New roles for renin in heart failure and cardio-renal interaction

Schroten, Nicolas

Chapter 4

Long term changes in renal function and perfusion in heart failure patients with reduced ejection fraction

Nicolas F. Schroten MD[1], Kevin Damman MD PhD[1], Mattia A.E. Valente MD[1], Tom D. Smilde MD PhD[2], Dirk J. van Veldhuisen MD PhD[1], Gerjan Navis MD PhD[3], Carlo A. Gaillard MD PhD[3], Adriaan A. Voors MD PhD[1], Hans L. Hillege MD PhD[1,4]

[1] University Medical Center Groningen, Department of Cardiology, Groningen, Netherlands
[2] Scheper Ziekenhuis, Emmen, Netherlands
[3] University Medical Center Groningen, Department of Internal Medicine, Groningen, Netherlands
[4] Trial Coordination Center, Groningen, Netherlands

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Abstract

Introduction – Little is known about the natural course of renal function and renal hemodynamics in heart failure patients with reduced ejection fraction (HFREF).

Methods & results – We prospectively studied effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) in 73 HFREF patients with 125I-Iothalamate/131I-Hippuran clearances with a mean follow up of 34.6±4.4 months. Fifteen percent was female, age 58±12yr, left ventricular ejection fraction (LVEF) 28.5±9.6% with a mean follow up of 34.6±4.4 months. Baseline GFR was 95±29 mL/min/1.73m^2 and declined 0.6±4.7 mL/min/1.73m^2 per year. Baseline ERPF was 592±194 mL/min/1.73m^2 and declined 4.3±19 mL/min/1.73m^2 per year. Of the baseline variables older age and high urinary kidney injury molecule-1 were the only variables associated univariably with GFR decline. Following stepwise backward analysis, only age ($p < 0.001$) remained significant. In addition, we found a univariable association between change in GFR and changes in ERPF, NT-proBNP and renovascular resistance. In the multivariable analysis, only the change in ERPF remained significantly associated with a change in GFR ($p < 0.001$).

Conclusion – In this cohort of stable chronic HFREF patients, the average decline in GFR over time was small. The decline of GFR was associated with a higher age, and a lower baseline GFR, and was strongly related to changes in renal perfusion.

Introduction

Both chronic kidney disease (CKD) and worsening of renal function are common in heart failure patients, (1) and among the most powerful predictors of morbidity and mortality in this population. (2) However, little is known on the natural course of renal function in heart failure patients and determinants of long-term renal function decline. The cause of renal dysfunction in HFREF is thought to be multifactorial. (3, 4) It has been attributed to medication, (5) renin-angiotensin-aldosterone system (RAAS) activation, (6) sympathetic nervous system (SNS) activation and inflammation. Decreased renal perfusion is likely the key determinant, (7) either via decreased renal perfusion pressure, an increase in renal vascular resistance (RVR), increase in renal venous pressure, or all of the above. {{96 Damman 2007}} However, these associations have mostly been described in cross-sectional studies. The limited number of longitudinal studies has mostly focused on acute worsening of renal function, and few data are available on predictors of long term estimated GFR changes in HFREF patients. (8-11) All these studies used changes in serum creatinine to estimate GFR, which is considered a surrogate for functioning kidney tissue. However, creatinine-based renal function estimates are not always accurate in estimating kidney function decline (21) and provide no information on renal hemodynamics.

Using gold standard techniques for measuring renal function, we studied the change in renal function over time and its clinical, biochemical and hemodynamic predictors in patients with heart failure. We previously described the cross-sectional associations. Renal blood flow showed the strongest association with GFR. In turn, NT-proBNP, PRA, sVCAM-1 levels and UAE showed the strongest associations with renal blood flow. (7) In the current analysis we investigated if these parameters are also associated with long term renal function decline, measured using radioactive labeled specific renal function tracers.

Methods

Patient population

Details on the study design and patient population have been published previously. (7) In brief, 120 clinically stable heart failure patients with reduced ejection fraction (HFREF), left ventricular ejection fraction (LVEF) < 45%, and stable heart failure medication for at least one month underwent renal function measurements using ^{125}I-iothalamate and ^{131}I-Hippuran clearances techniques at the University Medical Center Groningen, The Netherlands. Blood and urine samples were collected, a physical examination performed and the patient's history docu-

mented. Patients were contacted after three years and all investigations were repeated. The study was approved by the ethics committee of the study center, and all subjects gave written informed consent. The study was conducted in accordance with Declaration of Helsinki guidelines.

Renal function measurement

Renal function measurements were performed using radioactive labeled tracers, as described previously. (12) GFR was measured by continuous infusion of ^{125}I-Iothalamate, and Effective Renal Plasma Flow (ERPF) was measured by continuous infusion of ^{131}I-Hippuran. Filtration fraction was calculated as GFR/ERPF. Renovascular resistance (RVR) was calculated as (MAP/ERPF) x (1-haematocrit) and expressed in mmHg/ml/min. GFR and ERPF were corrected for 1.73 m^2 of body surface area, calculated using the Dubois formula.

Laboratory methods

Patients were all in the supine position during renal measurements, and a venous blood sample was drawn two hours after the start of the measurements. Routine hematology, blood chemistry and urinalysis were performed within an hour of collection. Additional blood and urine samples were immediately centrifuged and stored at -80 degrees Celsius. Serum creatinine levels were measured using an automated enzymatic method (Eastman Kodak, Rochester, New York, USA). The intra- and inter-assay coefficients of variation were < 4.1% and < 3.3%, respectively. Urinary markers of renal damage were measured in 24 hour urine collections and corrected for urinary creatinine as described previously. (13)

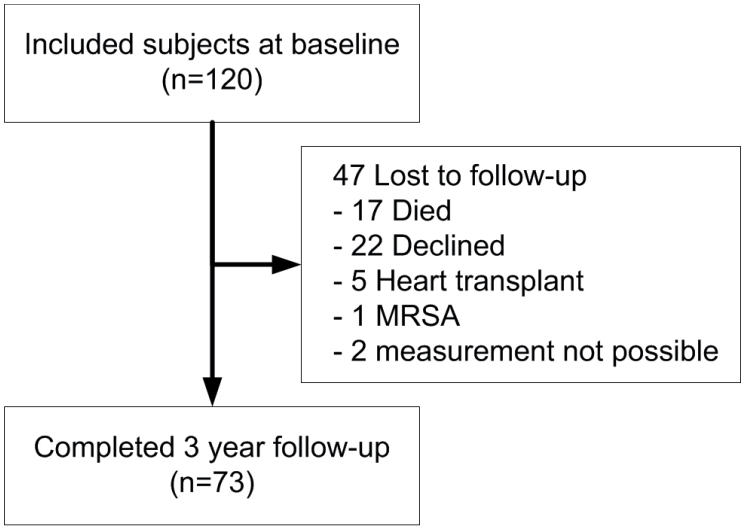
Follow-up

All patients were asked to return for a follow-up visit between 24 and 36 months after baseline renal function measurements. Adverse events during follow-up were determined via interview and case record extraction. Adverse events included death from any cause, heart transplantation, cardiovascular event (myocardial infarction or primary PCI or primary coronary artery bypass grafting) and first hospitalization for worsening heart failure.

Statistical analyses

Continuous data are presented as mean ± SD when normally distributed, as median and inter-quartile range (IGR) when non-normally distributed, and as frequencies and percentages for categorical variables. Differences between groups were tested using student's T-test, Kruskal-Wallis or Chi-square test as appropriate. Linear regression analysis was carried out to determine the association of baseline variables with change in GFR and to test the association of changes in hemodynamic parameters with changes in GFR. All analyses were corrected for baseline values of the outcome variable. Skewed variables were log-transformed where appropriate. Variables associated in the univariate model at $p < 0.1$ were included in a stepwise, backward multivariable regression analysis, with a threshold for variable retention of $p < 0.1$. All reported probability values are two-tailed, a p value < 0.05 was considered statistically significant. Statistical analyses were performed using STATA version 11.0, College Station, TX, USA.

Figure 1: Patient disposition



Results

Of the 120 patients included at baseline, 73 patients could be used for the present analysis. (Figure 1) Baseline characteristics of the study population are presented in table 1. In brief, 20% were female, with a mean age of 58±12 years. Left ventricular ejection fraction (LVEF) was 28.6±9.6%. Most patients had New

York Heart Association (NYHA) class II or III heart failure symptoms. All patients were on renin angiotensin aldosterone system (RAAS) inhibition, and most were on beta-blocker or diuretic therapy.

Baseline GFR was 80.8±23 mL/min/1.73m^2, baseline ERPF was 292±83 mL/ /min/1.73m^2. Mean follow-up time was 34.6±4.4 months. In patients with a complete follow-up mean decline in GFR was 0.60±4.7 ml/min/1.73m^2 per year and ERPF declined 4.3±19 ml/min/1.73m^2 per year.There was no significant difference in the rate of renal function decline between patients with a GFR below and above 60 mL/min/1.73m^2 at baseline (p = 0.81). Patients that were lost to follow-up are also presented in table 1. Patient that died or had a heart transplant during follow-up, had a lower blood pressure, GFR, ERPF, filtration fraction and a higher RVR, UAE, NT-proBNP and were more often using ARBs or ARAs compared to patients that completed follow-up. There were no significant differences between patients that completed follow-up and who were lost to follow-up for other reasons.

Baseline predictors of changes in GFR

Associations of baseline characteristics and laboratory tests with change in GFR are shown in Table 2. Baseline age, sex, MAP, log-NGAL, log-KIM-1 showed a univariate correlation with change in GFR at p < 0.1. Following stepwise backward analysis, only older age (p < 0.001) remained significantly associated with higher GFR decline in a multivariate model (Table 2).

Table 1: Baseline characteristics

Variable	With follow up	Lost to follow-up	Died / HTX
	(n = 73)	(n = 25)	(n = 22)
Age (yr)	57.9±11.8	58.4±11.8	61.5±12.4
Female sex, n (%)	11 (15.1%)	7 (28%)	6 (27.3%)
RR systolic (mmHg)	121±17.6	127±20.7	105±20.1#
RR diastolic (mmHg)	70.8±11	70.4±11.2	61.7±11#
Heart rate (bpm)	63.8±12.3	65.5±11.5	67.5±16
Ischemic etiology, n (%)	39 (53.4%)	11 (44%)	10 (45.5%)

Table 1 (cont)

Variable	With follow up	Lost to follow-up	Died / HTX
	(n = 73)	(n = 25)	(n = 22)
LVEF (%)	28.5 ± 9.58	29.5±9.94	27.7±9.81
GFR (ml/min/1.73m^2)	80.8 ± 22.7	74.6±27.8	50.1±26.1#
ERPF (ml/min/1.73m^2)	292 ± 82.5	264±89.9	202±72.8#
Filtration Fraction (%)	27.9 ± 3.4	27.8±5.5	24±7.5#
RVR (mmHg/ml/min)	0.17 (0.15-0.22)	0.19 (0.14-0.29)	0.22 (0.18-0.31)#
UAE (mg/24h)*	7.67 (5.64-12.2)	12.1 (7.36-34.5)	18.3 (7.42-49)#
NT-proBNP (ng/ml)	465 (219-1100)	635 (286-1700)	2200 (950-5000)#
Urine NGAL (µg/24h)*	15 (6.82-30.9)	16.7 (10.9-34.3)	9.23 (1.89-32.9)
Urine KIM (U/ 24h)*	408 (144-995)	416 (111-1800)	279 (20-1100)
Urine NAG (ng/24h)*	4.41 (2.15-6.61)	3.73 (2.46-7.92)	3.35 (2.41-7.53)
ACE inhibitor, n (%)	65 (89%)	21 (84%)	16 (72.7%)
ARB, n (%)	8 (11%)	3 (12%)	7 (31.8%)**
Beta blocker, n (%)	63 (86.3%)	20 (80%)	18 (81.8%)
Aldosterone antagonist, n (%)	18 (24.7%)	6 (24%)	13 (59.1%)#

Normally distributed data are presented as mean ± SD.

** Skewed data as median (p25-p75). RR, blood pressure; LVEF, left ventricular ejection fraction; GFR, glomerular filtration rate; ERPF, effective renal plasma flow; RVR reno-vascular resistance; UAE Urinary albumin excretion; NT-proBNP, N-terminal pro-brain natriuretic peptide; NGAL, neutrophil gelatinase associated lipocalin; KIM-1, kidney injury molecule 1; NAG, N-acetyl-b-D-glucosaminidase; ARB, angiotensin receptor blocker.*

*** p < 0.05 and #p < 0.01 compared to patients with complete follow-up*

Hemodynamics, Renal perfusion and changes in GFR

In general, patients that completed follow-up maintained a relatively stable hemodynamic profile. Changes in LVEF (+3.3±11 %), MAP (-0.13±10 mmHg), NT-proBNP (-0.6 (-265 to +250.6) ng/L), and RVR (0.01±0.05 mmHg/ml/min) were modest. In univariable analysis, a decrease in ERPF, NT-proBNP and increase in RVR were associated with a decrease in GFR. LVEF was not. In the multivariable analysis, only change in ERPF remained significantly associated with a change in GFR (Table 3, Figure 2). In parallel to changes in GFR, an increase in RVR and a decrease in NT-proBNP and LVEF were associated with a decrease in ERPF. In multivariate analysis, only RVR and NT-proBNP remained significantly associated with changes in ERPF (Table 6). Change in MAP and was not associated with a change in either GFR or ERPF.

Figure 2: Change in GFR and change in ERPF

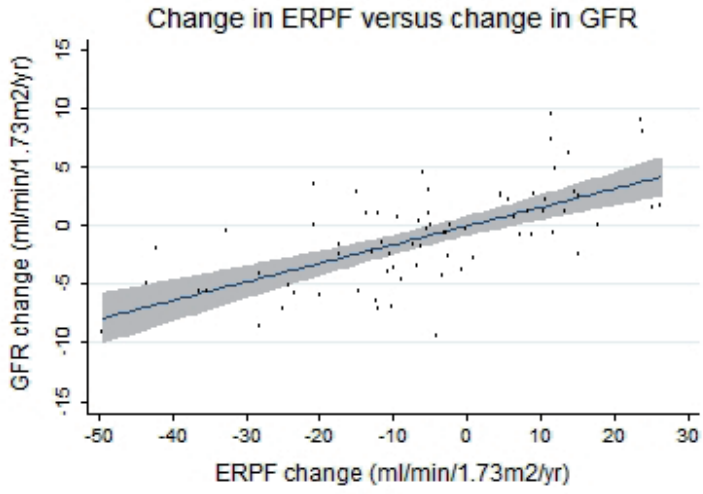


Table 2: Association of baseline markers with GFR change (ml/min/1.73m^2) per year corrected for baseline GFR

Variable	Beta	p-value	Beta	p-value
Age (years)	-0.41	< 0.001	-0.64	< 0.001
Female sex	0.21	0.077		
MAP (mmHg)	-0.22	0.064		

Table 2 (cont)

Variable	Beta	p-value	Beta	p-value
LVEF (%)	-0.17	0.20		
ERPF (ml/min/1.73m^2)	0.17	0.54		
RVR (mmHg/ml/min)	-0.15	0.38		
Filtration Fraction (%)	-0.06	0.61		
NT-proBNP (ng/ml)*	-0.11	0.41		
Hemoglobin (mmol/l)	-0.02	0.87		
CRP (mg/L)*	-0.05	0.67		
24h Urine Sodium (mmol)	-0.44	0.29		
UAE (mg/24h)*	-0.08	0.53		
NGAL (µg/24h)*	-0.21	0.096		
KIM-1 (U/24h)*	-0.27	0.027		
NAG (ng/24h)*	-0.11	0.36		

*GFR, glomerular filtration rate; ERPF, effective renal plasma flow; RVR renovascular resistance; MAP, mean arterial pressure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; UAE Urinary albumin excretion; CRP, C-reactive protein; NGAL, neutrophil gelatinase associated lipocalin; KIM-1, kidney injury molecule 1; NAG, N-acetyl-b-D--glucosaminidase; Correlations are corrected for age, sex and baseline GFR where appropriate. * log-transformed variables.*

Table 3: Associations between hemodynamic changes and changes in GFR

	Univariate			
	Coef	**95% CI**	**Beta**	**p-value**
Delta MAP (mmHg)	-0.17	(-0.47 to 0.13)	-0.14	0.25
Delta LVEF (%)	0.20	(-0.08 to 0.47)	0.16	0.16
Delta ERPF (ml/min/1.73m^2)	0.15	(0.11 to 0.19)	0.62	< 0.001
Delta RVR (mmHg/ml/min)	-110	(-172 to -47.9)	-0.43	0.001
Delta log-NT-proBNP (ng/ml)	3.20	(1.17 to 5.22)	0.34	0.002
	Multivariate			
Delta ERPF (ml/min/1.73m^2)	0.15	(0.11 to 0.19)	0.62	< 0.001

Discussion

In the present study of patients with stable HFREF, we found only a small decrease in true GFR over a longer period of time, in the order of magnitude also reported as the age-related decline in the general population. Likewise ERPF decline did not differ much from the age related decline rate in the general population. (14) Change in GFR was strongly associated with a parallel change in ERPF. Only higher age and lower baseline GFR predicted a greater decline in GFR over time, but none of the tested urinary biomarkers of renal damage, or hemodynamic parameters were associated with GFR decline.

Several studies have focused on markers predicting worsening renal function in chronic heart failure, with limited success. Identified risk factors include congestion, (15) vascular disease, diuretics, advanced age, left ventricular ejection fraction and worse renal function at baseline. (2, 5, 8) Furthermore NGAL and NT-proBNP have been linked to worsening renal function in acute decompensated heart failure, (16-18) and chronic heart failure. (20) However, all these studies used plasma creatinine to estimate GFR and cannot differentiate between changes in hemodynamics and kidney damage. In a previous analysis we demonstrated a strong relation of renal blood flow with GFR in HFREF patients. (7)

In the current analysis we found that none of the urinary biomarkers or hemodynamic parameters at baseline could predict renal function decline. Our study may have limited power, because of the small change in GFR over time; however, most of the aforementioned studies also demonstrated a limited estimated GFR decline over time and by using radioactive labeled tracers we can measure small changes in GFR more accurately. We cannot exclude that deceased subjects had a more rapid renal function decline. These subjects did have a lower GFR and ERPF and higher NT-proBNP at baseline, however, tubular damage markers were not elevated in these subjects. What is most remarkable is that they had a high RVR in combination with a low FF and low blood pressure. This may reflect the kidneys inability to maintain glomerular perfusion pressure. They were more often on double RAAS blockers, which may decrease FF by vasodilation of the efferent glomerular arteriole, however, this should cause a decrease in RVR. The high RVR therefore must reflect a different mechanism possibly compromised kidney perfusion by increased venous pressure, sympathetic nerve activation or a decreased amount of functioning glomeruli. It may be speculated that decreasing RVR may increase ERPF.

In our study we found that the change in ERPF was the strongest determinant of the change in GFR. In contrast, in healthy individuals, GFR remains relatively stable with moderate changes in renal blood flow. (19) It may be speculated that impaired systemic circulation causes decreased ERPF and, because of impaired intra-renal regulatory mechanisms, a parallel decline in GFR, but it may also imply that both ERPF and GFR are affected by intrarenal hemodynamic changes. Both

congestion and reduced cardiac output are thought to influence renal function in heart failure patients. In our study an increase in NT-proBNP was associated with an increase in ERPF and GFR, suggesting hypoperfusion rather than congestion causes renal function decline in these patients. Another explanation for the observed relationship is that kidney damage affects both ERPF and GFR. However, many patients showed an increase in ERPF and an associated increase in GFR, which suggests changes in hemodynamics rather than in viable kidney tissue.

This study has several limitations. First, not all patients were able to participate in the second measurement. The deceased patients had worse baseline renal function, lower blood pressure and higher NT-proBNP. Second, we only had two measurements; therefore we cannot establish if there is a linear trend over time and cannot account for fluctuations. The measurements performed, however, are the gold standard for measuring renal function, with a day-to-day variation coefficient of just 2.5 % for GFR and 5 % for ERPF. Finally, this was a relatively young cohort, with mostly male Caucasian patients.

Conclusion

In these stable chronic HFREF patients, long-term changes in GFR were small but strongly related to changes in ERPF. None of the investigated urinary biomarkers and hemodynamic parameters other than baseline GFR and age could predict changes in GFR. This underlines the need for the development of new renal risk markers and demonstrates that changes in GFR are mostly driven by changes in renal hemodynamics in chronic HFREF patients. Intervention trials should investigate whether targeting ERPF may improve GFR and reduce cardiac events and mortality.

Conflict of interest

C.A.J.M.G. received consultancy fees and/or research grants from: Novartis, Amgen, Roche, Baxter and Vifor. A.A.V received consultancy fees and/or research grants from: Alere, AstraZeneca, Bayer, Boehringer Ingelheim, Cardio3Biosciences, Celladon, Johnson and Johnson, Merck/MSD, Novartis, Servier, Torrent, Trevena, Vifor. The other authors report no conflicts of interest

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