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**Hisashi Kimura · Shinya Hiramitsu · Kenji Miyagishima
Kazumasa Mori · Ryuji Yoda · Shigeru Kato
Yasuchika Kato · Shin-ichiro Morimoto · Hitoshi Hishida
Yukio Ozaki**

Cardio-renal interaction: impact of renal function and anemia on the outcome of chronic heart failure

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Abstract The purpose of this study is to investigate the effects of renal function and anemia on the outcome of chronic heart failure (CHF). We targeted 711 consecutive patients who were hospitalized at the Division of Cardiology of Fujita Health University Hospital during a 5-year period. The subjects were divided into four groups according to their estimated glomerular filtration rate (e-GFR) calculated using the Modification of Diet in Renal Disease (MDRD) formula. Intergroup comparisons were conducted for underlying heart diseases, clinical findings at the time of hospitalization, treatment, and outcome. Moreover, the patients were divided into two groups according to their serum hemoglobin concentration at the time of hospitalization, using 12.0 g/dl as the dividing point, to study the effects of anemia on the outcome. In the group with decreased renal function, the average age was higher, and ischemic heart disease and associated conditions such as hypertension and diabetes mellitus were observed in most of the patients. In addition, the rate of anemia development and the plasma B-type natriuretic peptide concentration were also high. The greater the deterioration in renal function, the poorer the outcome became ($P < 0.0001$). Chronic heart failure complicated by anemia showed an especially poor outcome ($P < 0.0001$). As this study showed that renal function and anemia significantly affected the outcome of CHF, it is clear that the preservation of renal function and the management of anemia are important in addition to the conventional treatments for CHF.

Key words Chronic heart failure · Cardio renal anemia syndrome · Chronic kidney disease · Anemia · Prognosis

H. Kimura · S. Hiramitsu (✉) · K. Miyagishima · K. Mori · R. Yoda · S. Kato · Y. Kato · S. Morimoto · H. Hishida · Y. Ozaki
Division of Cardiology, Department of Internal Medicine, Fujita Health University School of Medicine, Toyoake 470-1192, Japan
Tel. +81-562-93-2312; Fax +81-562-93-2315
e-mail: hirazy@fujita-hu.ac.jp

Introduction

Chronic heart failure (CHF) is a systemic syndrome caused by various heart diseases. Its prevalence has been increasing every year in Japan due to aging of the population. Furthermore, heart failure carries a poor prognosis, comparable to that of malignant tumors. Because the involvement of renal failure and anemia in the outcome of CHF has become clear, the cardio-renal interaction has been actively studied.[1–3] Silverberg et al.[4] suggested the a new concept of cardio renal anemia syndrome and emphasized the importance of renal function in CHF. Nephrologists have also suggested that chronic kidney disease (CKD) is an independent risk factor for cardiovascular diseases.[5–8] In this study, the effects of renal function and anemia on the outcome of CHF were examined in patients with CHF admitted to our hospital.

Materials and methods

Patients with CHF who were hospitalized at the Division of Cardiology of Fujita Health University Hospital during the 5-year period from January 1, 2000 to December 31, 2004 were targeted for this study. Of 738 consecutive patients with a rapid deterioration of CHF, 711 patients were included, and their clinical findings and long-term outcome were investigated retrospectively. Twenty-seven patients were excluded from the study because they were already undergoing chronic hemodialysis. The average duration of follow-up prognosis was 791 ± 597 days. To determine the prognosis for those patients who had changed hospitals or stopped coming to our hospital, they or their families were contacted by telephone or letter to determine their survival status after following the necessary consent protocol.

The subjects were divided into four groups according to their estimated glomerular filtration rate (e-GFR) as follows: Group I (90 ml/min/1.73 m^2 or more), Group II (60–89 ml/min/1.73 m^2), Group III (30–59 ml/min/1.73 m^2),

and Group IV (30 ml/min/1.73 m^2 or less). Estimated glomerular filtration rate was calculated using the serum creatinine concentration at the time of hospitalization, age, and sex, and the formula of Modification of Diet in Renal Disease (MDRD): $194 \times SCr^{-1.094} \times Age^{-0.287} \times 0.739$ (if female).[9–11] The groups were then compared for any underlying heart diseases, clinical findings at the time of hospitalization, treatments, and outcome. Additionally, the subjects were divided into two groups according to their serum hemoglobin concentration at the time of hospitalization, using 12.0 g/dl as the dividing point (a nonanemic group with 12.0 g/dl or more, and an anemic group with less than 12.0 g/dl) to study the effects of anemia on outcome.

A rapid deterioration of CHF was diagnosed and treated by two or more cardiologists on the basis of the Framingham diagnostic criteria for heart failure.[12] Cardiomyopathy or ischemic heart diseases were defined according to heart catheterization, echocardiography, or previous diagnosis. A rapid deterioration of CHF was defined as a case with heart failure symptoms of II or higher in accordance with the New York Heart Association (NYHA) classification. Under the NYHA standard, some types of underlying heart disorder exist for a certain period of time as a result of discontinuation of medication or infection and require hospital treatment for the patient. Cases of acute heart failure associated with conditions such as acute coronary syndrome (ACS), acute myocarditis, and infective endomyocarditis were excluded from this study.

Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or previous history. Diabetes mellitus was defined as fasting plasma glucose concentration ≥126 mg/dl, hemoglobin A1c ≥6.5%, or a history of previous treatment. Anemia was defined as a serum hemoglobin concentration of <12 g/dl on admission. Hyperlipidemia was defined as serum total cholesterol concentration ≥220 mg/dl, or serum low-density lipoprotein-cholesterol concentration ≥140 mg/dl, or previous treatment.

Statistical analysis

Baseline characteristics of patients in the four groups specified above were compared using χ^2 test for dichotomous variables and Student's *t*-test for continuous variables. The crude survival curves were generated by the Kaplan–Meier method and compared with the Mantel–Haenszel log-rank test. Cox proportional hazards analyses were done to determine the association of e-GFR with all-cause mortality (over the entire follow-up period), adjusted for age, sex, NYHA functional classification, Killip classification, concomitant medication use, and any other variables that significantly differed between the patients with or without kidney disease or that predicted mortality in the multivariate model. As a sub-analysis, death risk of CKD and/or anemia in CHF patients are shown using the odds ratio. All analyses were performed using the JMP statistical software package (version 5).

Results

Clinical findings (Table 1)

Patients, sex, and age

Group I consisted of 88 patients (46 male patients, average age 58.5.1 ± 17.9 years), Group II of 235 patients (149 male patients, average age 68.8 ± 13.4 years), Group III of 263 patients (146 male patients, average age 71.7 ± 12.8 years), and Group IV of 125 patients (59 male patients, average age 72.1 ± 11.5 years). The average age increased significantly in parallel with the deterioration of renal function ($P < 0.0001$).

Basal heart disease

In the groups with good renal function (Groups I and II), higher rates of dilated cardiomyopathy (DCM) were observed in comparison with the other groups ($P = 0.027$). The rate of ischemic heart diseases increased in parallel with decreasing renal function ($P < 0.0001$).

Clinical findings at the time of hospitalization

According to the NYHA functional classification and the Killip classification, the greater the deterioration in the patient's renal function, the more severe was the patient's condition ($P = 0.0001$, $P = 0.012$). Although no significant differences were observed between the groups in terms of blood pressure or heart rate, the systolic blood pressure tended to be higher in the groups with poorer renal function ($P = 0.006$). The serum hemoglobin concentration decreased as the renal function worsened ($P < 0.0001$). The plasma B-type natriuretic peptide (BNP) concentration increased as the renal function deteriorated, and in Group IV, it increased to more than twice the level of that in Group I. In the echocardiographic findings, Left ventricular ejection fraction (LVEF) of Group III was lowest at 37.2% ± 15.4% ($P = 0.001$). Left ventricular mass index (LVMI) increased as the renal function deteriorated ($P = 0.021$).

Anemia (Table 2)

The anemic group consisted of 318 patients, accounting for 44.7% of all the patients. Patients in the anemic group were older, had poorer renal function, and showed high plasma BNP concentration. Neither the NYHA function classification nor the Killip classification differed significantly between the two groups. The LVEF was excellent in the anemic group.

Therapy (Table 3)

Treatment of heart failure

The drugs administered in the acute phase of a rapid deterioration of CHF and at the time of hospital discharge are

Table 1. Baseline characteristics of the study population according to their e-GFR on admission

e-GFR (*n* = 711)	Group I ≥90 (*n* = 88)	Group II 60–89 (*n* = 235)	Group III 30–59 (*n* = 263)	Group IV <30 (*n* = 125)	*P* value
Age (years)	58.5 ± 17.9	68.8 ± 13.4	71.7 ± 12.8	72.1 ± 11.5	<0.0001
Male:Female	46:42	149:86	146:117	59:66	0.162
Basal heart disease (%)					
IHD	19.3	37.4	44.1	52.8	<0.0001
Valvular disease	25.0	21.3	22.4	17.6	0.412
Hypertension	10.2	8.5	8.7	12.8	0.414
DCM	13.6	13.2	9.1	4.0	0.027
Others	27.9	22.6	15.1	12.3	0.005
Complication (%)					
Diabetes mellitus	23.9	28.5	35.4	56.8	<0.0001
Hypertension	34.1	56.2	61.6	66.4	<0.0001
Hyperlipidemia	20.5	25.5	34.6	34.4	0.020
Atrial fibrillation	46.7	46.0	32.4	23.2	<0.0001
VT, Vf	11.4	11.1	13.7	5.6	<0.0001
Characteristics					
NYHA functional classification	3.3 ± 0.6	3.4 ± 0.6	3.5 ± 0.6	3.6 ± 0.6	0.0001
Killip classification	2.0 ± 0.6	2.1 ± 0.7	2.2 ± 0.7	2.3 ± 0.7	0.012
Observation period (days)	1114 ± 593	857 ± 596	701 ± 545	630 ± 608	<0.0001
Systolic BP (mmHg)	131 ± 30	140 ± 31	138 ± 33	148 ± 35	0.006
Diastolic BP (mmHg)	70 ± 19	75 ± 18	75 ± 22	74 ± 20	0.221
Heart rate (beats/min)	99 ± 24	97 ± 27	100 ± 28	97 ± 23	0.456
BUN (mg/dl)	17.0 ± 8.3	18.1 ± 6.6	25.2 ± 11.0	48.9 ± 19.5	<0.0001
Serum creatinine (mg/dl)	0.5 ± 0.1	0.7 ± 0.1	1.1 ± 0.3	2.9 ± 1.5	<0.0001
Hemoglobin (g/dl)	13.1 ± 2.3	12.7 ± 2.2	12.4 ± 2.3	10.1 ± 2.1	<0.0001
BNP (pg/ml)	696 ± 795	694 ± 626	957 ± 965	1456 ± 1335	<0.0001
Echocardiogram					
LVEF (%)	42.7 ± 17.6	42.1 ± 15.4	37.2 ± 15.4	41.2 ± 12.9	0.001
LVDd (mm)	51.4 ± 11.5	52.2 ± 11.7	52.7 ± 10.5	49.9 ± 9.8	0.077
LVDs (mm)	40.9 ± 13.3	41.5 ± 13.3	42.9 ± 11.7	40.0 ± 10.4	0.134
IVS (mm)	10.4 ± 3.1	11.0 ± 3.5	11.0 ± 3.0	11.9 ± 2.9	0.001
PW (mm)	11.3 ± 2.8	11.9 ± 2.6	11.6 ± 2.5	12.5 ± 2.9	0.003
LVMI (g/m^2)	166.5 ± 75.3	178.0 ± 69.8	182.6 ± 73.7	193.4 ± 70.2	0.021

e-GFR, estimated glomerular filtration rate; IHD, ischemic heart disease; DCM, dilated cardiomyopathy; VT, ventricular tachycardia; Vf, ventricular fibrillation; NYHA, New York Heart Association; BP, blood pressure; BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; IVS, interventricular septum; PW, posterior wall; LVMI, left ventricular mass index

Table 2. Baseline characteristics of the study population according to their hemoglobin concentration on admission (*n* = 711)

	Hb ≥12.0 g/dl	Hb <12.0 g/dl	*P* value
n (%)	393 (55.3)	318 (44.7)	
Age (years)	66.2 ± 14.6	72.8 ± 12.8	<0.0001
Male:Female	269:124	131:187	<0.0001
NYHA class	3.5 ± 0.6	3.5 ± 0.6	0.697
Killip class	2.1 ± 0.7	2.2 ± 0.7	0.419
BUN (mg/dl)	21.5 ± 11.3	31.6 ± 19.0	<0.0001
Serum creatinine (mg/dl)	1.0 ± 0.5	1.5 ± 1.3	<0.0001
eGFR (ml/min/1.73 m^2)	65.2 ± 34.9	47.5 ± 30.3	<0.0001
Hemoglobin (g/dl)	14.0 ± 1.4	10.0 ± 1.4	<0.0001
BNP (pg/ml)	759 ± 808	1129 ± 1099	<0.0001
LVEF (%)	38.0 ± 15.8	43.0 ± 14.6	<0.0001

Hb, hemoglobin; NYHA, New York Heart Association; e-GFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction

shown in Table 3. In the acute phase, carperitide (hANP) was frequently used in each group. Catecholamines and nitrates were frequently used in the patients with poor renal function. At the time of hospital discharge, loop diuretics were most frequently administered in all four groups. Angiotensin-converting enzyme inhibitor (ACE-I) and/or angiotensin II receptor blocker (ARB) and spironolactone were used frequently but comparatively less so in Group IV. Nitrates and Ca channel blockers were frequently used in the groups with poor renal function.

Table 3. Therapy of the study population according to their e-GFR ($n = 711$)

Therapy (%) ($n = 711$)	Group I ≥90 ($n = 88$)	Group II 60–89 ($n = 235$)	Group III 30–59 ($n = 263$)	Group IV <30 ($n = 125$)	*P* value
Acute phase					
Carperitide	77.3	72.8	77.9	84.0	0.112
Nitrates	17.0	30.6	30.4	41.6	0.002
Catecholamines	18.2	15.7	28.9	39.2	<0.0001
PDE III inhibitor	8.0	2.6	0.8	3.2	0.004
Respirator	11.4	10.2	18.3	20.0	0.0001
IABP	4.5	3.8	5.3	3.2	0.764
Hemodialysis	2.3	1.7	4.6	33.6	<0.0001
Discharge					
Loop diuretics	90.2	89.5	94.4	85.6	0.243
ACE-I/ARB	82.9	90.4	87.4	68.0	<0.0001
ACE-I	54.9	50.7	45.9	30.9	0.0004
ARB	31.7	44.3	48.9	40.2	0.025
β-Blocker	51.2	53.9	62.3	50.5	0.124
Spironolactone	89.8	75.8	76.6	34.0	<0.0001
Nitrates	25.6	37.4	37.7	49.5	0.001
Calcium channel blocker	11.0	21.9	21.6	51.5	<0.0001
Pimobendan	22.0	13.2	15.6	17.5	0.449
Statin	24.4	26.5	33.8	30.9	0.240
Digitalis	43.9	41.1	41.6	23.7	0.008
Hemodialysis	2.3	1.7	4.6	33.6	<0.0001
Chronic hemodialysis	1.1	0.4	1.9	16.8	<0.0001

e-GFR, estimated glomerular filtration rate; PDE III, phosphodiesterase III; IABP, intra-aortic balloon pumping; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker

Hemodialysis

The patients who underwent any sort of hemodialysis during hospitalization and those who were transferred to chronic hemodialysis after their hospital discharge were compared. In Group I, hemodialysis was performed for 2 out of 88 patients (2.3%), one of whom was transferred to chronic hemodialysis. In Group II, hemodialysis was performed for 4 out of 235 patients (1.7%), 3 of whom died during hospitalization. In Group III, hemodialysis was performed in 12 out of 263 patients (4.6%), 5 of whom died during hospitalization. In Group IV, hemodialysis was performed in 42 out of 125 patients (33.6%), 18 of whom died during hospitalization.

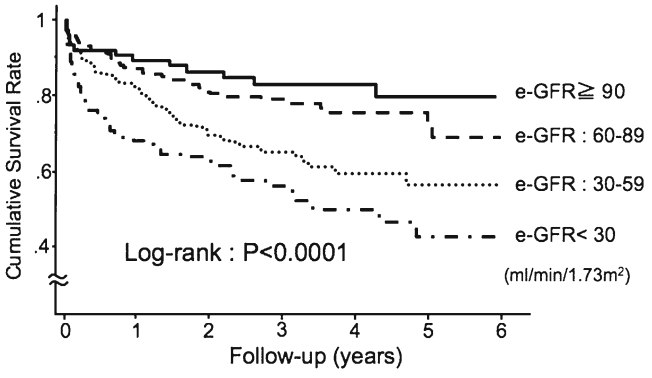

Fig. 1. Cumulative survival rate by baseline estimated glomerular filtration rate (*e-GFR*). Paralleling the deterioration in renal function, the outcome worsened

Outcome

The cumulative survival rates of the four groups are shown in Fig. 1 using Kaplan–Meier curves. The follow-up rate of the study population is 98.5%. Paralleling the deterioration in renal function, the outcome worsened ($P < 0.0001$). The in-hospital death rates were 6 cases (8.0%) (5 cases of heart failure and one case of myocardial infarction) in Group I, 14 cases (6.2%) (10 cases of heart failure, one case of myocardial infarction, one case of sudden death, and 2 cases of other causes) in Group II, 30 cases (11.0%) (20 cases of heart failure, 5 cases of myocardial infarction, 3 cases of sudden death, and 2 cases of other causes) in Group III, and 31 cases (22.5%) (22 cases of heart failure, 5 cases of sudden death, 3 cases of cerebrovascular disease, and one case of other cause) in Group IV. According to the presence or absence of anemia, a poorer outcome was noted in the anemic group ($P < 0.0001$) (Fig. 2).

In Table 4, the results of a multivariable analysis using the Cox proportional hazard model are shown. The following three items were detected as predictors of mortality: (1) an e-GFR <60 ml/min/1.73 m^2 (hazard ratio 1.865, $P = 0.0004$), (2) a serum hemoglobin concentration <12.0 g/dl (hazard ratio 1.622, $P = 0.004$), and (3) a plasma BNP concentration ≥700 pg/ml (hazard ratio 1.466, $P = 0.019$).

In the present study, when the risk of death in CHF patients with neither CKD nor anemia was set at 1.0, the odds ratio of death in CHF patients with CKD alone was 1.84 (95% confidence interval [CI]: 1.13–2.99), and in CHF

Table 4. Multivariate predictor of all-cause mortality by Cox proportional hazard model

Predictor	Category	*P* value	Hazard ratio	95% CI
e-GFR (ml/min/1.73 m^2)	<60 vs ≥60	0.0004	1.865	1.324–2.627
Hemoglobin (g/dl)	<12.0 vs ≥12.0	0.004	1.622	1.168–2.253
BNP (pg/ml)	≥700 vs <700	0.019	1.466	1.066–2.016

Hazard ratio and 95% confidence intervals (CI) were adjusted for age, sex, New York Heart Association functional classification, Killip classification, primary heart diseases, diabetes mellitus, hypertension, hyperlipidemia, and left ventricular ejection fraction. The index of BNP is a central value

CI, confidence interval; BNP, B-type natriuretic peptide; e-GFR, estimated glomerular filtration rate

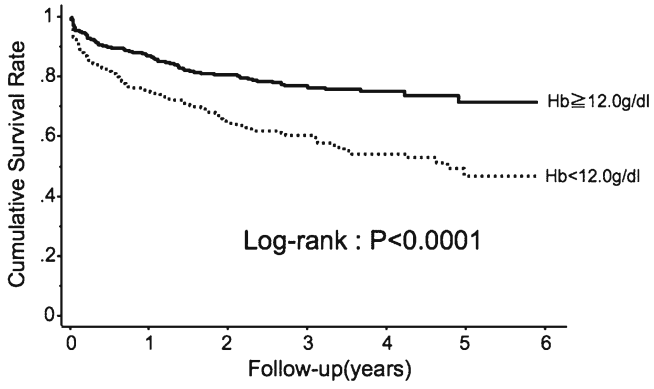

Fig. 2. Cumulative survival rate by baseline hemoglobin (*Hb*) level. Paralleling the deterioration in anemia, the outcome worsened

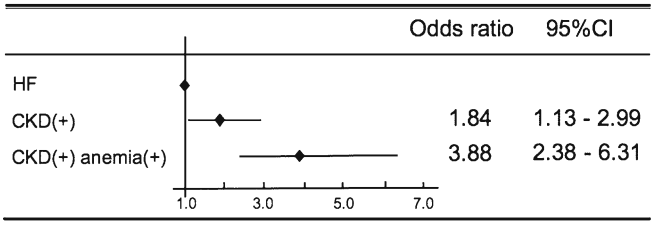

Fig. 3. Result of odds ratio according to chronic kidney disease and anemia. When the risk of death in chronic heart failure (CHF) patients with neither chronic kidney disease (*CKD*) nor anemia was set at 1.0, the odds ratio of death in CHF patients with CKD alone was 1.84 (95% confidence interval [*CI*]: 1.13–2.99), and in CHF patients with both CKD and anemia it was 3.88 (95% CI: 2.38–6.31)

patients with both CKD and anemia it was 3.88 (95% CI: 2.38–6.31) (Fig. 3).

Discussion

Chronic heart failure carries a poor prognosis. In this study, factors that influence the prognosis of CHF were investigated using the Cox hazard model. As a result, e-GFR, anemia, and BNP were identified as prognostic factors. It is well known that the heart and kidneys are closely related and that heart failure and renal failure significantly affect the outcome in patients with CHF.[13–15] However, few studies have been done on the influence of both renal function and anemia in the prognosis of CHF patients in Japan.

In the present study, approximately 60% of all subjects had an e-GFR of less than 60 ml/min/1.73 m^2, indicating the presence of CKD. It was further clarified that the cumulative survival rate in all four e-GFR groups significantly decreased as renal function decreased. Similarly, the report of McAlister et al.[13] suggested that decreased renal function greatly affects the outcome of heart failure. Although LVEF has long been considered a major determinant of outcome in heart failure, in recent years numerous reports have claimed that decreased LVEF does not greatly affect the outcome.[16–18] Various reports have instead demonstrated that renal dysfunction is an important factor determining the outcome of heart failure[6].

In cases of favorable renal function, the effect of ANP and BNP increases urinary volume, and the fluid volume in blood vessels is controllable. However, in cases of declining renal function, CHF symptoms such as lung congestion do not improve, and CHF further deteriorates. In the present study, the prognosis of CHF patients with CKD was not good. Our comparison of the drugs being administered at the time of hospital discharge showed that the rates of use of ACE-I, ARB, and spironolactone were lower in the groups with lower renal function, presumably because these drugs may elevate serum potassium concentration in the presence of decreased renal function. However, in CASE-J,[19] it has been reported that the lower the renal function is, the greater the renoprotective effect of ARB becomes. This suggests that ARB might be effective especially in patients with decreased renal function. It has also been demonstrated in various clinical trials that inhibition of the renin-angiotensin-aldosterone system inhibits progression of renal dysfunction and improves the outcome of heart failure.[20] The low-frequency use of these drugs in the groups with decreased renal function in the present study may have been one of the causes underlying the difference in the outcome.

Anemia is known to decrease the efficiency of systemic oxygen delivery, thereby resulting in increased heart rate, cardiac output, and heart strain.[21] Correction of anemia is therefore useful for the treatment of heart failure because it decreases both the heart rate and myocardial oxygen consumption.[22] Our results showed that the outcome was poorer in the anemic group than that in the group without anemia. Many reports have similarly shown that anemia

worsens the outcome of heart failure.[23–25] In our study, the outcome was worse in patients with serum hemoglobin concentration of less than 12 g/dl. Our results suggest that efforts should be made to maintain a serum hemoglobin concentration of 12 g/dl in patients with heart failure. Subjects with decreased renal function had decreased production of erythropoietin and frequently had renal anemia. Silverberg et al.[26] have reported that active correction of anemia using erythropoietin preparations and intravenous iron can help the heart function to recover while also inhibiting the progress of renal dysfunction. Similar treatments have been reported to help improve the NYHA functional classification while also reducing the number of hospitalizations.[27] In patients with both renal dysfunction and anemia, it is therefore important to consider administering an erythropoietin preparation. Among potential therapies, the use of erythropoietin-stimulating factor agents, usually together with iron to increase red blood cell production, represents a possible though not yet proven option.

It has been reported that if BNP is high in CHF patients, prognosis is poor.[28,29] Although no significant differences were observed among the four groups in our study in regard to the LVEF conventionally used in the clinical stratification of heart failure, the degree of heart failure according to the NYHA functional classification and the Killip classification, as well as the degree of heart failure according to the plasma BNP concentration, were shown to increase in severity as renal function decreased.[30,31] During heart failure, the secretion of ANP and BNP increases in association with atrial enlargement and cardiac chamber dilation. As mentioned earlier, in the patients with good renal function, endogenous ANP and BNP increased the urine volume thereby mitigating heart failure, whereas in the patients with decreased renal function, the urine volume did not increase sufficiently despite the increases in endogenous ANP and BNP, and the amount of circulating blood did not decrease. As a result, heart failure was exacerbated. In the patients with decreased renal function, the plasma BNP concentration therefore further increased and reached significantly high concentration. It has been surmised that the heart strain associated with decreased renal function and anemia likely increased the plasma BNP concentration. This suggests that anemia in patients with heart failure needs to be carefully managed. Decreased renal function and anemia are key factors associated with worsening heart failure. It is thus necessary to keep in mind the potential occurrence of cardio renal anemia syndrome during treatment of CHF.

Limitations

First, we used each patient's baseline weight in calculating their e-GFR. Although some patients were believed to be fluid overloaded on examination by experienced heart failure clinicians, it is possible that the baseline weight of some patients was higher than their true "dry" weights. Second, our cohort was derived from patients referred to only one hospital; as such, it does not represent an unselected population of CHF patients. However, our sample is consecutive and similar demographically and clinically to heart failure cohorts recruited in the community. The diagnoses of heart failure and comorbidities were rigorously confirmed at baseline, LVEF and the serum creatinine level were assessed objectively at baseline, and all clinical and laboratory data were collected prospectively during follow-up.

Conclusion

Chronic heart failure is associated with a poor prognosis. It has traditionally been believed that a decreased LVEF is the key indicator for formulating a prognosis. However, this study clarified that the degrees of renal function and anemia greatly affected the outcome of heart failure. In heart failure, it is not easy to recover heart function. Attempts to directly enhance the force of cardiac contractions increase the frequency of use of inotropic agents. However, these drugs tend to worsen the outcome of patients with heart failure. We therefore believe that when managing heart failure, it is important to improve extracardiac factors whenever possible, for example, by correcting neurohumoral factors and anemia.

References

1. Go AS, Yang J, Ackerson LM, Lepper K, Robbins S, Massie BM, Shlipak MG (2006) Hemoglobin level, chronic kidney disease, and the risks of death and hospitalization in adults with chronic heart failure: the anemia in chronic heart failure: outcomes and resource utilization (ANCHOR) Study. Circulation 113:2713–2723
2. Pocock SJ, Wang D, Pfeffer MA, Yusuf S, McMurray JJ, Swedberg KB, Östergren J, Michelson EL, Pieper KS, Granger CB (2006) Predictors of mortality and morbidity in patients with chronic heart failure. Eur Heart J 27:65–75
3. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Borenstein J (2002) Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. J Am Coll Cardiol 39:1780–1786
4. Silverberg D, Wexler D, Blum M, Wollman Y, Iaina A (2003) The cardio-renal anemia syndrome: does it exist? Nephrol Dial Transplant Suppl 8:7–12
5. Shiba N, Matsuki M, Takahashi J, Tada T, Watanabe J, Shimokawa H (2008) Prognostic importance of chronic kidney disease in Japanese patients with chronic heart failure. Implications of the CHART Study. Circ J 72:173–178
6. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson, PW (2003) Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. Circulation 108:2154–2169
7. Ninomiya T, Kiyohara Y, Kubo M, Tanizaki Y, Doi Y, Okubo K, Wakugawa Y, Hata J, Oishi Y, Shikata K, Yonemoto K, Hirakata H, Iida M (2005) Chronic kidney disease and cardiovascular disease in a general Japanese population: the Hisayama Study. Kidney Int 68:228–236
8. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY (2004) Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 351:1296–1305

9. Imai E, Horio M, Nitta K, Yamagata K, Iseki K, Tsukamoto Y, Ito S, Makino H, Hishida A, Matsuo S (2007) Modification of the modification of diet in renal disease (MDRD) study equation for Japan. Am J Kidney Dis 50:927–937
10. Imai E, Horio M, Nitta K, Yamagata K, Iseki K, Hara S, Ura N, Kiyohara Y, Hirakata H, Watanabe T, Moriyama T, Ando Y, Inaguma D, Narita I, Iso H, Wakai K, Yasuda Y, Tsukamoto Y, Ito S, Makino H, Hishida A, Matsuo S (2007) Estimation of glomerular filtration rate by the MDRD study equation modified for Japanese patients with chronic kidney disease. Clin Exp Nephrol 11:41–50
11. Imai E, Horio M, Iseki K, Yamagata K, Watanabe T, Hara S, Ura N, Kiyohara Y, Hirakata H, Moriyama T, Ando Y, Nitta K, Inaguma D, Narita I, Iso H, Wakai K, Yasuda Y, Tsukamoto Y, Ito S, Makino H, Hishida A, Matsuo S (2007) Prevalence of chronic kidney disease (CKD) in the Japanese general population predicted by the MDRD equation modified by a Japanese coefficient. Clin Exp Nephrol 11:156–163
12. McKee PA, Castelli WP, McNamara PM, Kannel WB (1971) The natural history of congestive heart failure: the Framingham study. N Engl J Med 285:1441–1446
13. McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW (2004) Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. Circulation 109: 1004–1009
14. Pitsavos C, Kourlaba G, Panagiotakos DB, Kogias Y, Mantas Y, Chrysohoou C, Stefanadis C (2007) Association of creatinine clearance and in-hospital mortality in patients with acute coronary syndromes: the GREECS study. Circ J 71:9–14
15. Nakamura K, Okamura T, Hayakawa T, Kadowaki T, Kita Y, Ohnishi H, Saitoh S, Sakata K, Okayama A, Ueshima H; The NIPPON DATA90 research group (2006) Chronic kidney disease is a risk factor for cardiovascular death in a community-based population in Japan: NIPPON DATA90. Circ J 70:954–959
16. Senni M, Redfield MM (2001) Heart failure with preserved systolic function: a different natural history? J Am Coll Cardiol 38: 1277–1282
17. Tsuchihashi M, Tsutsui H, Kodama K, Kasagi F, Takeshita A (2000) Clinical characteristics and prognosis of hospitalized patients with congestive heart failure, a study in Fukuoka, Japan. Circ J 64:953–959
18. Tsutsui H, Tsuchihashi M, Takeshita A (2001) Mortality and readmission of hospitalized patients with congestive heart failure and preserved versus depressed systolic function. Am J Cardiol 88:530–533
19. Ogihara T, Nakao K, Fukui T, Fukiyama K, Ueshima K, Oba K, Sato T, Saruta T; for the Candesartan Antihypertensive Survival Evaluation in Japan trial group (2008) Effects of candesartan compared with amlodipine in hypertensive patients trial with high cardiovascular risks: candesartan antihypertensive survival evaluation in Japan trial. Hypertension 51:393–398
20. Casas JP, Chua W, Loukogeorgakis S, Vallance P, Smeeth L, Hingorani AD, MacAllister RJ (2005) Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. Lancet 366: 2026–2033
21. Felker GM, Gattis WA, Leimberger JD, Adams KF, Cuffe MS, Gheorghiade M, O'Connor CM (2003) Usefulness of anemia as a predictor of death and rehospitalization in patients with decompensated heart failure. Am J Cardiol 92:625–628
22. Felker GM, Adams KF Jr, Gattis WA, O'Connor CM (2004) Anemia as a risk factor and therapeutic target in heart failure. J Am Coll Cardiol 44:959–966
23. Silverberg DS, Wexler D, Iaina A (2004) The role of anemia in the progression of congestive heart failure. Is there a place for erythropoietin and intravenous iron? J Nephrol 17:749–761
24. Silverberg DS, Wexler D, Blum B, Iaina A (2003) Anemia in chronic kidney disease and congestive heart failure. Blood Purif 21:124–130
25. Coats AJ (2004) Anaemia and heart failure. Heart 90:977–979
26. Silverberg DS, Wexler D, Sheps D, Blum M, Keren G, Baruch R, Schwartz D, Yachnin T, Steinbruch S, Shapira I, Laniado S, Iaina A (2001) The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. J Am Coll Cardiol 37:1775–1780
27. Silverberg DS, Wexler D, Blum M, Keren G, Sheps D, Leibovitch E, Brosh D, Laniado S, Schwartz D, Yachnin T, Shapira I, Gavish D, Baruch R, Koifman B, Kaplan C, Steinbruch S, Iaina A (2000) The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. J Am Coll Cardiol 35:1737–1744
28. Berger R, Huelsman M, Strecker K, Bojic A, Moser P, Stanek B, Pacher R (2002) B-type natriuretic peptide predicts sudden death in patients with chronic heart failure. Circulation 105:2392–2397
29. Maeda K, MD, Tsutamoto T, Wada A, Mabuchi N, Hayashi M, Tsutsui T, Ohnishi M, Sawaki M, Fujii M, Matsumoto T, Kinoshita M (2000) High levels of plasma brain natriuretic peptide and interleukin-6 after optimized treatment for heart failure are independent risk factors for morbidity and mortality in patients with congestive heart failure. J Am Coll Cardiol 36:1587–1593
30. Ueno H, Nakayama M, Kojima S, Kusuhara K, Nagayoshi Y, Yamamuro M, Nishijima T, Usuku H, Kaikita K, Sumida H, Yamabe H, Sugiyama S, Yoshimura M, Ogawa H (2008) The synergistic combined effect of anemia with high plasma levels of B-type natriuretic peptide significantly predicts an enhanced risk for major adverse cardiac events. Heart Vessels 23:243–248
31. Karavidas A, Lazaros G, Matsakas E, Farmakis D, Parissis J, Paraskevaidis IA, Michailidis C, Avramidis D, Zacharoulis A, Arapi S, Kaoukis A, Zacharoulis A (2008) Clinical value of B-type natriuretic peptide for the assessment of left ventricular filling pressures in patients with systolic heart failure and inconclusive tissue Doppler indexes. Heart Vessels 23:181–186