Urinary N-Terminal Prohormone Brain Natriuretic Peptide Excretion in Patients With Chronic Heart Failure

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Background—Urinary excretion is currently regarded as the main mechanism of elimination of N-terminal prohormone brain natriuretic peptide (NT-proBNP). The clinical implications and the value of measurement of urinary NT-proBNP in patients with heart failure are largely unknown.

Methods and Results—We studied 94 patients (age, 58±11 years; 79% men) with chronic heart failure (CHF) and 20 age- and sex-matched healthy control subjects. Glomerular filtration rate and effective renal plasma flow were measured as clearance of 125I-iothalamate and 131I-hippuran, respectively. NT-proBNP levels were determined in both plasma and 24-hour urine collections. Mean left ventricular ejection fraction of CHF patients was 0.28±0.09. Plasma NT-proBNP levels were higher in CHF patients compared with control subjects (median, 547 versus 41 pg/mL; P<0.001). Urinary NT-proBNP excretion, however, was substantially lower in CHF patients (median, 0.13 versus 2.3 mL/min; P<0.001). Urinary NT-proBNP excretion was independent of estimated glomerular filtration rate. In both CHF patients and control subjects, there was a strong and inverse relation between plasma NT-proBNP concentrations and urinary NT-proBNP excretion (r=−0.72 and r=−0.65 respectively; both P<0.001). Decreased renal plasma flow in CHF was significantly associated with a lower excretion of NT-proBNP (P=0.026).

Conclusions—Urinary NT-proBNP excretion is lower in patients with CHF compared with control subjects and is inversely related to plasma NT-proBNP. Urinary NT-proBNP is associated with renal plasma flow but not with estimated glomerular filtration rate. Elevated levels of plasma NT-proBNP in patients with CHF might be explained not only by myocardial stress but also by a marked decrease in urinary excretion. (Circulation. 2009;120:35-41.)

Key Words: heart failure ■ kidney ■ natriuretic peptides

Natriuretic peptides have beneficial effects by counteracting the activation of the renin-angiotensin-aldosterone system. Elevation of natriuretic peptide levels in heart failure is caused mainly by release from the ventricles in response to increased myocardial stress. Brain-type natriuretic peptide (BNP) and its inactive N-terminal fragment (NT-proBNP) are important markers for the diagnosis and prognosis of patients with suspected or established chronic heart failure (CHF).1–3

Clinical Perspective on p 41

The exact mechanism of elimination of NT-proBNP is still not well identified in health or in disease states. Besides an increased production, elevated natriuretic peptide levels might also be explained by an altered metabolism and decreased clearance from the circulation. The precise role of the kidney in eliminating NT-proBNP, however, remains unclear.

It is well known that renal dysfunction is relatively common in patients with heart failure and is an independent risk factor for cardiovascular morbidity and mortality.4–8 Several studies have been published on the inverse relationship between serum levels of natriuretic peptides and glomerular filtration rate (GFR). These peptides, although with higher optimal cutoff levels, remained diagnostic and predictive in all stages of CHF, despite the presence of significant renal dysfunction.9–18 Recently, the diagnostic and prognostic value of urinary concentrations of especially NT-proBNP has been evaluated in several small studies of patients with and without CHF.19–22

Our hypothesis was that part of the elevated concentrations of circulating natriuretic peptides in CHF is related to impaired renal function. The purpose of the present study was to investigate the impact of renal function on the excretion of NT-proBNP in the urine of patients with stable CHF.

Methods

Patient Population and Study Design

Details of the study design have been published elsewhere.23,24 The study was conducted in the outpatient clinic of the Department of Cardiology at the University Medical Center Groningen (Groningen, the Netherlands).

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A total of 94 patients were available for this analysis. Briefly, outpatient CHF patients >18 years of age with left ventricular ejection fraction <45% who were clinically stable were asked to participate. All CHF patients were given sodium-restricted dietary recommendations according to international and hospital heart failure guidelines. All patients were on angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers, and all medication had to be stable for at least 1 month. Additionally, 20 age- and sex-matched control subjects were studied for comparison purposes. Baseline measurements included standard weight, height, and systolic and diastolic blood pressures, as well as assessment of New York Heart Association functional class. All CHF patients underwent clearance measurements of renal function. GFR and effective renal plasma flow (ERPF) were measured by the clearance of 125I-iothalamate and 131I-hippuran, respectively.25,26 The filtration fraction was calculated as the ratio of GFR and ERPF and expressed as a percentage. In both CHF patients and control subjects, estimated GFR was calculated as the ratio of GFR and ERPF and expressed as a percentage. In both CHF patients and control subjects, estimated GFR (eGFR) was calculated from the simplified Modification of Diet in Renal Disease (mL · min⁻¹ · 1.73 m²) formula: 186.3 × (serum creatinine)¹·⁸⁵×(age)⁻¹·²⁰³×0.742 (if patient is female)×1.212 (if patient is black).²⁷,²⁸ Serum creatinine was measured by Jaffe alkaline picrate assay.

NT-proBNP measurements were performed in plasma and in urine on an Elecsys 2010 analyzer, a commercially available electrochemiluminescent sandwich immunoassay (Elecsys proBNP, Roche Diagnostics, Mannheim, Germany). The intra-assay and interassay coefficients of variation were 1.2% to 1.5% and 4.4% to 5.0%, respectively, with an analytical range of 5 to 35 000 pg/mL.²⁹ Both investigators and patients were blinded to the NT-proBNP results.

Urine Collection and Assays
All CHF patients and control subjects collected 24-hour urine. Urinary creatinine was determined by use of Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, NY), an automatic enzymatic method. Urinary NT-proBNP was determined by the same method as plasma NT-proBNP and expressed as picograms per milliliter. In addition, to account for possible differences in urine concentrations, we also corrected for urinary creatinine concentrations (nanograms per gram urinary creatinine). To evaluate the renal handling of NT-proBNP, we used different modalities to assess supply, handling, and excretion of NT-proBNP. As a measurement of supply, filtered load of plasma NT-proBNP was calculated as follows: eGFR × plasma NT-proBNP levels, which represents the amount of NT-proBNP freely filtered by glomeruli to the tubules. To assess the renal handling of NT-proBNP, we measured the renal excretion (rate) of NT-proBNP (or urinary clearance), which was calculated as follows: (urinary NT-proBNP concentrations × total urinary volume)/plasma NT-proBNP concentration. As a measurement of total NT-proBNP excretion, we also calculated the total amount of urinary NT-proBNP per day: urinary concentration of NT-proBNP × total 24-hour urine volume. Finally, to correct for a possible effect of glomerular filtration on NT-proBNP excretion, we also calculated the fractional NT-proBNP excretion as the ratio between NT-proBNP excretion rate and eGFR: NT-proBNP excretion/eGFR × 100%. This reflects the proportion of the filtered load that is actually excreted.

Statistical Analyses
Continuous variables with a normal distribution are expressed as means with SD. Levels of NT-proBNP are given as medians with interquartile range (IQR). Nominal variables are expressed as n (%). Plasma NT-proBNP levels were correlated with those in urine using Spearman’s rank correlation coefficient. Data with a skewed distribution were compared by means of the Mann–Whitney U tests, and categorical clinical variables were compared with the Fisher exact test. Kruskal-Wallis 1-way ANOVA test was used to determine differences in fractional NT-proBNP excretion across groups of ERPF.

All reported P values are 2-tailed, and values of P < 0.05 were considered statistically significant. Analyses were performed with Statistical Package for Social Sciences software (SPSS version 12.0 for Windows, SPSS Inc, Chicago, Ill) and STATA Statistical Software release 10.0 (Stata Corp LP, College Station, Tex).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Table 1. Baseline Characteristics of the Study Patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>CHF Patients (n=94)</th>
<th>Control Subjects (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58 ± 11</td>
<td>58 ± 4</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>74 (79)</td>
<td>16 (80)</td>
</tr>
<tr>
<td>NYHA class I/II/III or IV, %</td>
<td>15/49/36</td>
<td>NA</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>6 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>15 (16)</td>
<td>0</td>
</tr>
<tr>
<td>Ischemic origin, n (%)</td>
<td>43 (46)</td>
<td>0</td>
</tr>
<tr>
<td>Cardiorenal hemodynamic parameters</td>
<td></td>
<td></td>
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<tr>
<td>LVEF, %</td>
<td>0.28 ± 0.09</td>
<td>NA</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>121 ± 20</td>
<td>119 ± 11</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>70 ± 11</td>
<td>71 ± 8</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL†</td>
<td>1.26 ± 0.38</td>
<td>0.89 ± 0.15</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dL</td>
<td>22 ± 10</td>
<td>NA</td>
</tr>
<tr>
<td>eGFR, mL · min⁻¹ · 1.73 m⁻²†</td>
<td>64 ± 17</td>
<td>90 ± 12</td>
</tr>
<tr>
<td>GFRIOTH, mL · min⁻¹ · 1.73 m⁻²</td>
<td>78 ± 26</td>
<td>NA</td>
</tr>
<tr>
<td>ERPF, mL · min⁻¹ · 1.73 m⁻²</td>
<td>282 ± 84</td>
<td>NA</td>
</tr>
<tr>
<td>FF, %</td>
<td>28 ± 5</td>
<td>NA</td>
</tr>
<tr>
<td>UAE, mg/day*†</td>
<td>5.5 (3.4–10.7)</td>
<td>1.5 (1.2–1.9)</td>
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<table>
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<tr>
<th>Medication</th>
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</thead>
<tbody>
<tr>
<td>ACE-I/ARB, n (% use)</td>
<td>94 (100)</td>
<td>0</td>
</tr>
<tr>
<td>β-Blocker, n (% use)</td>
<td>79 (84)</td>
<td>0</td>
</tr>
<tr>
<td>Diuretic, n (% use)</td>
<td>64 (68)</td>
<td>0</td>
</tr>
<tr>
<td>Spironolactone, n (% use)</td>
<td>30 (32)</td>
<td>0</td>
</tr>
<tr>
<td>Calcium antagonist, n (% use)</td>
<td>13 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Nitrates, n (% use)</td>
<td>8 (9)</td>
<td>0</td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association functional class; LVEF, left ventricular ejection fraction; GFRIOTH, GFR measured by the clearance of 125I-iothalamate; FF, filtration fraction; UAE, urinary albumin excretion; ACE-I, angiotensin-converting enzyme inhibitors; and ARB, angiotensin II receptor blockers. All continuous variables are presented as mean ± SD.

*Median value with (25th to 75th percentile).
†P < 0.001.

14.0.1 for Windows, SPSS Inc, Chicago, Ill and STATA Statistical Software release 10.0 (Stata Corp LP, College Station, Tex).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Baseline Characteristics
Baseline characteristics of the study patients are presented in Table 1. Mean age of the CHF patients was 58 years, and 21% were female. The full range of severity of CHF from New York Heart Association class I to IV was present. Mean left ventricular ejection fraction was 0.28 ± 0.09%. All patients received renin-angiotensin-aldosterone system inhibitors, and a large proportion also received β-blockers (84%) and diuretics (68%). Mean GFR was 78 ± 25 mL · min⁻¹ · 1.73 m². Patients were classified according to the Kidney Disease Outcome Quality Initiative.³⁰ Only 6% of the patients had a GFR < 30 mL · min⁻¹ · 1.73 m², 19% had a GFR between 30 and 60 mL · min⁻¹ · 1.73 m², and 75% had a GFR ≥ 60 mL · min⁻¹ · 1.73 m². The healthy control subjects were 58 ± 4 years of age; 80% were male; and mean eGFR was 90 ± 12 mL · min⁻¹ · 1.73 m².
Plasma and Urinary NT-proBNP in CHF Patients and Control Subjects

Plasma levels of NT-proBNP of CHF patients were higher compared with control subjects (median, 547 pg/mL [IQR, 253 to 1,324 pg/mL] and 41 pg/mL [IQR, 28 to 69 pg/mL], respectively; P<0.001). Figure 1 demonstrates that urinary NT-proBNP levels were lower in CHF patients than in age- and sex-matched control individuals. In addition, urinary NT-proBNP excretion was substantially lower in CHF patients than in control subjects (0.13 mL/min [IQR, 0.04 to 0.32 mL/min] and 2.3 mL/min [IQR, 1.1 to 3.6 mL/min], respectively; P<0.001; see Table 2).

Plasma and Urinary NT-proBNP and Renal Function

Figure 2 shows the inverse and exponential relation between plasma levels and renal excretion of NT-proBNP in CHF patients and in healthy control individuals (r = −0.65, P<0.001; and r = −0.72, P<0.001, respectively). In Figure 3, study patients are stratified by the 4 Kidney Disease Outcome Quality Initiative stages of GFR. In CHF patients with moderately severe renal dysfunction (GFR, 30 to 60 mL · min⁻¹ · 1.73 m⁻²) and severe renal dysfunction (GFR <30 mL · min⁻¹ · 1.73 m⁻²), only slightly lower urinary NT-proBNP excretion was measured compared with patients with normal or mildly impaired renal function (GFR, 60 to 90 mL · min⁻¹ · 1.73 m⁻²).

The relation of ERPF and fractional NT-proBNP excretion (P for trend=0.026) in CHF is presented in Figure 4, showing that a decreased renal plasma flow in patients with CHF is associated with significantly lower excretion of NT-proBNP. All patients in the present study were on angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers.

There were no significant differences in urinary NT-proBNP levels, NT-proBNP excretion, or ERPF in patients on angiotensin II receptor blocker therapy compared with patients on angiotensin-converting enzyme inhibitors or a combination of both (all P>0.05). Patients on aldosterone antagonists had similar urinary NT-proBNP levels but tended to have lower NT-proBNP excretion (0.06 mL/min [IQR, 0.03 to 0.27 mL/min] versus 0.16 mL/min [0.05 to 0.45 mL/min]; P=0.06). However, it should be noted that plasma NT-proBNP concentrations were significantly higher in patients who used aldosterone antagonists (449 versus 1143 pg/mL; P=0.02).

Discussion

This is the first study that correlated plasma and urinary NT-proBNP with the exact quantitative assessment of GFR in

Table 2. Baseline Characteristics: NT-proBNP–Related Parameters

<table>
<thead>
<tr>
<th>Variables</th>
<th>CHF Patients (n=94)</th>
<th>Control Subjects (n=20)</th>
<th>P for Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma NT-proBNP, pg/mL</td>
<td>547 (253–1324)</td>
<td>41 (28–69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary NT-proBNP, pg/mL</td>
<td>55 (39–72)</td>
<td>84 (57–108)</td>
<td>0.001</td>
</tr>
<tr>
<td>Urinary NT-proBNP, ng/gCr</td>
<td>73 (57–93)</td>
<td>93 (63–123)</td>
<td>0.059</td>
</tr>
<tr>
<td>NT-proBNP excretion, mL/min</td>
<td>0.13 (0.04–0.32)</td>
<td>2.3 (1.1–3.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fractional NT-proBNP excretion, %</td>
<td>0.13 (0.06–0.40)</td>
<td>2.6 (1.2–3.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total urinary NT-proBNP, ng/24 h</td>
<td>99 (75–138)</td>
<td>154 (85–192)</td>
<td>0.036</td>
</tr>
<tr>
<td>Filtered load, μg/24 h</td>
<td>48 (23–106)</td>
<td>6.3 (3.2–8.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Cr indicates urinary creatine.

*Median value with (25th to 75th percentile).
patients with CHF. Interestingly, the urinary excretion of NT-proBNP in CHF was markedly reduced. In addition, in both CHF patients and control subjects, we found a strong and inverse relation between plasma NT-proBNP and urinary excretion of NT-proBNP. The reduced urinary NT-proBNP excretion was not related to concomitant impairment of GFR, as apparent from the reduced fractional excretion, although it was associated with impaired renal perfusion. These findings suggest that reduced NT-proBNP excretion is related to altered tubular handling of NT-proBNP in response to reduced renal perfusion and/or increased plasma NT-proBNP concentrations.

Urinary NT-proBNP and Heart Failure

There are only a few previous studies on the presence and clinical value of urinary NT-proBNP in CHF. Ng and coworkers\textsuperscript{19} compared urinary levels of N-terminal prohormone atrial natriuretic peptide, NT-proBNP, and C-type natriuretic peptide and plasma levels of NT-proBNP between 34 patients hospitalized for heart failure with 82 age- and sex-matched echocardiographically normal subjects. Urinary NT-proBNP was reported to have a diagnostic accuracy comparable to that of plasma NT-proBNP for the diagnosis of heart failure. Cortes and colleagues\textsuperscript{21,31} reported similar findings on both the diagnostic and the prognostic value of urinary NT-proBNP in 96 CHF patients. However, Michielsen and coworkers\textsuperscript{22} found a rather poor diagnostic performance of urinary NT-proBNP in 47 patients diagnosed with systolic heart failure (New York Heart Association class III and IV) and in 76 control subjects. The markedly impaired renal function in their patients with advanced heart failure could have influenced the diagnostic value of urinary NT-proBNP.

In these studies, spot morning urine samples were used to determine urinary NT-proBNP concentrations. However, plasma levels have a substantial diurnal variation, which may influence NT-proBNP excretion and consequently urinary concentration. Because we measured NT-proBNP in 24-hour urine collections, our study is devoid of such bias.

Clearance of NT-proBNP From the Circulation

The exact mechanism of NT-proBNP clearance remains to be elucidated, although renal clearance is currently regarded as its main mechanism.\textsuperscript{32} Only a few studies have explored the renal handling of proBNP-derived peptides. In healthy individuals, renal extraction ratios of \approx 0.15 to 0.20 were reported for both BNP and NT-proBNP.\textsuperscript{33–37} Similar values were found in patients with CHF, in patients with liver cirrhosis, and in subjects with hypertension. Interestingly, these ratios were not significantly influenced by body mass index, moderate dynamic exercise, and diuretic use.\textsuperscript{33–35,37} In our cohort of CHF patients, we found reduced GFR, which could theoretically contribute to the reduction in urinary clearance of NT-proBNP. Nevertheless, filtered load was markedly increased as a result of markedly elevated plasma NT-proBNP levels. Interestingly, despite much higher filtered load of NT-proBNP, the urinary excretion of this peptide was significantly decreased in patients with CHF. This finding indicates altered tubular handling of NT-proBNP in patients with CHF. The exact nature of the altered tubular handling, however, cannot be derived from our data and could involve changes in tubular reabsorption and an altered local degradation processes. So, changes in both glomerular filtration and tubular handling (reabsorption and/or local degradation processes) may account for the lower renal clearance of NT-proBNP in patients with CHF. The finding that fractional NT-proBNP excretion was found to be significantly reduced in patients with CHF suggests that the contribution of lower glomerular filtration in this process is at best minor and that, accordingly, altered tubular processing must predominantly be involved.

Cardiorenal Interactions in Heart Failure

Both BNP and NT-proBNP (3.5 and 8.5 kDa, respectively) are, by definition, small-molecular-weight proteins (1 to 50 kDa) and have a molecular weight of approximately 3.5 kDa. They are rapidly cleared from the circulation by the kidneys, and their plasma concentrations are highly influenced by renal function. The exact mechanism of NT-proBNP clearance remains to be elucidated, although renal clearance is currently regarded as its main mechanism.\textsuperscript{32} Only a few studies have explored the renal handling of proBNP-derived peptides. In healthy individuals, renal extraction ratios of \approx 0.15 to 0.20 were reported for both BNP and NT-proBNP.\textsuperscript{33–37} Similar values were found in patients with CHF, in patients with liver cirrhosis, and in subjects with hypertension. Interestingly, these ratios were not significantly influenced by body mass index, moderate dynamic exercise, and diuretic use.\textsuperscript{33–35,37} In our cohort of CHF patients, we found reduced GFR, which could theoretically contribute to the reduction in urinary clearance of NT-proBNP. Nevertheless, filtered load was markedly increased as a result of markedly elevated plasma NT-proBNP levels. Interestingly, despite much higher filtered load of NT-proBNP, the urinary excretion of this peptide was significantly decreased in patients with CHF. This finding indicates altered tubular handling of NT-proBNP in patients with CHF. The exact nature of the altered tubular handling, however, cannot be derived from our data and could involve changes in tubular reabsorption and altered degradation processes. So, changes in both glomerular filtration and tubular handling (reabsorption and/or local degradation processes) may account for the lower renal clearance of NT-proBNP in patients with CHF. The finding that fractional NT-proBNP excretion was significantly reduced in patients with CHF suggests that the contribution of lower glomerular filtration in this process is at best minor and that, accordingly, altered tubular processing must predominantly be involved.
kDa). These proteins are freely filtered by the glomeruli and catabolized by tubular epithelial cells without any other renal processing like tubular secretion as, for instance, in creatinine (0.1 kDa). In hypertensive patients, van Kimmenade and coworkers found no significant differences in fractional extraction of BNP and NT-proBNP between subjects with a GFR $\geq 60$ mL · min$^{-1}$ · 1.73 m$^{-2}$ and subjects with a GFR <60 mL · min$^{-1}$ · 1.73 m$^{-2}$. They suggest that elevated plasma levels of natriuretic peptide are governed mainly by the rate of production and to a lesser extent by renal clearance. This would imply that plasma levels of NT-proBNP predominantly represent modifications of cardiac function, also in the presence of renal function impairment. The reduction in fractional excretion of NT-proBNP in our study was associated with the reduction in renal blood flow. The reduction in renal blood flow in CHF has long been recognized as reflecting the inadequate tissue perfusion inherent to CHF, associated with an unfavorable shift in renal oxygen supply and hypoxia as indicated by an increase in renal oxygen extraction. Such tubular hypoxia may be involved in altered renal handling of NT-proBNP. It can be hypothesized that heart failure may influence tubular processes to maintain plasma natriuretic peptide at high circulating levels as a protective mechanism that counteracts the renin-angiotensin-aldosterone system by inducing vasodilation, diuresis, and natriuresis.

The use of heart failure medication also may have influenced the urinary NT-proBNP excretion. All heart failure medication that improves hemodynamics will potentially reduce plasma NT-proBNP and increase renal perfusion. Renin-angiotensin-aldosterone system blockers can reduce glomerular filtration rate by lowering intraglomerular pressures through vasodilatation of the efferent arteriole. However, we found a reduction in fractional excretion of NT-proBNP, which is, by definition, independent of changes in GFR, so effects on GFR cannot explain our findings. Diuretics will cause afferent vasoconstriction by a tubuloglomerular feedback mechanism, thereby also reducing GFR, but again, because we found a reduction in fractional excretion of NT-proBNP, this is independent of changes in GFR. On the other hand, diuretics will influence sodium absorption in the tubule, but it is unknown whether diuretics influence tubular handling of NT-proBNP. The effects of $\beta$-blockers on renal function in heart failure are not well understood. In patients with hypertension, bisoprolol did not affect renal hemodynamics. The results of our study indicate that the use of aldosterone antagonists was related to a trend toward a lower NT-proBNP excretion, but this might have been related to the higher plasma NT-proBNP levels in patients on aldosterone blockers, probably because they had more severe heart failure. Although we cannot rule out a direct effect of aldosterone blockers on renal/tubular function, the present results do not indicate this.

Whether the reduced renal excretion of NT-proBNP reflects a protective mechanism at any rate in CHF, the elevation of plasma NT-proBNP levels cannot be explained merely by increased cardiac generation but also are due to reduced renal excretion of NT-proBNP. In addition, our data do not enable quantification of the relative contributions of increased cardiac production and diminished renal clearance to elevated plasma levels of NT-proBNP in patients with CHF. This applies particularly to the tubular fate of reabsorbed NT-proBNP. We cannot establish to what extent the reabsorbed NT-proBNP is shunted back to the circulation (which increases circulating NT-proBNP) and to what extent it is metabolized (which would decrease circulating NT-proBNP). Experimental studies with labeled NT-proBNP and renal extraction studies could further clarify this. These and other unresolved issues on the role of natriuretic peptides and the altered tubular mechanisms in the context of the complex cardiorenal interactions merit further research.

### Implications

Urinary NT-proBNP excretion was markedly reduced in CHF. Our data indicate that CHF exerts specific effects on renal handling of NT-proBNP and reduces NT-proBNP excretion in relation to the reduction in renal blood flow. Sampling of 24-hour urine provided feasible and reliable NT-proBNP concentrations in our study population; however, these collections are not feasible in ambulatory patients compared with plasma samples. Furthermore, ease of spot urine sampling may facilitate community screening. Further research is needed to assess the value of this strategy in accurate risk stratification, monitoring, and guiding of therapy in patients with CHF.

### Limitations

In this study, all patients were using renin-angiotensin system inhibitors. These drugs are considered essential therapies in patients with CHF. The population consisted only of patients with systolic dysfunction. Renal NT-proBNP handling should also be studied in patients with preserved systolic function. All of our CHF patients were of white ethnicity and formed a representative sample of the Dutch population, but whether our results are the same for CHF patients with black or other ethnicity remains to be established. Patients in the present study were younger, were more often male, and had lower mean plasma NT-proBNP levels compared with a general outpatient CHF population. Although the results could theoretically have been different in patients with more advanced CHF, we demonstrated the strong inverse correlation between plasma and urinary NT-proBNP over a wide range of patients and even in healthy control subjects, and we did not find any suggestion that the observed relation was different in the more severely diseased heart failure patients.

Although the Modification of Diet in Renal Disease formula has been shown to be the most accurate and least biased estimate of GFR in CHF patients, it has not been validated in healthy subjects with higher GFR values. Therefore, the presented results are subject to this bias. However, based on quantitative considerations of the difference in fractional excretion of NT-proBNP between heart failure patients and control subjects, this would not alter the conclusions on the altered NT-proBNP handling to any relevant extent.

Although 25% of our patients had a GFR $<60$ mL · min$^{-1}$ · 1.73 m$^{-2}$, only 6% had a GFR $<30$ mL · min$^{-1}$ · 1.73 m$^{-2}$. In heart failure with comorbid end-stage renal disease, accumulation of NT-proBNP may be important. Therefore, our...
conclusions should not be extrapolated to patients with end-stage renal disease or undergoing dialysis.

Conclusions
Renal excretion of NT-proBNP in CHF is significantly lower compared with that in age- and sex-matched control patients, and plasma NT-proBNP concentrations are strongly and inversely related to urine NT-proBNP concentrations. Therefore, elevated levels of plasma NT-proBNP in patients with CHF might not be explained exclusively by myocardial stress but possibly also by a marked decrease in urinary excretion. The decrease in NT-proBNP excretion was not related primarily to GFR but seems to be related predominantly to altered tubular handling.

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Disclosures
None.

References
CLINICAL PERSPECTIVE

In patients with chronic heart failure, plasma N-terminal prohormone brain natriuretic peptide (NT-proBNP) levels are elevated, usually attributed to increased production by the ventricles. NT-proBNP is completely excreted by the kidneys, but the renal handling of increased levels of NT-proBNP in patients with heart failure and left ventricular dysfunction is not well understood. We studied renal handling of NT-proBNP in 94 patients with chronic heart failure. Renal function was assessed by clearance of $^{125}$I-iothalamate and $^{131}$I-hippuran. NT-proBNP levels were determined in both plasma and 24-hour urine collections. As expected, plasma NT-proBNP levels were $>10$ times higher in patients compared with 20 age- and sex-matched control subjects. However, urinary NT-proBNP excretion was $>10$ times lower in patients compared with control subjects. In both heart failure patients and control subjects, we found a strong and inverse relationship between plasma NT-proBNP and urinary NT-proBNP excretion. Interestingly, urinary NT-proBNP excretion was independent of glomerular filtration rate but was related to effective renal plasma flow. These findings suggest an active process of tubular NT-proBNP reabsorption, although this remains speculative. If true, elevated levels of NT-proBNP in chronic heart failure are related not only to increased production but also to decreased renal excretion.
Urinary N-Terminal Prohormone Brain Natriuretic Peptide Excretion in Patients With Chronic Heart Failure
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