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Effect of cardiac rehabilitation on the renal function in chronic kidney disease - Analysis using serum cystatin-C based glomerular filtration rate☆

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ABSTRACT

Background: Whether an individually determined appropriate level of cardiac rehabilitation (CR) has a favorable effect on the renal function still remains unclarified. The aim of this study was to confirm the effect of CR on the estimated glomerular filtration rate (eGFR) using cystatin C, which is known to be unaffected by physical exercise.
Methods: The study population was comprised of 86 patients (61 males; average age 74 y/o) with a lower-moderate level of chronic kidney disease (CKD) who was admitted to our hospital for treatment of cardiovascular disease (CVD) and who participated in our 3-month CR program. The exercise capacity was assessed by cardiopulmonary exercise testing (CPX) and the eGFR was measured by a formula based on the serum cystatin C concentration (eGFRcys) in each patient both at the beginning and end of the CR.
Results: In the CVD patients with CKD, both the peak oxygen uptake (VO_2) and peak work rate (WR) improved significantly after CR (15.0 ± 3 to 15.8 ± 3 ml/min/kg, $p = 0.002$. 65.5 ± 21 to 70.2 ± 25 W, $p = 0.001$). Regarding the renal function, the eGFRcys improved (45.2 ± 11 to 47.3 ± 13 ml/min/1.73 m^2, $p = 0.023$), however, the eGFR assessed by the serum creatinine (eGFRcr) did not improve after CR (45.1 ± 12 to 44.9 ± 13 ml/min/1.73 m^2, $p = 0.834$).
Conclusions: In CVD patients, a novel CR program significantly improved the exercise capacity. Further, CR was shown to have a favorable effect on the renal function when it was estimated by the eGFRcys.

1. Introduction

Strenuous exercise has been shown to possess unfavorable effects on the renal function and can be attributed to the reduction in the renal blood flow and glomerular filtration rate (GFR) [1–3]. For that reason, patients with chronic kidney disease (CKD) are usually advised to avoid any excessive exercise. On the other hand, comprehensive cardiac rehabilitation (CR), including an appropriate level of exercise training, has been shown to improve a variety of coronary risk factors, exercise capacity, quality of life [4] and even the prognosis [5]. In patients with CKD, exercise training has been proved to improve the coronary risk factors [6] and exercise capacity [7]. However, the influence of CR on the renal function still remains controversial, i.e., some investigators have demonstrated no significant difference in the renal function before and after CR [8,9], while CR was found to be associated with an obvious improvement in the renal function in some other reports [10–12].

In clinical practice, the GFR is commonly calculated using a formula mainly constructed using the serum creatinine concentration (eGFRcr) and age. The eGFRcr is inferred to be affected by exercise training due to muscle growth, and thus the eGFRcr may underestimate the actual renal function particularly in the patients undergoing chronic exercise training.

Recently, attention has been directed to the observation that the eGFR, based on the serum concentration of cystatin-C (eGFRcys), may overcome the aforementioned shortcoming of the eGFRcr. Cystatin-C is a single chain protein produced by all nucleated human cells and is suggested to be superior to creatinine in estimating the GFR [13].

Consequently, the aim of the present study was to evaluate the effects of the CR on the renal function using the eGFRcys in patients with both cardiovascular disease (CVD) and CKD. Another aim was to compare the change in the eGFRcys and eGFRcr in the same patient population. The results of this study may suggest the possibility of the CR improving the renal function in these patient populations that can be adequately estimated using the eGFRcys.

☆ These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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2. Methods

2.1. Study population

There were 240 patients who were admitted to our hospital for the evaluation and treatment of CVD and participated in and completed our 3-month CR program from April 2014 until March 2016. Out of them, we excluded 7 patients who were dependent on hemodialysis at the entry of this study, and 147 with a normal kidney function defined as an eGFRcys ≧ 60 ml/min/1.73 cm^2. Finally the study population was comprised of 86 patients with a mild-moderate level (G3-G4) of CKD (mean age: 74 ± 9 years, 61 male patients) (Fig. 1). We traced the patients' medical records retrospectively. This study has been approved by the research ethics committee of Tokai University.

2.2. CR program

Our CR program in this study was a comprehensive program consisting of exercise therapy, nutritional guidance, medication teaching, and attending a course on cardiopulmonary resuscitation. In the exercise therapy, our physiotherapists taught the patients an individual way to do aerobic exercises with walking or bicycle ergometer exercise and resistance training for 40 min per lesson. The exercise intensity was determined individually at a heart rate at the anaerobic threshold level obtained in a symptom-limited cardiopulmonary exercise test or at a level from 11 to 13 of the 6–20 scale training rating (original Borg's scale [14,15]). They were also encouraged to walk at a prescribed heart rate or do resistance training for 30–60 min, 3–7 times a week at home.

2.3. Cardiopulmonary exercise test

At the beginning and end of our 3-month CR program, a symptom limited exercise test was performed on a bicycle ergometer (Corival, Lode Co., Netherlands), which was coupled to a cardiopulmonary gas exchange system (Aero Monitor AE-310S, Minato medical science Co., Japan). The blood pressure was measured every minute and the 12-lead ECG was continuously monitored. The exercise protocol consisted of first a 4-minute resting period, followed by a 3-minute 10 or 20 watt warm up that was increased by 10 or 20 W per minute until one of the following occurred: (1) the patient requested to stop, (2) a plateau of the oxygen uptake, (3) an ischemic change in the electrocardiogram or symptoms, (4) an excessive rise or fall in the blood pressure, or (5) an onset of fatal arrhythmias. We measured the anaerobic threshold for an appropriate prescription of the exercise therapy, peak oxygen uptake (VO_2), and peak work rate (WR) as an index of their exercise capacity. The slope of the relationship between the ventilation (VE) and VCO_2 until the respiratory compensation point (VE/VCO_2 slope) was determined as an index of respiratory inefficiency. The peak respiratory exchange ratio (RER: ratio of carbon dioxide output and oxygen uptake at peak exercise) was used as a measure of the patient effort during the testing, and a value >1.05 was considered to be sufficient.

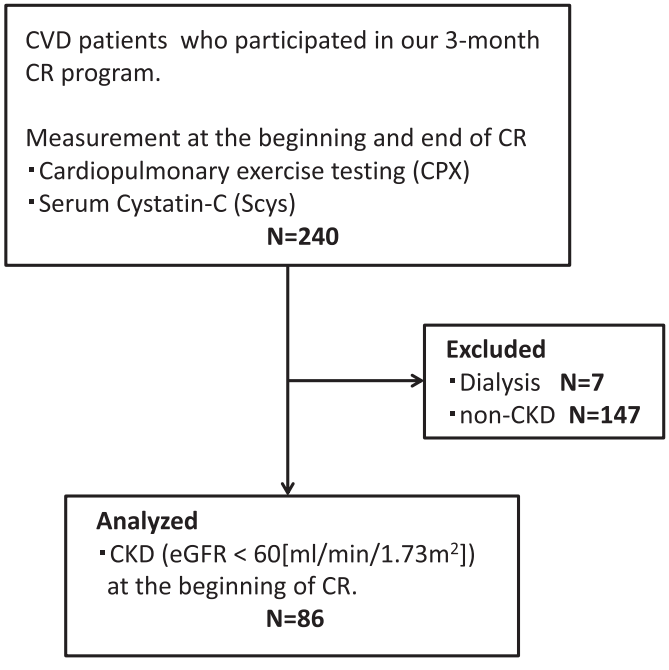

Fig. 1. Enrollment.

2.4. Kidney function

We measured the renal function by the serum creatinine (Scr, mg/dl) and a serum cystatin C (Scys, mg/l) levels. In this study, the eGFR was evaluated by the Japanese version of the equation: eGFRcr [ml/min/1.73 m^2] = 194 × Cr [mg/dl]$^{-1.094}$ × age [y.o.]$^{-0.287}$ (×0.739, if female), eGFRcys [ml/min/1.73 m^2] in male = (104 × CysC [mg/l]$^{-1.019}$ × 0.996$^{age\ [y.o.]}$) − 8, in female = (104 × CysC [mg/l]$^{-1.019}$ × 0.996$^{age\ [y.o.]}$ × 0.929) − 8.

2.5. Statistical analysis

Data are presented as the mean ± standard deviation or number (%). Data were analyzed for statistical significance using a Student's *t*-test for paired observations. All tests were assessed at a level of significance of a *p* value of <0.05. Statistical analyses were performed by SPSS, version16.0 software (SPSS Inc., Chicago, IL).

3. Results

3.1. Clinical characteristics of the participants

The demographic and clinical data are shown in Table 1. The mean age was 74 ± 9 years and approximately 71% of the patients were males. Basic heart disease consisted of angina pectoris in 31, myocardial infarctions in 22, silent myocardial ischemia in 15, non-ischemic heart failure in 18 and post-cardiac surgery in 30 patients, respectively. The patients had several coronary risk factors. More than a half of the patients were current smokers and/or had a history of smoking. Hypertension and dyslipidemia were also present in the majority of the patients.

More than half of the patients took renin-angiotensin system inhibitors (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers), diuretics, and beta blockers. No one took inotropic agents (Table 1). They were also able to maintain a good coronary risk control (serum triglycerides, cholesterol, and HbA1c) at the beginning of the CR (Table 1). With regards to the renal function, 51 patients (59%) had a grade G3a (mild-moderate grade of CKD; 45 ≦ eGFRcys < 60), 24 (28%) a grade G3b (moderate-severe grade of CKD; 30 ≦ eGFRcys < 45), and 11 patients (13%) had a grade G4 (severe grade of CKD): 15 ≦ eGFRcys < 30, respectively (Table 1). Further, most patients had a mildly reduced LV systolic function (LVEF < 40%: 19 pts, 40 < LVEF < 60%: 41 pts, and LVEF ≧ 60%: 26 pts) and diastolic function (E/e′ < 8: 13 pts, 8 ≦ E/e′ ≦ 14: 50 pts, and E/e′ > 14: 23pts) as shown in Table 1.

3.2. Exercise capacity

Most of the patients had a mild reduced exercise capacity and respiratory inefficiency detected by the cardiopulmonary exercise test at the beginning of the CR. Then, they also underwent an adequate inspection because of a peak RER (Table 1).

Our 3-month CR program improved their peak oxygen uptake (peak VO_2), from 15.0 ml/min/kg at baseline to 15.8 ml/min/kg at the