Optimal blockade of the renin angiotensin system in cardiorenal dysfunction
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High prevalence of microalbuminuria
in chronic heart failure patients

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Abstract

**Background** Microalbuminuria is associated with increased risk for cardiovascular morbidity and mortality. However, the relation between microalbuminuria and chronic heart failure has not been well described yet. In this cross-sectional study, we aimed to evaluate the prevalence of microalbuminuria and the association with neurohormonal parameters in severe chronic heart failure patients.

**Methods** We studied 94 stable chronic heart failure patients (New York Heart Association class III/IV) receiving therapy with angiotensin-converting enzyme inhibitors for over three months. In all patients, renal function and neurohormonal status were evaluated and correlated with urinary albumin/creatinine ratio.

**Results** The studied population consisted of 70 men and 21 women (mean age 69±12 years). Ischemia was the underlying cause of heart failure in 61 patients. Overall, 100% of the patients were treated with an ACE inhibitor, 72% with a β-blocker, and 47% with spironolactone. In 32% (95% confidence interval: 22-42) of the patients, microalbuminuria was present, which is significantly higher than in the general population. However, we found no significant association between the presence of microalbuminuria and renal function. Plasma NT-proBNP, active renin protein, angiotensin I, angiotensin II and aldosterone did not differ significantly between groups with and without microalbuminuria.

**Conclusion** In 32% of the patients microalbuminuria was present. No association was found with either renal, or neurohormonal parameters.
Introduction

Urinary albumin excretion (UAE) is a predictor of cardiovascular mortality in patients with diabetes and hypertension, but also in the general population.\(^1\)\(^-\)\(^2\) The prevalence of microalbuminuria in the general population is 6-8%, whereas in patients with hypertension and diabetes this percentage increases to 10-15% and 15-20%, respectively.\(^3\)\(^-\)\(^4\) However, literature data on the prevalence of microalbuminuria in advanced chronic heart failure (CHF) patients are scarce.\(^5\) The etiology of microalbuminuria remains uncertain, but a large body of evidence proves that treatment with an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker reduces microalbuminuria.\(^6\) In the present cross-sectional study, we therefore evaluate the prevalence of microalbuminuria in advanced chronic heart failure patients and its association with neurohormones and renal function.

Methods

We cross-sectionally evaluated 96 patients CHF New York Heart Association (NYHA) functional class III or IV, who visited the Heart Failure Clinic of the St. Antonius Hospital (Nieuwegein), the University Medical Center Groningen (Groningen), and the Deventer Hospital (Deventer), the Netherlands. All subjects were maintained on a stable dose of ACE inhibitor. Diagnosis had been made on the basis of medical history, ongoing symptoms, and physical examination. In all patients, left ventricular ejection fraction (LVEF) was assessed by echocardiography or radio nucleotide measurement. Patient had been clinically stable for at least three months before the study. Patients who used an angiotensin II receptor blocker were excluded from this study. The study was approved by each hospital’s ethics committee and written informed consent was obtained from all patients.

Venous blood samples and random spot urine samples were taken at the outpatient clinic while the patient was in an upright position. The blood and urine samples were transported to the local laboratory immediately and each aliquot was processed and stored according to protocol for later batched analysis. The concentration of aldosterone was measured by a sandwich radio immunoassay (Diagnostic Products Corporation, Breda, the Netherlands). Active renin protein was measured by an immunoradiometric assay (Nichols Institute Diagnostics, Middlesex, United Kingdom) and serum ACE activity was measured by an enzymatic assay (Bühlmann Laboratory AG, Schünenbuch, Switzerland).
Analyses were performed in a routine setting according to the guidelines of the manufacturer. Angiotensin I and II were measured by specific radioimmunoassays after SepPak extraction of plasma. NT-probrain natriuretic peptide (NT-proBNP) was measured by an Elecsys NT-proBNP immunoassay (Roche Diagnostics, Mannheim, Germany). Urinary creatinine and albumin were measured using a turbidimetric assay (Cobas Integra, Roche Diagnostics, Mannheim, Germany). Microalbuminuria was defined as a urinary albumin/creatinine ratio of 3.5 - 25 mg/mmol in male patients and 2.5 - 25 mg/mmol in female patients. Serum creatinine was measured using standard techniques. Serum creatinine, age, weight and gender were used to calculate glomerular filtration rate (GFRc) using the Cockcroft-Gault equation. The prevalence of microalbuminuria was compared to the prevalence of microalbuminuria in patients between 60 and 74 years old in the PREVEND study. The PREVEND (Prevention of Renal and Vascular ENDstage Disease) study was designed to investigate the natural course of microalbuminuria and its relation with renal and cardiovascular disease in the general population as described previously.

Values are expressed as mean values ± SD. Neurohormonal levels and urinary albumin/creatinine ratios were log-transformed before statistical comparison. Differences between groups were investigated by using the unpaired t-test for independent samples and the chi-square test, when appropriate.

Results

Average age in our population was 69 years (± 12), and 22% were female. Ninety-two patients were classified as CHF NYHA class III, whereas the remaining 4 patients were class IV. All patients used an ACE inhibitor, 72% used a beta-blocking agent, and 47% used spironolactone. Median albumin/creatinine ratio was 1.89 mg/mmol (interquartile range 1.29-3.72) and 5 patients (5.2%) were macroalbuminuric (all male, 2 diabetics). Because macroalbuminuria is often the result of intrinsic renal disease, we excluded these patients from further analysis. Microalbuminuria was present in 29 patients (31.9%; 95% confidence interval: 22.3-41.5). Patient characteristics are presented in Table 1. In 10 622 patients between 60 and 74 years old in the PREVEND study the prevalence of microalbuminuria was 10.4% (95% confidence interval: 9.8-11.0), which is significantly lower (p<0.001) than the prevalence we found in advanced chronic heart failure patients (Figure 1). GFRc was generally impaired, and tended to be slightly higher in patients without microalbuminuria (Table 1). However, this difference was small and not statistically significant. Other patient characteristics were not different between groups. In addition, no statistically
significant differences in active renin protein, angiotensin II, and aldosterone plasma levels were found in normoalbuminuric and microalbuminuric patients (Figure 2). Plasma NT-proBNP levels were slightly higher in the microalbuminuric group, but this difference did not reach statistical significance.

<table>
<thead>
<tr>
<th>No microalbuminuria (n = 62)</th>
<th>Microalbuminuria (n = 29)</th>
<th>Significance (two-tailed) p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex male (%)</td>
<td>74.2</td>
<td>82.8</td>
</tr>
<tr>
<td>Age (years)</td>
<td>68.2 ± 12.9</td>
<td>70.8 ± 11.2</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>27.4 ± 4.1</td>
<td>28.8 ± 5.0</td>
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<tr>
<td>ACE inhibitor (%)</td>
<td>100.0</td>
<td>100.0</td>
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<td>Beta Blocker</td>
<td>74.2</td>
<td>69.0</td>
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<tr>
<td>Diuretic</td>
<td>91.9</td>
<td>96.6</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>41.9</td>
<td>55.2</td>
</tr>
<tr>
<td>Anti arrhythmic</td>
<td>12.9</td>
<td>6.9</td>
</tr>
<tr>
<td>Calcium Blocker</td>
<td>11.3</td>
<td>13.8</td>
</tr>
<tr>
<td>Ischemic cause (%)</td>
<td>66.1</td>
<td>62.1</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>20.9</td>
<td>37.9</td>
</tr>
<tr>
<td>Smoking</td>
<td>16.1</td>
<td>13.8</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
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<td></td>
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<tr>
<td>Diastolic</td>
<td>74 ± 11</td>
<td>75 ± 8</td>
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<tr>
<td>Systolic</td>
<td>121 ± 21</td>
<td>122 ± 22</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>28 ± 11</td>
<td>30 ± 11</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>117 ± 29</td>
<td>125 ± 27</td>
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<tr>
<td>GFRc (ml/min/²)</td>
<td>64.6 ± 30.5</td>
<td>59.6 ± 25.2</td>
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<tr>
<td>Diet</td>
<td></td>
<td></td>
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<tr>
<td>Fluid restriction</td>
<td>29.0</td>
<td>27.6</td>
</tr>
<tr>
<td>Low sodium</td>
<td>56.5</td>
<td>69.0</td>
</tr>
</tbody>
</table>

Table 1. Patient characteristics at baseline
*Glomerular filtration rate calculated using the Cockroft-Gault equation
#Independent samples t-test *chi-square test
Abbreviation: LVEF, left ventricular ejection fraction

Discussion

In the present study we demonstrate that almost one third of a group of advanced CHF patients had microalbuminuria despite ACE inhibition. This finding demonstrates that the prevalence of microalbuminuria is much higher in CHF patients than in the comparable cohort of the PREVEND population, which was selected from the same geographical area as our CHF population.
The prevalence we found was also higher than in hypertensive patients and diabetics. It is well described that microalbuminuria is a risk factor for developing CHF and for cardiovascular mortality. However, published data on the prevalence of microalbuminuria in advanced CHF patients are scarce. Almost 25 years ago Carrie et al. suggested that either the fractional clearance for anionic albumin was disproportionately enhanced or the glomerular electrostatic barrier function was impaired in CHF patients. Since then, several pathophysiological mechanisms for the development of microalbuminuria have been proposed. First, microalbuminuria might be an early sign of renal damage. While the kidney function remains clinically stable, a reduced number of nephrons are trying to maintain normal homeostasis. The resulting augmented glomerular blood flow and hydraulic pressure lead to hyperfiltration and excretion of protein. Yet, the effects of an impaired left ventricular function on this compensation mechanism remain unclear. As most of the patients already had a mild to moderate renal dysfunction, we can merely speculate on the contribution of this mechanism to the occurrence of microalbuminuria in the present study.

Figure 1. The prevalence of microalbuminuria in 96 severe chronic heart failure patients is significantly higher than the prevalence in patients between 60 and 74 years old from the general population in the PREVEND study. 
Abbreviations: CHF, chronic heart failure.
Second, microalbuminuria is thought to be a reflection of generalized endothelial dysfunction, which results in leakage of albumin through the endothelium and glomerular basement membrane. Endothelial function is abnormal in CHF, and this hypothesis therefore provides a plausible explanation for the high prevalence of microalbuminuria in CHF patients.13;14 The Strong Heart study demonstrated that increased UAE is associated with systolic dysfunction in diabetic patients.15;16 The authors hypothesize that the urinary loss of albumin reflects cardiac systolic dysfunction and that this is mediated by extensive endothelial and vascular changes. However, our results do not confirm this, as left ventricular ejection fractions are comparable in both groups. Furthermore, another marker of systolic function, NT-proBNP, was not significantly increased in patients with microalbuminuria.

Because beneficial effects of both ACE inhibitors and angiotensin II receptor blockers on UAE have been described, activation of the renin angiotensin system seems to play an important role in the process.17;18 In CHF patients the renin angiotensin system is activated.19 Nevertheless, despite the use of ACE inhibitors a large number of our patients had microalbuminuria. Furthermore, the renin angiotensin system tended to be slightly, yet non-significantly, more activated in patients with microalbuminuria. However, the absence of statistical significance may have been caused by the wide range of medication used and by the relatively small number of patients. Theoretically, microalbuminuria could arise from the supplementary effect of various mildly activated neurohormonal

Figure 2. Neurohormonal concentrations and activities in patients without and with microalbuminuria.
systems. In this theory the renin angiotensin system is not the sole contributor to the development of microalbuminuria, which would explain the small differences we found.

Limitations

There are several limitations to the study. First, this was an observational, hypothesis-generating study in an out-patient clinical setting. Consequently, analysis revealed a wide variety of neurohormonal concentrations. This might be due to different levels of activation of the RAS under the circumstances we used. However, we believe that for revealing mechanisms within the RAS in a population-based study, it is a valuable tool. Secondly, we analyzed random spot urine samples. Previous reports indicate that the albumin/creatinine ratio in spot urine sample is a good screening test for microalbuminuria, but a poorer predictor of quantitative UAE than 24-hour UAE. Yet, this method can be easily used in daily clinical practice, and therefore our data are relevant.

Conclusion

In conclusion, in patients with advance heart failure UAE was increased. Furthermore, microalbuminuria was present in almost one third of the patients, despite ACE inhibition and normal blood pressures. These findings favor further studies into the natural course of microalbuminuria in CHF patients, and microalbuminuria as a treatment target in these patients.
Prevalence of Microalbuminuria in CHF

References


