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Original Paper

Impact of Chronic Kidney Disease and Anemia on Physical Function in Patients with Chronic Heart Failure

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Key Words
Chronic kidney disease · Anemia · Physical function · Heart failure

Abstract
Objective: The aim of this study was to confirm the effects of chronic kidney disease (CKD) and anemia on physical function and to clarify whether the interaction between CKD and anemia has an additive effect. ***Design:*** Eligible subjects were chronic heart failure (HF) patients who were discharged between March 2007 and August 2009. A total of 102 chronic HF patients (33% females; mean age: 68 ± 14 years) were enrolled in the present study. CKD was defined as an estimated glomerular filtration rate of <60 ml/min/1.73 m^2, and anemia was defined as a hemoglobin level of <12 g/dl in males and of <11 g/dl in females. The Short Physical Performance Battery (SPPB) was used to assess physical function. ***Results:*** The adjusted mean SPPB score was lower in patients with both CKD and anemia than in those with neither of the diseases or with either disease alone ($p < 0.05$). ***Conclusion:*** This study found that CKD and anemia are independently associated with reduced physical function.

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Introduction

Chronic kidney disease (CKD) and anemia are common comorbidities in patients with heart failure (HF) [1]. Several studies have shown that patients with CKD and/or anemia are more likely to have physical dysfunction and exercise intolerance [2–6]. Odden et al. [2] suggested that the impact of CKD and anemia on physical function is complicated because of their symptoms and overlap with aging and other common comorbidities such as malnutrition and HF. Other studies have found an association between anemia and physical function in patients with chronic HF or severe CKD [7, 8].

Most of the previous studies evaluated exercise capacity using the symptom-limited cardiopulmonary exercise test as a physical function test [7, 8]. However, the number of patients who cannot undergo this test is increasing because of comorbidities and/or age. Recently, there has been wide use of physical performance tests in community-dwelling elderly patients with chronic diseases such as renal disease, cancer and HF. In particular, the Short Physical Performance Battery (SPPB) was used for elderly patients with HF [2–4]. The SPPB is an easy test for evaluating physical function even in advanced-age or frail patients with comorbidities because there are no special modalities and special skills necessary to assess the SPPB. Moreover, the SPPB score has been widely used as a predictor of disability and readmission for patients with HF [9, 10]. The aim of this study was to confirm the effects of CKD and anemia on physical function, and to clarify whether the interaction between CKD and anemia has an additive effect.

Subjects and Methods

Patients with HF who underwent the SPPB at discharge between March 2007 and August 2009 were eligible for the study. A total of 102 HF patients (33% females; mean age: 68 ± 14 years) were enrolled in the present study. Patients on hemodialysis were excluded. All participants provided their written informed consent, and the protocol was approved by the institutional review boards.

Definitions of CKD and Anemia

CKD was defined as an estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m^2, which is defined as CKD stage 3 as suggested by the National Kidney Foundation classification [11]. The eGFR was calculated using the following formula: 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ (× 0.739 for females), which was recommended by the Japanese Society of Nephrology [12]. Hemoglobin (Hb) levels were measured in the hematology laboratory, and anemia was defined as an Hb level of <12 g/dl for males or <11 g/dl for females [13].

SPPB Score

Physical function was assessed by the SPPB at discharge. SPPB scores ranged from 0 to 12, with a higher score representing better physical function. The SPPB consists of the standing balance, gait speed and chair stand tests, as previously described in detail [14].

In the standing balance test, the patients were asked to attempt to maintain their feet in side-by-side, semitandem (heel of one foot beside the big toe of the other foot) and tandem (heel of one foot directly in front of the other foot) standing positions for 10 s each. Scoring was as follows: '0' if a patient was unable to do or hold the side-by-side standing position for 10 s; '1' if a patient could hold the side-by-side standing position for 10 s but was unable to hold the semitandem position for 10 s; '2' if a patient could hold the semitandem position for 10 s but was unable to hold the full tandem position for >3 s; '3' if a patient could stand in the full tandem position for 3–9.99 s, and '4' if a patient could stand in the full tandem position for 10 s.

In the gait speed test, a 4-meter walk at a comfortable speed was timed and scored according to quartiles for the length of time required. The faster time of 2 walks was used for scoring as follows: 0 = unable to do the test; 1 = 8.70 s; 2 = 6.20–8.70 s; 3 = 4.82–6.20 s, and 4 = ≤4.82 s.

Table 1. Comparison of baseline clinical characteristics of chronic HF patients with and those without CKD

	CKD (n = 70)	No CKD (n = 32)	p value
Age, years	71±13	61±14	<0.01
Male/female, n	43/27	25/7	0.07
BMI	22.4±3.7	21.5±3	0.24
Etiology, n			0.11
Ischemic	24	10	
Valvular	12	7	
Myopathy	14	13	
Hypertensive	5	0	
Arrhythmia	5	1	
Others	10	1	
Comorbidity, %			
Diabetes mellitus	40	34	0.37
Hypertension	61	28	<0.01
Dyslipidemia	39	34	0.42
LVEF, %	38±14.0	36±14	0.41
Left ventricular diastolic dimension, mm	54±10.0	56±11	0.55
Left ventricular systolic dimension, mm	48±12.0	46±12	0.74
Left atrial dimension, mm	44±9.0	43±10	0.53
E/E′	24.3±13.0	21.7±10.7	0.32
Hb, g/dl	12.3±2.2	13.1±1.9	0.07
Anemia, %	49	25	0.03
Serum creatinine, mg/dl	1.2±0.4	0.8±0.1	<0.01
eGFR, ml/min/1.73 m^2	44.5±12.8	77.8±13.1	<0.01
Albumin, mg/dl	3.4±0.4	3.6±0.5	0.62
Brain natriuretic peptide, pg/dl	898±778.0	650±765	0.18

Values denote means ± SD unless specified otherwise. E/E′ = Ratio of mitral early diastolic peak flow velocity (E) to tissue Doppler early mitral annular diastolic velocity (E′).

In the chair stand test, the patients were asked to fold their arms across their chests and stand up from a sitting position once. If successfully rising from the chair, the patients were asked to stand up and sit down 5 times, as quickly as possible. Quartiles for the length of time required for this test were used for scoring as follows: 0 = unable to do the test or required >60 s; 1 = 16.7 s; 2 = 13.70–16.69 s; 3 = 11.20–13.69 s, and 4 = ≤11.19 s.

The scores for all three tests were summed up to give the total SPPB score.

Statistical Analyses

This study evaluated the differences in baseline clinical characteristics between patients with and those without CKD. Similarly, this study also examined the differences in baseline clinical characteristics between patients with and those without anemia. Two groups were compared using the unpaired t test for continuous variables and the χ^2 test for dichotomous variables.

To investigate the level-dependent effect of eGFR and Hb on physical function, this study stratified patients by eGFR (stage 4: <30; stage 3: 30 to <60; stage 2: 60 to <90; stage 1: ≥90 ml/min/1.73 m^2) and by Hb level (<10; 10 to <11; 11 to <12; 12 to <13, and ≥13 g/dl).

Analysis of variance with Bonferroni post hoc testing was employed to evaluate physical function across the Hb and eGFR subgroups. Linear regression analysis was used to determine the independent association of the primary predictors with each outcome after adjustment for the clinical characteristics. Stepwise regression was used with a criterion of $p < 0.05$ for inclusion. Models that evaluated CKD as the primary predictor were adjusted for anemia, and models evaluating anemia as the primary predictor were adjusted for CKD. The adjusted mean physical function was calculated on the basis of the parameter estimates from the multivariate linear regression models. This study evaluated the differences in adjusted mean physical function between patients with and those without CKD or anemia, as well as between

Table 2. Comparison of baseline clinical characteristics of chronic HF patients with and those without anemia

	Anemia (n = 42)	No Anemia (n = 60)	p value
Age, years	72±15	65±12	<0.01
Male/female, n	26/16	42/18	0.40
BMI	21.5±5.3	22.6±3.6	0.13
Etiology, n			
Ischemic	15	19	0.08
Valvular	12	7	
Myopathy	6	21	
Hypertensive	1	4	
Arrhythmia	3	6	
Others	6	2	
Comorbidity, %			
Diabetes mellitus	43	35	0.53
Hypertension	50	52	1.00
Dyslipidemia	38	37	1.00
LVEF, %	42±14	34±14	<0.01
Left ventricular diastolic dimension, mm	52±10	56±10	0.05
Left ventricular systolic dimension, mm	41±11	47±12	<0.01
Left atrial dimension, mm	45±11	43±8	0.56
E/E′	25.5±13.0	22.1±12.0	0.18
Hb, g/dl	10.5±1.0	14.0±1.4	0.01
Serum creatinine, mg/dl	1.2±0.5	1.0±0.4	0.03
eGFR, ml/min/1.73 m^2	49.5±20.3	58.3±19.3	0.03
CKD, %	79	62	0.05
Albumin, mg/dl	3.4±0.4	3.6±0.5	0.56
Brain natriuretic peptide, pg/dl	846±734.0	650±812	0.79

Values denote means ± SD unless specified otherwise. E/E′ = Ratio of mitral early diastolic peak flow velocity (E) to tissue Doppler early mitral annular diastolic velocity (E').

patients with neither condition, those with either condition and those with both conditions. This study also aimed to examine the effects of left ventricular systolic dysfunction on physical function in HF patients. Therefore, we analyzed the difference in SPPB scores between HF patients with preserved ejection fraction (HFpEF; left ventricular ejection fraction, LVEF, >40%) and HF patients with reduced ejection fraction (HFrEF; LVEF ≤40%). All statistical analyses were performed using the statistical software SPSS version 19.0 (Chicago, Ill., USA).

Results

Clinical Characteristics

Of the 102 eligible patients, 70 (69%) had CKD and 42 (41%) had anemia. The age, rate of hypertension and rate of anemia were significantly higher in patients with CKD than in those without (table 1). The age, LVEF and rate of CKD were significantly higher in patients with anemia than in those without. Moreover, the left ventricular diastolic and systolic diameters were significantly lower in patients with anemia than in those without (table 2).

Physical Function

In the univariate analyses, both CKD (SPPB score: 11.6 ± 0.7 without vs. 10.1 ± 2.3 with CKD; $p < 0.01$) and anemia (SPPB score: 11.3 ± 1.3 without vs. 9.3 ± 2.6 with anemia; $p < 0.01$) were significantly associated with SPPB score. Figure 1 indicates the effects of Hb and eGFR

Table 3. Comparison of adjusted mean SPPB scores

	Patients, n	Adjusted mean SPPB score	95% CI	p value
Without CKD	32	11.6	10.94–12.28	<0.01
With CKD	70	9.8	9.31–10.22	
Without anemia	42	11.2	10.72–11.67	<0.01
With anemia	60	9.2	8.61–9.73	
Neither CKD nor anemia	30	11.5	10.82–12.14	
Either CKD or anemia	40	11.0[a]	10.48–11.52	
Both CKD and anemia	32	8.59[a, b]	8.01–9.18	

[a] $p < 0.05$ vs. neither CKD nor anemia; [b] $p < 0.05$ vs. either CKD or anemia.

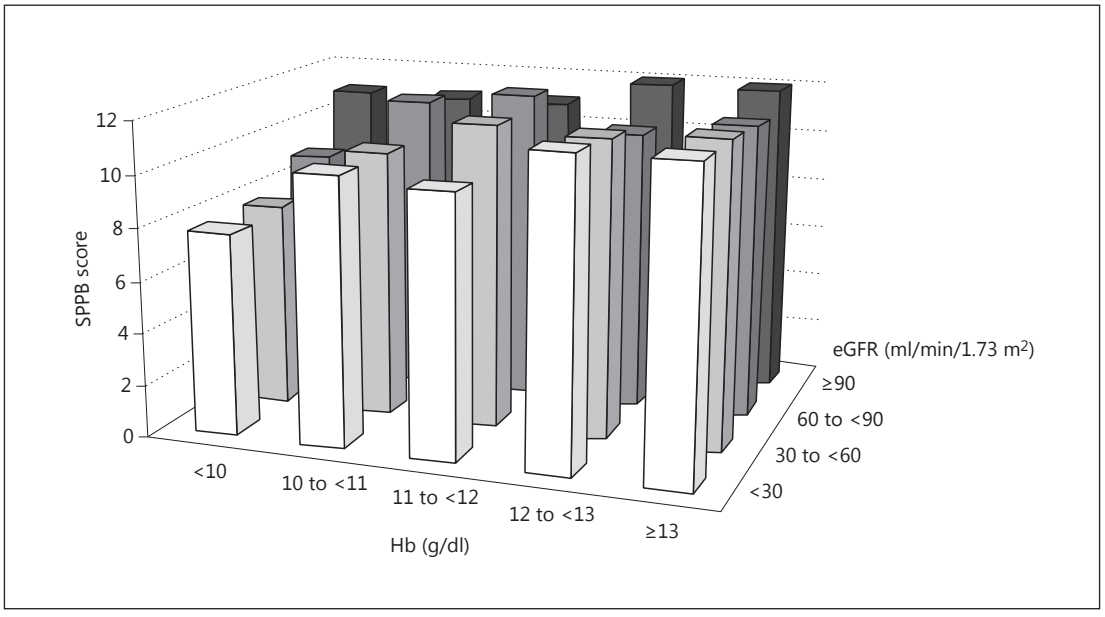

Fig. 1. Unadjusted association of eGFR and Hb level with SPPB score.

on SPPB score, with the category of Hb on the x-axis, the category of eGFR on the y-axis and the mean SPPB scores on the z-axis. There were no significant differences between the subcategories.

Multivariate adjustment clearly showed additive effects of the interaction between CKD and anemia on the SPPB score (table 3). The adjusted mean SPPB score was significantly lower in patients with both CKD and anemia than in those with neither CKD nor anemia or in those with either CKD or anemia.

There was no significant difference in SPPB scores between the HFpEF and HFrEF groups (10.4 ± 2.1 vs. 10.7 ± 2.0; $p = 0.493$). On the other hand, both the HFpEF and HFrEF groups showed that the SPPB scores in patients with both CKD and anemia were significantly lower than those in the group with neither CKD nor anemia and in the group with either CKD or anemia ($p < 0.05$; tables 4, 5).

Table 4. Comparison of adjusted mean SPPB scores for HFrEF patients

	HFrEF patients (LVEF ≤40%; n = 58)			
	n	adjusted mean	95% CI	p value
Without CKD	21	11.3	0.341–2.734	0.123
With CKD	37	10.1		
Without anemia	21	11.2	0.501–2.971	<0.01
With anemia	37	9.5		
Neither CKD nor anemia	23	11.1	9.139–12.725	
Either CKD or anemia	22	11.0	10.222–11.975	
Both CKD and anemia	13	9.6[a, b]	8.192–10.932	

[a] $p < 0.05$ vs. neither CKD nor anemia; [b] $p < 0.05$ vs. either CKD or anemia.

Table 5. Comparison of adjusted mean SPPB scores for HFpEF patients

	HFpEF patients (LVEF >40%; n = 44)			
	n	adjusted mean	95% CI	p value
Without CKD	11	11.2	0.382–1.906	0.186
With CKD	33	10.4		
Without anemia	21	11.1	0.237–2.582	0.101
With anemia	23	9.9		
Neither CKD nor anemia	7	11.8	10.409–13.187	
Either CKD or anemia	18	10.9	10.035–11.939	
Both CKD and anemia	19	9.1[a, b]	8.061–10.154	

[a] $p < 0.05$ vs. neither CKD nor anemia; [b] $p < 0.05$ vs. either CKD or anemia.

Discussion

The present study showed that both CKD and anemia were independently related to physical function, and the combined presence of CKD and anemia in chronic HF patients was associated with additive deterioration in physical function compared with the presence of CKD or anemia alone.

Effects of CKD and Anemia on Physical Function

The causes of low physical function in patients with CKD have not been clarified. Previous studies have found an association between malnutrition and low physical function in patients with CKD [7, 8, 15]; however, we found no association between CKD and serum albumin. Our study subjects received any cardiac rehabilitation during their hospital stays and underwent the physical performance test at discharge; therefore, our study population did not include patients who could not undergo any cardiac rehabilitation due to hemodynamic instability or patients who transferred to another institute such as a rehabilitation hospital or nursing home to receive hospital care or rehabilitation. Therefore, we thought the reason for the different results for nutritional status in patients with and those without CKD was a selection bias.

Activated inflammatory responses have been demonstrated in patients with CKD [16]; our study did not collect inflammatory biomarkers. These inflammatory responses were proposed to explain an association of CKD with skeletal muscle abnormalities and lower physical function [17, 18]. Those reports suggested that inflammation caused a loss of protein stores and muscle wasting because the serum levels of proinflammatory cytokines might be caused to increase by developed CKD or the presence of comorbidity.

Recently, there have been many studies examining the relationship between anemia and low physical function in HF patients [19]. Additionally, efforts to improve Hb levels using erythropoiesis-stimulating agents (ESA) and oral or intravenous (IV) iron, and even IV iron without ESA, have shown positive effects on hospitalization, New York Heart Association functional class, cardiac and renal function, quality of life and exercise capacity [20]. Therefore, we thought that HF patients limited in their activities of daily living due to severe anemia were better treated with EPO, ESA and oral or IV iron, or even IV iron without ESA, but most studies are poorly powered and therefore of limited validity, and the aim of Hb correction is also not well defined. Anemia has been suggested to be a marker of loss of lean body mass, presence of comorbidity and elevated inhibitory cytokine levels [21, 22]. Anemia and elevated inhibitory cytokine levels are determinants of skeletal muscle abnormality which might lead to physical dysfunction [22].

The present study showed that the relationship between anemia and low physical function was independent of CKD. In addition, it demonstrated an additive effect of CKD and anemia on physical function in HF patients in general as well as in the HFpEF and HFrEF subgroups. After adjusting for other covariates, HF patients – as well as patients from either the HFpEF or HFrEF subgroup – with both CKD and anemia had lower physical function than those with neither CKD nor anemia or those with either CKD or anemia. Low physical function in patients with both CKD and anemia was explained by abnormal energy metabolism, increased catabolism and malnutrition [23].

Cardiorenal Anemia Syndrome

Silverberg et al. [24–28] first proposed the 'cardiorenal anemia syndrome', a vicious circle that appears to be present in HF patients, in which HF itself causes both anemia and CKD. CKD increases the severity of anemia, and anemia and CKD can further worsen HF, which again aggravates anemia and CKD, and so on.

In the present study, HF patients with CKD and anemia had lower physical function, confirming previous findings. However, we did not evaluate exercise capacity and daily physical activity, which are counted as factors of physical function. HF patients with both CKD and anemia are at higher risk of physical functional deterioration. Therefore, a more detailed clinical research protocol is needed to explore effective interventions for preventing physical functional deterioration in HF patients.

Limitations of the Study

In our study, we did not find significant differences in SPPB scores (fig. 1), although the adjusted mean SPPB scores showed significant differences between the groups with neither CKD nor anemia, with either CKD or anemia and with both CKD and anemia. We suspect that this divergence was caused by our small sample size. As only 102 patients were included, the subgroups consisted of only a few patients each. Therefore, we assume that the small sample size may have caused type II errors (false negatives). We have to ascertain the effects of the subcategories of CKD and anemia on SPPB scores in the future.

Conclusion

In summary, this study found that CKD and anemia were independently associated with reduced physical function in HF patients. Further studies are needed to determine the cause of this lowered physical function and to explore whether there are effective interventions for HF patients with CKD and anemia.

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