reference group and eGFR groups 3 and 4. Third, the smoking status of the participants was not objectively validated. Because the self-reported smoking status is unreliable and the cholesterol levels were not available, the ORs for the presence of heart disease could not be adjusted for these confounders. Fourth, no data were available on the presence of albuminuria, which is associated with an increased cardiovascular risk [1]. Fifth, we did not adjust for current medications, which may interact with renal function and elicit cardiovascular effects. This limitation is unlikely to weaken the strength of our data because the lack of adjustment tends to dilute the impact of eGFR group membership on the NT-proBNP levels. Sixth, we did not measure BNP so we could not determine whether BNP was increased to a greater extent than NT-proBNP in eGFR group 1 [24–26]. Finally, our study involved only patients with dyspnea and included only 3 patients with an eGFR <30 ml/min per 1.73 m^2. Hence, these results should not be extrapolated to broader populations and to patients with severe impairment in renal function.

In summary, the results of this study show that an increased prevalence of heart disease is a major reason for the elevated NT-proBNP levels seen in patients with chronic dyspnea and moderately impaired renal function. The data do not support the widely held view that NT-proBNP accumulates in this condition because of impaired renal clearance. Rather, our findings suggest that a moderately impaired renal function induces additional cardiac stress in patients with heart disease. This excess burden of stress may further reduce exercise tolerance and contribute to the increased cardiovascular risk of cardiac disease patients with at least moderate renal dysfunction.

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