Circulation Reports
Circ Rep 2023; 5: 231–237
doi:10.1253/circrep.CR-23-0016

ORIGINAL ARTICLE
Heart Failure

Three Weeks of Inpatient Cardiac Rehabilitation Improves Metabolic Exercise Data Combined With Cardiac and Kidney Indexes Scores for Heart Failure With Reduced Ejection Fraction

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

Background: Heart failure with reduced ejection fraction (HFrEF) has a high mortality rate, and cardiac rehabilitation programs (CRP) reduce HFrEF rehospitalization and mortality rates. Some countries attempt 3 weeks of inpatient CRP (3w In-CRP) for cardiac diseases. However, whether 3w In-CRP reduces the prognostic parameter of the Metabolic Exercise data combined with Cardiac and Kidney Indexes (MECKI) score is unknown. Therefore, we investigated whether 3w In-CRP improves MECKI scores in patients with HFrEF.

Methods and Results: This study enrolled 53 patients with HFrEF who participated in 30 inpatient CRP sessions, consisting of 30 min of aerobic exercise twice daily, 5 days a week for 3 weeks, between 2019 and 2022. Cardiopulmonary exercise tests and transthoracic echocardiography were performed, and blood samples were collected, before and after 3w In-CRP. MECKI scores and cardiovascular (CV) events (heart failure rehospitalization or death) were evaluated. The MECKI score improved from a median 23.34% (interquartile range [IQR] 10.21–53.14%) before 3w In-CRP to 18.66% (IQR 6.54–39.94%; P<0.01) after 3w In-CRP because of improved left ventricular ejection fraction and percentage peak oxygen uptake. Patients' improved MECKI scores corresponded with reduced CV events. However, patients who experienced CV events did not have improved MECKI scores.

Conclusions: In this study, 3w In-CRP improved MECKI scores and reduced CV events for patients with HFrEF. However, patients whose MECKI scores did not improve despite 3w In-CRP require careful heart failure management.

Key Words: Cardiopulmonary exercise test; Heart failure; Heart failure rehospitalization; Inpatient cardiac rehabilitation; Metabolic Exercise data combined with Cardiac and Kidney Indexes (MECKI) score

Heart failure (HF) was a global pandemic before COVID-19,[1–3] and HF mortality and rehospitalization rates remain high, especially in Japan.[4–7] A cardiac rehabilitation program (CRP) improves exercise endurance and peak oxygen uptake ($\dot{V}O_2$). It also reduces rehospitalization and mortality rates for patients with HF with reduced ejection fraction (HFrEF). Therefore, many guidelines worldwide highly recommended CRP for patients with HFrEF.[2,3,8–15] In some European countries, 3 weeks of inpatient CRP (3w In-CRP) is provided to patients with heart disease.[16–19]

The Metabolic Exercise data combined with Cardiac and Kidney Indexes (MECKI) score is a prognostic parameter for patients with HFrEF and is superior to left ventricular ejection fraction (LVEF), minute ventilation ($\dot{V}E$) vs. carbon dioxide production ($\dot{V}CO_2$) slope, peak $\dot{V}O_2$, and some other HF scores.[20–23] However, whether 3w In-CRP improves MECKI scores remains unknown.

Thus, in this study we investigated whether 3w In-CRP improves the MECKI score and its relationship with cardiovascular (CV) events in patients with HFrEF.

Methods

From 2019 to 2022, outpatient CRP 3 times a week for 5 months was recommended for patients with HFrEF. Despite

Received April 11, 2023; accepted April 12, 2023; J-STAGE Advance Publication released online May 19, 2023 Time for primary review: 1 day

Department of Cardiology (S.S., 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

this, many patients could not visit Gunma Prefectural Cardiovascular Center because they were unable to drive, had no one to pick them up, or because of the distance. Subsequently, we recommended 3w In-CRP, and included 53 patients with HFrEF who met the inclusion and exclusion criteria (**Supplementary Figure 1**) and agreed to take part in the present study. Patients performed a 10-min warm-up exercise, a 30-min anaerobic threshold (AT)-based cycle ergometer exercise, and a 10-min cool-down exercise program twice daily, 5 days a week. In addition, patients undertook resistance training and were provided with food, self-control, and self-management education. During the 3 weeks, 30 inpatient CRP sessions were performed. Before and after the 3w In-CRP, patients underwent transthoracic echocardiography (TTE) and cardiopulmonary exercise testing (CPET), and blood samples were collected. We investigated the MECKI score, its components, and CV events after discharge from 3w In-CRP.

Cardiopulmonary Exercise Tests

The ventilatory pattern at the AT and peak $\dot{V}O_2$ were evaluated using symptom-limited CPET during incremental exercise testing on an upright cycle ergometer (StrengthErgo 8; Mitsubishi Electric Engineering, Tokyo, Japan), as reported previously.[18] The test started with a 3-min rest, followed by a 3-min warm-up performed at 0-W intensity using the mask method. Subsequently, exercise intensity was increased continuously by 1 W every 6 s. To ensure a high-intensity CPET sufficient to achieve exhaustion, patients were instructed to maintain a sufficient work rate (WR) to achieve a gas respiratory exchange ratio ($\dot{V}CO_2/\dot{V}O_2$) >1.10. $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}E$ 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 WR, and the percentage peak (%peak) $\dot{V}O_2$ was estimated among healthy Japanese participants.[24] Before the respiratory compensation point, the $\dot{V}E$ vs. $\dot{V}CO_2$ slope demonstrated a linear relationship between $\dot{V}E$ and $\dot{V}CO_2$.

Transthoracic Echocardiography

An experienced sonographer obtained TTE data according to the guidelines reported by Nakatani et al[25,26] using a GE Vivid E9 equipped with a 1.75- to 3.5-MHz transducer. LVEF was determined using the modified Simpson's rule. HFrEF was defined as LVEF ≤40%.

MECKI Scores

The MECKI score was estimated using the formula $\exp(k)/(1+\exp(k))$, where $k = 10.3464 - 0.0262 \times \%\text{peak } \dot{V}O_2 + 0.0472 \times \dot{V}E \text{ vs. } \dot{V}CO_2 \text{ slope} - 0.1086 \times \text{hemoglobin (g/dL)} - 0.0615 \times \text{sodium (mEq/L)} - 0.0699 \times \text{LVEF (\%)} - 0.0136 \times \text{GFR (mL/min)}$,[20] and the glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease equation.[27]

Follow-up After Discharge

Hospital records of regular checkups were investigated after the discharge of patients with HFrEF. CV events were defined as HF rehospitalization and all-cause death after discharge. HF rehospitalization included 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

All data are expressed as the mean ± SD, median with interquartile range (IQR), or number and percentage, as appropriate for the data type and distribution. Data were analyzed using Student's t-test, paired t-test, Mann-Whitney U test, the Wilcoxon signed-rank test, or Chi-squared test, 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 each parameter of the area under the curve (AUC) for the ROC curve. Kaplan-Meier analyses helped identify predictors of CV events. 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.

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

Baseline Patient Clinical Characteristics

Patients' characteristics are presented in **Table 1**. The mean age of patients was 69±12 years, and 83% were male. Mean LVEF was 25.6±8.5% and mean peak $\dot{V}O_2$ was 11.6±3.3 mL/min/kg. Patients were followed up for 309±275 days (median 196 days; IQR 75–483 days), during which 17 were rehospitalized for HF, and 4 died. The mortality rate within this period was 7.5%.

MECKI Scores Before and After 3w In-CRP

The median MECKI score decreased significantly (P<0.01) from 23.34% (IQR 10.21–53.14%) to 18.66% (IQR 6.54–39.94%) after 3w In-CRP, with an absolute reduction of −3.41% (−12.85% to 4.10%). The mean percentage decrease in MECKI score was 80.5±48.0% (**Figure 1**). Both LVEF (25.6±8.5% vs. 29.7±11.9%) and %peak $\dot{V}O_2$ (49.1±13.5% vs. 54.5±16.9%) increased after 3w In-CRP (**Supplementary Figure 2**). Furthermore, ROC curve analysis for CV events revealed that the post-3w In-CRP MECKI score showed a significantly higher AUC (**Figure 2**).

CV Events and MECKI Scores

Patients were classified into 2 groups, those with (+) and without (−) CV events (heart failure rehospitalization or death) after discharge. Although before 3w In-CRP there was no significant difference in MECKI score between the CV(+) and CV(−) groups, after 3w In-CRP the MECKI score was significantly lower in the CV(−) than CV(+) group (**Figure 3**). The percentage decrease in MECKI score was significantly higher in patients in the CV(−) than CV(+) group (68.3±41.1% vs. 99.0±52.6%; P=0.02; **Figure 4**).

Furthermore, ROC curve analysis for CV events revealed that the percentage decrease in MECKI score showed a significantly higher AUC (**Figure 2**). There was no significant difference in the AUC for the post-3w In-CRP MECKI score and the AUC for the percentage decrease in MECKI score. The cut-off value for the percentage decrease

Table 1. Patient Characteristics

	Overall (n=53)	CV event (–) (n=32)	CV event (+) (n=21)	P value
Age (years)	69±12	67±13	72±10	0.15
Male sex (%)	44 (83)	25 (78)	19 (91)	0.29
Body weight (kg)	55.7±12.7	56.4±14.0	54.5±10.7	0.60
BMI (kg/m²)	23.1±15.0	24.9±18.9	20.4±3.4	0.29
Heart diseases				
Ischemic heart disease	21 (33)	8 (25)	13 (62)	0.05
Cardiomyopathy	23 (43)	17 (53)	6 (29)	
Valve disease	2 (3)	2 (6)	0 (0)	
Other heart disease	7 (13)	5 (17)	2 (10)	
Comorbidities				
Smoking	30 (57)	17 (53)	13 (62)	0.58
Hypertension	19 (36)	13 (41)	6 (28)	0.40
Diabetes	25 (47)	11 (34)	14 (67)	0.03
Dyslipidemia	23 (43)	12 (38)	11 (52)	0.39
Medications				
β-blocker	51 (96)	31 (97)	20 (95)	1.00
ACEI	22 (42)	11 (34)	11 (52)	0.26
ARB	7 (13)	6 (19)	1 (5)	0.23
ARNI	10 (19)	7 (22)	3 (14)	0.72
MRA	42 (72)	25 (78)	17 (81)	1.00
SGLT2-I	29 (55)	10 (31)	9 (42)	0.26
Ivabradine	10 (19)	8 (25)	2 (10)	0.28
Diuretics	33 (62)	17 (53)	16 (76)	0.15

Unless indicated otherwise, data are given as the mean±SD or n (%). Data were analyzed using Student's t-test or the Chi-squared test, with P<0.05 considered significant. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BMI, body mass index; CV events, cardiovascular events (heart failure rehospitalization or death) after discharge; MRA, mineralocorticoid receptor antagonist; SGLT2I, sodium-glucose cotransporter 2 inhibitor.

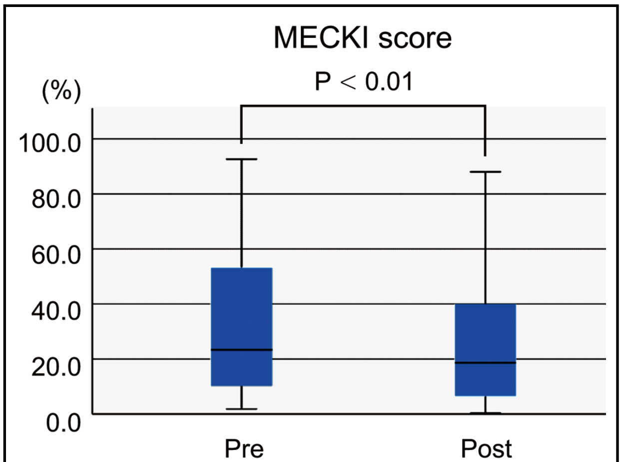

Figure 1. Metabolic Exercise data combined with Cardiac and Kidney Indexes (MECKI) scores before and after 3 weeks of an inpatient cardiac rehabilitation program (3w In-CRP). There was a significant (P<0.01) decrease in the median MECKI score after 3w In-CRP, from 23.34% (interquartile range [IQR] 10.21–53.14%) to 18.66% (IQR 6.54–39.94%).

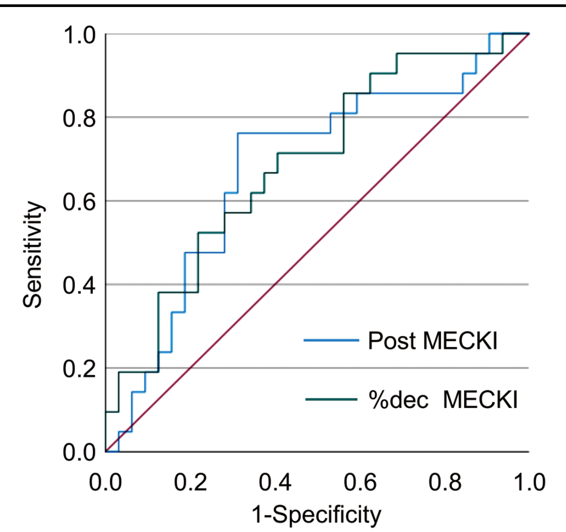

Figure 2. Receiver operating characteristic curve analysis of cardiovascular (CV) events (heart failure rehospitalization or death) after discharge. The area under the curve for Metabolic Exercise data combined with Cardiac and Kidney Indexes (MECKI) score after 3 weeks of an inpatient cardiac rehabilitation program (CRP) was 0.677 (95% confidence interval [CI] 0.526–0.828; P<0.01), whereas that for the percentage decrease (%dec) in the MECKI score was 0.688 (95% CI 0.542–0.833; P<0.01). The cut-off value was 99% (sensitivity 0.571, specificity 0.781).

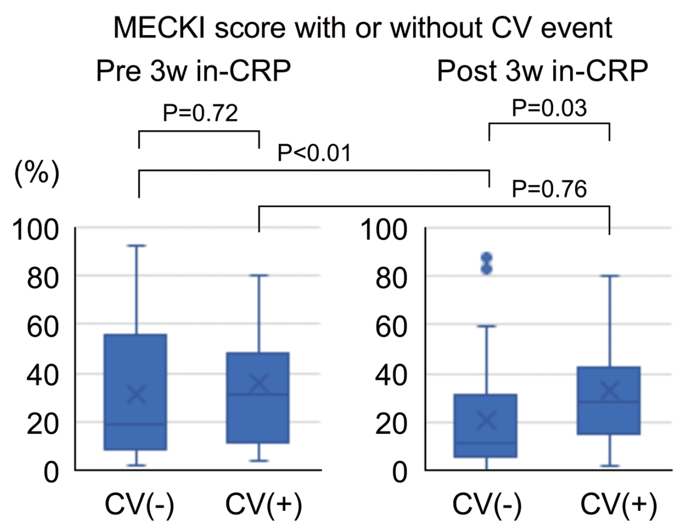

Figure 3. Metabolic Exercise data combined with Cardiac and Kidney Indexes (MECKI) scores before and after 3 weeks of an inpatient cardiac rehabilitation program (3w In-CRP) in patients with or without cardiovascular (CV) events (rehospitalization for heart failure or death) after discharge. In patients without CV events, the median MECKI score decreased after 3w In-CRP (from 18.76% [IQR 8.44–55.1%] to 11.84% [IQR 5.7–30.8%]; P<0.01). However, in patients with CV events, the median MECKI score remained almost unchanged after 3w In-CRP (from 30.76% [IQR 12.09–43.95%] to 28.81% [IQR 18.75–41.13%]; P=0.76). Moreover, regardless of the presence of CV events before 3w In-CRP, the MECKI score decreased significantly among patients without CV events after 3w In-CRP (P=0.03). The boxes show the interquartile range, with the median value indicated by the horizontal line; crosses indicate mean values. Whiskers show the range.

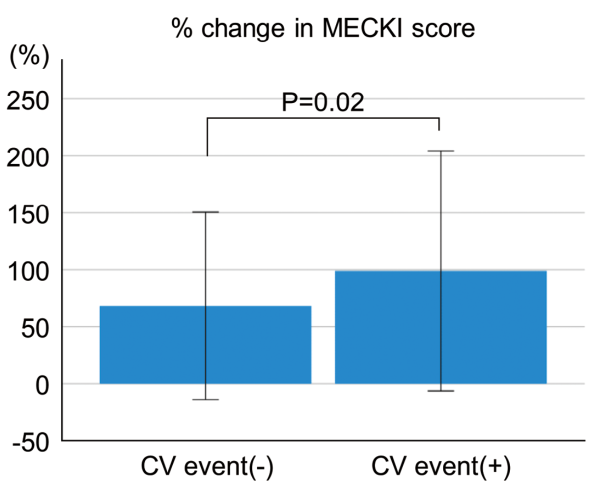

Figure 4. Mean (±SD) percentage change in Metabolic Exercise data combined with Cardiac and Kidney Indexes (MECKI) scores in patients with or without cardiovascular (CV) events (rehospitalization for heart failure or death) after discharge. The percentage decrease in the MECKI score was significantly higher in patients without than with CV events (68.3±41.1% vs. 99.0±52.6%; P=0.02).

in MECKI score for predicting CV events was 99.0%.

Using 99.0% as the cut-off value, Kaplan-Meier analysis revealed that patients with a higher percentage decrease in MECKI score during 3w In-CRP had fewer CV events than those with a lower percentage decrease in MECKI score after discharge (log-rank [Mantel-Cox] χ^2=8.108, P>0.01; hazard ratio 0.291, 95% confidence interval 0.118–0.719, P<0.01; **Figure 5**).

MECKI Score Components and Risk Factors for Non-Improvement in MECKI Score

LVEF and %peak $\dot{V}O_2$ before 3w In-CRP did not differ between patients with and without CV events. These parameters improved significantly only in patients without CV events. Moreover, in patients with CV events, hemoglobin levels decreased significantly (**Table 2**). The main factors associated with non-improvement in the MECKI score were non-improvements in LVEF and %peak $\dot{V}O_2$ and decreased hemoglobin levels.

Peak WR was also increased only in patients without CV events (**Table 2**).

Discussion

This study investigated the effects of 3w In-CRP in patients with HFrEF. After 3w In-CRP, the MECKI score improved from 23.34% to 18.66%. The primary reason for its improvement was increased LVEF and %peak $\dot{V}O_2$. In addition, the group with improved MECKI scores experienced fewer CV events (death or HF rehospitalization) after discharge. In contrast, patients who died or were rehospitalized for HF after discharge did not have improved MECKI scores, despite the 3w In-CRP. The main factors in contributing to the stable MECKI scores in this group were non-improvements in LVEF, %peak $\dot{V}O_2$, and peak WR and decreased hemoglobin levels. In this study, we showed that 3w In-CRP could significantly improve MECKI scores in patients with HFrEF and that the improved MECKI scores were associated with a reduction in CV events. The group of patients who undertook 3w In-CRP

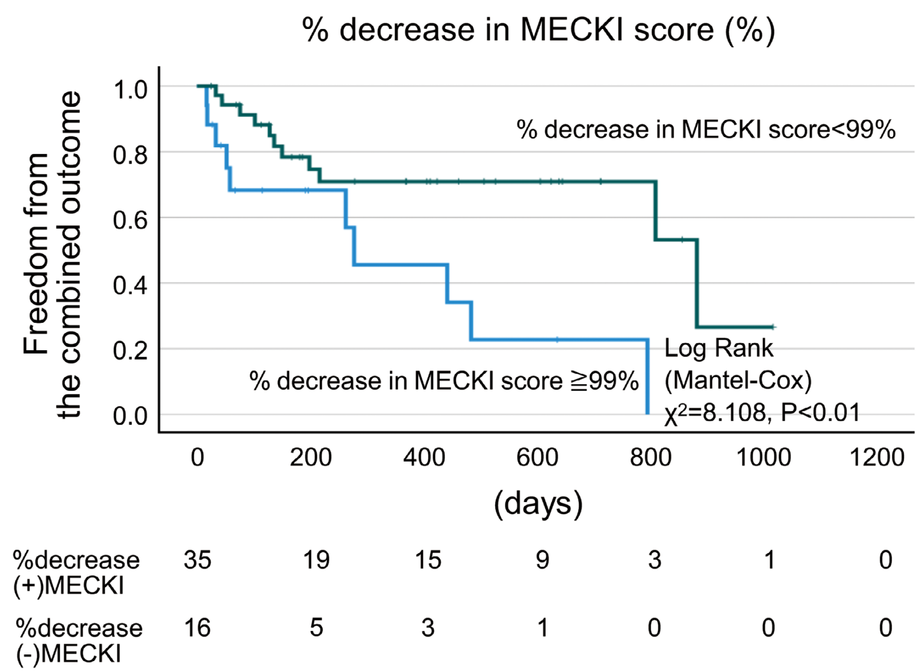

Figure 5. Kaplan-Meier curves showing freedom from cardiovascular events in patients with high and low percentage decreases in the Metabolic Exercise data combined with Cardiac and Kidney Indexes (MECKI) score (i.e., MECKI score after 3 weeks of an inpatient cardiac rehabilitation program [3w In-CRP] <99% vs. ≥99%, respectively). Patients with a high percentage decrease in MECKI score after 3w In-CRP had significantly fewer CV events than patients with a low percentage decrease in MECKI score (log-rank [Mantel-Cox] X^2=8.108, P<0.01).

Table 2. Effects of 3w In-CRP in Patients With or Without CV Events

	CV event (–)			CV event (+)			P value (A vs. C)
	Before 3w In-CRP (A)	After 3w In-CRP (B)	P value (A vs. B)	Before 3w In-CRP (C)	After 3w In-CRP (D)	P value (C vs. D)	
LVEF (%)	25±9	31±12	<0.01	26±8	28±11	0.31	0.66
%Peak $\dot{V}O_2$ (%)	51±14	59±14	<0.01	46±12	47±17	0.69	0.13
$\dot{V}E$ vs. $\dot{V}CO_2$ slope	46.8±18.6	42.6±13.5	0.11	53.4±14.2	52.1±9.3	0.58	0.17
MDRD (mL/min)	44.0±20.9	44.1±23.6	0.94	56.3±44.0	54.1±53.3	0.55	0.19
Sodium (mEq/L)	139±3	139±4	0.99	138±4	139±3	0.15	0.83
Hemoglobin (g/dL)	13.8±2.1	13.4±2.2	0.12	12.3±1.3	11.7±1.5	0.11	0.01
Peak work rate (W)	53±19	64±23	<0.01	42±15	45±16	0.17	0.03

Unless indicated otherwise, data are presented as the mean±SD. Data were analyzed using Student's t-test or paired t-tests, as appropriate. P<0.05 was considered significant. %Peak $\dot{V}O_2$, percentage peak oxygen uptake; 3w In-CRP, 3 weeks of an inpatient cardiac rehabilitation program; CV events, cardiovascular events (heart failure rehospitalization or death) after discharge; LVEF, left ventricular ejection fraction; MDRD, Modification of Diet in Renal Disease estimate of glomerular filtration rate; $\dot{V}CO_2$, carbon dioxide production; $\dot{V}E$, minute ventilation.

without any improvement in their MECKI score experienced more CV events.

The MECKI score is a novel parameter for HFrEF prognosis. It is significantly more accurate for mortality, heart transplantation, and left ventricular assist device implantation in patients with HFrEF than LVEF, $\dot{V}E$ vs. $\dot{V}CO_2$ slope, and peak $\dot{V}O_2$ alone.[20–23] Moreover, the MECKI score is more accurate for prognosis than the HF survival score and the Seattle heart failure model, which estimates the HF score. It is even more useful because of the few requirements: blood sample, TTE, and CPET.[23]

We revealed that MECKI scores improved among patients with HFrEF who undertook 3w In-CRP. The primary reasons for the improvement in the MECKI score are increased peak $\dot{V}O_2$ and LVEF. In addition, 3w In-CRP consisted of 30 CRP sessions. Generally, cardiac rehabilitation guidelines require many outpatient sessions.[15,28] However, because of the rapidly aging society, most patients with HF cannot attend sufficient outpatient CRP sessions according to the guidelines.[29] Thus, 3w In-CRP could solve this problem in Japan. CRP improves peak $\dot{V}O_2$, and some reports have indicated that LVEF is also improved.[11,12,30] Our results showed effects similar to those reported previously, along with an improvement in the

MECKI score.

Conversely, patients with HFrEF rehospitalized for HF or who died after discharge from the 3w In-CRP did not have improved MECKI scores after 3 weeks. These patients attended 30 CRP sessions; nevertheless, they did not experience an improvement in %peak $\dot{V}O_2$. Peak $\dot{V}O_2$ involves cardiac output and arteriovenous oxygen difference (Fick method), and exercise therapy generally increases peripheral skeletal muscles and the arteriovenous oxygen difference.[31] In the present study, patients with CV events had unchanged peak WR. Therefore, there were probably no improvements in the skeletal muscles of the patients' legs within the 3 weeks of the program, despite the 30 CRP sessions. Therefore, these patients may experience future CV events and should undergo additional management of HF after discharge.

This study has some limitations. First, this was a single-center study with relatively few patients. Future multicenter studies are warranted to confirm our findings. However, we revealed that 3w In-CRP increased peak $\dot{V}O_2$, improved the MECKI score, and reduced CV events. It is applicable in Japan as well as in other countries.[16–19] Second, we excluded patients who could not cycle on the ergometer without support to avoid falling. Thus, we included patients with HF who had a sufficient daily activity level to be able to ride the bicycle without help but with low exercise endurance. Third, we added some medications during inpatient CRP. However, most participants had sufficient medications prescribed during previous hospitalizations or outpatient treatments. Therefore, only a few patients had medications added, and the effects of the additional medications are expected to be quite low. Moreover, in Japan, the cost of congestive HF is approximately US$8,115 (US$5,302–13,023),[32] and the cost of 3w In-CRP is approximately US$7,300–6,500 to prevent HF hospitalizations or death. Thus, although CRP seems safer and cheaper than hospitalization for congestive HF, further long-term investigations are needed.

Conclusions

The MECKI score is a prognostic parameter for HFrEF, superior to cardiac parameters or other HF scores. Because of increases in LVEF and %peak $\dot{V}O_2$, 3w In-CRP improves MECKI scores. The group with improved MECKI scores experienced fewer deaths or HF rehospitalizations after discharge compared with the group of patients with HFrEF who underwent 3w In-CRP without an improvement in MECKI scores. Thus, patients who do not see an improvement in MECKI scores after CRP require additional HF management. In conclusion, 3w In-CRP may help reduce HFrEF hospitalizations and improve prognosis.

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 grants 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).

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, Böhm 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, Bäck M, et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021; **42:** 3227–3337.
16. Karoff M, Held K, Bjarnason-Wehrens B. Cardiac rehabilitation in Germany. *Eur J Cardiovasc Prev Rehabil* 2007; **14:** 18–27.
17. 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.
18. 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.
19. 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.

20. Agostoni P, Corrà U, Cattadori G, Veglia F, La Gioia R, Scardovi AB, et al. Metabolic exercise test data combined with cardiac and kidney indexes, the MECKI score: A multiparametric approach to heart failure prognosis. *Int J Cardiol* 2013; **167:** 2710–2718.
21. Corrà U, Agostoni P, Giordano A, Cattadori G, Battaia E, La Gioia R, et al. The Metabolic Exercise test data combined with Cardiac And Kidney Indexes (MECKI) score and prognosis in heart failure: A validation study. *Int J Cardiol* 2016; **203:** 1067–1072.
22. Salvioni E, Bonomi A, Re F, Mapelli M, Mattavelli I, Vitale G, et al. The MECKI score initiative: Development and state of the art. *Eur J Prev Cardiol* 2020; **27:** 5–11.
23. Agostoni P, Paolillo S, Mapelli M, Gentile P, Salvioni E, Veglia F, et al. Multiparametric prognostic scores in chronic heart failure with reduced ejection fraction: A long-term comparison. *Eur J Heart Fail* 2018; **20:** 700–710.
24. Itoh H, Ajisaka R, Koike A, Makita S, Omiya K, Kato Y, et al. Heart rate and blood pressure response to ramp exercise and exercise capacity in relation to age, gender, and mode of exercise in a healthy population. *J Cardiol* 2013; **61:** 71–78.
25. 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.
26. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 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.
27. Hillege HL, Nitsch D, Pfeffer MA, Swedberg K, McMurray JJ, Yusuf S, et al. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. *Circulation* 2006; **113:** 671–678.
28. Santiago de Araújo Pio C, Marzolini S, Pakosh M, Grace SL. Effect of cardiac rehabilitation dose on mortality and morbidity: A systematic review and meta-regression analysis. *Mayo Clin Proc* 2017; **92:** 1644–1659.
29. 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.
30. 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.
31. Sullivan MJ, Higginbotham MB, Cobb FR. Exercise training in patients with severe left ventricular dysfunction: Hemodynamic and metabolic effects. *Circulation* 1988; **78:** 506–515.
32. Kanaoka K, Okayama S, Nakai M, Sumita Y, Nishimura K, Kawakami R, et al. Hospitalization costs for patients with acute congestive heart failure in Japan. *Circ J* 2019; **83:** 1025–1031.

Supplementary Files

Please find supplementary file(s);
https://doi.org/10.1253/circrep.CR-23-0016