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Sydney Tang

Editor-in-Chief

Nephrology

Re: Impact of Worsening Renal Function on Peak Oxygen Uptake in Patients with Acute Myocardial Infarction

Dear Dr. Tang:

We would like to re-submit our manuscript entitled “*Impact of Worsening Renal Function on Peak Oxygen Uptake in Patients with Acute Myocardial Infarction*” to be considered for publication as a scientific research article in the *Nephrology*.

We have revised this manuscript based on the reviewer’s comments for us.

All authors have approved the submission of this manuscript to your journal, have taken due care to ensure the integrity of the work, and confirm that neither the manuscript nor any part of it has been published or is under consideration for publication elsewhere. Asami Ogura and Kazuhiro P. Izawa contributed to the conception and design of the study. Asami Ogura, HidetoTawa, Fumie Kureha and Masaaki Wada contributed to the acquisition of data or analysis and interpretation of data. Kazuhiro P. Izawa, Ikko Kubo, Masashi Kanai, Fumie Kureha, Ryohei Yoshikawa and Yuichi Matsuda drafted the article or critically revised it for important intellectual content. All of the authors gave final approval and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

We hope that our findings are of interest to you, the editorial staff, and readers of the *Nephrology* and that you will find our manuscript suitable for publication.

Sincerely,

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Impact of Worsening Renal Function on Peak Oxygen Uptake in Patients with Acute Myocardial Infarction

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Impact of Worsening Renal Function on Peak VO₂

Abstract

Aim

Worsening renal function (WRF) induced by acute myocardial infarction is a strong predictor of cardiovascular events and mortality. Peak oxygen uptake may contribute to prognosis in acute myocardial infarction (AMI) patients with WRF; however, the impact of WRF on peak oxygen uptake is unclear.

Methods

Among 154 patients with AMI who underwent emergency percutaneous coronary intervention and participated in phase II cardiac rehabilitation, those who underwent cardiopulmonary exercise testing were consecutively enrolled. WRF was defined as a $\geq 20\%$ decrease in estimated glomerular filtration rate (eGFR [mL/min/1.73 m²]) from admission to that at cardiopulmonary exercise testing. The association of WRF with peak oxygen uptake was evaluated by multivariate regression analysis. The non-WRF group was divided into two subgroups according to eGFR $<60/\geq 60$ at cardiopulmonary exercise testing, and eGFR at cardiopulmonary exercise testing and peak oxygen uptake of all three groups were compared.

Results

Ninety-four patients were enrolled in the final analysis. Multiple linear regression analysis showed that WRF was associated with peak oxygen uptake ($p=0.003$). Comparing the non-WRF group with eGFR at cardiopulmonary exercise testing <60 and the WRF group,

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4 although eGFR at cardiopulmonary exercise testing was similar ($p=1.000$), peak oxygen
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7 uptake in the WRF group was significantly lower ($p=0.026$).
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10 **Conclusion**

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13 WRF, not eGFR at cardiopulmonary exercise testing was significantly associated with peak
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16 oxygen uptake in patients with acute myocardial infarction. This result suggests that when
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19 considering the relationship between renal function and peak oxygen uptake, WRF must be
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22 taken into account.
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28 *Keywords:* Acute myocardial infarction, Peak oxygen uptake, Worsening renal function
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Peak oxygen uptake (VO_2) measured during cardiopulmonary exercise testing (CPX) is the gold standard for assessing cardiovascular functional capacity and cardiorespiratory fitness.¹ Peak VO_2 is also an independent predictor of all-cause and cardiovascular-specific mortality in patients with coronary artery disease.² Patients with chronic kidney disease (CKD) have reduced peak VO_2 ^{3,4} as do patients with acute myocardial infarction (AMI) and CKD.⁵ Additionally, in regard to renal function in patients with AMI, it is important to consider AMI-induced worsening renal function (WRF). In previous reports, the prevalence of WRF ranged from 7.34 to 37%,⁶⁻¹⁰ indicating that it is not uncommon. WRF patients have higher mortality and cardiovascular event rates than non-WRF patients,⁶⁻⁹ and similar results have been reported in studies adjusted for CKD.¹⁰ Therefore, it is expected that WRF patients would have lower peak VO_2 caused by a different mechanism than that of CKD. However, few studies have examined the impact of WRF on peak VO_2 . **Examining the effect of WRF on peak VO_2 may improve the prognosis of WRF patients.** In this study, we hypothesized that WRF patients would have a lower peak VO_2 than non-WRF patients. The purpose of this study was to clarify the effect of WRF on peak VO_2 in patients with AMI.

1. Methods

1.1. Study design and patients

This was a retrospective observational cohort study performed in a single center. From April

2016 to December 2019, 154 patients with AMI who underwent an emergency percutaneous coronary intervention treated and participated in cardiac rehabilitation in Sanda City Hospital were consecutively enrolled in this study. The inclusion criterion was having undergone CPX between 1 and 6 months after AMI onset.¹¹ Exclusion criteria included patients with peak respiratory exchange ratio (RER) <1.10 at CPX,¹² TIMI grade ≤ 2 and atrial fibrillation. Patients' characteristics and clinical parameters including age, sex, body mass index, peak creatine phosphokinase, ST-elevation myocardial infarction, left ventricular ejection fraction (LVEF) during hospitalization, contrast volume, pain-to-balloon time (ischemic time), medical history, laboratory values on admission (estimated glomerular filtration rate [eGFR (mL/min/1.73 m²)], blood urea nitrogen (BUN), serum creatinine (sCr), brain natriuretic peptide concentration, serum C-reactive protein, hemoglobin, hemoglobin A1c), laboratory values at CPX (eGFR, BUN, sCr, hemoglobin), medications at the time of CPX and the results of CPX were obtained from the electronic medical records by two physical therapists. Laboratory values at CPX were extracted within 2 weeks around the date of CPX. 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 no.2019017). Written informed consent was obtained from each patient.

1.2. Symptom-limited CPX

All patients underwent symptom-limited maximal CPX using a cycle ergometer (Strength Ergo 8; Mitsubishi Electric Engineering Co., Ltd., Tokyo, Japan) with a 10 watt/min continuous ramp exercise protocol, after a 3-min period of rest and a 4-min period of warm-up at 0 or 20 watts. During CPX, expired gas analysis (AE-310S; Minato Medical Science, Osaka, Japan) was performed, and the electrocardiogram and blood pressure of the patients were recorded. The patients were encouraged to reach a maximal or near maximal effort by monitoring the RER at >1.10 .¹² Peak VO_2 was defined as the VO_2 attained at peak exercise, and %peak VO_2 ¹³ was also calculated. Anaerobic threshold (AT) was determined using the V-slope, ventilatory equivalents and end-tidal pressure methods¹⁴ by at least 2 experts in CPX. Peak oxygen pulse (peak O_2 pulse), minute ventilation at maximal exercise (peak VE), minute ventilation-carbon dioxide production linear regression slope (VE vs. VCO_2 slope) and minimum ventilatory equivalent for carbon dioxide (minimum VE/VCO_2) were also obtained. Peak work rate (WR) was defined as the work rate at peak VO_2 . The following heart rate (HR) parameters were calculated: increases from Rest HR to Peak HR (ΔHR peak-rest), from Rest HR to AT HR (ΔHR AT-rest), and from AT HR to peak HR (ΔHR peak-AT). %HR reserve was calculated as $(\text{Peak HR} - \text{Rest HR}) / (220 - \text{age} - \text{Rest HR}) \times 100$.¹⁵ HR recovery was defined as the difference in HR between the HR from peak exercise to 1 min and to 2 min after exercise.

1.3. Definition

WRF was defined as a $\geq 20\%$ decrease in eGFR from baseline based on 2016 ESC heart failure guidelines.¹⁶ Baseline renal function was defined as eGFR at admission based on previous studies.⁷⁻⁹ In this study, eGFR was evaluated with the Japanese version of the equation (JMDRD): $\text{eGFR} = 194 \times (\text{serum creatinine})^{-1.094} \times \text{age}^{-0.287} (\times 0.739 \text{ if female})$.¹⁷ We divided the patients into two groups, the WRF group and the non-WRF group.

1.4. Statistical analysis

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. Continuous variables were compared by Student *t*-test or Mann-Whitney test, and categorical data were compared by Fisher's exact test. Univariate and multivariate linear regression analyses were performed to identify WRF associated with peak VO_2 , with age, sex, LVEF, diabetes mellitus, hemoglobin at CPX and eGFR at CPX defined as confounding factors according to previous studies.^{5,13,18-21} Variables with $p < 0.05$ in univariate regression analysis were entered into multiple regression analysis. Furthermore, the non-WRF group was divided into two subgroups according to $\text{eGFR} < 60 / \geq 60 \text{ mL/min/1.73 m}^2$ at CPX, and the eGFR at CPX and peak VO_2 of these subgroups were compared with those of the WRF group using one-way ANOVA, followed by the Bonferroni multiple

comparison post hoc test. A p value of <0.05 was considered to indicate statistical significance. A post-hoc power calculation was performed. Using a two-sided α level of 0.05, our sample size yielded sufficient power to detect a 4.5 mL/min/kg difference between groups in Peak VO_2 with over 80% power. All 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). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

2. Results

In total, 94 patients were enrolled in the final analysis. The WRF group comprised 20 patients (21.3%). Figure 1 shows a flowchart of the study population selection. Clinical characteristics of the patients are shown in Table 1. Patients in the WRF group had longer pain-to-balloon time, higher BNP and higher eGFR at admission, lower eGFR, higher BUN and higher BUN/creatinine ratio at CPX, than those in the non-WRF group. Medications were not significantly different between the two groups. Regarding the CPX parameters, patients in the WRF group had lower peak VO_2 , lower %peak VO_2 , lower peak O_2 pulse, lower peak WR and higher VE vs. VCO_2 slope and higher minimum VE/ VCO_2 . Although peak RER was not significantly different between the groups, AT RER was significantly higher in the WRF

group. Patients in the WRF group had lower peak HR, lower %HR reserve, lower Δ HR (peak-rest) and, especially, a lower Δ HR (peak-AT).

Multivariate linear regression analysis showed that peak VO_2 correlated significantly with age ($\beta = -0.110$, $p = 0.035$), sex ($\beta = -4.138$, $p = 0.003$), LVEF ($\beta = 0.167$, $p < 0.001$), hemoglobin at CPX ($\beta = 0.641$, $p = 0.045$) and WRF ($\beta = -3.161$, $p = 0.003$). eGFR at CPX was associated with peak VO_2 in the univariate analysis but not in the multivariate analysis (Table 2). Furthermore, a comparison between the non-WRF group with eGFR at CPX < 60 mL/min/1.73 m² and the WRF group showed that although the eGFR at CPX was essentially the same (WRF group: 54.6 ± 20.4 mL/min/1.73 m², non-WRF group with eGFR at CPX < 60 mL/min/1.73 m²: 54.5 ± 5.6 mL/min/1.73 m², $p = 1.000$), peak VO_2 in the WRF group was significantly lower (WRF group: 17.0 ± 3.3 mL/min/kg, non-WRF group: 20.7 ± 4.8 mL/min/kg, $p = 0.026$) (Figure 2).

3. Discussion

This study assessed, for the first time to our knowledge, the effect of WRF on peak VO_2 .

Although not only CKD but also WRF is important in the prognosis of AMI patients,⁶⁻⁹ only the effect of CKD on peak VO_2 has been reported,^{3,4} whereas that of WRF is unclear.

Our study showed that WRF was associated with lower peak VO_2 independent of other established factors such as age, sex, LVEF and hemoglobin at CPX.^{13,19-21} Interestingly,

eGFR at CPX had no association with peak VO_2 . Furthermore, even at a similar level of eGFR at CPX, peak VO_2 was significantly lower in the WRF group. Our study suggests that when considering renal function in patients with AMI, it is important to also consider AMI-induced WRF.

Previous studies have shown that eGFR at CPX is an independent factor associated with peak VO_2 ,^{3,4} but no significant association was found in the present study after adjustment for WRF. In our results, as the eGFR at CPX was around 60 mL/min/1.73 m², we thought that the influence of kidney dysfunction was small. It has been reported that if the eGFR is 60 mL/min/1.73 m² or more, the effect on peak VO_2 is relatively small.⁴ However, we found that WRF had a significant effect on peak VO_2 even if the decrease in eGFR was very slight. Therefore, we suggest that even in patients with an eGFR of around 60 mL/min/1.73 m², the presence of WRF can reduce peak VO_2 .

In the WRF group, % peak VO_2 , with peak VO_2 adjusted by age and sex, was also significantly lower than that in the non-WRF group. As a cause for WRF to affect peak VO_2 , according to the Fick formula, peak VO_2 is determined by stroke volume \times heart rate \times arteriovenous oxygen difference. Based on this formula, regarding stroke volume, since LVEF was 55.3% in the WRF group, it is considered that there is little influence of hypofunction of the heart function, but since BUN/creatinine ratio in the WRF group was high, poor stroke volume may have affected peak VO_2 .²² Furthermore, the WRF group had

significantly poor HR response, especially from AT to peak. Poor HR response is caused by desensitization or down-regulation of myocardial β -receptor to sympathetic nerve stimulation.^{23,24} In particular, as exercise intensity increases, cardiac control shifts from predominantly parasympathetic control to predominantly sympathetic control,²⁵ so this may be the reason for the low Δ HR after AT. It has been reported that sympathetic desensitization, which indicates hyporesponsiveness, and down-regulation, which is indicative of a decrease in receptor due to prolonged sympathetic hyperactivity, occur about one month after AMI onset.²⁶ Neurohormonal factors such as the renin-angiotensin-aldosterone system and the sympathetic nervous system are known to be activated in patients after acute coronary syndrome and to be involved in cardiorenal syndrome.⁸ Moreover, sympathetic hyperactivity after AMI was reported to persist for 9 months after onset.²⁷ In the present study, several results suggesting sympathetic hyperactivity in the WRF group were shown. First, the WRF group had significantly longer pain-to-balloon time than the non-WRF group. Previous studies reported that pain-to-balloon time is associated with WRF,²⁸ and sympathetic hyperactivity in AMI patients is associated with ischemic time.²⁹ Next, although BUN was not significantly different on admission, it was significantly higher in the WRF group at CPX. The increase in BUN may be contributed to by an increase in the activity of both the renin-angiotensin aldosterone system and sympathetic nervous system,³⁰ even in patients with AMI.³¹ Therefore, it is presumed that the neurohormonal activity at the time of CPX was

higher in the WRF group. Although it is unclear in this study why sympathetic hyperactivity occurred in the WRF group, previous studies have shown that the pathophysiology of the cardiorenal syndrome involves interrelated hemodynamic and neurohormonal mechanisms, including the sympathetic nervous system, the renin-angiotensin-aldosterone system, and endothelin and arginine vasopressin system activation.^{32,33} From the above, we considered that the patients in the WRF group had high sympathetic nerve activity for a long time and that poor HR response through sympathetic nerve desensitization or down-regulation caused their low peak VO_2 values.

Another factor in the Fick formula, arteriovenous oxygen difference, indicates skeletal muscle abnormalities.³ Despite the two groups having the same level of peak RER, the WRF group may have had some skeletal muscle abnormalities because peak WR was significantly lower in this group.

It is considered that the activation of neurohumoral systems also affects skeletal muscle abnormalities as activation of these systems has been reported to result in skeletal muscle catabolism.^{34, 35} In the WRF group, skeletal muscle catabolism due to the activation of neurohumoral systems may have reduced the arteriovenous oxygen difference.

However, impairment of bicarbonate regeneration due to WRF is compensated for by a decrease in PETCO_2 and thus enhances ventilation, which reduces respiratory reserve.³⁶ In the present study as well, minimum VE/VCO_2 and VE/VCO_2 slopes were significantly high,

and it is possible that the decrease in ventilation reserve in the WRF group affected the low peak VO_2 .

Activation of neurohumoral systems and skeletal muscle abnormalities suggested by this study to be responsible for low peak VO_2 can be prevented or improved by exercise. Exercise therapy has been reported to suppress sympathetic hyperactivity.³⁷ It is well known that exercise therapy is effective for skeletal muscle abnormalities,³⁸ and exercise can also effectively inhibit skeletal muscle abnormalities due to myocardial infarction.³⁹ Improvement of peak VO_2 by exercise therapy may improve the prognosis of WRF patients.

This study has several limitations need to be acknowledged. First, this was a single-center, retrospective study consisting of a relatively small number of patients. Second, this study is affected by selection bias as patients who were unable to undergo symptom-limited CPX due to frailty were excluded from the study. Therefore, the subjects in this study consisted of relatively young patients. Third, the value of serum creatinine on admission may not reflect true baseline renal function as we included patients with acute coronary syndrome, left ventricular dysfunction, heart failure and cardiogenic shock.

In conclusion, WRF, not eGFR at cardiopulmonary exercise testing was significantly associated with peak oxygen uptake in patients with acute myocardial infarction. This result

suggests that when considering the relationship between renal function and peak oxygen uptake, WRF must be taken into account.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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Figure Legend

Fig. 1. Flow of patients through the study. PCI, percutaneous coronary intervention; AMI, acute myocardial infarction; CPET, cardiopulmonary exercise testing; WRF, worsening renal function.

Fig. 2. eGFR at CPET and peak VO_2 in patients in the WRF group compared with those in the non-WRF group divided by eGFR $<60/\geq 60$ mL/min/1.73 m² at CPET. eGFR, estimated glomerular filtration rate; CPET, cardiopulmonary exercise testing; VO_2 , oxygen uptake; WRF, worsening renal function.

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Table 1. Clinical characteristics of the patients.				
	WRF n = 20	Non-WRF n = 74	<i>t</i> value	P value
Age, yrs	65.7 ± 11.0	61.5 ± 10.3	-1.559	.123
Male, n (%)	16 (80.0)	67 (90.5)	-	.239
Body mass index, kg/m ²	23.8 ± 3.7	23.9 ± 3.1	.111	.913
Peak CPK, IU/L	2617.0 (881.8–4313.5)	1969.0 (679.8–4049.5)	-	.602
STEMI, n (%)	13 (65.0)	56 (75.7)	-	.395
LVEF, %	55.3 ± 11.1	57.3 ± 9.8	.798	.427
Contrast volume, mL	146.4 ± 29.9	151.4 ± 41.6	.504	.615
Pain-to-balloon time, min	294.0 (217.5–356.8)	157.0 (112.3–271.3)	-	.003**
Smoking, n (%)	15 (75.0)	54 (73.0)		1
Medical history				
Hypertension, n (%)	15 (75.0)	50 (67.6)	-	.596
Diabetes mellitus, n (%)	4 (20.0)	26 (35.1)	-	.281
eGFR, mL/min/1.73 m ²				
Admission	76.3 ± 26.6	64.3 ± 13.6	-2.787	.006**
At CPX	55.3 ± 20.1	65.9 ± 12.1	3.527	.004**
Δ (at CPX – admission)	-21.0 ± 7.8	1.2 ± 10.1	9.389	<.001**
Laboratory values on admission				
BUN, mg/dL	14.6 (13.4–17.8)	16.3 (13.2–20.3)		.307
sCr, mg/dL	0.71 (0.63–0.91)	0.93 (0.82–1.08)		.007**
BUN/creatinine ratio	18.2 (15.8–23.6)	18.0 (14.1–22.3)	-	.485
BNP, pg/mL	46.5 (26.4–71.4)	20.0 (8.0–66.0)	-	.034*
Serum CRP, nmol/L	0.08 (0.04–0.32)	0.10 (0.05–0.31)	-	.677
Hemoglobin, mg/dL	14.8 ± 1.4	14.9 ± 1.7	.257	.798
HbA1c, %	6.0 (5.9–6.5)	6.0 (5.8–6.7)	-	.673
Laboratory values at CPX				
BUN, mg/dL	19.5 (16.7–24.4)	16.0 (14.3–18.7)		.009**
sCr, mg/dL	0.98 (0.86–1.24)	0.91 (0.79–1.02)		.046*
BUN/creatinine ratio	24.2 (21.6–29.1)	16.8 (14.9–20.9)		<.001**
Hemoglobin, mg/dL	13.8 ± 1.5	14.0 ± 1.5	.616	.539
Medications at CPX				
Beta blocker, n (%)	16 (80.0)	58 (78.4)	-	1
ACE-I, n (%)	7 (35.0)	28 (35.1)	-	1
ARB, n (%)	10 (50.0)	23 (31.1)	-	.186
CCB, n (%)	3 (15.0)	11 (14.9)	-	1
Diuretic, n (%)	7 (35.0)	13 (17.6)	-	.123
Oral diabetic drug, n (%)	5 (25.0)	21 (28.4)		1
Statin, n (%)	19 (95.0)	70 (94.6)	-	1
CPX parameters				
Peak VO ₂ , mL/min/kg	17.4 ± 3.7	21.9 ± 5.0	3.723	<.001**
%Peak VO ₂ , %	71.9 ± 12.8	88.7 ± 19.3	3.678	<.001**
AT VO ₂ , mL/min/kg	12.2 (11.0–13.8)	13.1 (11.4–15.1)	-	.152

Peak RER	1.17 ± 0.07	1.18 ± 0.06	1.017	.421
AT RER	0.98 ± 0.03	0.95 ± 0.03	-3.408	<.001**

Table 2Univariate and multivariate linear regression models testing for peak VO₂.

	Univariate		Multivariate		
	β	P-value	β	95% CI	P-value
Age	-0.201	<.001**	-0.110	-0.191, -0.007	.035*
Sex	-5.549	<.001**	-4.138	-6.790, -1.486	.003**
LVEF	0.166	.001**	0.167	0.082, 0.253	<.001**
WRF	-4.437	<.001**	-3.161	-5.214, -1.109	.003**
eGFR at CPX	0.123	<.001**	-0.006	-0.074, 0.062	.869
Diabetes mellitus	-1.397	0.213			
Hemoglobin at CPX	1.148	<.001**	0.641	0.015, 1.264	.045*
R²					0.407

Abbreviations: CI, confidence interval; CPX, cardiopulmonary exercise testing; eGFR, estimated

VE vs. VCO ₂ slope	32.7 (29.1–35.8)	28.8 (26.1–31.8)	-	.018*
Minimum VE/VCO ₂	35.2 ± 6.5	32.2 ± 4.1	-2.490	.015*
Peak O ₂ pulse	9.2 ± 2.5	10.9 ± 2.5	2.572	.012*
ΔVO ₂ /ΔWR	8.7 ± 1.6	8.9 ± 1.4	.379	.706
Peak WR, watt	89.0 (79.3–107.3)	112.0 (93.8–130.0)	-	.002**
AT WR, watt	58.0 (46.8–71.3)	64.0 (53.0–77.0)	-	.156
Rest HR, bpm	70.5 ± 12.2	68.1 ± 10.6	-.841	.403
AT HR, bpm	97.1 ± 15.5	94.3 ± 12.3	-.836	.405
Peak HR, bpm	124.8 ± 18.2	135.7 ± 17.5	2.380	.019*
ΔHR (peak-rest), bpm	54.4 ± 13.5	67.3 ± 17.4	3.070	.003**
ΔHR (AT-rest), bpm	31.2 ± 8.1	29.9 ± 10.5	-.461	.646
ΔHR (peak-AT), bpm	23.1 ± 12.9	41.4 ± 14.5	3.821	<.001**
%HR reserve, %	65.9 ± 16.7	75.1 ± 17.8	2.065	.042*
HR recovery 1 min, bpm	20.1 ± 8.3	23.6 ± 9.6	1.481	.142
Days from onset to CPX, days	79.0 ± 50.0	85.1 ± 50.2	0.486	.628

Abbreviations: ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AT, anaerobic threshold; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CCB, calcium channel blocker; CPX, cardiopulmonary exercise testing; CPK, **creatinine** phosphokinase; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HR, heart rate; LVEF, left ventricular ejection fraction; O₂, oxygen; RER, respiratory exchange ratio; sCr, serum creatinine; STEMI, ST-elevation myocardial infarction; VCO₂, carbon dioxide output; VE, expiratory minute volume; VO₂, oxygen uptake; WR, work rate; WRF, worsening renal function.

Values shown are n (%), mean ± standard deviation, or median (interquartile range).

* $P < .05$.

** $P < .01$.

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glomerular filtration rate; LVEF, left ventricular ejection fraction; VO₂, oxygen uptake; WRF, worsening renal function.

* $P < .05$.

** $P < .01$.

For Peer Review

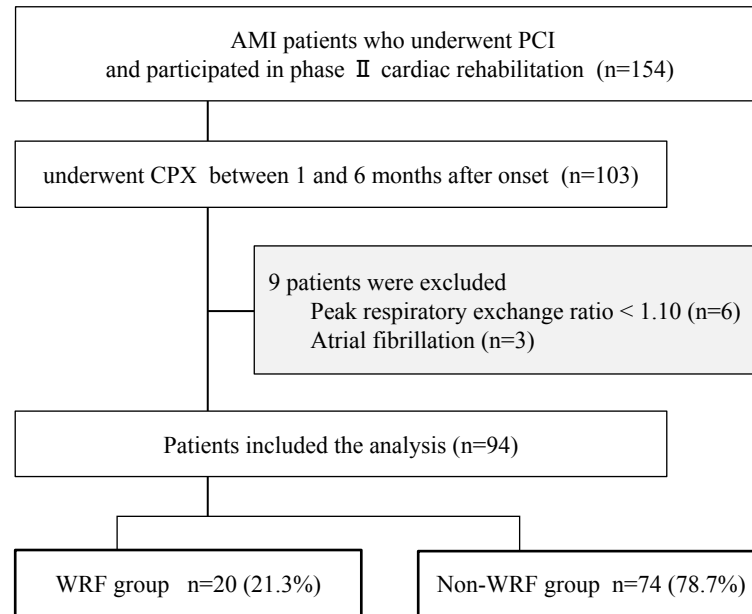


Figure 1

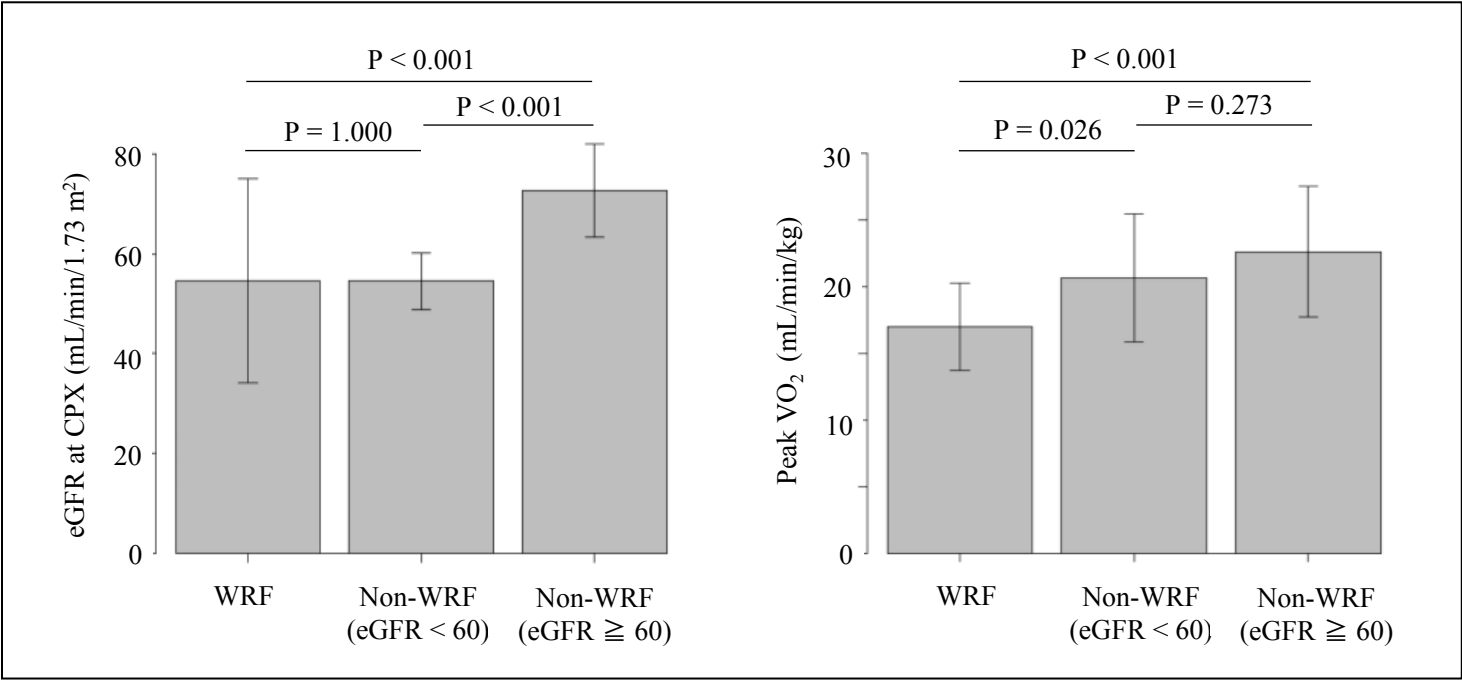


Figure 2