

Effect of Cardiac Rehabilitation on Glomerular Filtration Rate Using Serum Cystatin C Concentration in Patients With Cardiovascular Disease and Renal Dysfunction

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Purpose: Among patients with chronic kidney disease (CKD), little is known about whether the effect of cardiac rehabilitation (CR) on renal function differs across baseline estimated glomerular filtration rate using the serum concentration of cystatin C (eGFRcys). The aim of this study was to evaluate the effect of CR on renal function in patients with CKD.

Methods: We performed a retrospective cohort study of patients with CKD ($15 \leq \text{eGFRcys} < 60 \text{ mL/min/1.73 m}^2$) who participated in our CR program for cardiovascular disease. First, the patients were divided into three groups according to the baseline severity of the eGFRcys: G3a, G3b, and G4 groups. We compared the eGFRcys before and after the CR in each group. Second, to determine the association of baseline eGFRcys with the effect of CR, we fitted a linear regression model using the percent change in the eGFRcys (% $\Delta\text{eGFRcys}$) as an outcome.

Results: Of the 203 patients, 122 were in G3a, 60 were in G3b, and 21 were in G4 groups. The mean improvement of eGFRcys in each group was 1.3, 3.1, and 4.8 mL/min/1.73 m², respectively. The % $\Delta\text{eGFRcys}$ was larger among patients with lower baseline eGFRcys (0.47% greater improvement of % $\Delta\text{eGFRcys}$ /one lower baseline eGFRcys; 95% CI, 0.23-0.72%). This association remained significant after adjustment for potential confounders (0.63% greater improvement of % $\Delta\text{eGFRcys}$ /one lower baseline eGFRcys; 95% CI, 0.35-0.91%).

Conclusions: The effect of CR on renal function was greater in patients with worse renal dysfunction measured by eGFRcys. A CR program could be useful for patients with severe renal dysfunction and it might have a beneficial effect on their renal function.

Key Words: cardiac rehabilitation • chronic kidney disease • cystatin C • severe renal function

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The authors declare no conflicts of interest.

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Cardiac rehabilitation (CR),¹ including an appropriate level of exercise training, has been proved to improve coronary risk factors² and exercise capacity³ in patients with chronic kidney disease (CKD). However, the effects of CR on renal function in patients with CKD remain controversial. It is important to evaluate the effect on renal function in CKD patients with cardiovascular disease (CVD) because a previous study showed that CKD patients with higher renal dysfunction severity had higher risks of death, CVD events, and hospitalization than those with lower renal dysfunction.⁴ Some previous studies have suggested the potential benefit of exercise training on renal function.^{3,5,6} However, the results are not definitive and their findings may be affected by the use of serum creatinine to evaluate renal function,⁷ as resistance training can lead to elevated serum creatinine level.⁸⁻¹⁰

Recent studies have recommended the use of serum concentration of cystatin C (Scys) to evaluate renal function in patients with CKD. Since Scys is not affected by muscle mass, Scys can be an optimal marker of renal function in patients who undergo CR.¹¹⁻¹³ Recently, some studies using estimated glomerular filtration rate using the serum concentration of cystatin C (eGFRcys) evaluated the effect of CR on renal function of CVD patients, and they showed a favorable effect of CR on renal function.^{14,15} However, for patients with CVD, little is known about whether CR improves renal function, as measured by Scys, particularly in patients with severe CKD. A previous small observational study using Scys (n = 41) demonstrated that high physical activity may suppress renal function decline in patients after acute myocardial infarction.¹⁶ Another pilot randomized controlled trial reported a 1-yr exercise intervention on the progression of renal function was inconclusive.¹⁷ Even assuming the potential benefit of CR on renal function, it remains unclear whether CR has a beneficial effect on patients with severe renal dysfunction (eg, patients who are eligible for dialysis), and whether the effect differs across the baseline CKD severity. We hypothesized that CR would have a beneficial effect on glomerular filtration rate (GFR) measured by Scys in patients with CKD, even in those with severe renal dysfunction.

To address the knowledge gap in the literature, we aimed to evaluate the effect of CR on renal function in patients with CKD, particularly in those with severe CKD. In addition, we investigated the association of the baseline renal function with the degree of CR effects on the renal function using Scys.

METHODS

This was a retrospective cohort study using data of patients who were admitted to the Tokai University Hachioji Hospital

for the evaluation and treatment of CVD and participated in the 3-mo CR program from April 2014 to October 2018. This study was approved by the research ethics committee of Tokai University (20R-377). Among patients who completed the CR program, we further identified patients with CKD ($15 \leq \text{eGFR}_{\text{cys}} < 60 \text{ mL/min/1.73 m}^2$). To test our hypothesis of the beneficial effect of CR on GFR measured by Scys in patients with CKD, we enrolled pre-dialysis CKD patients with CVD. In this study, CKD was defined as $15 \leq \text{eGFR}_{\text{cys}} < 60 \text{ mL/min/1.73 m}^2$.¹⁸ The exclusion criterion in this study was if the patient was being dialyzed. All data were abstracted from medical records in the hospital. Patient medical records were retrospectively reviewed, and the investigational items were collected, including age, sex, body mass index, underlying diseases for CR (ischemic heart disease, nonischemic heart failure, post-cardiac surgery, and aortic disease), chronic obstructive pulmonary disease, coronary risk factors (smoking, hypertension, diabetes mellitus, dyslipidemia, and family history), current medications (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β -blockers, calcium channel blockers, diuretics, and antihyperlipidemic drugs), blood examinations (triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, glycosylated hemoglobin, brain natriuretic peptide, hemoglobin, serum creatinine concentration [Scr], estimated glomerular filtration rate based on Scr [eGFR_{cr}], Scys, and eGFR_{cys}), echocardiographic findings (left atrial diameter, left ventricular end-diastolic diameter, and left ventricular ejection fraction), cardiopulmonary exercise testing at the beginning of the CR (heart rate and blood pressure at pre-exercise, heart rate and blood pressure at peak exercise, peak oxygen uptake [$\dot{V}O_{2\text{peak}}$], peak work rate, the slope of the relationship between the minute ventilation and carbon dioxide output until the respiratory compensation point, and the ratio of the carbon dioxide output and $\dot{V}O_2$ at peak exercise), and amount of exercise during the CR at the outpatient visit.

CARDIAC REHABILITATION PROGRAM

The CR program was a comprehensive program including exercise therapy, nutritional guidance, medication education, and attending an educational class of cardiopulmonary resuscitation according to the *Guidelines for Rehabilitation in Patients With Cardiovascular Disease*.¹⁹ For the exercise therapy, the physiotherapists guided the patients to undergo the most appropriate aerobic exercises, including walking or bicycle ergometer exercise for 20 min and resistance training for 20 min/session at the outpatient department. The intensity of the aerobic exercise is determined individually at the heart rate during the anaerobic threshold level obtained by a symptom-limited cardiopulmonary exercise test or at a level from 11-13 of the 6-20-scale training rating (original Borg Rating of Perceived Exertion Scale^{20,21}). Patients were also prompted to do aerobic exercise at the prescribed heart rate or resistance training for 30-60 min, 3-7 times/wk at home.

At the beginning and end of our 3-mo CR program, a symptom-limited exercise test was performed on a bicycle ergometer Corival (Lode Co) with a cardiopulmonary gas exchange system Aero Monitor AE-310S (Minato Medical Science Co). The blood pressure was measured every minute and the 12-lead electrocardiogram was continuously monitored. The exercise protocol consisted of first a 4-min resting period, followed by a 3-min 10- or 20-W warm-up that was increased by 10 or 20 W/min until one of the following events occurred: (1) the patient dictated the test stop, (2) a $\dot{V}O_2$ plateau, (3) an ischemic change in the electrocardiogram or symptoms, (4) an excessive rise or fall in the

blood pressure, or (5) an occurrence of fatal arrhythmias (sustained ventricular tachycardia, multifocal premature ventricular contractions, triplets of premature ventricular contractions, supraventricular tachycardia, heart block, or bradyarrhythmias).²² We measured the anaerobic threshold for an appropriate prescription of the exercise therapy and $\dot{V}O_{2\text{peak}}$ as an index parameter of their exercise capacity. The anaerobic threshold was determined with the V-slope method.²³ The slope of the relationship between the minute ventilation and carbon dioxide output until the respiratory compensation point was determined as an index parameter of respiratory inefficiency. The ratio of carbon dioxide output and $\dot{V}O_2$ at peak exercise was used as a measure of the patient effort during the testing, and a value >1.05 was considered to be a sufficient load on the test.

RENAL FUNCTION MEASURES

Renal function was measured by serum cystatin C (Scys, mg/L) and serum creatinine (Scr, mg/dL) levels before (baseline) and after the CR program. In this study, eGFR_{cys} and eGFR_{cr} (both, mL/min/1.73 m²) were calculated using the following equations for Japanese population^{24,25}:

$$\begin{aligned} \text{eGFR}_{\text{cys}} \text{ in male} &= (104 \times \text{Scys}^{-1.019} \times 0.996^{\text{age [y.o.]}}) - 8 \\ \text{eGFR}_{\text{cys}} \text{ in female} &= (104 \times \text{Scys}^{-1.019} \times 0.996^{\text{age [y.o.]}} \\ &\quad \times 0.929) - 8 \\ \text{eGFR}_{\text{cr}} \text{ in male} &= 194 \times \text{Scr}^{-1.094} \times \text{age [y.o.]}^{-0.287} \\ \text{eGFR}_{\text{cr}} \text{ in female} &= 194 \times \text{Scr}^{-1.094} \times \text{age [y.o.]}^{-0.287} \\ &\quad (\times 0.739) \end{aligned}$$

We categorized patients with CKD severity into three groups based on eGFR_{cys} according to the 2012 Clinical Practice Guidelines^{18,26}: CKD G3a group (mild to moderate renal dysfunction; $45 \leq \text{eGFR}_{\text{cys}} < 60 \text{ mL/min/1.73 m}^2$), CKD G3b group (moderate to severe renal dysfunction; $30 \leq \text{eGFR}_{\text{cys}} < 45 \text{ mL/min/1.73 m}^2$), and CKD G4 group (severe renal dysfunction; $15 \leq \text{eGFR}_{\text{cys}} < 30 \text{ mL/min/1.73 m}^2$).

STATISTICAL ANALYSIS

Data are presented as mean \pm SD or n (%). Analyses of variance tests were used for comparisons of continuous variables, χ^2 tests for comparisons of categorical variables between three groups, and paired *t* tests for comparisons of the continuous variables before and after the CR.

To determine the association of baseline eGFR_{cys} and the effect of CR, we fitted an unadjusted linear regression model using $\% \Delta \text{eGFR}_{\text{cys}}$ as an outcome, which was defined as follows: $\% \Delta \text{eGFR}_{\text{cys}} = (\text{eGFR}_{\text{cys}} \text{ after the CR} - \text{baseline eGFR}_{\text{cys}}) / \text{baseline eGFR}_{\text{cys}}$. Then, we fitted a linear regression model adjusting for age, sex, patient comorbidities (ischemic heart disease, nonischemic heart failure, hypertension, diabetes mellitus, and dyslipidemia), current medication (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, calcium channel blockers, β -blockers, and diuretics), brain natriuretic peptide, hemoglobin, and session attendance.

All tests were assessed at a level of significance of a *P* value of $< .05$. Statistical analyses were performed using SPSS, version 16.0 (IBM).

RESULTS

Baseline characteristics of study participants are provided in Table 1. The patient age was 73 ± 9 yr, and 76% (155/203) were male. The underlying CVDs for CR were ischemic heart disease in 110, nonischemic heart failure in 49, post-cardiac surgery in 52, and aortic disease in 18 patients, respectively (26 patients had multiple CVDs). The

Table 1

Baseline Characteristics of 203 Patients Who Underwent Cardiac Rehabilitation, According to the Chronic Kidney Disease Stage^a

Variables	Overall (N = 203)	CKD Grade			P Value
		CKD G3a (n = 122)	CKD G3b (n = 60)	CKD G4 (n = 21)	
<i>Patient demographics</i>					
Age, yr	73 ± 9	73 ± 9	75 ± 9	73 ± 10	.17
Male/female	155 (76)/48	93 (76)/29	44 (73)/16	18 (86)/3	.52
Body mass index, kg/m ²	22.8 ± 4	22.4 ± 3	23.2 ± 3	23.5 ± 5	.21
<i>Underlying diseases for cardiac rehabilitation</i>					
Ischemic heart disease	110 (54)	73 (60)	30 (50)	7 (33)	.06
Nonischemic heart failure	49 (24)	25 (20)	17 (28)	7 (33)	.30
Post-cardiac surgery	52 (26)	27 (22)	16 (27)	9 (43)	.13
Aortic disease	18 (9)	10 (8)	6 (10)	2 (10)	.42
COPD	10 (5)	7 (6)	3 (5)	0 (0)	.242
<i>Coronary risk factors</i>					
Smoking (current and ever)	132 (65)	80 (66)	36 (60)	16 (76)	.40
Hypertension	132 (65)	71 (58)	43 (72)	18 (86)	.02
Diabetes mellitus	63 (31)	34 (28)	21 (35)	8 (38)	.47
Dyslipidemia	113 (56)	67 (55)	35 (58)	11 (52)	.86
Family history	39 (19)	24 (20)	11 (18)	4 (19)	.50
<i>Current medications</i>					
ACE-I / ARBs	105 (52)	58 (48)	38 (63)	9 (43)	.09
β-Blockers	144 (71)	82 (67)	45 (75)	17 (81)	.31
Bisoprolol	93 (46)	50 (41)	32 (53)	11 (52)	.237
Daily dosage, mg/d	1.54 ± 1.30	1.33 ± 1.11	1.93 ± 1.58	1.36 ± 0.88	.193
Carvedilol	50 (25)	31 (25)	13 (22)	6 (29)	.779
Daily dosage, mg/d	6.1 ± 4.7	5.3 ± 4.6	6.9 ± 5.1	7.9 ± 2.7	.353
Atenolol	1 (0.5)	1 (0.8)	0	0	
Daily dosage, mg/d	50	50			
CCBs	63 (31)	32 (26)	22 (37)	9 (43)	.167
Diuretics	131 (65)	71 (58)	45 (75)	15 (71)	.08
Antihyperlipidemic drugs	137 (67)	84 (69)	43 (72)	10 (48)	.11
<i>Blood examinations</i>					
Triglyceride (casual), mg/dL	137 ± 63	139 ± 67	135 ± 55	133 ± 65	.88
LDL-Chol, mg/dL	95 ± 33	95 ± 35	96 ± 31	93 ± 29	.90
HDL-Chol, mg/dL	50 ± 15	50 ± 15	48 ± 13	54 ± 17	.25
HbA1c, %	6.2 ± 0.8	6.2 ± 0.8	6.2 ± 0.7	6.1 ± 0.9	.85
BNP, pg/mL	199 ± 249	172 ± 193	196 ± 222	364 ± 462	.17
Hemoglobin, g/dL	12.6 ± 1.8	12.9 ± 1.7	12.4 ± 1.6	11.3 ± 2.0	<.001
Scr, mg/dL	1.24 ± 0.36	1.09 ± 0.21	1.30 ± 0.25	1.96 ± 0.39	<.001
eGFRcr, mL/min/1.73 m ²	44.9 ± 11.2	50.0 ± 9.2	40.5 ± 7.4	27.5 ± 7.2	<.001
Scys, mg/L	1.49 ± 0.39	1.26 ± 0.10	1.63 ± 0.16	2.45 ± 0.26	<.001
eGFRcys, mL/min/1.73 m ²	45.5 ± 10.8	52.9 ± 4.2	38.4 ± 4.1	23.2 ± 3.3	<.001

(continues)

Table 1

Baseline Characteristics of 203 Patients Who Underwent Cardiac Rehabilitation, According to the Chronic Kidney Disease Stage^a (Continued)

Variables	Overall (N = 203)	CKD Grade			P Value
		CKD G3a (n = 122)	CKD G3b (n = 60)	CKD G4 (n = 21)	
<i>Echocardiographic findings</i>					
LAD, mm	44 ± 10	44 ± 12	44 ± 6	44 ± 6	.99
LVDd, mm	50 ± 9	50 ± 8	50 ± 8	50 ± 9	.93
LVEF, %	50 ± 13	50 ± 13	48 ± 14	49 ± 13	.65
<40%	53 (26)	29 (24)	18 (30)	6 (29)	.643
≥50%	125 (62)	76 (62)	34 (57)	15 (71)	.472
<i>Cardiopulmonary exercise testing at the beginning of the CR</i>					
Pre-exercise					
Heart rate, bpm	76 ± 15	76 ± 15	78 ± 14	71 ± 13	.19
Systolic BP, mm Hg	132 ± 23	131 ± 24	130 ± 21	142 ± 22	.10
Diastolic BP, mm Hg	72 ± 13	73 ± 13	71 ± 12	70 ± 14	.42
Peak exercise					
Heart rate, bpm	120 ± 23	123 ± 22	117 ± 22	109 ± 22	.02
Systolic BP, mm Hg	168 ± 30	171 ± 30	162 ± 29	168 ± 29	.15
Diastolic BP, mm Hg	77 ± 17	79 ± 18	75 ± 16	74 ± 17	.22
$\dot{V}O_{2peak}$, mL/kg/min	15.2 ± 3.5	16.2 ± 3.5	13.8 ± 2.7	13.6 ± 2.9	<.001
Peak WR, W	68 ± 22	73 ± 13	62 ± 18	63 ± 16	.003
$\dot{V}E/\dot{V}CO_2$ Slope	38.1 ± 7.0	37.3 ± 7.0	39.4 ± 7.0	39.5 ± 5.7	.09
Peak RER	1.16 ± 0.11	1.16 ± 0.10	1.15 ± 0.11	1.17 ± 0.09	.80
<i>Amount of exercise during the CR at the outpatient visit</i>					
Session attendance, times/3 mo	7.0 ± 3.4	6.9 ± 3.6	7.5 ± 2.9	6.5 ± 3.2	.44

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP, brain natriuretic peptide; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CR, cardiac rehabilitation; eGFRcr, estimated glomerular filtration rate serum creatinine concentration; eGFRcys, eGFR based on serum concentration of cystatin C; HbA_{1c}, glycosylated hemoglobin; HDL-Chol, high-density lipoprotein cholesterol; LAD, left atrial diameter; LDL-Chol, low-density lipoprotein cholesterol; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; peak RER, the ratio of the carbon dioxide output and oxygen uptake at peak exercise; peak WR, peak work rate; Scr, serum creatinine concentration; Scys, serum concentration of cystatin C; $\dot{V}E/\dot{V}CO_2$ slope, the slope of the relationship between the minute ventilation and carbon dioxide output until the respiratory compensation point; $\dot{V}O_{2peak}$, peak oxygen uptake.

^aData are presented as mean ± SD or n (%).

most frequent comorbidities were hypertension (65%), followed by dyslipidemia (56%), and diabetes mellitus (31%). Approximately half of the patients had renin-angiotensin system inhibitors. About 70% of the patients had β -blockers, diuretics, or antihyperlipidemic drugs, with a good coronary risk control before CR (within the normal range of serum triglycerides, cholesterol, and glycosylated hemoglobin).

The left ventricular systolic function in the participants was modestly impaired. Forty-two percent (86/203) had a moderate to severely reduced exercise capacity, and 76% (154/203) had respiratory inefficiency detected by the cardiopulmonary exercise test at the beginning of the CR.

With regard to the renal function, 122 patients (122/203, 60%) were grade G3a (mild-moderate grade of CKD), 60 patients (60/203, 30%) were grade G3b (moderate-severe grade of CKD), and 21 patients (21/203, 10%) were grade G4 (severe grade of CKD). The proportion of comorbid hypertension was higher in patients with worse renal function. The patients with CKD G4 had higher serum brain

natriuretic peptide levels and lower hemoglobin levels than those with CKD G3a and G3b.

Changes in CVD risks and renal function after CR are shown in Table 2. Overall, $\dot{V}O_{2peak}$, high-density lipoprotein cholesterol, and brain natriuretic peptide statistically improved after CR. As regard renal function, eGFRcr did not improve after CR, whereas eGFRcys statistically improved (45.5-47.7 mL/min/1.73 m², $P < .001$). The Figure shows the temporal course of eGFRcys according to the three groups based on the grade of renal dysfunction. In the CKD G3a group, the eGFRcys did not improve after CR (52.9-54.2 mL/min/1.73 m², $P = .07$). By contrast, the eGFRcys statistically improved in the CKD G3b and G4 groups after CR (38.4-41.5 mL/min/1.73 m², $P = .001$; 23.2-28.0 mL/min/1.73 m², $P = .02$).

The association between the baseline eGFRcys and the percent change in the eGFRcys after CR (% Δ eGFRcys) is shown in Table 3. In the unadjusted linear regression model, the improvement of eGFRcys was greater among patients with a lower baseline eGFRcys (0.47% greater

Table 2

Changes in the Biomarkers Between the Beginning and End of the Cardiac Rehabilitation According to the Chronic Kidney Disease Stage^a

Biomarkers	Overall (N = 203)			CKD G3a (n = 122)			CKD G3b (n = 60)			CKD G4 (n = 21)		
	Before CR	After CR	P Value	Before CR	After CR	P Value	Before CR	After CR	P Value	Before CR	After CR	P Value
$\dot{V}O_{2peak}$, mL/kg/min	15.2 ± 3.5	16.0 ± 3.6	<.001	16.2 ± 3.5	17.0 ± 3.6	<.001	13.8 ± 2.7	14.6 ± 3.1	.01	13.6 ± 2.9	14.4 ± 3.4	.01
Triglyceride (casual), mg/dL	137 ± 63	146 ± 90	.08	139 ± 67	154 ± 100	.02	135 ± 55	129 ± 71	.42	133 ± 65	144 ± 71	.49
LDL-Chol, mg/dL	95 ± 33	93 ± 29	.43	95 ± 35	94 ± 31	.85	96 ± 31	92 ± 26	.19	93 ± 29	93 ± 29	.96
HDL-Chol, mg/dL	50 ± 14	55 ± 15	<.001	50 ± 15	54 ± 15	<.001	48 ± 13	55 ± 14	<.001	54 ± 17	62 ± 18	.003
HbA _{1c} , %	6.2 ± 0.8	6.1 ± 0.6	.06	6.2 ± 0.8	6.2 ± 0.6	.49	6.2 ± 0.7	6.1 ± 0.5	.07	6.1 ± 0.9	6.0 ± 0.9	.12
BNP, pg/mL	199 ± 249	148 ± 221	<.001	172 ± 193	114 ± 132	<.001	196 ± 221	153 ± 213	.01	364 ± 462	331 ± 446	.55
Hemoglobin, g/dL	12.6 ± 1.8	12.8 ± 1.6	.02	12.9 ± 1.7	13.1 ± 1.6	.06	12.4 ± 1.6	12.4 ± 1.5	.72	11.3 ± 2.0	12.1 ± 1.2	.05
eGFRcr, mL/min/1.73m ²	44.9 ± 11.2	44.8 ± 12.0	.94	50.0 ± 9.2	49.4 ± 10.6	.31	40.5 ± 7.4	40.9 ± 9.0	.60	27.5 ± 7.2	29.4 ± 10.5	.22
eGFRcys, mL/min/1.73m ²	45.5 ± 10.8	47.7 ± 12.3	<.001	52.9 ± 4.2	54.2 ± 8.8	.07	38.4 ± 4.1	41.5 ± 7.9	.001	23.2 ± 3.3	28.0 ± 9.6	.02

Abbreviations: BNP, brain natriuretic peptide; CKD, chronic kidney disease; CR, cardiac rehabilitation; eGFRcr, estimated glomerular filtration rate based on serum creatinine concentration; eGFRcys, estimated glomerular filtration rate based on serum concentration of cystatin C; HbA_{1c}, glycosylated hemoglobin; HDL-Chol, high-density lipoprotein cholesterol; LDL-Chol, low-density lipoprotein cholesterol; $\dot{V}O_{2peak}$, peak oxygen uptake.
^aData are presented as mean ± SD.

improvement of %ΔeGFRcys/one lower baseline eGFRcys; 95% CI, 0.23-0.72%). This association remained after adjustment for age, sex, ischemic heart disease, non-ischemic heart failure, hypertension, diabetes mellitus, dyslipidemia, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, calcium channel blockers, β-blockers, diuretics, brain natriuretic peptide, hemoglobin, and session attendance (0.63% greater improvement of %ΔeGFRcys/one lower baseline eGFRcys; 95% CI, 0.35-0.91%).

DISCUSSION

In this study of 203 CVD patients with CKD, we found that CR statistically improved renal function measured by eGFRcys among patients with moderate to severe renal dysfunction (CKD grades 3b and 4). Furthermore, the worse baseline renal function, the greater effect of CR. Our observations indicate that CR could be performed in patients with severe renal dysfunction and might have a beneficial effect on their renal function.

Several studies have investigated the effects of CR including exercise training on renal function in patients with severe renal dysfunction. A small randomized controlled study of 30 patients with severe renal dysfunction showed that exercise did not have a beneficial effect on their eGFRcr³. Another small (n = 10), observational study also showed that the GFR did not change after exercise training in pre-dialytic uremic patients with an average GFR of 15 mL/min/1.73 m².⁴ Furthermore, CR did not improve eGFRcr among 22 patients with acute myocardial infarction and severe CKD (eGFRcr < 30 mL/min/1.73 m²), suggesting that functional renal reserve capacity may be irreversibly deteriorated in severe CKD patients.²⁷ Nevertheless, our findings demonstrated the statistically improved eGFRcys after CR, while these small studies collectively suggest no clinical benefit of CR for patients with severe CKD. The reason for the differences is largely attributable to the types of measured markers of renal function. The use of eGFRcr may not be optimal because eGFRcr is affected by muscle mass. Indeed, in our study, the eGFRcr, which is not affected by muscle mass and exercise, was improved after CR, while there were no significant improvements in eGFRcr across CKD groups. In addition, two earlier, prospective studies using eGFRcys showed that CR and high physical activity improved renal function. Because these studies have several potential limitations (one study had a small sample size of patients with severe renal function,¹⁴ and the other study did not divide study patients into renal function severity¹⁵), our findings should enhance the earlier knowledge.

Previous studies showed that a minimally clinically important difference of increase in eGFR was 5 mL/min/1.73 m².²⁸ The increase of eGFRcys in this study was statistically an improvement but did not reach this minimally clinically important difference. Nevertheless, the observed findings should be an important basis for future investigations because limited evidence demonstrated the beneficial effects of CR on patients with severe CKD.^{14,15}

Although the mechanisms for the improvement of renal function have remained unclear, several potential mechanisms have been suggested. The decline of renal function is affected by coronary risk factors such as hypertension, hyperlipidemia, and diabetes mellitus. One study reported that normalizing the blood pressure leads to a decrease in the proteinuria of patients with chronic renal failure.²⁹ Other studies showed that hyperlipidemia may affect the renal

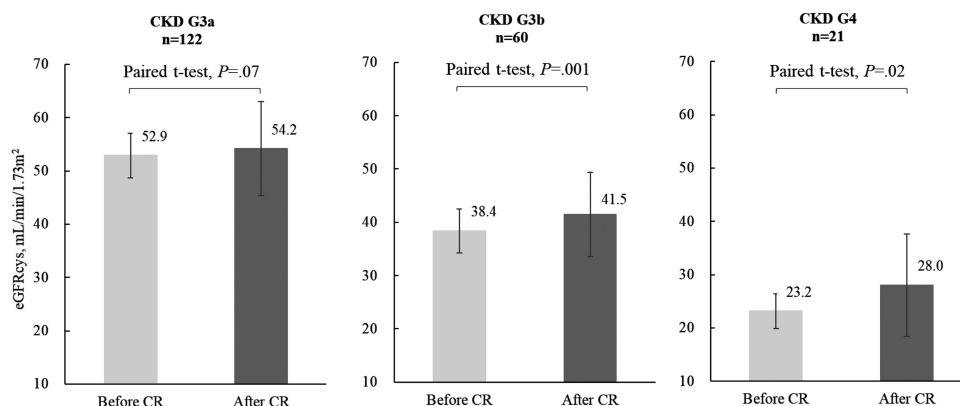


Figure. The changes in the eGFRcys between the beginning and end of the cardiac rehabilitation in each of the three groups. Abbreviations: CR, indicates cardiac rehabilitation; eGFRcys, estimated glomerular filtration rate based on serum concentration of cystatin C.

function decline and an increase in high-density lipoprotein cholesterol related to an improvement in renal function.^{30,31} Another report indicated that an improvement in insulin sensitivity was an independent predictor of an increase in eGFR.³² Because a comprehensive CR program is widely known to improve the effect of risk factors, CR might have favorable effects to improve their kidney function directly or indirectly.

We also found that the improvement of eGFRcys after CR was relatively greater in patients with worse baseline eGFRcys compared with those with better. To the best of our knowledge, this is the first study that demonstrates

the association of baseline eGFRcys and the effect of CR in CKD patients. The observed results imply that the lower the baseline renal function was, the larger the space for a beneficial change of renal function was. Yet, little is known about the potential underlying mechanism of the improvement in renal function of CKD patients and the association of baseline renal function and the effect of CR. Our findings should drive further research to validate these findings and to elucidate the underlying mechanisms of the association of interest.

The most important finding in this study is the possibility of a beneficial effect of a comprehensive CR program

Table 3

Univariable and Multivariable Linear Regression Analyses of the Percent Change in the eGFRcys (%ΔeGFRcys)

Variables	Univariable			Multivariable		
	β	95% CI	P Value	β	95% CI	P Value
eGFRcys at the beginning of the CR (/one lower eGFRcys), mL/min/1.73 m ²	0.47	0.23 to 0.72	<.001	0.63	0.35 to 0.91	<.001
Covariates						
Age, yr				0.24	-0.08 to 0.55	.143
Male				2.41	-4.30 to 9.12	.480
Ischemic heart disease				0.69	-6.96 to 8.34	.859
Nonischemic heart failure				-3.42	-12.79 to 5.95	.472
Hypertension				-3.48	-9.40 to 2.45	.249
Diabetes mellitus				3.71	-2.36 to 9.78	.229
Dyslipidemia				6.80	1.02 to 12.57	.021
ACE-I/ARBs				1.99	-4.04 to 8.01	.516
CCBs				2.26	-3.83 to 8.35	.464
β-Blockers				2.07	-4.15 to 8.29	.513
Diuretics				1.42	-4.88 to 7.73	.657
BNP, pg/mL				0.02	0.009 to 0.033	.001
Hemoglobin, g/dL				-0.44	-2.24 to 1.36	.633
Session attendance, times/3 mo				0.63	-0.18 to 1.45	.126

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP, brain natriuretic peptide; CCB, calcium channel blocker; CR, cardiac rehabilitation; eGFRcys, estimated glomerular filtration rate based on serum concentration of cystatin C.

for renal function in CVD patients even with severe renal dysfunction. To date, physicians are likely to deem the severe chronic renal dysfunction to be accumulated irreversible renal damage. However, our findings might facilitate patients with severe renal dysfunction to proactively participate in the CR program because they could receive benefits to improve their renal function.

This study has several limitations. First, there might be unmeasured confounding factors (eg, patient adherence to the home exercise program and body composition data³³) in the present study because of the nature of the retrospective design. Yet, we have adjusted clinically relevant and important confounders, and therefore the confounding bias should be minimized. Second, the sample size, especially patients with CKD G4, was relatively limited, while the current study is one of the largest studies that investigates the effect of CR using eGFRcys. Third, we do not have long-term follow-up data. Therefore, the effect of CR on the long-term renal prognosis remains unclarified. Fourth, the observed improvement in the present study did not reach this minimally clinically important difference (eGFR, 5 mL/min/1.73 m²; $\dot{V}O_{2peak}$ 1.5 mL/min/kg).^{7,34-36} However, our study aim was to examine whether CR can be performed for these patients. The observed, potential beneficial effect of CR program on patients with severe CKD should facilitate further investigation to develop the optimal CR program for patients with severe CKD. Lastly, the single-center design limits the generalizability of the current findings. Thus, further studies are needed to validate the current findings.

CONCLUSIONS

We found that CR statistically improved renal function using eGFRcys among CVD patients with CKD, particularly in those with severe renal dysfunction, although it did not exceed the minimally clinically important difference. The baseline renal function was associated with the degree of improvement in renal function after participating in the CR program. Our findings should facilitate further prospective randomized controlled trials to verify the effect of CR on renal function and long-term prognosis in CVD patients with CKD using eGFRcys.

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