Renal and intraglomerular haemodynamics in chronic heart failure with preserved and reduced ejection fraction

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Abstract

Aims Congestive heart failure (CHF) and impaired renal function are two often co-existing medical conditions and associated with adverse cardiovascular outcome. The aim of the current study was to assess renal and intraglomerular haemodynamics by constant infusion input clearance technique in subjects with CHF.

Methods and results The group of subjects with CHF consisted of 27 individuals with HFpEF and 27 individuals with HFrEF and were compared with 31 healthy controls. Subjects underwent renal clearance examination to measure glomerular filtration rate (GFR) and renal blood and plasma flow (RBF and RPF) and to calculate intraglomerular haemodynamics such as resistances of the afferent (RA) and efferent arterioles (RE) as well as intraglomerular pressure (P glom). Measured GFR was lower in CHF subjects (68.1 ± 10.1 mL/min/1.73 m²) compared with controls (83.6 ± 13.4 mL/min/1.73 m², P adj < 0.001) as was P glom (P adj < 0.001). Total renal vascular resistance (RVR) was higher in CHF subjects (87.3 ± 20.1 vs. 73.8 ± 17.1 dyn × s/cm², P adj < 0.001) mediated by an increased resistance at the afferent site (3201 ± 1084 vs. 2181 ± 796 dyn × s/cm², P adj < 0.001). Comparing HFpEF and HFrEF subjects, RA was higher in HFrEF subjects. The severity of CHF assessed by NT-proBNP revealed an inverse association with renal perfusion (RPF r = −0.421, P = 0.002, RBF r = −0.414, P = 0.002) and a positive relation with RVR (r = 0.346, P = 0.012) at the post-glomerular site (RE: r = 0.318, P = 0.022).

Conclusions Renal function assessed by measured GFR is reduced and renal vascular resistance at the preglomerular, afferent site is increased in HFpEF and, to greater extent, in HFrEF. Our data indicate a close cardiorenal interaction in CHF.

Keywords Heart failure; Preserved ejection fraction; Reduced ejection fraction; Renal haemodynamics; Cardiorenal interaction

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Introduction

With life expectancy increasing, the prevalence and incidence of chronic heart failure (CHF) and chronic kidney disease (CKD) have been growing in parallel.1,2 CHF and impaired renal function are two often co-existing medical conditions, and the combination is known to be associated with adverse cardiovascular outcome and increased mortality.3−5 Therefore, detailed analysis of the pathophysiological mechanisms that connect CHF and renal function represents a matter of major research activities.

The relationship between CHF and impaired renal function is bidirectional. Renal dysfunction has been shown to be an independent risk factor for the development of CHF,6,7 and conversely, an increase in central venous pressure leads to renal dysfunction by reducing renal blood flow (RBF) and perfusion pressure in patients with CHF, which is related to the activation of the renin-angiotensin-aldosterone system.8−10 This cardiorenal relationship has been demonstrated for...
subjects with CHF and both preserved (HFpEF) and reduced ejection fraction (HFrEF).8,11–15

Hillegae et al. found a close relation between renal function and mortality in a total of 1906 subjects with HFrEF.16 In a retrospective analysis of the Studies of LV Dysfunction (SOLVD) cohort, renal dysfunction could be identified as an independent risk factor for mortality in subjects with left ventricular dysfunction.17 Similarly, estimated creatinine clearance was shown to be an important predictor for all-cause mortality in subjects with CHF.18 Unger et al. retrospectively examined the relationship between renal function and echocardiographic parameters in 299 patients with HFpEF, revealing that CKD was independently associated with worse cardiac mechanics and outcomes.13 Studying 217 participants from the PARAMOUNT trial with HFpEF, Gori et al. demonstrated that renal dysfunction was associated with abnormal left ventricular geometry, lower midwall fractional shortening, and higher NT-proBNP.19

In the majority of the studies published so far, renal function has been assessed with readily available tests such as determination of serum creatinine, estimated glomerular filtration rate (eGFR) and urinary albumin to creatinine ratio. However, these parameters, while established in clinical practice, only allow an approximate estimation of renal function. Constant infusion input clearance technique offers a more precise and detailed approach of evaluating renal function and perfusion.20 With this technique, a reliable and valid measurement of GFR and renal plasma flow (RPF) is available for clinical studies, thus allowing us to further assess renal haemodynamic parameters such as RBF, renal vascular resistance (RVR), and intraglomerular haemodynamic parameters.20 To the best of our knowledge, such a detailed analysis of renal and also intraglomerular haemodynamics has not yet been performed in subjects with CHF.

Therefore, the aim of the present study was to precisely assess renal function and intraglomerular haemodynamics by means of constant infusion input clearance technique in subjects with CHF—with both HFpEF and HFrEF—compared with healthy controls.

Methods

Study design

This was a cross-sectional, observational single centre study performed at the Clinical Research Center of the Department of Nephrology and Hypertension, University Hospital Erlangen-Nuremberg, Germany (www.crc-erlangen.de). Between March and July 2019, subjects with HFrEF, HFpEF and healthy controls were recruited from the University outpatient clinics, by means of local newspaper advertisement and referring physicians. Written informed consent was obtained from each subject before study inclusion. The study was conducted according to the tenets of the Declaration of Helsinki and the principles of good clinical practice guidelines. The study protocol has been approved by the local Ethics Committee of the University of Erlangen-Nuremberg. The study was registered at http://www.clinicaltrials.gov (NCT03672591).

Study population

A total of 85 subjects were included into this study. The group of subjects with CHF and clinical stable conditions consisted of 27 individuals suffering from HFpEF and 27 individuals suffering from HFrEF according to 2016 European Guidelines for the diagnosis and treatment of acute and chronic heart failure.21 Thereby, subjects were defined as suffering from HFpEF if they had a left ventricular ejection fraction (LVEF) of at least 50% and symptoms and/or signs of HF, N-terminal pro-B-type natriuretic peptide (NT-proBNP) values above 125 pg/mL, and evidence of relevant structural heart disease such as left ventricular hypertrophy or atrial enlargement and/or diastolic dysfunction. Subjects were defined as suffering from HFrEF if they had a left ventricular ejection fraction below 40% and had symptoms and/or signs of CHF. The group of healthy controls consisted of 31 subjects who had to be in good and stable health condition without any relevant preexisting medical condition or long-term medication. Key exclusion criteria for all groups were acute cardiac decompensation, dyspnoea at rest, uncontrolled diabetes [fasting plasma glucose ≥240 mg/dL, glycated haemoglobin (HbA1c) ≥ 10%, uncontrolled arterial hypertension (≥180/110 mmHg), any history of stroke, transient ischaemic attack, instable angina pectoris or myocardial infarction within the last 6 months prior to study inclusion, significant valvular heart disease, known hypertrophic obstructive cardiomyopathy or known pericardial constriction as well as atrial fibrillation with a resting heart rate above 90 bpm. Subjects were also excluded if they suffered from subclinical or clinical hyperthyroidism, known allergic reaction to iodine, or medication with amiodarone. Other exclusion criteria were an eGFR below 30 mL/min/1.73 m² and a body mass index higher than 40 kg/m².

Clinical parameters

At Visit 1, demographic data of all participants including medical history and concomitant medication were obtained. In addition, fasting blood samples were drawn to measure NT-proBNP, creatinine (with eGFR calculated), fasting plasma glucose, HbA1c, lipid levels, and other biochemical parameters such as liver enzymes and lipid levels.
Assessment of office blood pressure and heart rate was carried out in standard fashion by validated devices (DINAMAP® PRO 100 V2, GE Critikon) in a seated position after 5 min of rest according to European Society of Cardiology/European Society of Hypertension guideline recommendations.22

Renal clearance examination

Figure 1 shows an example of a renal clearance examination protocol. Renal haemodynamic parameters were determined by constant infusion input clearance technique with iohexol and p-aminohippuric acid for measuring GFR and RPF, respectively.23–26 Clearance examinations were performed at the same time in the morning in a quiet and temperature-controlled room. After bolus infusion of iohexol and p-aminohippuric acid over 15 min and a subsequent constant infusion over 90 min, a steady state between input and renal excretion of the tracer substances was reached. With respect to the application of iohexol, we followed the methodological approach of Dixon et al.27–30 Target steady state concentration of iohexol was 100 μmol/L. This required a loading dose of 16.5 × body weight (kg). Thereafter, the constant infusion started with 0.5 mL/h of ACCUPAQUE 300™ (containing 647 mg iohexol/mL or 300 mg iod/mL), corresponding to 323 mg iohexol/h or 150 mg iodine/h. Renal haemodynamic parameters such as RBF and RVR were derived in standard fashion.20 Total serum concentration and mean arterial pressure at the end of the infusion period were measured. Subsequently, intraglomerular pressure (Pglom) as well as resistances of the afferent (Ra) and efferent arterioles (Re) were calculated according to previously described formulas.20,23,31,32

Statistical analysis

Data are expressed as mean ± standard deviation or median and 95% confidence interval depending on data distribution. A two-sided P value <0.05 was considered statistically significant. According to our statistical analysis plan we compared first all subjects with CHF (both HFpEF and HFrEF taken together) to healthy controls and then as a second step subjects with HFpEF versus those with HFrEF by Student’s t-test. Due to significant differences in age and systolic blood pressure between the three groups, we adjusted our results for these 2 cofactors by applying analysis of covariance. As a third step, bivariate correlation analyses were performed to assess the relation between NT-proBNP and renal haemodynamic and intraglomerular parameters in subjects with CHF. All analyses were performed using SPSS software, version 21.0 (IBM Corporation, Chicago, IL, USA).

Results

Clinical characteristics of the study population

Table 1 provides the clinical characteristics of the study groups. Comparing the total group of subjects with CHF to healthy controls, CHF subjects were older (74.1 ± 7.5 vs. 43.0 ± 14.8 years, P < 0.001) and had a higher body mass index (28.7 ± 4.5 vs. 25.9 ± 5.1 kg/m², P = 0.006) than healthy controls. There was no significant difference in gender distribution between the two groups (P = 0.392). Similarly, office systolic blood pressure was higher in the group of subjects with CHF compared with healthy controls (130.9 ± 18.0 vs. 123.2 ± 13.4 mmHg, P = 0.006). In CHF subjects, mean LVEF was 48.1 ± 11.4% and mean NT-proBNP levels were 990.0 ± 1492.7 ng/L.
Serum creatinine concentrations were higher (1.1 ± 0.3 vs. 0.8 ± 0.2 mg/dL, P < 0.001) and the derived eGFR (according to CKD-EPI formula) lower (68.2 ± 17.3 vs. 102.3 ± 18.0 mL/min/1.73 m², P < 0.001) in CHF subjects compared with healthy controls.

With respect to the cause of heart failure, n = 36 individuals (66.7%) suffered from ischaemic cardiomyopathy and n = 18 (33.3%) from non-ischaemic (e.g. dilated or hypertensive) cardiomyopathy.

With respect to concomitant medication in the group of subjects with CHF, n = 21 (38.9%) were treated with angiotensin-converting enzyme (ACE) inhibitors, n = 20 (37.0%) with angiotensin type 1 (AT₁) receptor antagonists, n = 5 subjects (9.3%) with sacubitril/valsartan, n = 34 (63.0%) with beta-blockers, n = 16 (29.6%) with spironolactone and n = 32 (59.3%) with thiazide or loop diuretics.

Comparing the two entities of CHF, subjects with HFrEF were older (76.7 ± 7.0 years) than subjects with HfPEF (71.2 ± 7.2 years, P = 0.003) and had a higher office systolic blood pressure (136.7 ± 15.8 vs. 125.3 ± 18.5, P = 0.018). Mean LVEF was 56.3 ± 3.7% in HfPEF and 36.7 ± 3.2% in HFrEF subjects (P < 0.001), respectively. Of interest, in our study, NT-proBNP levels and serum creatinine as well as derived eGFR did not differ significantly between the 2 groups, although NT-proBNP levels tended to be higher in HFrEF subjects (1214.9 ± 1929.9 ng/L) compared with HfPEF subjects (786.1 ± 927.7 ng/L, P = 0.266).

### Renal function, perfusion, and intraglomerular haemodynamics

**Table 2** shows a comparison of renal haemodynamic parameters between subjects with CHF and healthy controls. Measured GFR was lower in subjects with CHF (68.1 ± 10.1 mL/min/1.73 m²) compared with the control group (83.6 ± 13.4 mL/min/1.73 m²) before (P < 0.001) and after adjustment for age and systolic blood pressure (Padj < 0.001). RVR was significantly higher in subjects with CHF (87.3 ± 20.1 dyn × s/cm⁵) compared with healthy controls (73.8 ± 17.1 dyn × s/cm⁵, Padj < 0.001), as was Rglomerular (547.3 ± 3.8 mmHg, Padj < 0.001). RPF and RBF as well as Rglomerular did not differ significantly between subjects with CHF and control subjects after adjustment for age and systolic blood pressure. Comparing subjects with HFPREF to those with HFrEF, there were no significant differences in measured GFR, RPF, RBF, Rglomerular, or Rglomerular (Table 3). However, after adjustment for age

### Table 2 Comparison of renal haemodynamic parameters between subjects with HF and healthy controls

| Parameter            | CHF (n = 54) | Healthy controls (n = 31) | P value | Padj valuea |
|----------------------|--------------|---------------------------|---------|-------------|
| GFR (mL/min/1.73 m²) | 68.1 ± 10.1  | 83.6 ± 13.4               | <0.001  | <0.001      |
| RPF (mL/min/1.73 m²) | 565.0 ± 143.3| 627.1 ± 161.8              | 0.070   | 0.245       |
| RBF (mL/min/1.73 m²) | 959.1 ± 244.8| 1105.7 ± 258.6             | 0.012   | 0.067       |
| MAP (mmHg)           | 91.7 ± 10.3  | 90.7 ± 9.7                | 0.675   | -           |
| RVR (dyn × s/cm⁵)    | 87.3 ± 20.1  | 73.8 ± 17.1               | 0.003   | <0.001      |
| Pglomerular (mmHg)   | 497.3 ± 2.6  | 54.7 ± 3.8                | <0.001  | <0.001      |
| Rglomerular (dyn × s/cm⁵)| 3201 ± 1084 | 2181 ± 796                | <0.001  | <0.001      |
| Rglomerular (dyn × s/cm⁵)| 1307 ± 298  | 1414 ± 344                | 0.143   | 0.147       |

Data are given as mean ± standard deviation (SD). CHF, heart failure; GFR, glomerular filtration rate; MAP, mean arterial pressure; Pglomerular, intraglomerular pressure; Rglomerular, resistance of the afferent arteriole; RBF, renal blood flow; Rglomerular, resistance of the efferent arteriole; RPF, renal plasma flow; RVR, renal vascular resistance.

aAdjusted for age and systolic blood pressure.
of systolic blood pressure, RA was higher in subjects with HFrEF compared with those with HFpEF ($P_{adj} = 0.001$).

Bivariate correlation analysis in the group of subjects with CHF revealed a significant inverse correlation between NT-proBNP levels and RPF ($r = -0.421$, $P = 0.002$) as well as RBF ($r = -0.414$, $P = 0.002$), whereas there was no significant association between NT-proBNP and measured GFR ($r = -0.071$, $P = 0.619$). Of interest, there was a positive correlation between NT-proBNP levels and RVR ($r = 0.346$, $P = 0.012$) as well as $R_e$ ($r = 0.318$, $P = 0.022$), but not with RA ($r = 0.191$, $P = 0.176$) and $P_{glomer}$ ($r = 0.048$, $P = 0.733$) (Figure 2).

**Discussion**

Detailed exploration of the pathophysiological mechanisms behind the relationship of CHF and renal function represents...
a matter of major research interest. Several studies have attempted to investigate the association between renal (dys-)function and CHF. In all of these studies, renal function was assessed by estimated GFR (eGFR), determined by serum creatinine concentration.\textsuperscript{13,16–19} However, eGFR provides only an approximate estimation of renal function. In order to understand cardiorenal interaction, complete assessment of renal haemodynamics is required.

In subjects with CHF, we precisely investigated renal haemodynamics (measured GFR, RPF, RBF, and RVR) by means of constant infusion input clearance technique, which is considered to be the gold standard technique for the measurement of renal function and perfusion.\textsuperscript{33} We observed that measured GFR was significantly lower in subjects with CHF compared with healthy controls. After adjustment for age and systolic blood pressure, renal perfusion as assessed by RPF and RBF did not differ significantly between the groups, but total renal vascular resistance was higher in CHF subjects, which was mediated by an increase at the preglomerular, afferent site, suggesting preserved tubuloglomerular feedback. There was no significant difference in vascular resistance at the post-glomerular, efferent site between patients with CHF and healthy controls, which can be attributed to the fact that the majority of subjects with CHF in this group were under medication with renin angiotensin system inhibitors known to decrease vascular resistance at the post-glomerular, efferent site. Diuretics also affect renal haemodynamics and 59.3\% of our population were on diuretics. Comparing CHF subjects with and without diuretic treatment, there were no significant differences (all $P > 0.20$) with respect to renal and intraglomerular haemodynamics (data not shown), which may be related to the fact that we excluded patients with decompensated CHF.

The findings of the current study should be interpreted in the context of neuroendocrine activation known to occur with progression of CHF.\textsuperscript{34,35} In order to maintain the function of vital organs such as heart, kidney, and brain in case of hypoperfusion, neuroendocrine activation—in particular of the sympathetic nervous system and renin angiotensin aldosterone system—initially leads to increased chronotropia, inotropia, and vasoconstriction in the systemic circulation. We now observed that with increasing severity of CHF, as assessed by NT-proBNP, vasoconstriction increases in parallel in the renal vasculature. Further analysis of total RVR disclosed that NT-proBNP was closely related to the post-glomerular, efferent resistance which is known to be the target of angiotensin II.

The role of NT-proBNP in CHF and cardiorenal syndrome has been previously described. NT-proBNP has been found to be among the best indicators for severity of CHF and a predictor for short-term mortality.\textsuperscript{36} The observed associations between NT-proBNP and renal haemodynamics confirm the concept of a cardiorenal interaction. In the current study, we observed an association between reduced renal perfusion and renal vasoconstriction with progressive severity of CHF. The haemodynamic relation of NT-proBNP with an increased resistance of the post-glomerular efferent arterioles, which are the primary target of renin and angiotensin II, suggests that the neuroendocrine activation helps to preserve renal function.\textsuperscript{37} A decrease in renal perfusion might cause tubular hypoxic injury and thereby progressive renal dysfunction as a long-term consequence.\textsuperscript{38}

In patients with HFrEF, renal dysfunction is highly prevalent (30–60\%) and associated with cardiac remodelling.\textsuperscript{12,13,39} Our data do not indicate a substantial difference in renal and intraglomerular haemodynamics between patients with HFrEF and HFpEF. Only the resistance at the preglomerular afferent site was found to be increased in patients with HFrEF, pointing to either increased efferent sympathetic activity to the kidney or more advanced vascular remodelling in these patients.

However, renal and intraglomerular function can be affected by renal congestion in subjects with CHF. Due to increasing cardiac preload and therefore central venous pressure, renal venous pressure increases in parallel, subsequently leading to a reduction of RBF and GFR, as effective glomerular pressure may decrease. However, decompensated CHF and NYHA IV were exclusion criteria in this study. All subjects participating in this project were clinically recompensated and euvoalaemic under diuretic treatment. No measurement of central venous pressure or other parameters of left ventricular preload was performed, which may be considered as a limitation of this study.

Treatment with the dual-acting angiotensin receptor neprilysin inhibitor LCZ696 was associated with lower levels of creatinine and higher eGFR indicating a better preservation of renal function in comparison to treatment with valsartan only.\textsuperscript{14,15} In our study, only five patients were treated with sacubitril/valsartan, and we therefore did not conduct any analysis of intraglomerular haemodynamics to further elucidate the renoprotective effects of sacubitril/valsartan. Another limitation of the current study is its cross-sectional design without follow-up examination, but in this study, we addressed the open question of altered renal and in particular glomerular haemodynamics in HFrEF and HFpEF by measuring (and estimating) glomerular filtration rate in parallel to renal perfusion. Structural and functional alterations of the kidney with increasing age have been described previously, including a decrease in GFR and RBF as well as alterations in intraglomerular haemodynamics such as a reduction in $R_x$.\textsuperscript{40–43} To compensate for the significant difference in age between CHF subjects and healthy controls, adjustment for age was performed in the current study by statistical means. CHF is a predominantly a disease of the elderly, with increased prevalence, incidence and severity with progressive aging. In contrast, recruitment of elderly healthy control subjects is challenging, some may consider it nearly impossible in
the Western world, and we therefore relied on statistical adjustments to take age into account as a confounder.

Conclusions

In conclusion, the findings of the current study should be interpreted in the context of neuroendocrine activation in subjects suffering from CHF. In compensated CHF, both HfPEF and HFREF, renal perfusion is preserved, renal function (assessed by measured GFR) is reduced and renal vascular resistance at the preglomerular, afferent site is increased in HfPEF and, to greater extent, in HFREF. With progressive severity of CHF—as indicated by increasing NT-proBNP—renal vascular resistance at the post-glomerular site increases in parallel, potentially reflecting the predominantly intraglomerular action of angiotensin II at the glomerular vessels. The association between NT-proBNP and renal haemodynamic parameters documents a close cardiorenal interaction by neuroendocrine activation due to CHF. Insofar, the results of the current study can help us to better understand the pathophysiological background of future results of larger studies in subjects with both HfPEF and HFREF.

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Conflict of interest

R. E. S. has received speaker fees and advisory board fees from Novartis Pharma GmbH, Germany, during the conduct of the study. The other authors declare that they have no competing interests.
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