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【 ORIGINAL ARTICLE 】

Possibility of Cardio-renal Protection by Long-term Cardiac Rehabilitation in Elderly Patients with Cardiovascular Diseases

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Abstract:

Objective Cardiac rehabilitation (CR) improves the mortality in patients with cardiovascular disease (CVD). Even in elderly patients with CVD, CR may improve the activities of daily living (ADL).

Methods Eighty-eight outpatients over 65 years of age at the beginning of a CR program (baseline) at Fukuoka University Hospital who had CVD and could be followed-up for up to 5 years were enrolled. CVD included ischemic heart disease, postoperative valvular heart disease, dissecting aneurysm of the aorta and peripheral artery disease. The patients were divided into 2 groups according to the average estimated glomerular filtration rate (eGFR) at baseline (55.4±14.8 mL/min/1.73 m^2): high (≥55.4, n=44) and low (<55.4, n=44)-eGFR groups. The anaerobic threshold (AT) during exercise and left ventricular ejection fraction (LVEF) were measured by cardiopulmonary exercise (CPX) and ultrasound cardiography, respectively. The serum brain natriuretic protein (BNP) was also measured every year.

Results The average age at baseline in all patients was 73±6 years. In all patients, the level of eGFR did not significantly change for 5 years (55±15 mL/min/1.73 m^2 at baseline vs. 48±14 at the end of the study). The AT (3.7±1.0 METs at baseline vs. 3.3±0.5), LVEF (57±13% vs. 64±10%) and BNP (260±452 pg/mL vs. 308±345) were also maintained for 5 years. In both the low- and high-eGFR groups, the eGFR, AT during exercise, LVEF and BNP at the end of the study were not significantly changed compared to the baseline values, although some changes were observed during the follow-up period.

Conclusion Long-term CR in CVD outpatients over 65 years of age helped maintain the AT, LVEF, BNP and eGFR for 5 years. CR afforded cardio-renal protection in elderly patients with CVD.

Key words: elderly patients, cardiac rehabilitation, cardio-renal protection

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Introduction

In association with the growing number of elderly people in developed countries, the number of patients with heart failure (HF) in Japan may reach pandemic levels by around 2025 (1). Cardiac rehabilitation (CR) is a method for coping with this HF pandemic and has been shown to prevent secondary cardiovascular diseases worldwide (2-4). However, there are few reports of CR improving the activities of daily living or organic function in elderly patients, perhaps because only a small number of these patients participate in CR as outpatients after hospital discharge.

We previously reported that patients with mild to moderate chronic kidney disease (CKD) who participated in our CR program for one year showed an increase in the esti-

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mated glomerular filtration rate (eGFR) (5). Cardio-renal syndrome refers to a condition where acute or chronic dysfunction of either the heart or kidneys leads to dysfunction of the other (6). Thus, CR may improve and maintain the cardiac function as well as the renal function over the long term. Fukuoka University Hospital has had a CR program for more than seven years, and each year we collect the clinical data of patients who participate in this program.

In this study, we hypothesized that CR could help maintain the exercise capacity and cardiac and renal function in elderly patients over 65 years of age for up to five years.

Materials and Methods

Study population and protocol

This study was a retrospective trial that evaluated the efficacy of CR in elderly patients. It was approved by the institutional review board; i.e., the ethics committee of Fukuoka University Hospital. The outpatients who had cardiovascular diseases (CVD) and participated in a CR program at Fukuoka University Hospital and were over 65 years old at the beginning of the CR program patients were enrolled as of the beginning of November 2017. The cardiac events and withdrawal patients were defined until the end of October 2018. Patients who had hemodialysis were excluded.

Exercise protocol

At the beginning of the CR program, the patients underwent a cardiopulmonary exercise test (CPX) using Cpex1 (Inter Riha, Tokyo, Japan) and a stress test system with an ML9000 electrocardiogram (Fukuda Denshi, Tokyo, Japan). The CR program was the same as in our previous report (5). In brief, the patients participated in a supervised exercise training program at the hospital's gym one to three times a week. The exercise workload was based on the anaerobic threshold (AT) according to the CPX results. Each session lasted 1 hour, beginning with a warm-up exercise for 5 minutes, followed by 30 minutes of cycling with an aero bike (75XLIII; Combi, Tokyo, Japan) or walking on a treadmill (TRD-350; Sakai Medical, Tokyo, Japan) at the patient's indicated exercise intensity and 25 minutes of cooling down and stretching. The blood pressure (BP) and heart rate (HR) were measured at rest before and after exercise. The BP was measured after at least 1 minute of rest in the sitting position by an automated sphygmomanometer (HEM-8723; Omron Healthcare, Kyoto, Japan), and an electrocardiogram was obtained using a central monitor (DS-5700; Fukuda Denshi). The Borg rating of perceived exertion (RPE) was also recorded during exercise.

Data collection

At the beginning of the CR program and yearly thereafter, the ejection fraction (EF) obtained by modified Simpson's method was analyzed by a Vivid E9 echocardiogram (GE Healthcare, Tokyo, Japan). Serum biochemical data, including serum creatinine (Cr) and brain natriuretic peptide (BNP), were analyzed by enzymatic methods in the clinical laboratory of Fukuoka University Hospital. In this study, the eGFR was evaluated by the Japanese version of the equation using serum Cr: eGFRcr [mL/min/1.73 m^2]=194×Cr [mg/dL]$^{-1.094}$×age [years]$^{-0.287}$(×0.739, if a woman). The patients' general information and background profiles were obtained from an electronic medical recording system. The follow-up period was up to five years.

Statistical analyses

Data are presented as the mean and standard deviation (SD) for continuous variables and the number and percentage of patients for categorical variables. The continuous results from the beginning of CR and yearly thereafter in the low- and high-eGFR groups were compared with a one-way analysis of variance followed by Tukey-Kramer's post-hoc test (Figure). The categorical variables were analyzed by the unpaired samples Student's *t*-test when normally distributed and Wilcoxon's ranked-sum test when not normally distributed between the low- and high-eGFR groups (Table 1, 2). P values below 0.05 were regarded as statistically significant. Statistical analyses were performed using the IBM SPSS Statistics software program, version 25.0 (IBM, Armonk, USA) at Fukuoka University Hospital (Fukuoka, Japan).

Results

Patient characteristics at baseline

The baseline patient characteristics are shown in Table 1. The 88 patients were enrolled and divided into two groups depending on the eGFR at the beginning of the CR program: below 55.4±14.8 mL/min/1.73 m^2, which was the average eGFR in all patients (low-eGFR group), and above this value (high-eGFR group). Overall, the mean age at the beginning of the CR program and the observation period was 73±6 years and 3.2±1.8 years, respectively. Men comprised 75% of the patients in the low-eGFR group but only 43% in the high-eGFR group (p=0.002 vs. low-eGFR group). The number of CKD patients in the low-eGFR group was greater than that in the high-eGFR group (p< 0.001 vs. low-eGFR group). There were no differences in other basic diseases or medications between the low and high-eGFR groups (Table 1). At the beginning of CR, there were no significant differences in the AT exercise capacity, BNP or LVEF between the low- and high-eGFR groups (Table 2). After starting CR, the rates of cardiac events and withdrawal were not markedly different between the two groups.

Time of eGFR

In all patients, the eGFR changed from 55.4±14.8 mL/min/1.73 m^2 to 48.1±13.6 mL/min/1.73 m^2 at 5 years (Figure A). In the low-eGFR group, the eGFR increased to 42.9

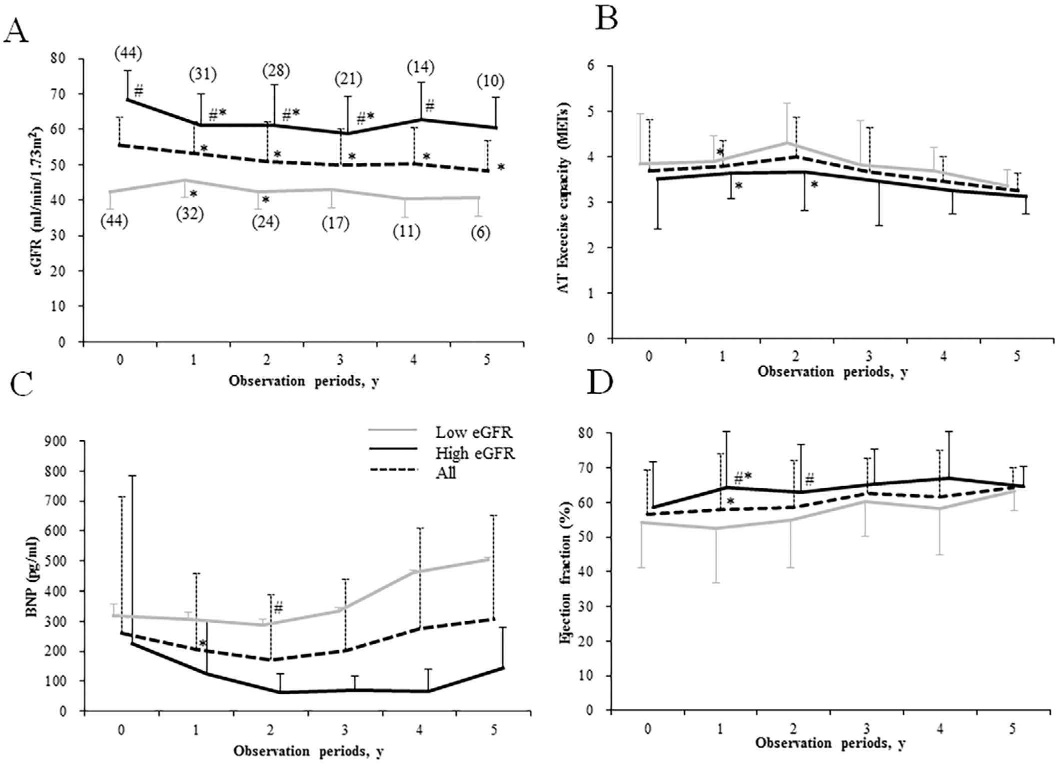

Figure. **The eGFR (A), exercise capacity at AT by CPX (B), serum BNP (C) and EF by ultrasound echocardiography (D) as cardio-renal parameters. Data are presented as the mean±SD. *p<0.05 vs. 0 year, s #p<0.05 vs. the low-eGFR group. The numbers in parentheses indicate the number of patients per year. eGFR: estimated glomerular filtration rate, AT: anaerobic threshold, CPX: cardiopulmonary exercise test, BNP: brain natriuretic peptide, EF: ejection fraction, SD: standard deviation**

±7.9 mL/min/1.73 m^2 at one year and then decreased to 41.1 ±8.6 mL/min/1.73 m^2 at five years. In the high-eGFR group, the eGFR changed from 67.8±7.8 mL/min/1.73 m^2 to 59.9± 12.4 mL/min/1.73 m^2 at five years. In both groups, the eGFR increased and decreased slowly. As a result, the eGFR was maintained throughout the five-year observation period.

Time course of exercise capacity at AT

In all patients, the exercise tolerance at AT measured by CPX changed from 3.7±1.0 METs at baseline to 3.3±0.5 METs at five years (Figure B). Over five years, the AT changed from 3.7±1.1 to 3.2±0.4 METs in the low-eGFR group and from 3.7±0.9 to 3.3±0.6 METs in the high-eGFR group. If we account for the normal effects of aging in elderly cardiovascular patients, the exercise capacity seemed to decrease naturally and may actually have been maintained by the CR program.

Time course of BNP

In all patients, the BNP changed from 260±452 pg/mL at baseline to 308±345 pg/mL at five years (Figure C). The BNP changed from 288±37 to 467±6 pg/mL in the low-eGFR group and from 229±538 to 148±132 pg/mL in the high-eGFR group over this period. Due to the large SD, it is difficult to conclude whether or not there was a marked difference between the low- and high-eGFR groups. However, there may have been a trend toward an increasing and decreasing BNP in the low- and high-eGFR groups, respectively.

Time course of LVEF

In all patients, the LVEF measured by echocardiography increased from 56.5±13.1% at baseline to 64.3±9.9% at 5 years (Figure D). The LVEF changed from 56±13% to 65± 6% in the low-eGFR group and from 57±13% to 63±15% in the high-eGFR group over this period. There were no significant differences after the three-year time point between the groups.

Discussion

Participating in a CR program is known to be able to increase the exercise capacity and cardiac protection in elderly CVD patients. The present study showed that the exercise capacity at AT and CVD parameters, such as BNP, LVEF and eGFR, were maintained by participating in CR for up to five years.

We expected that the prognosis of CVD would be improved by long-term CR in patients over 65 years of age (7). Since CVD patients often have several risk factors, such as hypertension (8), diabetes (9), dyslipidemia and obesity (10), we must offer comprehensive care for their health problems in addition to care for CVD. CKD is also common in the elderly (11). The eGFR is a useful tool for estimating

Table 1. Patient Characteristics at Baseline in All Patients, the Low- and High-eGFR Groups.

	All (n=88)	Low-eGFR (n=44)	High-eGFR (n=44)	p value low vs. high
Age, year	73±6	74±6	72±5	0.15
Observation periods, year	3.2±1.8	3.5±1.9	3.0±1.7	0.12
Gender (male), n (%)	52 (59)	33 (75)	19 (43)	0.002
Smoking, n (%)	33 (38)	20 (45)	13 (30)	0.86
BMI, kg/m^2	24±4	24±4	23±4	0.19
HTN, n (%)	74 (84)	38 (86)	36 (82)	0.56
DM, n (%)	28 (32)	16 (36)	12 (27)	0.36
DL, n (%)	72 (82)	36 (82)	36 (82)	1.00
CKD, n (%)	55 (63)	44 (100)	7 (16)	<0.001
CVD				
IHD, n (%)	47 (53)	28 (64)	19 (43)	0.05
HF, n (%)	59 (67)	29 (66)	30 (68)	0.82
Valvular disease, n (%)	29 (33)	14 (32)	15 (34)	0.82
PAD, n (%)	17 (19)	10 (23)	7 (16)	0.41
Others, n (%)	20 (23)	12 (27)	8 (18)	0.31
Medications				
ARB/ACE-I, n (%)	55 (63)	30 (68)	25 (57)	0.27
Diuretics, n (%)	28 (32)	15 (34)	13 (30)	0.26
Furosemide, n (%)	16 (17)	8 (18)	8 (18)	1.00
Azosemide, n (%)	4 (4.5)	3 (6.8)	1 (2.3)	0.17
Torasemide, n (%)	1 (1.1)	1 (2.3)	0 (0)	1.00
Hydrochlorothiazide, n (%)	1 (1.1)	0 (0)	1 (2.3)	1.00
Trichlormethiazide, n (%)	2 (1.1)	1 (2.3)	1 (2.3)	1.00
Spironolactone, n (%)	15 (17)	7 (16)	8 (18)	0.10
Eplerenone, n (%)	4 (4.5)	3 (6.8)	1 (2.3)	0.17
Tolvaptan, n (%)	1 (1.1)	0 (0)	1 (2.3)	1.00
β-blocker, n (%)	54 (61)	31 (70)	23 (52)	0.08
CCB, n (%)	44 (50)	24 (55)	20 (45)	0.39
Statin, n (%)	62 (50)	32 (77)	30 (68)	0.64

eGFR: estimated glomerular filtration rate, BMI: body mass index, HTN: hypertension, DM: diabetes mellitus, DL: dyslipidemia, CVD: cardiovascular disease, IHD: ischemic heart disease, HF: heart failure, PAD: peripheral artery disease, ARB/ACE-I: angiotensin II receptor blocker/angiotensin converting enzyme inhibitor, CCB: calcium channel blocker

Table 2. Clinical Data from All Patients, the Low- and High-eGFR Groups.

	All (n=88)	Low-eGFR (n=44)	High-eGFR (n=44)	p value low vs. high
eGFR at starting CR (mL/min/1.73 m^2)	55±15	43±9	68±8	<0.001
AT at starting CR (METs)	3.7±1.0	3.7±1.1	3.7±0.9	0.200
BNP at starting CR (pg/mL)	279±473	288±361	229±538	0.274
LVEF at starting CR (%)	57±13	56±13	57±13	0.453
CVD events after starting CR, n (%)	14 (16)	9 (21)	6 (14)	0.500
Withdrawal patients after starting CR, n (%)	21 (24)	11(25)	10 (23)	0.622

eGFR: estimated glomerular filtration rate, CR: cardiac rehabilitation, AT: anaerobic threshold, METs: metabolic equivalents, BNP: brain natriuretic peptide, LVEF: left ventricular ejection fraction, CVD: cardiovascular diseases

the renal function, even though elderly individuals may show a biased eGFR based on serum Cr due to their lower muscle mass and dietary protein intake (12). As shown in Figure, the eGFR decreased yearly for three years and then was maintained until five years from the baseline. This is not a problem, as the eGFR generally decreases by 1 mL/min/year. The present data showed that continuous CR prevented the progression of CKD.

For CVD patients in a long-term CR program, we should revise the exercise prescription according to the patient's capacity for physical activity, since physical activity was shown to be associated with a reduction in the risk of CVD death in a Japanese population (13). CPX is the best way to determine the appropriate exercise prescription (14). As shown in Figure, the exercise capacity at AT as determined by CPX increased for the first two years and then decreased. There was ultimately no significant difference in the exercise capacity between the baseline and the end of the study. The exercise tolerance remained sufficient for activities of daily living, since the capacity at AT was over 3.0 METs even after five years.

The low physical strength in elderly patients who are at risk of becoming frail must be addressed (15). The present study showed that the exercise capacity at AT was maintained by continuous CR for up to five years. Once patients become frail, it is difficult to determine their exercise capacity at AT. In patients who are in a frail state, we can use HR calculated by the Karvonen formula or RPE which is the same as the score of 13 on the Borg's scale (16) instead of the oxygen uptake (VO_2) according to CPX results to approximately determine AT. We need to help patients avoid frailty, which has been associated with an increased risk of CVD events (17), hospitalization and an impaired quality of life (18). While resistance training is the primary method used to forestall frailty (19), intervention by a CR team approach is also applied (20). For example, depression and anxiety as psychogenic factors can be treated by clinical psychologists, total energy intake as a nutrition factor can be treated by nutritionists (21), and low adherence as a pharmacological factor can be addressed by pharmacists. We also used our team approach to improve the motivation for continuous exercise, so a CR program should include interprofessional work (22). CR improves the patient's quality of life and promotes healthy aging through tailor-made CR (23). Of note, while CR involves individual exercise and is not group-based, it may be important for CVD patients to socialize with the CR medical stuff and other CVD patients in order to receive motivation to continue the CR program (24). Since we used a team approach in addition to regular exercise, the exercise capacity at AT was maintained by continuous CR for up to five years.

In conclusion, a continuous outpatient CR program for up to five years afforded persistent exercise tolerance with cardiac and kidney protection in elderly patients with CVD.

The authors state that they have no Conflict of Interest (COI).

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