Circulation Reports
Circ Rep 2023; 5: 238–244
doi:10.1253/circrep.CR-23-0040

ORIGINAL ARTICLE
Heart Failure

Improved Peak Oxygen Uptake Reduces Cardiac Events After 3 Weeks of Inpatient Cardiac Rehabilitation for Chronic Heart Failure Patients

Makoto Murata, PhD, MD; Saya Yanai; Shogo Nitta; Yuhei Yamashita; Tatsunori Shitara; Hiroko Kazama; Masanori Ueda; Yasuyuki Kobayashi; Yoshihisa Namasu; Hitoshi Adachi, MD, PhD

Background: The incidence of heart failure (HF) is increasing, and the mortality from HF remains high in an aging society. Cardiac rehabilitation (CR) programs (CRP) increase oxygen uptake ($\dot{V}O_2$) and reduce HF rehospitalization and mortality. Therefore, CR is recommended for every HF patient. However, the number of outpatients undergoing CR remains low, with insufficient attendance at CRP sessions. In this study we evaluated the outcomes of 3 weeks of inpatient CRP (3w In-CRP) for HF patients.

Methods and Results: This study enrolled 93 HF patients after acute-phase hospitalization between 2019 and 2022. Patients participated in 30 sessions of 3w In-CRP (30 min aerobic exercise twice daily, 5 days/week). Before and after 3w In-CRP, patients underwent a cardiopulmonary exercise test, and cardiovascular (CV) events (mortality, HF rehospitalization, myocardial infarction, and cerebrovascular disease) after discharge were evaluated. After 3w In-CPR, mean (±SD) peak $\dot{V}O_2$ increased from 11.8±3.2 to 13.7±4.1 mL/min/kg (116.5±22.1%). During the follow-up period (357±292 days after discharge), 20 patients were rehospitalized for HF, 1 had a stroke, and 8 died for any reasons. Proportional hazard and Kaplan-Meier analyses demonstrated that CV events were reduced among patients with a 6.1% improvement in peak $\dot{V}O_2$ than in patients without any improvement in peak $\dot{V}O_2$.

Conclusions: 3w In-CRP for HF patients improved peak $\dot{V}O_2$ and reduced CV events in HF patients with a 6.1% improvement in peak $\dot{V}O_2$.

Key Words: Cardiac rehabilitation; Cardiopulmonary exercise test; Heart failure; Heart failure rehospitalization; Inpatient cardiac rehabilitation

Heart failure (HF) is a burden worldwide because of an aging society.[1–3] HF mortality and rehospitalization rates remain high, especially in Japan.[4–7] Cardiac rehabilitation (CR) programs (CRP) improve the quality of life, exercise endurance, and peak oxygen uptake ($\dot{V}O_2$) of patients with HF, which then reduces the HF rehospitalization and mortality rates. Therefore, after HF discharge, every HF patient is highly recommended to participate in CRP according to HF and CR guidelines across the world.[2,3,8–15]

However, the number of participants for outpatient CRP remains low.[16] As a consequence of an aging society, one possible reason why older patients cannot attend outpatient CRP is difficulty getting there: they may not be able to drive themselves, they may not have anyone to take them, or the distance may be prohibitive.[17,18] In some European countries, a 3-week inpatient CRP (3w In-CRP) is provided for patients with heart disease. Although this may help increase the number of participants in CRPs given the problems associated with accessing outpatient CR in Japan, there have been no trials of inpatient CRP in Japan.

Therefore, this study investigated whether 3w In-CRP improved peak $\dot{V}O_2$ and reduced cardiovascular (CV) events after CRP among HF patients.

Methods

From 2019 to 2022, patients with HF were recommended to attend outpatient CRP 3 times a week for 5 months.

Received April 11, 2023; accepted April 12, 2023; J-STAGE Advance Publication released online May 17, 2023 Time for primary review: 1 day

Department of Cardiology (M.M., H.A.), Department of Rehabilitation (S.Y., S.N., Y.Y., T.S., H.K., Y.N.), Department of Physiological Examination (M.U., Y.K.), Gunma Prefectural Cardiovascular Center, Maebashi, Japan

H.A. is a member of *Circulation Reports*' Editorial Team.

Mailing address: Makoto Murata, MD, PhD, Department of Cardiology, Gunma Prefectural Cardiovascular Center, 3-12 Kameizumimachi, Maebashi 371-0004, Japan. email: yarukimanmann2000@yahoo.co.jp

ISSN-2434-0790

However, some patients had difficulty attending CRP at Gunma Prefectural Cardiovascular Center because of transportation problems. Subsequently, we recommended that these patients participate in 3w In-CRP, and they accepted. As part of the 3w In-CRP, patients performed a 10-min warm-up exercise, 30 min of anaerobic threshold (AT) exercises based on a cycle ergometer, and a 10-min cool down exercise program, twice a day for 5 days each week. Subsequently, resistance training was conducted as appropriate. During the 3-week period, 30 sessions of inpatient CRP were performed. Before and after the 3w In-CRP, patients also underwent transthoracic echocardiography (TTE) and cardiopulmonary exercise testing (CPET). TTE and CPET data and CV events were evaluated after patients had been discharged from the 3w In-CRP. All patients except 2 completed the 3w In-CRP. Of the 2 patients who did not complete the program, 1 had a joint problem and the other could not complete the 3w In-CRP because the ward was closed due to COVID-19.

Cardiopulmonary Exercise Tests

The ventilatory pattern at the AT and the peak $\dot{V}O_2$ were evaluated using symptom-limited CPET during incremental exercise testing on an upright cycle ergometer (Strength-Ergo 8; Mitsubishi Electric Engineering, Tokyo, Japan), as reported previously.[19] The test started with a 3-min rest period, followed by a 3-min warm-up performed at 0-W intensity using the mask method. After this warm-up, the exercise intensity was increased continuously at a rate of 1 W every 6 s until exhaustion. To ensure CPET was performed at a sufficiently high intensity to reach exhaustion, patients were instructed to maintain a sufficient work rate (WR) to achieve a gas respiratory exchange ratio (RER; carbon dioxide production [$\dot{V}CO_2$]/$\dot{V}O_2$) of >1.10. $\dot{V}O_2$, $\dot{V}CO_2$, and minute ventilation ($\dot{V}E$) were measured on a breath-by-breath basis using a gas analyzer (MINATO AE-310S; Minato Science Co., Ltd., Osaka, Japan).

Peak $\dot{V}O_2$ was determined at the highest exercise WR, and AT was measured using the V-slope method.[20] The improvement in peak $\dot{V}O_2$ (%) was calculated as by dividing peak $\dot{V}O_2$ after 3w In-CRP by the peak $\dot{V}O_2$ before 3w In-CRP and multiplying by 100. Before the respiratory compensation point, the $\dot{V}E$ vs. $\dot{V}CO_2$ slope was a measured linear relationship between $\dot{V}E$ and $\dot{V}CO_2$.[21,22] Minimum $\dot{V}E/\dot{V}CO_2$ was determined as the nadir of the $\dot{V}E/\dot{V}CO_2$ ratio during incremental exercise testing and the 30-s average data.[21]

TTE

TTE data were obtained by an experienced sonographer according to the guidelines reported by Nakatani et al.[23,24] A GE Vivid E9 equipped with a 1.75- to 3.5-MHz transducer was used for the evaluation. Left ventricular ejection fraction (LVEF) was calculated using the modified Simpson's rule. According to the LVEF, HF was classified as either HF with reduced ejection fraction (HFrEF; LVEF ≤40%), HF with preserved ejection fraction (HFpEF; LVEF ≥50%), or HF with mildly reduced ejection fraction (HFmrEF; 40%<LVEF<50%).

Follow-up After Discharge

Hospital records of regular checkups after the discharge of HF patients were investigated. CV events were defined as HF rehospitalization, myocardial infarction, cerebrovascular disease, and other causes of death. HF rehospitalization was defined as major symptoms (breathlessness, orthopnea, fatigue, and ankle swelling) and signs (elevated jugular venous pressure, hepatojugular reflux, third heart sound, and laterally displaced apical impulse) of HF[9] in patients hospitalized to receive intravenous therapy (diuretics, catecholamines, or carperitide).

Statistical Analysis

Data are expressed as the mean ± SD, median with interquartile range (IQR), or numbers and percentages, as appropriate for the data type and distribution. Student's t-test, paired t-test, or the Chi-squared test were used for data analysis, as appropriate. Receiver operating characteristic (ROC) curve analysis was used to identify the optimal cut-off for CV events. The Delong method was used to compare the area under the curve (AUC) for each parameter on ROC analysis. Predictors of CV events were identified using Cox proportional hazard analysis for univariate and multivariable logistic analyses and Kaplan-Meier analysis. For the multivariate analysis, we selected parameters that differed significantly after the intervention between the groups with and without CV events (**Table**), except other CPET data. Statistical significance was set at P<0.05 for all analyses, which were performed using SPSS version 28 (IBM Corp., Armonk, NY, USA) or EZR version 2.7-x analysis, as appropriate.[25]

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and the ethical standards of the responsible committee on institutional human experimentation, and was approved by the Ethics Committee of the Gunma Prefectural Cardiovascular Center (Reference no. 2022018).

Results

Patients' Baseline Clinical Characteristics

The patients' characteristics at baseline are presented in the **Table**. The mean age of the patients was 69±13 years, and 72% were men. The mean LVEF was 40±18%. Overall, 64%, 7%, and 29% of patients had HFrEF, HFmrEF, and HFpEF, respectively. After 3w In-CRP, peak $\dot{V}O_2$ increased significantly from 11.8±3.2 to 13.6±4.1 mL/min/kg (P<0.01; **Figure 1**) and the mean improvement of peak $\dot{V}O_2$ was 116.5±22.1%. Patients were followed up for 357±292 days (median 277 days; IQR 102–612 days), during which time 20 patients were rehospitalized for HF, 1 patient experienced a stroke, and 6 patients died for any reasons.

Identification of Indicators Most Sensitive to CV Events

In univariate and multivariate analyses, after adjustment for LVEF after 3w In-CRP, the use of angiotensin-converting enzyme inhibitors, diuretics, and mineralocorticoid receptor antagonists, postintervention B-type natriuretic peptide, hemoglobin, and peak $\dot{V}O_2$, and improvement of peak $\dot{V}O_2$ were independent risk factors for CV events. **Figure 2** shows ROC curve analysis for CV events. After 3w In-CRP, peak $\dot{V}O_2$ had a larger AUC. The cut-off value for peak $\dot{V}O_2$ was 11.6 mL/min/kg (AUC 0.777; 95% confidence interval [CI] 0.671–0.884; P<0.01). The ROC curve for improvement in peak $\dot{V}O_2$ was not significantly different to that of post-CRP peak $\dot{V}O_2$, with a cut-off value for improvement in peak $\dot{V}O_2$ of 6.1% (AUC 0.724; 95% CI 0.599–0.849; P<0.01).

Table. Patient Characteristics

	Overall (n=93)	CV event (–) (n=66)	CV event (+) (n=27)	P value
Age (years)	69±13	68±14	72±10	0.15
Male sex (%)	67 (72)	45 (68)	22 (82)	0.22
Body weight (kg)	57.1±14.4	57.8±14.9	55.2±13.2	0.43
BMI (kg/m²)	23.1±11.6	23.9±13.5	21.2±4.3	0.31
Heart disease				
Ischemic heart disease	35 (38)	21 (32)	14 (52)	0.35
Cardiomyopathy	26 (28)	20 (30)	6 (22)	
Valve disease	19 (20)	16 (24)	3 (11)	
Other heart diseases	13 (14)	10 (15)	3 (11)	
Comorbidity				
Smoking	48 (52)	33 (50)	15 (56)	0.66
Hypertension	36 (39)	26 (39)	10 (37)	1.00
Diabetes	40 (43)	25 (38)	15 (56)	0.17
Dyslipidemia	38 (41)	25 (38)	13 (48)	0.49
Pre-intervention physical condition				
AT (mL/min/kg)	8.9±1.9	9.2±1.9	8.0±1.4	<0.01
Predicted AT (%)	57.1±12.2	59.8±12.5	50.7±8.8	<0.01
Peak $\dot{V}O_2$ (mL/min/kg)	11.8±3.2	12.4±3.3	10.3±2.3	<0.01
Predicted peak $\dot{V}O_2$ (%)	50±13	52±13	45±11	0.01
$\dot{V}E$ vs. $\dot{V}CO_2$ slope	46.9±15.4	44.0±14.4	53.9±15.8	<0.01
Minimum $\dot{V}E/\dot{V}CO_2$	46.1±11.8	44.32±11.0	50.6±12.5	0.02
Peak gas exchange ratio	1.14±0.08	1.13±0.07	1.15±0.10	0.09
LVEF (%)	40±18	45±17	34±16	0.01
Creatine (mg/dL)	1.30±0.64	1.28±0.67	1.35±0.59	0.61
Hemoglobin (g/dL)	12.9±2.4	13.4±2.6	11.9±1.4	<0.01
Sodium (mEq/L)	139.0±4.0	140.0±3.0	138.0±4.0	0.02
BNP (pg/mL)	260 [94–529]	212 [58–478]	394 [208–619]	0.03
Medications				
β-blocker	81 (87)	56 (85)	25 (93)	0.50
ACEI	26 (28)	14 (21)	12 (44)	0.04
ARB	20 (22)	17 (26)	3 (11)	0.17
ARNI	13 (14)	9 (14)	4 (15)	1.00
Diuretics	52 (56)	31 (47)	21 (78)	0.01
MRA	55 (59)	33 (50)	22 (82)	<0.01
SGLT2-I	42 (45)	32 (49)	10 (37)	0.36
Ivabradine	10 (11)	8 (12)	2 (7)	0.72
Postintervention physical condition				
AT (mL/min/kg)	10.0±2.3	10.5±2.2	8.7±1.8	<0.01
Predicted AT (%)	64.0±14.0	67.5±13.5	55.2±11.1	<0.01
Peak $\dot{V}O_2$ (mL/min/kg)	13.6±4.1	14.7±3.9	10.9±3.1	<0.01
Predicted peak $\dot{V}O_2$ (%)	57±17	61±15	47±16	<0.01
$\dot{V}E$ vs. $\dot{V}CO_2$ slope	43.9±11.8	41.0±11.3	50.9±9.9	<0.01
Minimum $\dot{V}E/\dot{V}CO_2$	44.7±11.1	41.6±8.7	52.3±12.8	<0.01
Change in peak $\dot{V}O_2$ (%)	116.5±22.1	120.8±22.0	106.2±19.1	<0.01
Peak gas exchange ratio	1.17±0.09	1.17±0.08	1.18±0.09	0.55
LVEF (%)	42±18	45±17	34±16	<0.01
Creatine (mg/dL)	1.26±0.54	1.24±0.53	1.43±0.54	0.12
Hemoglobin (g/dL)	12.8±2.0	13.3±2.0	11.5±1.4	<0.01
Sodium (mEq/L)	139.0±4.0	139.6±3.6	138.6±4.1	0.29
BNP (pg/mL)	176 [90–511]	140 [48–322]	347 [223–666]	<0.01

Unless indicated otherwise, data are given as the mean ± SD, median [interquartile range], or n (%). P values are for comparisons of groups with (+) and without (–) a cardiovascular (CV) event after discharge from a 3-week an inpatient cardiac rehabilitation program. Data were analyzed using Student's t-test, Chi-squared test, or Mann-Whitney U test, as appropriate. Significance was set at P<0.05. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; AT, anaerobic threshold; BMI, body mass index; BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; SGLT2-I, sodium-glucose cotransporter 2 inhibitor; $\dot{V}CO_2$, carbon dioxide production; $\dot{V}E$, minute volume; $\dot{V}O_2$, oxygen uptake.

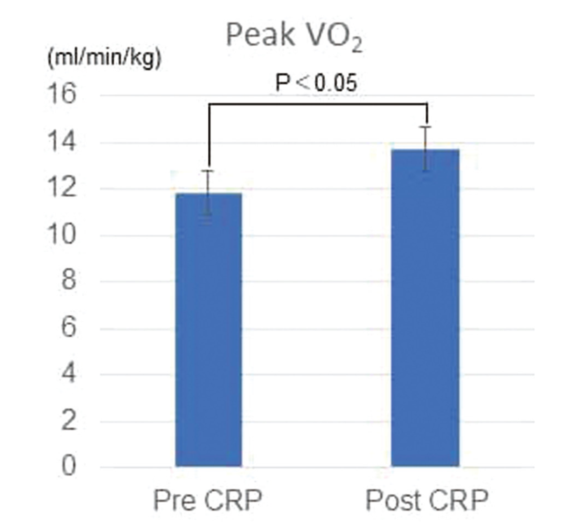

Figure 1. Peak oxygen uptake ($\dot{V}O_2$) before and after 3 weeks of an inpatient cardiac rehabilitation program (CRP). Data are the mean±SD.

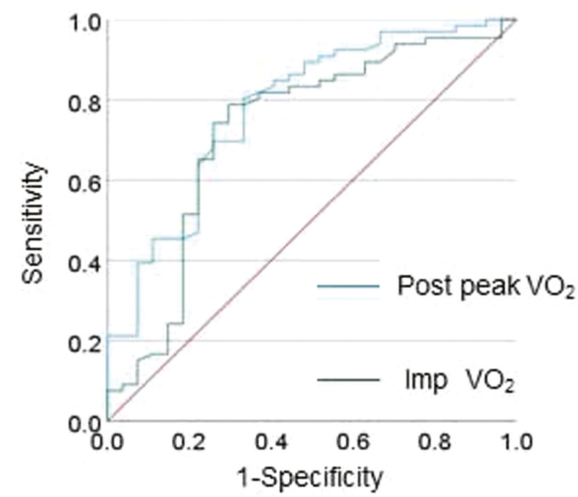

Figure 2. Receiver operating characteristic (ROC) curve analysis of peak oxygen uptake ($\dot{V}O_2$) and improvements in $\dot{V}O_2$ for predicting cardiovascular (CV) events. After 3 weeks of an inpatient cardiac rehabilitation program (3w In-CRP), the area under the curve (AUC) of peak $\dot{V}O_2$ (Post peak $\dot{V}O_2$) was 0.777 (95% confidence interval [CI] 0.671–0.884; P<0.01), with a cut-off of 11.6 mL/min/kg having a sensitivity of 0.621 and a specificity of 0.805 for predicting future CV events. The AUC for the improvement in $\dot{V}O_2$ (Imp $\dot{V}O_2$) was 0.724 (95% CI 0.599–0.849; P<0.01), with a cut-off of 6.1% having a sensitivity of 0.655 and a specificity of 0.805 for predicting future CV events.

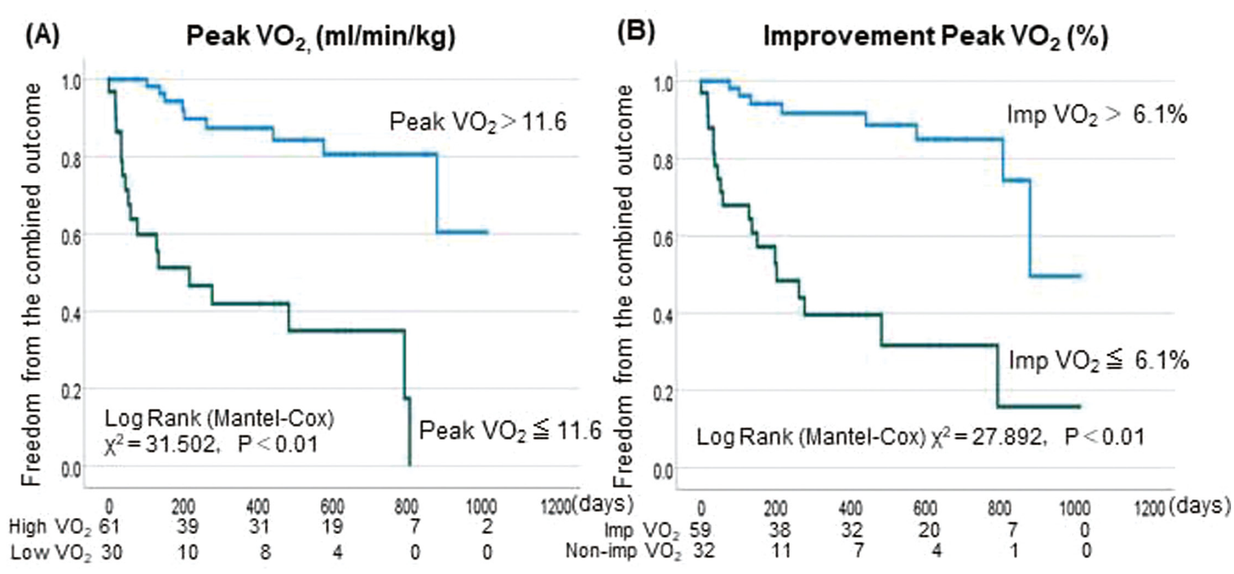

Figure 3. Kaplan-Meier curves for cardiovascular (CV) event-free survival in patients with (**A**) higher (>11.6 mL/min/kg) and lower (≤11.6 mL/min/kg) peak oxygen uptake ($\dot{V}O_2$) and (**B**) higher (>6.1%) and lower (≤6.1%) improvements (Imp) in peak $\dot{V}O_2$ after 3 weeks of an inpatient cardiac rehabilitation program (3w In-CRP). (**A**) There were fewer CV events in the group with higher (>11.6 mL/min/kg) than lower (≤11.6 mL/min/kg) peak $\dot{V}O_2$ after 3w In-CRP (log-rank [Mantel-Cox] χ^2=31.502, P<0.01). (**B**) Similarly, there fewer CV events in the group with a higher (>6.1%) than lower (≤6.1%) improvement in peak $\dot{V}O_2$ (log-rank [Mantel-Cox] χ^2=27.892; P<0.01).

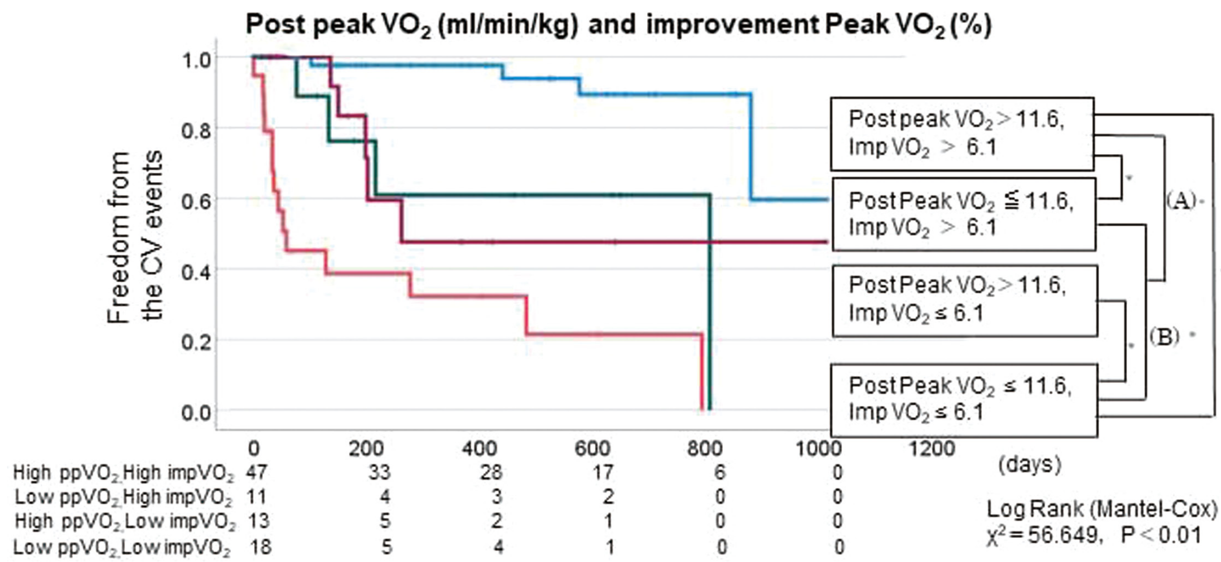

Figure 4. Kaplan-Meier curves for cardiovascular (CV) event-free survival according to levels of peak oxygen uptake ($\dot{V}O_2$; high [>11.6 mL/min/kg] or low [≤11.6 mL/min/kg]), and improvements in peak $\dot{V}O_2$ (high [>6.1%] or low [≤6.1%]) after 3 weeks of an inpatient cardiac rehabilitation program (3w In-CRP). There were significantly fewer CV events in the group with high peak $\dot{V}O_2$ and high improvements in peak $\dot{V}O_2$ after 3w In-CRP than in the other groups. In addition, there were fewer CV events among patients with a high improvement in peak $\dot{V}O_2$ than among those with a low improvement peak $\dot{V}O_2$ and either a high peak $\dot{V}O_2$ (log-rank [Mantel-Cox] X^2=9.741, P<0.01; "A") or a low peak $\dot{V}O_2$ (log-rank [Mantel-Cox] X^2=5.118, P=0.02; "B"). (All, log-rank (Mantel-Cox) X^2=56.649, P<0.01.) pp$\dot{V}O_2$, post-3w In-CRP peak $\dot{V}O_2$; imp $\dot{V}O_2$, improvement in peak $\dot{V}O_2$. *P value <0.05.

CV Events According to Postintervention Peak $\dot{V}O_2$ and Improvement in Peak $\dot{V}O_2$

Kaplan-Meier analysis demonstrated that patients with higher peak $\dot{V}O_2$ after 3w In-CRP (>11.6 mL/min/kg) had fewer CV events than those with lower peak $\dot{V}O_2$ (≤11.6 mL/min/kg; hazard ratio [HR] 0.129; 95% CI 0.056–0.299; P<0.01; **Figure 3A**). The group of patients with a greater improvement in peak $\dot{V}O_2$ after 3w In-CRP (>6.1%) had fewer CV events than the group with a lower improvement in peak $\dot{V}O_2$ (≤6.1%; HR 0.141; 95% CI 0.061–0.326; P<0.01; **Figure 3B**).

Furthermore, as shown in **Figure 4**, Kaplan-Meier analysis revealed that patients with a higher (>6.1%) improvement in peak $\dot{V}O_2$ and a higher peak $\dot{V}O_2$ (>11.6 mL/min/kg) after 3w In-CRP had fewer CV events than those with a lower improvement in peak $\dot{V}O_2$ (≤6.1%) and either a higher peak $\dot{V}O_2$ (>11.6 mL/min/kg; HR 0.151; 95% CI 0.039–0.583; P<0.01) or a lower peak $\dot{V}O_2$ (≤11.6 mL/min/kg; HR 0.261; 95% CI 0.075–0.914; P=0.03).

Discussion

This study investigated the effects of 3w In-CRP for HF patients. After a 3w In-CRP, peak $\dot{V}O_2$ increased from 11.8±3.2 to 13.7±4.1 mL/min/kg, with an improvement in peak $\dot{V}O_2$ of 116.5±22.1%. After 3w In-CPR, patients with higher peak $\dot{V}O_2$ and a higher improvement in peak $\dot{V}O_2$ had fewer CV events (mainly rehospitalization and all-cause death). Regardless of whether peak $\dot{V}O_2$ was high (>11.6 mL/min/kg) or low (≤11.6 mL/min/kg), an improvement in peak $\dot{V}O_2$ of >6.1% reduced CV events compared with no improvement in peak $\dot{V}O_2$. We demonstrated that 3w In-CRP for HF patients improved peak $\dot{V}O_2$ and reduced CV events among those HF patients with a >6.1% improvement in peak $\dot{V}O_2$.

HF has been increasing worldwide as a result of the increasing number of older adults.[1–3] Mortality and rehospitalization rates are still increasing in Japan after index HF hospitalizations.[4] The Japanese HF registries have reported a 24.4–27.1% HF rehospitalization rate.[5–7] In the present study, over a follow-up period of nearly 1 year, 27.4% of HF patients experienced a CV event, which is consistent with the previous reports. Outpatient CRP is a common CRP in Japan for patients with heart disease. Generally, outpatient CRP for HF involves aerobic exercise 3 times a week for 3–12 months, which has been reported to reduce HF rehospitalization or mortality[10,11] and to improve peak $\dot{V}O_2$ by 4–18% in both HFrEF[11–13] and HFpEF patients.[14] In Germany, 3w In-CRP is more common than outpatient CRP.[26] For older patients, after transcatheter aortic valve replacement, 3w In-CRP reduces mortality.[27] In Italy, Scrutinio et al reported that inpatient CRP increased the 6-min walk distance (6MWD) and reduced heart transplantation and mortality rates among patients with HFrEF.[28,29] In the present study, 3w In-CRP, evaluated with CPET, increased peak $\dot{V}O_2$ by 116.5±22.1% within 3 weeks. Moreover, it reduced CV events. We demonstrated that 3w In-CRP resulted in similar incremental peak $\dot{V}O_2$ improvements to several months of outpatient CRP, and thus was effective for HF.

We found that the number of CV events was lower among patients with higher peak $\dot{V}O_2$ and a >6.1% improvement in peak $\dot{V}O_2$ after 3w In-CRP. Generally, higher peak $\dot{V}O_2$ is related to lower mortality in both healthy people and patients with CV conditions.[30,31] Paolillo et al reported that a peak $\dot{V}O_2$ of 10.8 mL/min/kg is the cut-off value for 10% of death, heart transplantation, or left ventricular assist device implantation risk in patients with HFrEF.[32] Although our definition of CV events did not include only mortality, the cut-off value of 11.6 mL/min/kg we found seems compatible with previous reports. We identified patients who had improved CV events after 3w In-CRP. There was no relationship between incremental peak $\dot{V}O_2$ and CV events. However, Passantino et al similarly reported that a 70 metre increase in the 6MWD reduced mortality in HFrEF patients who participated in inpatient CRP.[33] Therefore, we can infer that HF patients who do not exhibit a >6.1% improvement in peak $\dot{V}O_2$ after 3w In-CRP are at a high risk of CV events and must be cautious with their treatments.

Despite the poor prognosis and marked increase in the prevalence of HF, and despite CR guidelines strongly recommending patients with HF participate in CRP,[8,9] in Japan only 7% of HF patients take part in outpatient CRP.[16] Moreover, both Japanese and European guidelines for HF recommend that patients take part in 3 sessions of CRP per week for 5 months or 36 sessions within 5 months.[8,15] However, because patients with HF are older and are likely to live alone or with an aging partner, they may not be able to attend outpatient CRP locations due to transportation problems. Therefore, most CRP participants can only attend 1 session per week or 2 or 3 sessions per month. The number of patients who cannot attend CRP or attend enough sessions is increasing, possibly due to single households and the aging society in Japan.[17,18] The Japanese social environment may increase the difficulty of participant recruitment and adherence to CRP. Conversely, inpatient CRP has the potential to solve these problems, with participants able to attend the recommended number of sessions, as demonstrated in the present study. It is possible that 3w In-CRP may help increase peak $\dot{V}O_2$ and reduce CV events for HF patients in Japan.

The study had some limitations. First, this was a single-center study with a relatively small number of patients. Future multicenter studies are needed to confirm our findings. Second, we excluded the patients who could not ride a cycle ergometer themselves because of a falling risk. This study was for HF patients with low exercise endurance but sufficient activities of daily living to ride the bicycle themselves. Third, some medications were added during inpatient CRP. However, most of the participants had sufficient medications prescribed during a previous hospitalization or outpatient periods and so only a few patients had added medications, and the effects of these additional medications were assumed to be limited.

Conclusions

Three weeks of inpatient CRP improved peak $\dot{V}O_2$ and reduced CV events after discharge in patients with HF. Given the social and environmental conditions in Japan, 3w In-CRP can provide patients with the opportunity to attend a sufficient (recommended) number of CRP sessions and increase the number of CRP participants after hospitalization for congestive HF. Thus, 3w In-CRP may help reduce the burden of the HF pandemic in Japan.

Acknowledgments

The authors thank their colleagues in the Physiological Examination Department and the Cardiac Rehabilitation Team at Gunma Prefectural Cardiovascular Center.

Sources of Funding

This research did not receive any grant from any funding agency in the public, commercial, or not-for-profit sectors.

Disclosures

H.A. is a member of *Circulation Reports*' Editorial Team. The remaining authors have no conflicts of interest to disclose.

IRB Information

This study was approved by the Ethics Committee of the Gunma Prefectural Cardiovascular Center (Reference no. 2022018). The requirement for written informed consent was waived due to the retrospective nature of the study.

References

1. Okura Y, Ramadan MM, Ohno Y, Mitsuma W, Tanaka K, Ito M, et al. Impending epidemic: Future projection of heart failure in Japan to the year 2055. *Circ J* 2008; **72:** 489–491.
2. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022; **145:** e895–e1032.
3. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021; **42:** 3599–3726.
4. Shiraishi Y, Kohsaka S, Sato N, Takano T, Kitai T, Yoshikawa T, et al. 9-year trend in the management of acute heart failure in Japan: A report from the national consortium of acute heart failure registries. *J Am Heart Assoc* 2018; **7:** e008687.
5. Shiraishi Y, Kohsaka S, Abe T, Mizuno A, Goda A, Izumi Y, et al. Validation of the Get With The Guideline-Heart Failure risk score in Japanese patients and the potential improvement of its discrimination ability by the inclusion of B-type natriuretic peptide level. *Am Heart J* 2016; **171:** 33–39.
6. Sato N, Kajimoto K, Asai K, Mizuno M, Minami Y, Nagashima M, et al. Acute decompensated heart failure syndromes (ATTEND) registry. A prospective observational multicenter cohort study: Rationale, design, and preliminary data. *Am Heart J* 2010; **159:** 949–955.e1.
7. Matsue Y, Damman K, Voors AA, Kagiyama N, Yamaguchi T, Kuroda S, et al. Time-to-furosemide treatment and mortality in patients hospitalized with acute heart failure. *J Am Coll Cardiol* 2017; **69:** 3042–3051.
8. Makita S, Yasu T, Akashi YJ, Adachi H, Izawa H, Ishihara S, et al. JCS/JACR 2021 guideline on rehabilitation in patients with cardiovascular disease. *Circ J* 2022; **87:** 155–235.
9. Tsutsui H, Isobe M, Ito H, Ito H, Okumura K, Ono M, et al. JCS 2017/JHFS 2017 guideline on diagnosis and treatment of acute and chronic heart failure: Digest version. *Circ J* 2019; **83:** 2084–2184.
10. Long L, Mordi IR, Bridges C, Sagar VA, Davies EJ, Coats AJ, et al. Exercise-based cardiac rehabilitation for adults with heart failure. *Cochrane Database Syst Rev* 2019; **1:** CD003331.
11. Belardinelli R, Georgiou D, Cianci G, Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: Effects on functional capacity, quality of life, and clinical outcome. *Circulation* 1999; **99:** 1173–1182.
12. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009; **301:** 1439–1450.
13. Passino C, Severino S, Poletti R, Piepoli MF, Mammini C, Clerico A, et al. Aerobic training decreases B-type natriuretic peptide expression and adrenergic activation in patients with heart failure. *J Am Coll Cardiol* 2006; **47:** 1835–1839.
14. Kitzman DW, Brubaker PH, Morgan TM, Stewart KP, Little WC. Exercise training in older patients with heart failure and preserved ejection fraction: A randomized, controlled, single-blind trial. *Circ Heart Fail* 2010; **3:** 659–667.
15. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Back M, et al. 2021 ESC guidelines on cardiovascular dis-

ease prevention in clinical practice. *Eur Heart J* 2021; **42:** 3227–3337.
16. Kamiya K, Yamamoto T, Tsuchihashi-Makaya M, Ikegame T, Takahashi T, Sato Y, et al. Nationwide survey of multidisciplinary care and cardiac rehabilitation for patients with heart failure in Japan: An analysis of the AMED-CHF study. *Circ J* 2019; **83:** 1546–1552.
17. Ministry of Health Labour and Welfare, Japan. Kokuminseikatukisotyosa [Basic survey of living conditons in Japan]. 2021. https://www.mhlw.go.jp/toukei/saikin/hw/k-tyosa/k-tyosa21/index.html (accessed December 24, 2022).
18. Ministry of Land, Infrastructure and Transport, Transport and Tourism, Japan Kokudonotyoukitenbou [Long-term outlook for nation]. 2021. https://www1.mlit.go.jp/policy/shingikai/kokudo03_sg_000243.html (accessed December 24, 2022).
19. Buchfuhrer MJ, Hansen JE, Robinson TE, Sue DY, Wasserman K, Whipp BJ. Optimizing the exercise protocol for cardiopulmonary assessment. *J Appl Physiol Respir Environ Exerc Physiol* 1983; **55:** 1558–1564.
20. Beaver WL, Wasserman K, Whipp BJ. Bicarbonate buffering of lactic acid generated during exercise. *J Appl Physiol (1985)* 1986; **60:** 472–478.
21. Sun XG, Hansen JE, Garatachea N, Storer TW, Wasserman K. Ventilatory efficiency during exercise in healthy subjects. *Am J Respir Crit Care Med* 2002; **166:** 1443–1448.
22. Wasserman K. Principles of exercise testing & interpretation: Including pathophysiology and clinical applications. 3rd edn. Philadelphia: Lippincott Williams & Wilkins, 1999.
23. Nakatani S, Akaishi M, Asanuma T, Hashimoto S, Izumi C, Iwanaga S, et al. Guidelines from the Japanese Society of Echocardiography: Guidance for the management and maintenance of echocardiography equipment. *J Echocardiogr* 2015; **13:** 1–5.
24. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016; **29:** 277–314.
25. Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. *Bone Marrow Transplant* 2013; **48:** 452–458.
26. Karoff M, Held K, Bjarnason-Wehrens B. Cardiac rehabilitation in Germany. *Eur J Cardiovasc Prev Rehabil* 2007; **14:** 18–27.
27. Butter C, Gross J, Haase-Fielitz A, Sims H, Deutsch C, Bramlage P, et al. Impact of rehabilitation on outcomes after TAVI: A preliminary study. *J Clin Med* 2018; **7:** 326.
28. Scrutinio D, Passantino A, Catanzaro R, Farinola G, Lagioia R, Mastropasqua F, et al. Inpatient cardiac rehabilitation soon after hospitalization for acute decompensated heart failure: A propensity score study. *J Cardiopulm Rehabil Prev* 2012; **32:** 71–77.
29. Scrutinio D, Guida P, Passantino A, Scalvini S, Bussotti M, Forni G, et al. Characteristics, outcomes, and long-term survival of patients with heart failure undergoing inpatient cardiac rehabilitation. *Arch Phys Med Rehabil* 2022; **103:** 891–898.e4.
30. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation* 1991; **83:** 778–786.
31. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 2002; **346:** 793–801.
32. Paolillo S, Veglia F, Salvioni E, Corra U, Piepoli M, Lagioia R, et al. Heart failure prognosis over time: How the prognostic role of oxygen consumption and ventilatory efficiency during exercise has changed in the last 20 years. *Eur J Heart Fail* 2019; **21:** 208–217.
33. Passantino A, Lagioia R, Mastropasqua F, Scrutinio D. Short-term change in distance walked in 6 min is an indicator of outcome in patients with chronic heart failure in clinical practice. *J Am Coll Cardiol* 2006; **48:** 99–105.