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Original Research

Determinants of Peak Oxygen Uptake at Each Stage of Renal Dysfunction in Patients with Heart Disease

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Abstract

Background: Identifying the causes of low peak oxygen uptake (peak $\dot{V}O_2$) in heart disease patients with renal dysfunction is necessary for prognostic improvement strategies. The purpose of this study was to verify the determinants of peak $\dot{V}O_2$ for each stage of renal function in heart disease patients, focusing on end-tidal oxygen partial pressure ($PETO_2$). **Methods**: Two hundred fifty heart disease patients who underwent cardiopulmonary exercise testing (CPET) in our institution were consecutively enrolled. Patients were divided into three groups by their estimated glomerular filtration rate (eGFR): $<$45, 45–59 and $\geq$60 mL/min/1.73 m^2. Patient characteristics and CPET parameters including $\Delta PETO_2$ (rest—anaerobic threshold) were compared between the groups. The relationship between $\Delta PETO_2$ and peak $\dot{V}O_2$ was also investigated for each group. **Results**: In total, 201 patients were analyzed. $\Delta PETO_2$ decreased with the deterioration of renal function (eGFR $<$45, 0.1 mmHg vs. eGFR 45–59, 2.4 mmHg vs. eGFR $\geq$60, 5.2 mmHg, $p < 0.001$). In the eGFR $<$45 group, left ventricular ejection fraction (LVEF) and hemoglobin (Hb) were significantly associated with peak $\dot{V}O_2$ ($\beta = 0.518$, $p < 0.001$ and $\beta = 0.567$, $p < 0.001$, respectively), whereas $\Delta PETO_2$ was not. In the eGFR 45–59 group, age, Hb, and $\Delta PETO_2$ showed a significant association with peak $\dot{V}O_2$ ($\beta = -0.354$, $p = 0.006$; $\beta = 0.258$, $p = 0.007$; $\beta = 0.501$, $p < 0.001$; respectively). In the univariate analysis, eGFR 45–59 group showed the highest coefficient of determination of $\Delta PETO_2$ to peak $\dot{V}O_2$ ($R^2 = 0.247$, $p <$ 0.001). **Conclusions**: The determinants of peak $\dot{V}O_2$ in heart disease patients depended on the stage of renal function. The determinants of peak $\dot{V}O_2$ in patients with eGFR $<$45 were LVEF and Hb, while $\Delta PETO_2$ was the strongest predictor of peak $\dot{V}O_2$ in patients with eGFR 45–59.

Keywords: peak oxygen uptake; heart disease; renal dysfunction; end-tidal oxygen partial pressure

1. Introduction

The prevalence of chronic kidney disease (CKD) is increasing steadily around the world, and a "CKD epidemic" is being warned against [1]. As well, the rate of complications from renal dysfunction in patients with heart disease is also rising. In recent reports, the proportion of patients with renal dysfunction was 48% for those with coronary artery disease [2], 41% for heart failure with reduced ejection fraction [3], and 51% for heart failure with preserved ejection fraction [4]. In fact, about half of all heart disease patients have renal dysfunction. These patients have lower peak oxygen uptake (peak $\dot{V}O_2$) [5], and it decreases as renal dysfunction progresses [6]. Lower peak $\dot{V}O_2$ is a serious problem in this cohort as it is a predictor of cardiovascular events and mortality [6–8]. To improve peak $\dot{V}O_2$, it is necessary to verify the cause of the low peak $\dot{V}O_2$ and take appropriate countermeasures. However, the factors that influence low peak $\dot{V}O_2$ in heart disease patients are diverse [9], and the addition of renal dysfunction further complicates the search for causative factors [10]. This problem cannot be overlooked in improving the prognosis of heart disease patients with renal dysfunction. Since the pathophysiology of renal dysfunction and cardiorenal syndrome differs depending on the stage of renal dysfunction [11], it is necessary to verify the determinants of peak $\dot{V}O_2$ in heart disease patients by stage of renal dysfunction. On the basis of the above, we hypothesized that the determinants of peak $\dot{V}O_2$ in heart disease patients with renal dysfunction depend on the stage of renal dysfunction. The determinants of peak $\dot{V}O_2$ are dividing into the oxygen delivery and oxygen extraction [9,10]. It has been clarified that the contributions of oxygen extraction are greater than those of oxygen delivery in CKD patients [12]. Therefore, in this study, we focused on end-tidal oxygen partial pressure ($PETO_2$), which has been reported to be associated with renal dysfunction and to show oxygen extraction capacity in skeletal muscle [13–16]. The purpose of this study was to verify the determinants of peak $\dot{V}O_2$ for each stage of renal function in

heart disease patients, including $PETO_2$.

2. Methods

2.1 Study Design and Patients

This was a retrospective, single-center, observational study. From April 2016 to August 2021, 250 patients with heart disease (defined as myocardial infarction, angina, and chronic heart failure) who underwent cardiopulmonary exercise testing (CPET) in our institution were consecutively enrolled in the study. Exclusion criteria included patients with a resting respiratory exchange ratio (RER) $\geq$1.00 due to resting hyperventilation and abnormal breathing [17] and peak RER $<$1.10 during CPET [18], AT impossible to determine, and no laboratory data measured during CPET. Patients' characteristics and clinical parameters including age, sex, body mass index, left ventricular ejection fraction (LVEF), medical history, laboratory values during CPET (estimated glomerular filtration rate [eGFR (mL/min/1.73 m^2)], hemoglobin [Hb (g/dL)]), medications, and the results of CPET were obtained from the electronic medical records by two physical therapists. Laboratory values at CPET were extracted within 2 weeks around the date of CPET.

2.2 Definition

eGFR in this study was evaluated with the Japanese version of the following equation: eGFR = 194 $\times$ (serum creatinine) – 1.094 $\times$ age – 0.287 ($\times$ 0.739 if female) [19].

2.3 Cardiopulmonary Exercise Testing

All patients underwent symptom-limited maximal CPET using a cycle ergometer (Strength Ergo 8; Mitsubishi Electric Engineering Co., Ltd., Tokyo, Japan) with a 10 watt/min continuous ramp exercise protocol after an initial 3-min rest period and a 4-min warm-up period. The warm-up wattage was chosen to be 0 watts or 20 watts in consideration of age, sex, cardiac function, and exercise habits. During CPET, analysis of expired gas was performed with an AE-310S analyzer (Minato Medical Science, Osaka, Japan). The patients were encouraged to perform a maximal or near maximal effort by monitoring the RER at $\geq$1.10 [18]. Peak $\dot{V}O_2$ was defined as the mean value of $\dot{V}O_2$ during the last 15 s of the test, and %peak $\dot{V}O_2$ was also calculated. AT was determined using the V-slope, ventilatory equivalents, and end-tidal pressure methods based on the statement from the American Heart Association [17] by at least two experts in CPET. Resting $PETO_2$ was determined as the mean value during the last 30 s of the rest, and AT $PETO_2$ was the $PETO_2$ at AT. $\Delta PETO_2$ was the difference between the resting $PETO_2$ and AT $PETO_2$. Peak oxygen pulse (peak O_2 pulse), minute ventilation-carbon dioxide production linear regression slope ($\dot{V}E$ vs. $\dot{V}CO_2$ slope), and minimum ventilatory equivalent for carbon dioxide ($\dot{V}E/\dot{V}CO_2$) were also obtained. Peak work rate was defined as the work rate at peak $\dot{V}O_2$.

2.4 Statistical Analysis

Patients were stratified according to their eGFR into three clinically meaningful strata: $<$45, 45–59, and $\geq$60 mL/min/1.73 m^2 [20]. Data are expressed as mean values $\pm$ standard deviation (SD) or median (interquartile range) for continuous variables, as appropriate. Normality of distribution was verified using the Shapiro-Wilk test. Categorical variables are presented as numbers and percentages. One-way ANOVA test and the Kruskal-Wallis test were used for comparison between groups, and the χ^2 test and Fisher's exact test were used for comparing categorical variables. We used the Bonferroni test as post hoc test. Multivariate linear regression analysis was performed to evaluate independent determinants of peak $\dot{V}O_2$ after adjusting for all significant determinants on univariate linear regression analyses. In addition, resting $PETO_2$ was also included as a confounding factor to rule out the effect of resting $PETO_2$ on $\Delta PETO_2$. Univariate linear regression analyses were performed to evaluate the contribution of each determinant to peak $\dot{V}O_2$. A p-value of $<$0.05 was considered to indicate statistical significance. The statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Of the 250 heart disease patients who underwent CPET, 49 patients were excluded because of rest RER $\geq$1.00 (n = 6), peak RER $<$1.10, judgement of AT impossible (n = 8), and no laboratory data (n = 4). Finally, 201 patients were enrolled in the analysis. All patients were divided into three groups by eGFR level: eGFR $<$45 group (n = 30, 14.9%), eGFR 45–59 (n = 59, 29.4%), and eGFR $\geq$60 group (n = 112, 55.7%). Table 1 shows the clinical characteristics and CPET parameters of the three groups. The patients in the eGFR $<$45 group were older and had a higher proportion of chronic heart failure and lower LVEF and Hb. There was a significant difference in peak $\dot{V}O_2$ between the three groups (eGFR $<$45, 16.2 $\pm$ 3.9 mL/min/kg vs. eGFR 45–59, 19.7 $\pm$ 4.7 mL/min/kg vs. eGFR $\geq$60, 23.0 $\pm$ 4.5 mL/min/kg, $p < 0.002$). $\Delta PETO_2$ decreased with the deterioration of renal function (eGFR $<$45, 0.1 mmHg vs. eGFR 45–59, 2.4 mmHg vs. eGFR $\geq$60, 5.2 mmHg, $p <$ 0.001) (Fig. 1). There was no significant difference in peak RER and rest $PETO_2$ between the three groups.

The results of univariate and multivariate linear regression analysis in all subjects showed that age (β = –0.142, p = 0.023), LVEF (β = 0.150, p = 0.006), eGFR strata (β = 0.154, p = 0.026), Hb (β = 0.167, p = 0.005), and $\Delta PETO_2$ (β = 0.356, $p < 0.001$) were significantly associated with peak $\dot{V}O_2$ (Table 2).

The results of univariate and multivariate linear regression analyses differed between the eGFR strata. In the eGFR $<$45 group, LVEF and Hb were significantly associ-

Table 1. Patient characteristics and CPET parameters.

	eGFR <45	eGFR 45–59	eGFR ≥60	*p*-value		
	(n = 30)	(n = 59)	(n = 112)	eGFR <45 vs. eGFR 45–59	eGFR 45–59 vs. eGFR ≥60	eGFR <45 vs. eGFR ≥60
Age, years	71.4 ± 7.7	67.8 ± 7.8	61.2 ± 10.8	0.300	<0.001	<0.0001
Male, n (%)	29 (96.7)	50 (84.7)	104 (92.9)	0.46	0.33	1
Body mass index, kg/m^2	23.2 ± 2.8	23.1 ± 3.2	23.8 ± 2.9	1	0.45	0.88
MI, n (%)	19 (63.3)	43 (72.9)	86 (76.8)	1	1	0.63
AP, n (%)	0 (0)	4 (6.8)	16 (14.3)	0.887	0.632	0.071
CHF, n (%)	24 (80.0)	19 (32.2)	25 (22.3)	<0.001	0.666	<0.001
LVEF, (%)	51.2 (38.9–54.4)	58.7 (49.0–65.4)	59.3 (51.5–68.2)	0.090	0.384	<0.001
Hypertension, n (%)	24 (80.0)	36 (61.0)	74 (66.1)	0.35	1	0.64
Diabetes, n (%)	17 (56.7)	20 (33.9)	36 (32.1)	0.201	1	0.073
Laboratory values						
eGFR, mL/min/1.73 m^2	36.8 (32.2–40.5)	54.6 (51.7–57.0)	71.2 (65.2–80.0)	<0.001	<0.001	<0.001
Hemoglobin, g/dL	12.7 ± 1.8	13.3 ± 1.5	14.2 ± 1.3	0.221	<0.001	<0.001
Medications						
Beta blockers, n (%)	23 (76.7)	45 (77.6)	72 (64.9)	1	0.38	0.95
ACE-I, n (%)	8 (26.7)	9 (15.3)	33 (29.5)	0.94	0.19	1
ARB, n (%)	15 (50.0)	24 (40.7)	39 (34.8)	1	1	0.57
CCB, n (%)	9 (30.0)	6 (10.2)	21 (18.8)	0.12	0.64	0.83
Diuretics, n (%)	19 (63.3)	16 (27.1)	14 (12.5)	0.006	0.088	<0.001
Statin, n (%)	19 (63.3)	49 (83.1)	95 (84.8)	0.212	1	0.054
CPET parameters						
Peak $\dot{V}O_2$, mL/min/kg	16.2 ± 3.9	19.7 ± 4.7	23.0 ± 4.5	0.002	<0.001	<0.001
%Peak $\dot{V}O_2$, %	70.6 ± 16.4	82.8 ± 18.7	92.8 ± 19.0	0.011	0.003	<0.001
AT $\dot{V}O_2$, mL/min/kg	10.9 ± 2.1	12.4 ± 2.5	14.0 ± 2.6	0.029	<0.001	<0.001
Peak RER	1.20 ± 0.05	1.20 ± 0.06	1.18 ± 0.06	1	0.086	0.382
AT RER	0.96 ± 0.02	0.96 ± 0.03	0.95 ± 0.04	1	0.14	0.11
Peak WR, watts	86.2 ± 17.2	102.3 ± 28.6	122.9 ± 28.3	0.028	<0.001	<0.001
$\dot{V}E$ vs. $\dot{V}CO_2$ slope	33.9 (30.8–38.5)	30.6 (27.9–33.5)	29.2 (26.3–31.7)	0.007	0.137	<0.001
Minimum $\dot{V}E/\dot{V}CO_2$	36.1 (33.5–39.9)	33.9 (30.9–37.4)	30.8 (28.8–34.5)	0.173	0.002	<0.001
Peak O_2 pulse	8.6 ± 2.0	9.6 ± 2.5	11.1 ± 2.2	0.181	<0.001	<0.001
$\Delta\dot{V}O_2/\Delta WR$	8.1 ± 1.6	8.8 ± 1.4	9.4 ± 1.3	0.051	0.030	<0.001
Rest $PETO_2$, mmHg	107.2 ± 5.5	107.8 ± 4.9	108.1 ± 4.2	1	1	0.88
AT $PETO_2$, mmHg	107.1 ± 5.4	105.0 ± 5.5	102.4 ± 4.7	0.216	0.004	<0.001
$\Delta PETO_2$, mmHg	0.1 (–1.1–1.4)	2.4 (0.8–4.0)	5.2 (3.7–7.4)	<0.001	<0.001	<0.001

CPET, cardiopulmonary exercise testing; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; AP, angina pectoris; CHF, chronic heart failure; LVEF, left ventricular ejection fraction; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; $\dot{V}O_2$, oxygen uptake; AT, anaerobic threshold; RER, respiratory exchange ratio; WR, work rate; $\dot{V}E$, expiratory minute volume; $\dot{V}CO_2$, carbon dioxide output; $\dot{V}E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide; O_2, oxygen; $PETO_2$, end-tidal oxygen partial pressure. Values shown are % (n), mean ± standard deviation, or median (interquartile range).

ated with peak $\dot{V}O_2$ ($\beta = 0.518$, $p < 0.001$ and $\beta = 0.567$, $p < 0.001$, respectively). In the eGFR 45–59 group, age, Hb, and $\Delta PETO_2$ showed a significant association with peak $\dot{V}O_2$ ($\beta = -0.354$, $p = 0.006$; $\beta = 0.258$, $p = 0.007$; $\beta = 0.501$, $p < 0.001$; respectively). In the eGFR ≥60 group, $\Delta PETO_2$ was significantly associated with peak $\dot{V}O_2$ ($\beta = 0.308$, $p = 0.003$) (Table 3).

Fig. 2 summarizes the coefficients of determination of age, LVEF, Hb, and $\Delta PETO_2$ for peak $\dot{V}O_2$ by eGFR level. In the eGFR 45–59 group, the coefficient of determination for peak $\dot{V}O_2$ was higher in age and $\Delta PETO_2$ than in the other groups ($R^2 = 0.241$, $p < 0.001$; $R^2 = 0.247$, $p < 0.001$; respectively). The eGFR <45 group showed higher coefficients of determination for peak $\dot{V}O_2$ in LVEF and Hb than in the other groups ($R^2 = 0.327$, $p < 0.001$; $R^2 = 0.380$, $p < 0.001$; respectively). The p value for interaction analysis of the slope difference was <0.001.

4. Discussion

This study revealed that the determinants of peak $\dot{V}O_2$ depend on the stage of renal function in heart disease patients. In the group with eGFR <45, the determinants of peak $\dot{V}O_2$ were LVEF and Hb. In the group with eGFR 45–59, $\Delta PETO_2$ was the most influential determinant of

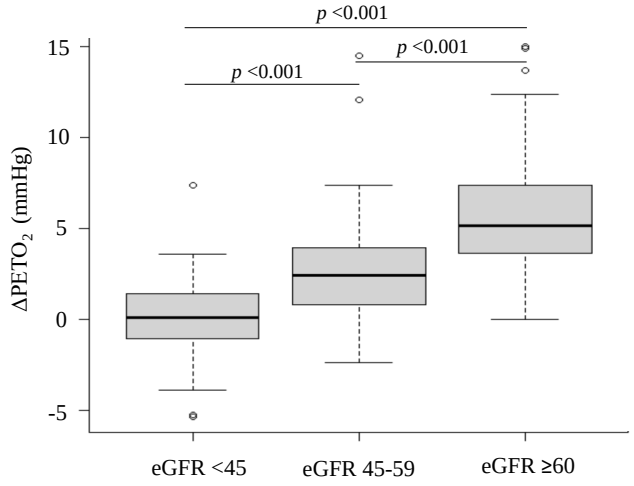

Fig. 1. Comparison of the change in end-tidal oxygen partial pressure ($\Delta PETO_2$) at different values of estimated glomerular filtration rate (eGFR).

Table 2. Univariate and multivariate linear regression analyses for peak $\dot{V}O_2$ in all subjects.

	Univariate		Multivariate		
	β	p-value	β	95% CI	p-value
Age	–0.451	<0.001	–0.142	–0.128, –0.009	0.023
LVEF	0.113	<0.001	0.150	0.018, 0.110	0.006
eGFR strata	0.508	<0.001	0.154	0.128, 2.000	0.026
Hb	0.148	<0.001	0.167	0.164, 0.914	0.005
$\Delta PETO_2$	0.552	<0.001	0.356	0.308, 0.690	<0.001
Rest $\Delta PETO_2$	0.121	0.020	–0.194	–0.335, –0.092	<0.001
R^2					*0.462*

$\dot{V}O_2$, oxygen uptake; CI, confidence interval; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; $PETO_2$, end-tidal oxygen partial pressure.

peak $\dot{V}O_2$. As a result of examining the determinants of peak $\dot{V}O_2$ in all subjects, age, LVEF, Hb, and $\Delta PETO_2$ were all determinants independently of eGFR strata. Thus, the present study clarified that in patients with heart disease with renal dysfunction, it is necessary to investigate the determinants for each level of renal dysfunction. The decrease in peak $\dot{V}O_2$ is observed in the stage of mild renal dysfunction [21]. In this study as well, peak $\dot{V}O_2$ was significantly decreased even in the eGFR 45–59 group. In this group, age, Hb and $\Delta PETO_2$ were the determinants of peak $\dot{V}O_2$, and both oxygen delivery capacity and oxygen extraction capacity affected peak $\dot{V}O_2$ in this group. Among these factors, multivariate analysis showed that $\Delta PETO_2$ had the highest β for peak $\dot{V}O_2$. Furthermore, in the univariate analysis, this group showed the highest contribution of $\Delta PETO_2$ to peak $\dot{V}O_2$.

$PETO_2$ reflects the oxygen extraction capacity of skeletal muscle during incremental exercise up to AT [13, 14], it is also reported to reflect mitochondrial oxygen uptake [15]. Although the subjects of these prior studies were mainly healthy individuals, in our study of patients with myocardial infarction, $PETO_2$ at AT was affected by abnormal ventilation, whereas $\Delta PETO_2$ from rest to AT reflected peripheral factors of peak $\dot{V}O_2$ [16].

Table 3. Univariate and multivariate linear regression analyses for peak $\dot{V}O_2$ by eGFR strata.

	Univariate		Multivariate		
	β	p-value	β	95% CI	p-value
eGFR <45 group					
Age	–0.358	0.052			
LVEF	0.572	<0.001	0.518	0.086, 0.229	<0.001
Hb	0.616	<0.001	0.567	0.728, 1.766	<0.001
$\Delta PETO_2$	0.175	0.356			
Rest $\Delta PETO_2$	0.121	0.059			
R^2					*0.620*
eGFR 45–59 group					
Age	–0.521	<0.001	–0.354	–0.297, –0.052	0.006
LVEF	0.183	0.166			
Hb	0.365	0.004	0.258	0.241, 1.449	0.007
$\Delta PETO_2$	0.523	<0.001	0.501	0.402, 1.013	<0.001
Rest $\Delta PETO_2$	0.062	0.058	–0.181	–0.384, –0.016	0.035
R^2					*0.538*
eGFR ≥60 group					
Age	–0.236	0.012	–0.215	–0.140, 0.017	0.125
LVEF	0.198	0.036	0.146	–0.014, 0.137	0.113
Hb	0.078	0.416			
$\Delta PETO_2$	0.314	<0.001	0.308	0.154, 0.716	0.003
Rest $\Delta PETO_2$	0.036	0.045	–0.193	–0.154, –0.013	0.037
R^2					*0.194*

$\dot{V}O_2$, oxygen uptake; CI, confidence interval; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; Hb, hemoglobin; $PETO_2$, end-tidal oxygen partial pressure.

Therefore, it is highly possible that $\Delta PETO_2$ represents the oxygen extraction capacity of skeletal muscle, that is, mitochondrial function. This study showed that $\Delta PETO_2$ decreased as renal dysfunction progressed.

Heart disease patients have decreased mitochondrial function due to oxidative stress, inflammation, and insulin resistance due to heart disease [22,23]. In addition, heart disease risk factors such as hyperglycemia, hyperlipidemia, and smoking also reduce mitochondrial function [24]. With the addition of renal dysfunction in these patients, oxidative stress, inflammation, and uremic toxins from the renal dysfunction cause further mitochondrial dysfunction [25–27]. Furthermore, in heart failure patients with renal dysfunction, the relation between the cardiac and renal dysfunction of cardiorenal syndrome, which adversely affect each other [11], may contribute to a further decline in mitochondrial function. A report that mitochondrial dysfunction worsens as renal dysfunction progresses also supports this result [28].

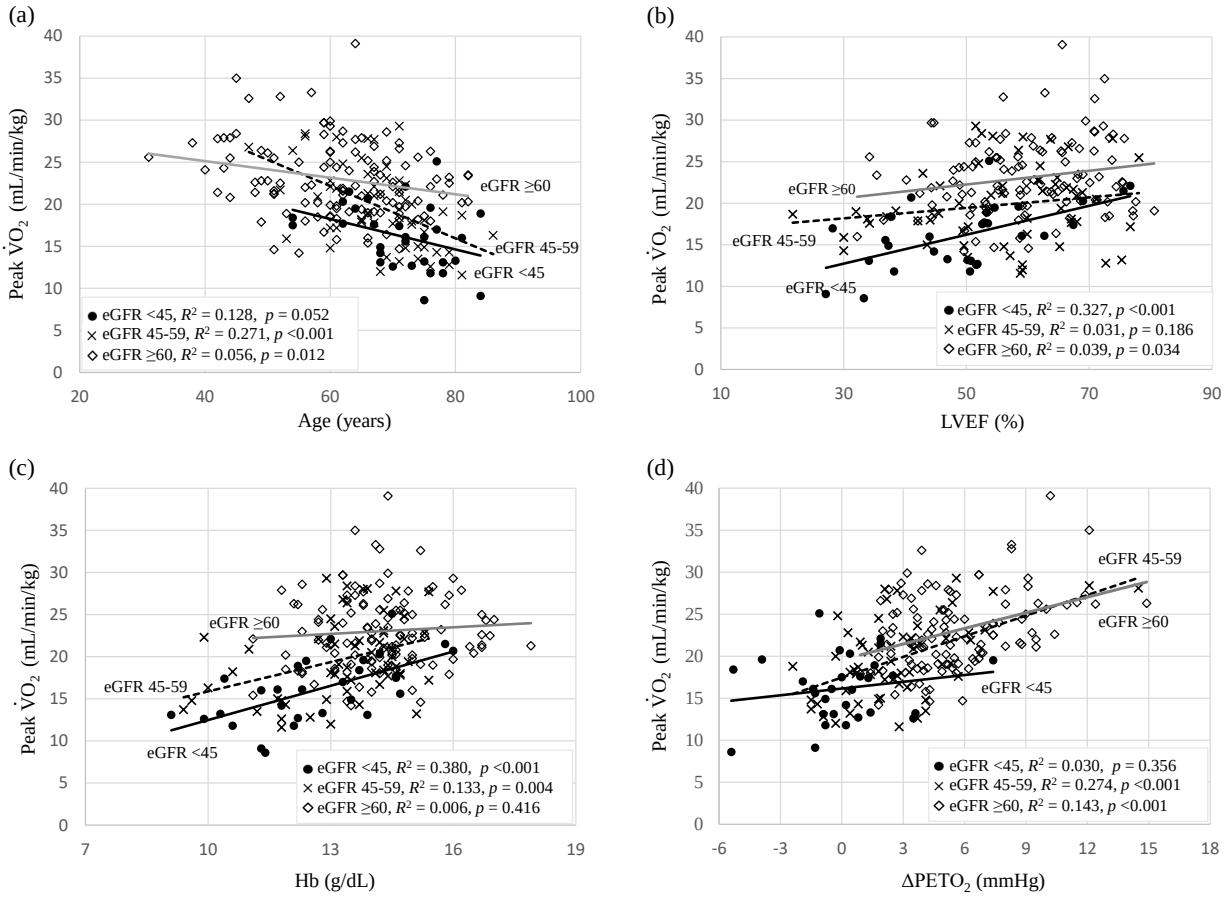

Fig. 2. Coefficients of determination for peak $\dot{V}O_2$ for each group. Coefficients of determination of the (a) age, (b) left ventricular ejection fraction (LVEF), (c) hemoglobin (Hb), and (d) change in end-tidal oxygen partial pressure ($\Delta PETO_2$) to peak $\dot{V}O_2$ for each group.

The most interesting finding in this study was that although $\Delta PETO_2$, which represents oxygen extraction capacity, decreased as renal dysfunction progressed, $\Delta PETO_2$ was not a determinant of peak $\dot{V}O_2$ in the eGFR <45 group. As peak $\dot{V}O_2$ is composed of the product of oxygen delivery capacity times oxygen extraction capacity, there is no doubt that a decrease in oxygen extraction capacity will lead to a decrease in peak $\dot{V}O_2$. However, in this study, the determinants of peak $\dot{V}O_2$ in the eGFR <45 group were LVEF and Hb, which are mainly related to oxygen delivery capacity. In this regard, as the eGFR <45 group had significantly lower LVEF and Hb than the other two groups, decreased oxygen delivery capacity may be the main contributor to the decrease in peak $\dot{V}O_2$. A previous study also reported that LVEF is not a determinant of peak $\dot{V}O_2$ [29]. However, LVEF in the present study was the determinant in heart disease patients with moderate to severe renal dysfunction. The mechanism for this is unknown, but it may be a characteristic of heart disease patients with an eGFR <45. This result also contrasted with recent reports that low oxygen extraction capacity is the main factor for low peak $\dot{V}O_2$ in CKD patients [5,12]. The $\Delta PETO_2$ of the eGFR <45 group was very low at 0.1 mmHg, and it is estimated that oxygen extraction of skeletal muscle would hardly increase during incremental exercise in these patients. As skeletal muscle oxygen extraction cannot be increased, it may be necessary for these patients to rely on oxygen delivery to increase oxygen uptake. Thus, this may be the reason why the only determinants of peak $\dot{V}O_2$ were the factors related to oxygen delivery capacity. This also supports the finding that the contribution of LVEF and Hb to peak $\dot{V}O_2$ in this group was higher than that in the other groups. The effects of exercise training aimed at improving mitochondrial function and oxygen extraction capacity to improve peak $\dot{V}O_2$ have been reported [30], but in heart disease patients with eGFR <45, such interventions may not lead to improvement in peak $\dot{V}O_2$. Improving oxygen delivery capacity may be more important. Further verification is needed on interventions to improve peak $\dot{V}O_2$ in this group.

Heart disease patients with eGFR <45 experience increased cardiovascular events [31]. One of the causes is suggested to be that cardiac load is increased due to the abnormally low value of oxygen extraction capacity being compensated for by oxygen delivery capacity.

Regarding the clinical implication of this study, the

first was that decrease in $\Delta PETO_2$ with the progression of renal dysfunction revealed that the oxygen extraction capacity of skeletal muscle decreased as renal dysfunction progressed. Second, in the eGFR <45 group, $\Delta PETO_2$ was not a determinant, and the determinant of peak $\dot{V}O_2$ was different depending on the degree of renal dysfunction. Therefore, intervention strategies for improving peak $\dot{V}O_2$ in heart disease patients should be considered for each stage of renal dysfunction. The effects of exercise training aimed at improving mitochondrial function and oxygen extraction capacity to improve peak $\dot{V}O_2$ have been reported [31], but in heart disease patients with eGFR <45, such interventions may not lead to improvement in peak $\dot{V}O_2$. Improving oxygen delivery capacity may be more important. A meta-analysis has been reported that Fe therapy improved peak $\dot{V}O_2$ in patients with heart failure with reduced EF [32]. Further verification is needed on interventions to improve peak $\dot{V}O_2$ in this group. On the other hand, in heart disease patients with eGFR 45–59, interventions that improve skeletal muscle oxygen extraction, i.e., mitochondrial function, may be effective. In recent years, it has been reported that exercise improves mitochondrial function in heart disease patients [33,34].

Study Limitations

This study has several limitations. First, this was a single-center, retrospective study consisting of a relatively small number of patients. Second, there is potential selection bias as patients who were unable to undergo CPET due to frailty and sarcopenia were excluded. Because these factors themselves are associated with mitochondrial dysfunction [35,36], further investigation of these patients is needed. Third, eGFR calculated with serum creatinine is affected by skeletal muscle mass and may not accurately reflect renal function [37]. Fourth, renal dysfunction is classified into acute kidney injury, CKD, and worsening renal function [38]. Further studies are needed to determine whether each clinical status may have different effects on skeletal muscle oxygen extraction capacity. Fifth, there was a significant difference in the etiology between the groups. Future studies will need to be validated for association with etiology. Finally, we could not evaluate cardiac output, vascular function including that of the capillaries, and skeletal muscle mass, which are additional determinants of peak $\dot{V}O_2$.

5. Conclusions

$\Delta PETO_2$, which indicates the oxygen extraction capacity of skeletal muscle, decreased with the progression of renal dysfunction. In the eGFR 45–59 group, $\Delta PETO_2$ was the strongest determinant of peak $\dot{V}O_2$, but the determinants in the eGFR <45 group were LVEF and Hb, and $\Delta PETO_2$ was not included. This study suggests that intervention strategies should be considered for each stage of renal dysfunction to improve peak $\dot{V}O_2$ in heart disease patients.

Abbreviations

CKD, chronic kidney disease; CPET, cardiopulmonary exercise testing; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; peak $\dot{V}O_2$, peak oxygen uptake; $PETO_2$, end-tidal oxygen partial pressure; RER, respiratory exchange ratio; $\dot{V}CO_2$, carbon dioxide production; $\dot{V}E$, minute ventilation.

Author Contributions

AO—Conceptualization, Methodology, Formal analysis, Investigation, Writing-Original Draft. KPI—Conceptualization, Methodology, Writing-Review & Editing, Supervision. SS—Conceptualization, Methodology. HT—Investigation, Writing-Review & Editing. FK—Investigation, Writing-Review & Editing. MW—Formal analysis, Investigation. MK—Writing-Review & Editing. IK—Writing-Review & Editing. RY—Supervision. YM—Project administration. All authors approved the manuscript for submission.

Ethics Approval and Consent to Participate

This study complied with the Declaration of Helsinki with respect to investigation in humans and was approved by the Ethics Committee of Sanda City Hospital (approval number: 2021009). Written informed consent was obtained from each patient.

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Conflict of Interest

The author declares no conflict of interest. Kazuhiro P. Izawa is serving as one of the guest editor of this journal. We declare that Kazuhiro P. Izawa had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Brian Tomlinson.

References

[1] Ng JK, Li PK. Chronic kidney disease epidemic: how do we deal with it? Nephrology. 2018; 23: 116–120.

[2] Tanaka K, Jujo K, Yamaguchi J, Ogawa H, Hagiwara N. Optimal Blood Pressure in Patients with Coronary Artery Disease and Chronic Kidney Disease: HIJ-CREATE Substudy. The American Journal of the Medical Sciences. 2019; 358: 219–226.

[3] Jhund PS, Solomon SD, Docherty KF, Heerspink HJL, Anand IS, Böhm M, *et al*. Efficacy of Dapagliflozin on Renal Function and Outcomes in Patients with Heart Failure with Reduced Ejection Fraction. Circulation. 2021; 143: 298–309.

[4] Patel RB, Mehta R, Redfield MM, Borlaug BA, Hernandez AF, Shah SJ, *et al*. Renal Dysfunction in Heart Failure with Preserved Ejection Fraction: Insights from the RELAX Trial. Journal of Cardiac Failure. 2020; 26: 233–242.

[5] Takaya Y, Kumasaka R, Arakawa T, Ohara T, Nakanishi M, Noguchi T, *et al*. Impact of Cardiac Rehabilitation on Renal Function in Patients with and without Chronic Kidney Disease after Acute Myocardial Infarction. Circulation Journal. 2014; 78: 377–384.

[6] Scrutinio D, Agostoni P, Gesualdo L, Corrà U, Mezzani A, Piepoli M, *et al*. Renal Function and Peak Exercise Oxygen Consumption in Chronic Heart Failure with Reduced Left Ventricular Ejection Fraction. Circulation Journal. 2015; 79: 583–591.

[7] Ezzatvar Y, Izquierdo M, Núñez J, Calatayud J, Ramírez-Vélez R, García-Hermoso A. Cardiorespiratory fitness measured with cardiopulmonary exercise testing and mortality in patients with cardiovascular disease: a systematic review and meta-analysis. Journal of Sport and Health Science. 2021; 10: 609–619.

[8] Cahalin LP, Chase P, Arena R, Myers J, Bensimhon D, Peberdy MA, *et al*. A meta-analysis of the prognostic significance of cardiopulmonary exercise testing in patients with heart failure. Heart Failure Reviews. 2013; 18: 79–94.

[9] Del Buono MG, Arena R, Borlaug BA, Carbone S, Canada JM, Kirkman DL, *et al*. Exercise Intolerance in Patients with Heart Failure. Journal of the American College of Cardiology. 2019; 73: 2209–2225.

[10] Van Craenenbroeck AH, Van Craenenbroeck EM, Van Ackeren K, Hoymans VY, Verpooten GA, Vrints CJ, *et al*. Impaired vascular function contributes to exercise intolerance in chronic kidney disease. Nephrology Dialysis Transplantation. 2016; 31: 2064–2072.

[11] Ronco C, Bellasi A, Di Lullo L. Cardiorenal Syndrome: an Overview. Advances in Chronic Kidney Disease. 2018; 25: 382–390.

[12] Chinnappa S, Lewis N, Baldo O, Shih M, Tu Y, Mooney A. Cardiac and Noncardiac Determinants of Exercise Capacity in CKD. Journal of the American Society of Nephrology. 2021; 32: 1813–1822.

[13] Binder RK, Wonisch M, Corra U, Cohen-Solal A, Vanhees L, Saner H, *et al*. Methodological approach to the first and second lactate threshold in incremental cardiopulmonary exercise testing. European Journal of Cardiovascular Prevention & Rehabilitation. 2008; 15: 726–734.

[14] Salvadori A, Fanari P, Mazza P, Agosti R, Longhini E. Work Capacity and Cardiopulmonary Adaptation of the Obese Subject during Exercise Testing. Chest. 1992; 101: 674–679.

[15] Baumbach P, Schmidt-Winter C, Hoefer J, Derlien S, Best N, Herbsleb M, *et al*. A pilot study on the association of mitochondrial oxygen metabolism and gas exchange during cardiopulmonary exercise testing: Is there a mitochondrial threshold? Frontiers in Medicine. 2020; 7: 585462.

[16] Ogura A, Izawa KP, Sato S, Tawa H, Kureha F, Wada M, *et al*. Relationship of end-tidal oxygen partial pressure to the determinants of anaerobic threshold in post-myocardial infarction patients. Heart and Vessels. 2021; 36: 1811–1817.

[17] Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, *et al*. Clinician's Guide to Cardiopulmonary Exercise Testing in Adults. Circulation. 2010; 122: 191–225.

[18] Pescatello LS. ACSM's Guidelines for Exercise Testing and Prescription (pp. 151). Wolters Kluwer/Lippincott Williams & Wilkins Health: Philadelphia. 2014.

[19] Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, *et al*. Collaborators developing the Japanese equation for estimated GFR. Revised equation for estimated GFR from serum creatinine in Japan. American Journal of Kidney Diseases. 2009; 53: 982–992.

[20] Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL, *et al*. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, KDIGO clinical practice guideline for acute kidney injury. Kidney International Supplements. 2012; 2: 1–138.

[21] McCullough PA, Franklin BA, Leifer E, Fonarow GC. Impact of Reduced Kidney Function on Cardiopulmonary Fitness in Patients with Systolic Heart Failure. American Journal of Nephrology. 2010; 32: 226–233.

[22] Kinugawa S, Takada S, Matsushima S, Okita K, Tsutsui H. Skeletal Muscle Abnormalities in Heart Failure. International Heart Journal. 2015; 56: 475–484.

[23] Keshavarz-Bahaghighat H, Darwesh AM, Sosnowski DK, Seubert JM. Mitochondrial dysfunction and inflammaging in heart failure: novel roles of CYP-derived epoxylipids. Cells. 2020; 9: 1565.

[24] Poznyak AV, Ivanova EA, Sobenin IA, Yet SF, Orekhov AN. The role of mitochondria in cardiovascular diseases. Biology. 2020; 9: 137.

[25] Yokoi H, Yanagita M. Decrease of muscle volume in chronic kidney disease: the role of mitochondria in skeletal muscle. Kidney International. 2014; 85: 1258–1260.

[26] Alcalde-Estévez E, Sosa P, Asenjo-Bueno A, Plaza P, Olmos G, Naves-Díaz M, *et al*. Uraemic toxins impair skeletal muscle regeneration by inhibiting myoblast proliferation, reducing myogenic differentiation, and promoting muscular fibrosis. Scientific Reports. 2021; 11: 512.

[27] Yazdi PG, Moradi H, Yang JY, Wang PH, Vaziri ND. Skeletal muscle mitochondrial depletion and dysfunction in chronic kidney disease. International Journal of Clinical and Experimental Medicine. 2013; 6: 532–539.

[28] Adey D, Kumar R, McCarthy JT, Nair KS. Reduced synthesis of muscle proteins in chronic renal failure. American Journal of Physiology-Endocrinology and Metabolism. 2000; 278: E219–E225.

[29] Roibal Pravio J, Barge Caballero E, Barbeito Caamaño C, Paniagua Martin MJ, Barge Caballero G, Couto Mallon D, *et al*. Determinants of maximal oxygen uptake in patients with heart failure. ESC Heart Failure. 2021; 8: 2002–2008.

[30] Guimarães GV, Ribeiro F, Castro RE, Roque JM, Machado ADT, Antunes-Correa LM, *et al*. Effects of the exercise training on skeletal muscle oxygen consumption in heart failure patients with reduced ejection fraction. International Journal of Cardiology. 2021; 343: 73–79.

[31] Tedeschi A, Agostoni P, Pezzuto B, Corra' U, Scrutinio D, La Gioia R, *et al*. Role of comorbidities in heart failure prognosis Part 2: Chronic kidney disease, elevated serum uric acid. European Journal of Preventive Cardiology. 2020; 27: 35–45.

[32] Zhang S, Zhang F, Du M, Huang K, Wang C. Efficacy and safety of iron supplementation in patients with heart failure and iron deficiency: a meta-analysis. British Journal of Nutrition. 2019; 121: 841–848.

[33] Mafra D, Gidlund E, Borges NA, Magliano DC, Lindholm B, Stenvinkel P, *et al*. Bioactive food and exercise in chronic kidney disease: Targeting the mitochondria. European Journal of

Clinical Investigation. 2018; 48: e13020.
[34] Gu C, Yan J, Zhao L, Wu G, Wang YL. Regulation of mitochondrial dynamics by aerobic exercise in cardiovascular diseases. Frontiers in Cardiovascular Medicine. 2022; 13: 788505.
[35] Cardoso AL, Fernandes A, Aguilar-Pimentel JA, de Angelis MH, Guedes JR, Brito MA, *et al*. Towards frailty biomarkers: Candidates from genes and pathways regulated in aging and age-related diseases. Ageing Research Reviews. 2018; 47: 214–277.
[36] Kameda M, Teruya T, Yanagida M, Kondoh H. Reduced uremic metabolites are prominent feature of sarcopenia, distinct from antioxidative markers for frailty. Aging. 2021; 13: 20915–20934.
[37] Potok OA, Ix JH, Shlipak MG, Katz R, Hawfield AT, Rocco MV, *et al*. The Difference between Cystatin C– and Creatinine-Based Estimated GFR and Associations with Frailty and Adverse Outcomes: a Cohort Analysis of the Systolic Blood Pressure Intervention Trial (SPRINT). American Journal of Kidney Diseases. 2020; 76: 765–774.
[38] Damman K, Testani JM. The kidney in heart failure: an update. European Heart Journal. 2015; 36: 1437–1444.