Renal Function, Neurohormonal Activation, and Survival in Patients With Chronic Heart Failure

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Background—Because renal function is affected by chronic heart failure (CHF) and it relates to both cardiovascular and hemodynamic properties, it should have additional prognostic value. We studied whether renal function is a predictor for mortality in advanced CHF, and we assessed its relative contribution compared with other established risk factors. In addition, we studied the relation between renal function and neurohormonal activation.

Methods and Results—The study population consisted of 1906 patients with CHF who were enrolled in a recent survival trial (Second Prospective Randomized study of Ibopamine on Mortality and Efficacy). In a subgroup of 372 patients, plasma neurohormones were determined. The baseline glomerular filtration rate (GFR_c) was calculated using the Cockroft Gault equation. GFR_c was the most powerful predictor of mortality; it was followed by New York Heart Association functional class and the use of angiotensin-converting enzyme inhibitors. Patients in the lowest quartile of GFR_c values (<44 mL/min) had almost 3 times the risk of mortality (relative risk, 2.85; $P<0.001$) of patients in the highest quartile (>76 mL/min). Impaired left ventricular ejection fraction (LVEF) was only modestly predictive ($P=0.053$). GFR_c was inversely related with N-terminal atrial natriuretic peptide (ANP; $r=-0.53$) and, to a lesser extent, with ANP itself ($r=-0.35$; both $P<0.001$).

Conclusions—Impaired renal function (GFR_c) is a stronger predictor of mortality than impaired cardiac function (LVEF and New York Heart Association class) in advanced CHF, and it is associated with increased levels of N-terminal ANP. Moreover, impaired renal function was not related to LVEF, which suggests that factors other than reduced cardiac output are causally involved. **(*Circulation*. 2000;102:203-210.)**

Key Words: heart failure ■ prognosis ■ kidney ■ hormones

Chronic heart failure (CHF) is caused by a loss of ventricular function and by various adaptational responses, including neurohormonal activation, peripheral vasoconstriction, and salt and water retention.[1] A large number of clinical, hemodynamic, biochemical, and electrophysiological factors have now been identified that are related to prognosis in patients with CHF.[2] In routine clinical practice, left ventricular function (including left ventricular ejection fraction [LVEF]), the clinical severity of the disease (eg, New York Heart Association functional class ([NYHA]), and cause of the disease all carry independent prognostic value. Biochemical markers, including serum sodium, urea, and creatinine, and neurohormones may have additive value.[3,4] It has been suggested that the activation of the renin-angiotensin-aldosterone system (RAAS), which occurs when renal perfusion pressure is reduced in CHF, is not primarily a response to preserve circulatory homeostasis, but a renal compensatory reaction to preserve renal function.[5] It could thus be postulated that renal function can indirectly be used as an indicator of cardiovascular status in CHF and may, therefore, potentially be a powerful prognostic indicator.

Two previous studies reported the prognostic value of renal function (serum creatinine) in patients with CHF, but whether renal function contributed independently to mortality was not discussed.[6,7] Therefore, we examined renal function as a predictor of mortality in advanced CHF. Our secondary aim was to identify the relative contribution of renal function compared with established risk factors to the prognosis of the disease. Finally, we determined whether the relation between renal function and mortality was linked through neurohormonal activation. The study population consisted of patients who were enrolled in a recent survival trial (Second Prospective Randomized study of Ibopamine on Mortality and Efficacy [PRIME-II]).[8] In a subgroup of 372 patients, a predefined neurohormonal substudy was conducted.[9]

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TABLE 1. Baseline Characteristics of the Study Population

	Total Population (n=1906)	Neurohormone Subset (n=372)
Age, y	64.7±9.5	67.7±8.0
Male sex	1532 (80.4%)	288 (77.4%)
Diabetes	394 (20.7%)	82 (22.0%)
History of myocardial infarction	1025 (53.9%)	280 (75.3%)
Duration of heart failure, mo	30 (12–60)	24 (11–48)
Heart rate, bpm	81.0±14.8	81.1±14.8
Blood pressure, mm Hg		
Systolic	121.6±19.8	124.4±18.1
Diastolic	75.1±11.1	76.1±9.4
Atrial fibrillation	453 (23.8%)	78 (21.0%)
Calculated GFR, mL/min	62.9±26.2	59.6±22.5
NYHA class		
III	1138 (59.7%)	253 (68.0%)
III/IV	607 (31.8%)	107 (28.8%)
IV	161 (8.4%)	12 (3.2%)
Cause of CHF		
Ischemic heart disease	1120 (58.8%)	284 (76.3%)
Cardiomyopathy	600 (31.5%)	61 (16.4%)
Hypertension	106 (5.6%)	18 (4.8%)
Other	106 (5.6%)	14 (3.8%)
Current treatment of heart failure		
Digitalis	1222 (64.1%)	221 (59.4%)
Diuretics (furosemide)	1882 (98.7%)	369 (99.2%)
≤80 mg	1154 (61.3%)	232 (62.9%)
>80 mg	728 (38.7%)	137 (37.1%)
ACE inhibitors	1745 (91.6%)	352 (94.6%)
High dose	479 (27.4%)	84 (23.9%)
Moderate dose	953 (54.6%)	169 (48.0%)
Low dose	313 (17.9%)	99 (28.1%)
β-Blockers	118 (6.2%)	33 (8.9%)
Antiarrhythmics	463 (24.3%)	69 (18.5%)
Anticoagulants	819 (43.0%)	265 (71.2%)
Evidence of severity of heart failure		
LVEF, %	26.2±9.1	23.4±7.5
Left ventricular end internal diastolic diameter, cm	6.9±1.0	6.8±0.8
Serum		
Creatinine, μmol/L	120.5±45.5	118.2±37.6
Potassium, mmol/L	4.3±0.5	4.2±0.5
Sodium, mmol/L	138.5±4.9	139.0±3.4
Urea, mmol/L	27.7±34.9	9.6±4.5
Plasma neurohormones		
Norepinephrine, pg/mL	...	501 (363–696)
Epinephrine, pg/mL	...	39 (27–66)
Aldosterone, pg/mL	...	113 (67–220)
Dopamine, pg/mL	...	20 (13–32.3)
Epinine, pg/mL	...	6 (2–22)
Renin, μU/mL	...	86.2 (34.8–226.1)
ANP, pmol/L	...	103 (63–174)
N-terminal ANP, pmol/L	...	1088 (628–1798)
Endothelin, pg/mL	...	5.4 (3.4–11.4)

Continuous variables are expressed as mean±SD, duration of heart failure and plasma neurohormones are expressed as median (25^{th}–75^{th} percentiles), and other variables are n (%).

Methods

The details of PRIME-II have been described previously.[8] Briefly, the study was designed to investigate the effect of the oral dopamine agonist ibopamine on mortality in advanced CHF. The study was conducted in 13 European countries, and 1906 patients were included. PRIME-II was prematurely discontinued in August 1995 when a significantly higher fatality rate was observed in the ibopamine group. Patients, aged 18 to 80 years, were eligible for PRIME-II if they had moderate to severe CHF (NYHA class III to IV) and evidence of left ventricular dysfunction (including LVEF<0.35). In the predefined substudy, which was performed only in the Netherlands, blood for plasma neurohormone detection was collected from 372 patients.[9]

Renal Function

The glomerular filtration rate (GFR) is the standard indicator of renal function. Under steady-state conditions, GFR is estimated from serum creatinine using a formula that accounts for the influence of age and body weight on creatinine production (the Cockroft Gault equation)[10,11]: GFR_c=[(140−age in years)×(body weight in kg)]/(72×serum creatinine in mg/dL). In women, the value is multiplied by 0.85. This formula has been validated in several studies of CHF and renal dysfunction, and it showed a correlation >0.90, with accurately measured GFR.[10–15]

Neurohormonal Measurements

The method of handling, storing, and determining neurohormonal levels has been previously described in detail.[9,10] Plasma norepinephrine, epinephrine, and dopamine levels were determined by high-performance liquid chromatography with fluorometric detection. Active plasma renin concentration was measured by a radioimmunoassay of generated angiotensin I. To measure aldosterone, endothelin, atrial natriuretic peptide (ANP), and plasma N-terminal ANP, commercially available kits were used.

Statistical Methods

The influence of baseline renal function on survival in the total study population was studied with Kaplan Meier methods and Cox regression. To isolate the independent effect of GFR_c on overall mortality, the statistical analysis included adjustments for several possible risk factors, including age, sex, blood pressure, heart rate, rhythm, cause and duration of CHF, and concomitant medication (in particular, angiotensin-converting enzyme [ACE] inhibitors, diuretics, digoxin, and antiarrhythmic drugs). The effects of ibopamine on survival and other baseline characteristics that were prognostically relevant were also used in this analysis. A further description of risk factors can be found elsewhere.[8,10]

Continuous variables were modelled with indicator variables into quartiles, and relative risks with the lowest risk quartile were calculated for those in the second, third, and fourth quartiles. Test for trends are presented. Only variables with $P<0.10$ in the univariate Cox regression analysis were used in the multiple Cox regression analysis. Cumulative relative risks were calculated within the subgroups defined by GFR_c strata with degree of LVEF and NYHA class. Interaction terms were used to examine effect modification.

To reduce the risk of bias by the empirical use of arbitrary values for missing items of data, we excluded observations with missing values for contributing variables in the multivariate model. Stepwise linear regression analysis was used to determine the relationship between each of the plasma neurohormones with GFR_c and LVEF and other relevant, significant baseline variables. Plasma neurohormone values were not normally distributed, and their natural logarithms were incorporated. Pearson or Spearman correlation coefficients were calculated to determine which independent variables had a significant univariate association with serum creatinine. To examine all possible interactions of the effects of various variables, a secondary analysis that included interaction terms was performed. In addition, we performed a separate analysis of the subgroups with and without ibopamine. All reported probability values are 2-tailed, and $P<0.05$ was considered statistically significant.

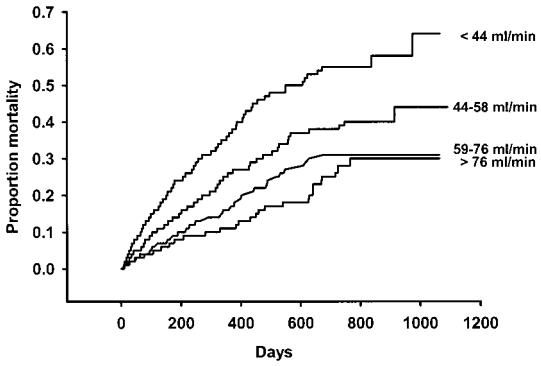

Figure 1. Kaplan-Meier mortality curves for quartiles of GFR_c.

Results

Patient Characteristics

Table 1 shows the baseline characteristics of the total population (n=1906) and the neurohormonal subgroup (n=372). In 204 of the 1906 patients, values were missing for ≥1 contributing variable in the multivariate model; these patients were excluded from the analysis. Therefore, full analyses of GFR_c were performed on 1702 patients. No significant demographic or clinical differences were found between the total and actual study populations.

Renal Function and Overall Mortality

After a median follow-up of 277 days (range, 0 to 1091 days), 343 patients had died. In unadjusted analyses, GFR_c at baseline was strongly associated with all-cause mortality, with a clear separation of curves and a marked stepwise increase in the cumulative incidence of mortality for successively lower quartiles of GFR_c (Figure 1).

Table 2 summarizes the univariate and multivariate results of independent predictors that remained significantly associated (with the exception of LVEF) with mortality. GFR_c was the most powerful predictor of mortality, as expressed by the Wald statistics; this was followed by NYHA class and use of ACE inhibitors. Patients in the lowest quartile of GFR_c values (<44 mL/min) had almost 3 times the risk of mortality (relative risk, 2.85; $P<0.001$) of the patients in the highest quartile (>76 mL/min). LVEF contributed only modestly to mortality ($P=0.053$ for trend). The risk of mortality was almost equal for the first 2 GFR_c quartiles. A similar observation was present for the first 3 quartiles of LVEF (Figure 2). Weak prognostic values for mortality (relative risks <2.0) were found for NYHA class, systolic blood pressure, digitalis use, history of myocardial infarction, sodium level, β-blocker use, use of anticoagulants, LVEF, and ibopamine use. The proportional relationship of GFR_c with mortality was also evident in the Cox-adjusted survival plot (Figure 3).

When performing secondary analyses, no interaction term was statistically significant in the multivariate analysis, including ibopamine treatment and renal function ($P=0.194$). In the separate subgroup analyses according to treatment with and without ibopamine, similar highly significant trends in relative risks for successively lower quartiles were observed

TABLE 2. Stepwise Cox Proportional Hazard Analysis of Risk Factors at Baseline for Overall Mortality (Total Population)

	No. of Subjects	No. of Deaths	Univariate RR (95% CI)	Multivariate RR (95% CI)	*P* for Trend	*P*	Wald Statistic
Baseline GFR_c, mL/min							
>76	466	64	1.00	1.00	0.0000		55.20
76–59	467	82	1.32 (0.95–1.82)	1.27 (0.90–1.80)		0.1749	
58–44	467	116	1.95 (1.44–2.65)	1.91 (1.38–2.64)		0.0001	
<44	466	170	3.23 (2.42–4.31)	2.85 (2.08–3.90)		0.0000	
NYHA class							
III	1138	197	1.00	1.00	0.0000		26.25
III/IV	607	186	1.96 (1.60–2.40)	1.51 (1.21–1.89)		0.0003	
IV	161	56	2.55 (1.89–3.43)	2.13 (1.55–2.93)		0.0000	
ACE inhibitors							
No	161	66	1.00	1.00	0.0000		19.53
Yes	1745	373	0.43 (0.33–0.56)	0.51 (0.38–0.69)			
Systolic blood pressure, mm Hg							
>133	479	77	1.00	1.00	0.0025		14.21
133–120	611	131	134 (1.01–1.18)	1.24 (0.92–1.68)		0.1585	
119–110	367	92	1.73 (1.28–2.34)	1.48 (1.06–2.06)		0.0217	
<110	448	139	2.14 (1.62–2.83)	1.78 (1.29–2.43)		0.0004	
Sodium, mmol/L							
>141	419	76	1.00	1.00	0.0108		11.12
141–139	597	113	1.05 (0.79–1.40)	1.05 (0.78–1.43)		0.7457	
139–137	380	98	1.56 (1.16–2.11)	1.39 (1.01–1.90)		0.0422	
<137	487	149	1.97 (1.50–2.60)	1.51 (1.12–2.03)		0.0075	
Digitalis							
No	607	132	1.00	1.00	0.0049		7.93
Yes	1098	307	1.48 (1.21–1.82)	1.37 (1.10–1.71)			
LVEF, %							
>30	449	98	1.00	1.00	0.0528		7.71
30–26	403	73	0.85 (0.63–1.15)	0.94 (0.69–1.29)		0.7151	
25–21	404	93	1.05 (0.79–1.40)	1.16 (0.87–1.56)		0.3184	
<21	492	135	1.33 (1.02–1.72)	1.35 (1.03–1.77)		0.0281	
β-Blockers							
No	1788	429	1.00	1.00	0.0090		6.83
Yes	118	10	0.40 (0.22–0.75)	0.39 (0.19–0.79)			
Ibopamine							
No	953	199	1.00	1.00	0.0206		5.17
Yes	953	240	1.26 (1.05–1.52)	1.27 (1.03–1.55)			
History of myocardial infarction							
No	878	171	1.00	1.00	0.0367		4.36
Yes	1025	268	1.30 (1.07–1.58)	1.25 (1.01–1.54)			

RR indicates relative risk; CI, confidence interval.

when compared with the highest quartile of GFR_c (relative risks of 1.31, 2.36, and 2.48, respectively, for the ibopamine group [$P<0.001$] and of 1.35, 1.66, and 3.41, respectively, for the placebo group [$P<0.001$]).

Additional adjustments for univariate prognostic variables for mortality, such as age, heart rate, body weight, diastolic blood pressure, serum potassium level, urea and creatinine levels, cause of CHF, diabetes mellitus, intraventricular conduction disorders, absence of sinus rhythm, orthopnea, dyspnea, peripheral edema, fatigue, nitrate use, use of direct vasodilators, the administered dose of ACE inhibitors, and furosemide use were nonsignificant in the multivariate model and were not included.

Mortality and the Relationship Between GFR_c, LVEF, and NYHA Class

Cumulative relative risk estimates for the GFR_c categories in combination with NYHA classes and LVEF are shown in

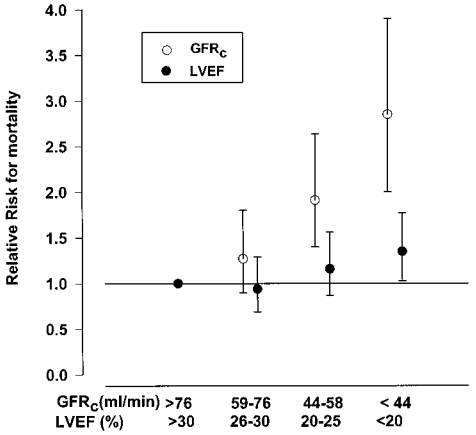

Figure 2. Relation, in quartiles, of LVEF and GFR_c to the risk of mortality using the multivariate proportional hazards regression model.

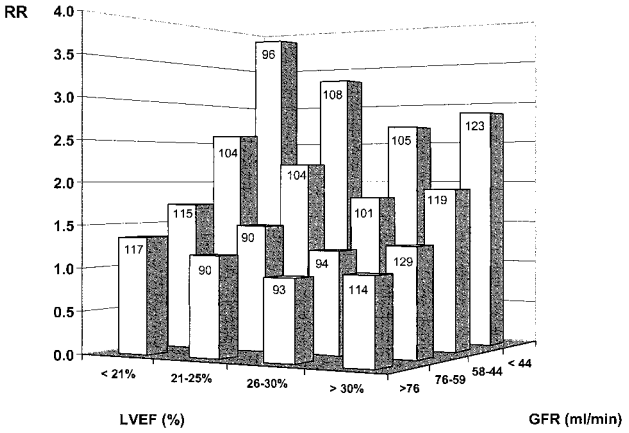

Figure 4. Three-dimensional bar graph showing risk of mortality (vertical axis) in relation to decreasing quartiles of LVEF (horizontal axis) and decreasing quartiles of GFR_c (diagonal axis).

Figures 4 and 5. A stepwise increase in mortality risks with decreasing GFR_c and LVEF was present. When divided into quartiles, LVEF showed lower risk estimates than GFR_c. No interaction between GFR_c and LVEF was observed, so GFR_c and LVEF had an effect that was additive in terms of predicting mortality. An identical analysis of GFR_c with NYHA class revealed a similar pattern. In addition, only weak inverse correlations were observed between baseline GFR_c and NYHA class and between LVEF and NYHA class ($r=-0.062$, $P=0.002$ and $r=-0.030$, $P=0.142$, respectively). There was no correlation between GFR_c and LVEF ($r=-0.013$, $P=0.422$).

GFR_c, LVEF, and Plasma Neurohormones

The neurohormonal subpopulation was largely similar to the general PRIME-II population (Table 1). Most neurohormones were elevated compared with normal values, but epinephrine, dopamine, and aldosterone levels were within the normal range. Univariate correlation coefficients for neurohormones with GFR_c and LVEF and the results of the stepwise multivariate regression analyses are presented in Table 3. The majority of plasma neurohormones showed a statistically significant, but only moderate, relation with GFR_c and LVEF. In general, a more pronounced association was found with GFR_c, and the strongest associations were found for ANP ($r=-0.35$) and N-terminal ANP ($r=-0.53$).

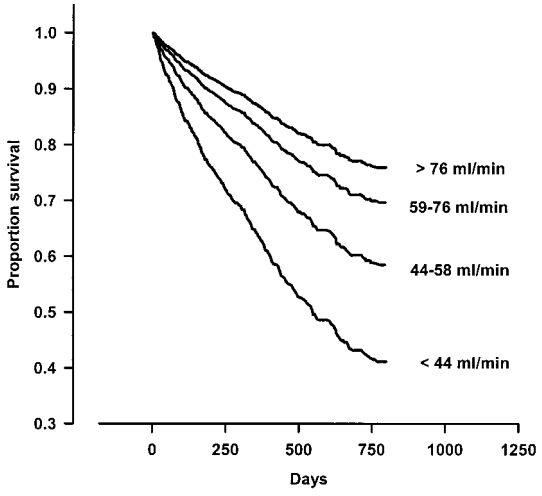

Figure 3. The proportional relationship of GFR_c with mortality in Cox-adjusted survival analysis.

Discussion

The important new finding in this study is that renal function, as measured by GFR_c, is strongly associated with mortality in patients with advanced CHF; it seems to be independent of the impaired LVEF found in these patients. Renal function was more closely associated with mortality in patients with advanced CHF than any other established risk factor, including NYHA class and LVEF. In addition, renal function correlated significantly, and more strongly than LVEF, with plasma neurohormones (in particular, N-terminal ANP).

Renal Function as a Marker of Prognosis and Clinical Status?

Patients with renal dysfunction had a significantly poorer prognosis compared with patients with relatively preserved

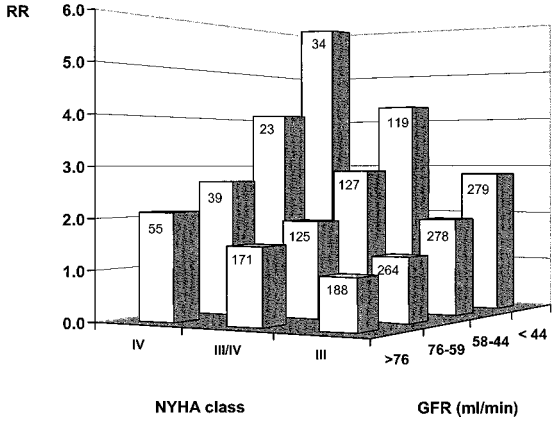

Figure 5. Three-dimensional bar graph showing risk of mortality (vertical axis) in relation to decreasing NYHA class (horizontal axis) and decreasing quartiles of GFR_c (diagonal axis).

TABLE 3. Relationship Between Neurohormones and LVEF and GFR_c

	GFR_c			LVEF		
		Univariate	Multivariate		Univariate	Multivariate
	r	*P*	*P*	*r*	*P*	*P*
Norepinephrine	−0.28	<0.001	0.001	−0.15	0.004	NS
Epinephrine	−0.05	0.365	NS	−0.15	0.004	0.007
Dopamine	−0.23	<0.001	0.001	−0.08	0.143	NS
Renin	−0.13	0.013	0.005	−0.22	<0.001	NS
Aldosterone	−0.15	0.005	0.006	−0.04	0.501	NS
ANP	−0.35	<0.001	<0.001	−0.27	<0.001	0.002
N-terminal ANP	−0.53	<0.001	<0.001	−0.33	<0.001	<0.001
Endothelin	−0.10	0.069	NS	−0.18	0.001	0.046
Epinine	−0.07	0.201	NS	−0.01	0.899	NS

NS indicates not significant.

renal function, despite a similar NYHA functional class and LVEF. A number of studies focusing on specific groups such as hypertensive individuals, the elderly, patients with recent stroke, survivors of myocardial infarction, and patients after open heart surgery indicated that elevated serum creatinine may be an independent predictor of all-cause and of cardiovascular disease mortality.[16–19] Two previous studies have reported the prognostic value of renal function in patients with CHF; both used serum creatinine as a measure for renal function.[6,7] However, the patient characteristics of those populations were limited and, remarkably, the impact of this observation was not discussed in either article. In another study, it was speculated that renal function might carry prognostic information, but this study mainly dealt with changes in serum creatinine.[20]

In several studies, LVEF has been shown to correlate directly with survival in patients with CHF. Although LVEF is an indicator of left ventricular dysfunction, it does not have a strong relationship with clinical symptoms.[4,21] Renal function includes both cardiovascular and hemodynamic properties and, thus, its prognostic value in CHF could be expected. It may be postulated that because renal function is measured on a continuous scale, it is more likely to be a more powerful predictor of the clinical status of the patient than, for example, NYHA class. However, the present study shows that LVEF, GFR_c, and NYHA class are prognostically important and that they act in part independently and show only weak correlations with each other. This is demonstrated by the relatively large number of patients with severely impaired renal function who do not have severely impaired cardiac function and vice versa. Further, it supports the hypothesis that cardiac function, clinical status, and renal function represent, in part, different prognostic entities of CHF.

Treatment with ibopamine was a unique aspect of this study. Ibopamine is an oral dopamine analogue with vasodilatory, positive inotropic, and diuretic effects.[22] In the PRIME-II study, ibopamine increased the risk of death among patients with advanced CHF, but the reasons for this increase are not clear. In a post hoc subgroup analysis, antiarrhythmic treatment was a significant predictor of increased mortality in ibopamine-treated patients.[8] The possibility that ibopamine may have contributed to the relationship between GFR_c and mortality was investigated by interaction analysis in the total population and in a separate analysis of the subgroups. Although in this exploratory analysis ibopamine did not seem to modify this effect, a confounding influence still may have been present. The present findings must, therefore, be viewed cautiously.

Relation Between Renal and Cardiac Dysfunction and Neurohormonal Activation

In the early stages of CHF, GFR is well maintained by compensatory increases in filtration fraction; in patients with more severe CHF, GFR becomes more dependent on afferent arteriolar flow and the stimulation of hemodynamic and hormonal pathways.[20,23] Furthermore, the fall in effective renal blood flow is relatively more pronounced and therefore disproportional to the reduction in cardiac output.[23,24] Nevertheless, it was recently demonstrated that renal hemodynamic reserve is already impaired in patients with asymptomatic left ventricular dysfunction.[25] Traditionally, the contribution of the kidneys to CHF has been considered an adaptive response mechanism evoking a series of compensatory neurohormonal changes, in particular, increased adrenergic drive and activation of the RAAS to maintain perfusion to vital organs and to expand the inadequate arterial blood volume.[20,23–31] With respect to the kidneys, however, activation of the RAAS is not only a response to preserve systemic circulatory volume; indeed, it is primarily a response to preserve GFR as renal blood flow decreases and renal perfusion pressure declines.[5] Therefore, it could be postulated that the association between renal function and prognosis is linked by neurohormonal activation.

In our study, renal function correlated significantly, and more strongly than LVEF, with neurohormonal activation (in particular, with N-terminal ANP). N-terminal ANP is a powerful predictor of cardiovascular mortality.[32] The majority of the other vasoactive neurohormones, including those related to the RAAS, however, were only weakly associated

with renal function. A direct relationship between the kidney and natriuretic peptides has never been demonstrated, but the main counteracting mechanism available to the circulation to break through the vicious circle of salt and water retention induced by the failing kidneys is the production of ANP. In the present study, a relation between renal function and ANP and N-ANP was indeed observed. Renal responsiveness to natriuretic peptides, however, seems to decrease as CHF worsens, even in the presence of rising plasma concentrations of these peptides.[33]

Limitations of the Study

This study is limited by its observational nature. GFR was calculated using the Cockroft Gault equation. Thus, GFR in patients with severe CHF could potentially be overestimated because serum creatinine is dependent on muscle mass, which may be lowered in patients with CHF, particularly in those with cachexia. However, if one takes that into account, the results would be even more convincing. Also, this study constitutes cross-sectional observational data and, thus, can only be used to generate new hypotheses. In this respect, it must be noted that half of the patients were treated with ibopamine, which showed an increased risk for mortality in the original study. Further, although medication was in general similar, not all patients were using the same drugs or doses of drugs. Although we corrected for these differences, their true influence may not have been adequately represented by the multivariate analysis.

Clinical Implications

Our findings have several clinical implications; the most important is that renal function may serve as one of the most important determinants of prognosis in advanced CHF and that it seems to be more powerful than cardiac parameters (such as LVEF) in discriminating patients at risk. Moreover, in a substantial number of patients, the compromised renal function is probably not caused by cardiac disease. We speculate that nephrosclerosis, which seems to run in parallel with systemic atherosclerosis, accounts for the impaired renal function.[34] A strong, direct relationship between renal function and activation of the RAAS could not be established, but a significant correlation between plasma levels of N-terminal ANP and GFR_c was found. Therefore, determination of renal function may serve to identify CHF patients at risk, which may have therapeutic implications. This hypothesis will require further prospective studies. It must be emphasised, however, that a population with severe CHF was studied, and the results cannot be automatically extrapolated to patients with less severe CHF.

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References

1. Packer M. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. *J Am Coll Cardiol*. 1992;20:248–254.
2. Cowburn PJ, Cleland JG, Coats AJ, et al. Risk stratification in chronic heart failure. *Eur Heart J*. 1998;19:696–710.
3. Francis GS, Benedict C, Johnstone DE, et al. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure: a substudy of the Studies of Left Ventricular Dysfunction (SOLVD). *Circulation*. 1990;82:1724–1729.
4. Parameshwar J, Keegan J, Sparrow J, et al. Predictors of prognosis in severe chronic heart failure. *Am Heart J*. 1992;123:421–426.
5. Packer M. Why do the kidneys release renin in patients with congestive heart failure? A nephrocentric view of converting-enzyme inhibition. *Eur Heart J*. 1990;11(suppl D):44–52.
6. Feenstra J, in't Veld BA, van der Linden PD, et al. Risk factors for mortality in users of ibopamine. *Br J Clin Pharmacol*. 1998;46:71–77.
7. Madsen BK, Keller N, Christiansen E, et al. Prognostic value of plasma catecholamines, plasma renin activity, and plasma atrial natriuretic peptide at rest and during exercise in congestive heart failure: comparison with clinical evaluation, ejection fraction, and exercise capacity. *J Card Fail*. 1995;1:207–216.
8. Hampton JR, Van Veldhuisen DJ, Kleber FX, et al. Randomised study of effect of ibopamine on survival in patients with advanced severe heart failure: Second Prospective Randomised Study of Ibopamine on Mortality and Efficacy (PRIME II) Investigators. *Lancet* 1997;349:971–977.
9. Van Veldhuisen DJ, Boomsma F, de Kam PJ, et al. Influence of age on neurohormonal activation and prognosis in patients with chronic heart failure. *Eur Heart J*. 1998;19:753–760.
10. Ajayi AA. Estimation of creatinine clearance from serum creatinine: utility of the Cockroft and Gault equation in Nigerian patients. *Eur J Clin Pharmacol*. 1991;40:429–431.
11. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31–41.
12. Luke DR, Halstenson CE, Opsahl JA, et al. Validity of creatinine clearance estimates in the assessment of renal function. *Clin Pharmacol Ther*. 1990;48:503–508.
13. Robert S, Zarowitz BJ, Peterson EL, et al. Predictability of creatinine clearance estimates in critically ill patients. *Crit Care Med*. 1993;21:1487–1495.
14. Robertshaw M, Lai KN, Swaminathan R. Prediction of creatinine clearance from plasma creatinine: comparison of five formulae. *Br J Clin Pharmacol*. 1989;28:275–280.
15. Waller DG, Fleming JS, Ramsey B, et al. The accuracy of creatinine clearance with and without urine collection as a measure of glomerular filtration rate. *Postgrad Med J*. 1991;67:42–46.
16. Damsgaard EM, Froland A, Jorgensen OD, et al. Microalbuminuria as predictor of increased mortality in elderly people. *BMJ*. 1990;300:297–300.
17. Friedman PJ. Serum creatinine: an independent predictor of survival after stroke. *J Intern Med*. 1991;229:175–179.
18. Matts JP, Karnegis JN, Campos CT, et al. Serum creatinine as an independent predictor of coronary heart disease mortality in normotensive survivors of myocardial infarction: POSCH group. *J Fam Pract*. 1993;36:497–503.
19. Shulman NB, Ford CE, Hall WD, et al. Prognostic value of serum creatinine and effect of treatment of hypertension on renal function: results from the hypertension detection and follow-up program: the hypertension detection and follow-up program cooperative group. *Hypertension*. 1989;13:I80–I93.
20. Ljungman S, Kjekshus J, Swedberg K. Renal function in severe congestive heart failure during treatment with enalapril (the Cooperative North Scandinavian Enalapril Survival Study [CONSENSUS] trial). *Am J Cardiol*. 1992;70:479–487.
21. Van den Broek SAJ, Van Veldhuisen DJ, De Graeff PA, et al. Comparison between New York Heart Association classification and peak oxygen consumption in the assessment of functional status and prognosis in patients with mild to moderate chronic congestive heart failure secondary to either ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol*. 1992;70:359–363.
22. Lieverse AG, Van Veldhuisen DJ, Smit AJ, et al. Renal and systemic hemodynamic effects of ibopamine in patients with mild to moderate congestive heart failure. *J Cardiovasc Pharmacol*. 1995;25:361–367.
23. Ljungman S, Laragh JH, Cody RJ. Role of the kidney in congestive heart failure: relationship of cardiac index to kidney function. *Drugs*. 1990;39(suppl 4):10–21.
24. Leithe ME, Margorien RD, Hermiller JB, et al. Relationship between central hemodynamics and regional blood flow in normal subjects and in patients with congestive heart failure. *Circulation*. 1984;69:57–64.

25. Magri P, Rao MA, Cangianiello S, et al. Early impairment of renal hemodynamic reserve in patients with asymptomatic heart failure is restored by angiotensin II antagonism. *Circulation*. 1998;98: 2849–2854.
26. Anand IS, Ferrari R, Kalra GS, et al. Edema of cardiac origin: studies of body water and sodium, renal function, hemodynamic indexes, and plasma hormones in untreated congestive cardiac failure. *Circulation*. 1989;80:299–305.
27. Dzau VJ, Colucci WS, Hollenberg NK, et al. Relation of the renin-angiotensin-aldosterone system to clinical state in congestive heart failure. *Circulation*. 1981;63:645–651.
28. Dzau VJ. Renin-angiotensin system and renal circulation in clinical congestive heart failure. *Kidney Int Suppl*. 1987;20:S203–S209.
29. Elsner D. Changes in neurohumoral systems during the development of congestive heart failure: impact on cardiovascular and renal function. *Eur Heart J*. 1995;16(suppl N):52–58.
30. Merrill AJ, Morrison JL, Brannon ES. Concentration of renin in renal venous blood in patients with chronic heart failure. *Am J Med*. 1946;1: 468–472.
31. Zhang PL, Mackenzie HS, Totsune K, et al. Renal effects of high-dose natriuretic peptide receptor blockade in rats with congestive heart failure. *Circ Res*. 1995;77:1240–1245.
32. Hall C, Rouleau JL, Moye L, et al. N-terminal proatrial natriuretic factor: an independent predictor of long-term prognosis after myocardial infarction. *Circulation*. 1994;89:1934–1942.
33. Cody RJ, Atlas SA, Laragh JH, et al. Atrial natriuretic factor in normal subjects and heart failure patients: plasma levels and renal, hormonal, and hemodynamic responses to peptide infusion. *J Clin Invest*. 1986;78: 1362–1374.
34. Tracy RE, MacLean CJ, Reed DM, et al. Blood pressure, nephrosclerosis, and age autopsy findings from the Honolulu Heart Program. *Mod Pathol*. 1988;1:420–427.

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