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Original Article

Tailored BEST Exercise Protocol in Heart Failure Rehabilitation: Intracardiac and Extracardiac Benefits for All Responders

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Abstract

Introduction: Heart failure with a reduced ejection fraction (HFrEF) significantly contributes to global morbidity and mortality, necessitating effective rehabilitation programs. Exercise-based rehabilitation improves functional capacity and quality of life in HFrEF patients, though responses vary. The tailored BEST (Breathing, Endurance, and Strengthening) exercise protocol addresses both cardiac and extracardiac rehabilitation, benefiting all patients regardless of response status. This study evaluated the protocol's effects on HFrEF patients and classified rehabilitation responses based on changes in aerobic capacity.

Methods: In this etiologic study with a prospective cohort design, all participants underwent a three-month cardiac rehabilitation program using the BEST Exercise Protocol. Assessments included the 6-minute walk test (6MWT), short physical performance battery (SPPB), handgrip strength, chest expansion, ultrasonographic measurements, and NT-proBNP levels before and after the intervention, with statistical comparisons made within and between groups. Groupings of responder level will be reliant on 6MWT distance achievement at the end of the program, with ≥6% improvement classified as good responders.

Results: Out of 107 HFrEF patients (median age 55 years, ejection fraction 29.50±7.34%), 63.56% were good responders and 36.44% were poor responders (<6% improvement). Good responders showed significant improvements in most extracardiac parameters, including a 20% increase in 6MWT distance (470.96±69.21 meters post-rehabilitation), chest expansion, handgrip strength, and SPPB scores ($p<0.001$ for all). Poor responders also improved in chest expansion, sit-to-stand time, and postural balance, with minor 6MWT gains (407.33±72.50 meters). NT-proBNP levels decreased in both groups but were not statistically significant ($p=0.288$ and 0.368 for good and poor responders, respectively).

Conclusion: The tailored BEST Exercise Protocol offers substantial cardiac and extracardiac benefits for HFrEF patients by enhancing functional capacity and muscle strength. Both good and poor responders exhibited significant improvements, indicating the protocol's broad applicability. However, the lack of statistically significant NT-proBNP reduction suggests further studies on cardiac biomarkers are needed. The 6MWT provides accessible rehabilitation insights, though more precise evaluations like Cardiopulmonary Exercise Testing (CPET) can offer clearer insights into cardiopulmonary adaptations.

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Keywords: *Heart failure with reduced ejection fraction (HFrEF); Endurance Exercise; Breathing Exercise; Strengthening Exercise; Heart failure rehabilitation.*

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Introduction

Heart failure with reduced ejection fraction (HFrEF) is a prevalent condition associated with significant morbidity and mortality that necessitates effective rehabilitation strategies.[1] Exercise-based cardiac rehabilitation programs have shown promise for improving the functional capacity and quality of life of patients with HFrEF.[2] The breathing, endurance, and strengthening (BEST) protocol aims to optimize cardiovascular and muscular adaptations using a tailored approach.[3,4] This personalized exercise regimen may address the diverse needs of patients with HFrEF and potentially lead to better outcomes across a broader spectrum of responders.

Initially, the ARISTOS-HF trial demonstrated the importance of a comprehensive exercise program in patients with HFrEF.[4] This program combines endurance, resistance, and inspiratory muscle training.[4] Endurance exercises focus on improving cardiovascular endurance and overall aerobic capacity.[4] Breathing exercises target strengthening of the respiratory muscles to enhance lung function.[4] Strengthening exercises aim to increase muscle mass and improve overall muscle strength and endurance.[4]

The study's findings revealed that the combined Aerobic, Resistance, and Inspiratory Strengthening (ARIS) program yielded superior benefits compared to aerobic alone or aerobic combined with either resistance or inspiratory muscle strengthening, as they would affect the extracardiac ergoceptors.[2,3,5] The ARIS group showed trends towards greater improvement in aerobic capacity, with a 19% increase in peak VO2 compared to 9-11% in the other groups.[4] Additionally, the combined program demonstrated significant benefits in terms of cardiac function, aerobic capacity, quality of life, respiratory function, and skeletal muscle function.[4,5] These results support the muscle training hypothesis for HFrEF, suggesting that addressing multiple aspects of physical fitness through a combined training approach would eventually provide optimal benefits for patients with HFrEF.5 Unfortunately, the ARISTOS study did not classify rehabilitation responder levels, which has been shown to affect rehabilitation impacts between subjects.[6,7]

Despite the increasing body of evidence supporting its benefits, HFrEF rehabilitation continues to face numerous barriers, exhibits low participation rates, and the optimal exercise protocol with individualization of rehabilitation programs remains unclear.[6,8–10] In addition to insufficient knowledge regarding exercise safety for patients with HFrEF between care providers, another contributing factor is the low proportion of favorable responders after a three-month rehabilitation period, resulting in minimal or no improvement in aerobic capacity as depicted by VO2 max upon program completion.[8,11,12] This study aimed to address this knowledge gap by investigating the impact of a tailored rehabilitation program based on the BEST Exercise protocol on both intracardiac and extracardiac outcomes in patients with HFrEF, and presenting the number of good and poor responders while exhibiting which extracardiac factors had obtained the best improvement. The rationale is to provide evidence-based recommendations for designing individualized rehabilitation programs that improve the overall physical function and quality of life in patients with HFrEF. We hypothesize that this tailored BEST protocol in HF rehabilitation will significantly improve cardiac and extracardiac parameters among patients with HFrEF, regardless of their responder status.

Methods

Study Participants

From April 2022 to April 2023, the research group initially screened 125 patients in the Holistic Assessment and Rehabilitation toolKIT for Heart Failure (HARKIT-HF) cohort. Of these, 107 individuals with HFrEF were selected for the study after completing a 3-month cardiac rehabilitation program. These participants were all rehabilitation patients between 18 and 65 years of age who had been diagnosed with chronic HFrEF by their cardiologist. Prior to rehabilitation referrals, all patients had received optimal guideline-directed medical therapy (GDMT) for at least two months. These individuals had to achieve hemodynamic stability for a minimum of one week following their most recent hospitalization before being included in the program. Regarding etiology, only ischemic and cardiomyopathy causes of HFrEF were included, whereas severe valvular disorders and congenital heart disease were excluded from the study.

Subjects were also excluded if they experienced impaired mobility due to neuromuscular conditions, amputation, or severe pain that hindered their movement.

Examination

This etiologic study had a pre-post design in which all subjects received the same BEST exercise protocol for three months, 2 3 days per week in a structure-based rehabilitation facility. Before enrollment in the program, subjects underwent initial measurements of cardiac parameters, including echocardiographic values, such as left ventricular ejection fraction (LVEF) and tricuspid annular plane systolic excursion (TAPSE). Subjects had their physical parameters measured, namely, 6-minute walk test (6MWT) distance, handgrip strength, chest expansion, and short physical performance battery (SPPB). Supporting diagnostics such as ultrasonographic parameters (diaphragm thickness during inspiration and expiration, anterior forearm muscle thickness) and laboratory values (NT-proBNP) were additionally assessed pre-post to enhance the overall results. The above parameters will be measured before and after the completion of the rehabilitation program by 3 months. Follow-up protocol includes measurement of all the components, being both physical and laboratory examinations. All measurements were standardized to mitigate measurement bias. Responder categories were stratified based on the improvement in 6MWT distance at the end of the program as previously published within the HF-ACTION study chain, with those demonstrating an improvement of ≥6% classified as good responders.[9]

Ethical Clearance Statement

The National Cardiovascular Center Harapan Kita Institutional Review Board granted ethical clearance for this study (Approval Number: DP.04.03/KEP238/EC105/2023), and informed consent was obtained from all participants prior to assessments.

Exercise Protocol

A description of the BEST exercise protocol (Figure 1) begins with breathing exercises that involve 10 min of deep breathing in a corrective thoracal posture combined with upper extremity range of motion exercise to optimize chest expansion. Endurance exercise began with 10 min of warm-up through general flexibility exercises for the upper and lower extremities, followed by 20 min of core exercise through brisk walking or treadmill exercise at moderate intensity (40-59% Heart Rate Reserve). Subjective maintenance of aerobic intensity was performed through a talk test to ensure that the patient could converse in full sentences while performing the required exercise intensity. The last element consisted of strength training exercises conducted on alternating days each week. On one day, the session targeted major upper body muscles (pectorals, deltoids, biceps, triceps, and forearm) using lightweight dumbbells of 1-2 kg, with participants performing three sets of 10-12 repetitions for each exercise. On other days, the session focused on the major core and lower body muscles (gluteus, quadriceps, hamstring, and latissimus dorsi), employing calisthenics and chair-based exercises. Details on all the strengthening exercises can be seen in Table 1. Overall, the patient received 3-5 days of breathing and endurance exercises, and 1-2 days of strengthening exercises on alternating days for each major muscle group, as recommended by the ESC guidelines. The patient had to complete the program for 3 months before undergoing a follow-up examination of all intra- and extracardiac parameters.

Statistical Analysis

SPSS for Macintosh version 29.0 (IBM, New York, USA) was used for the statistical analysis in this study. The Kolmogorov-Smirnov test was initially used to examine all numeric data for a normal distribution. Most variables in the study were continuous and thus expressed as mean±SD or median (minimum-maximum values), while categorical variables are shown as proportions with percentages. To compare between responder groups, independent Student's t-test and Mann-Whitney U test were used, while intragroup comparisons were analyzed with dependent Student’s t-test and Wilcoxon test. Spearman correlation analysis was used to evaluate nonparametric NT-proBNP values in relation to extracardiac parameters.

Results

The study recruited 107 subjects with baseline characteristics and changes after three months of

Table 1. Protocol of Strengthening Exercises.

No.	Upper Extremities Exercises	Form and Weight	Muscles Affected	Lower Extremities Exercises	Form	Muscles Affected
1	Core Sides	1 kg Dumbbell Side Bends	Ext Obliques and Quadratus Lumborum	Core Extension/ Flexion	Wood Chop Exercise and Trunk Extension	Rectus Abdominis and Erector Spinae
2	Shoulder Abduction/ Adduction	Shoulder raise with 1 kg Dumbbells	Middle Deltoids and Rotator Cuff	Hip Abduction/ Adduction	Standing Hip Abduction	Adductor group and Tensor Fascia Latae
3	Shoulder Flexion/ Extension	Shoulder press with 1 kg Dumbbells	Anterior Deltoid, Biceps, Triceps	Hip Flexion/ Extension	Squat and Lunges	Iliopsoas, Gluteus
4	Rhomboids Retraction	Bent over row with 1 kg Dumbbells	Rhomboids, Latissimus Dorsi	Knee Flexion	Standing Hamstring Curls	Hamstring
5	Elbow Flexion/ Extension	Curl exercise with 1 kg Dumbbells	Biceps, triceps	Knee Extension	Seated Leg Extension	Quadriceps
6	Wrist Flexion/ Extension & Deviation	Hammer exercise 1 kg Dumbbells	Forearm Flexors – Extensors	Ankle Dorsi/ Plantarflexion	Standing	Gastrocsoleus and Anterior Tibialis

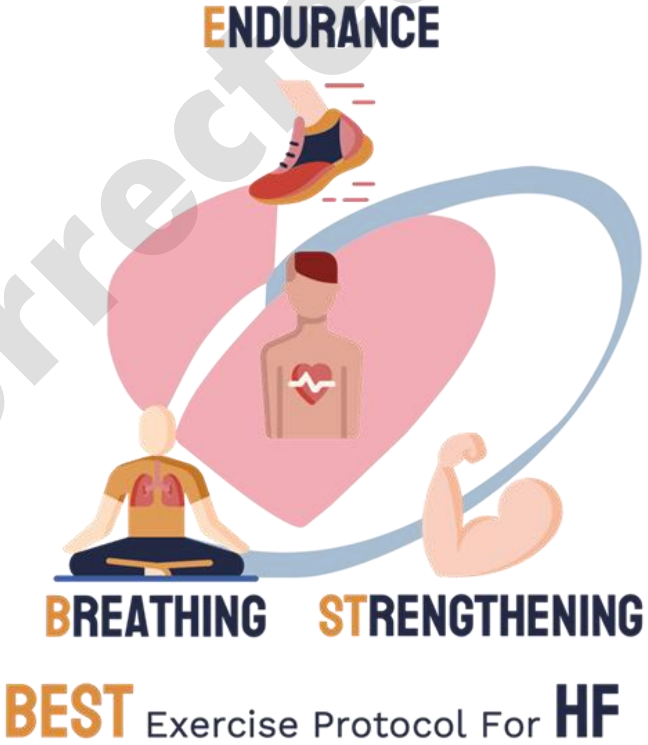

Figure 1. BEST exercise Protocol graphical representation .

Table 2. Patient baseline characteristics and overall improvement.

Variables	Baseline (n=107)	After 3 months CR (n=107)	Mean Difference±SD	p-value
Age (years)	55 (39-65)			
Female (n,%)	10 (9.35%)			
BMI (kg/m2)	26.44±4.90	26.46±4.93	0.01±0.43	0.739b,
Ejection fraction (%)	29.50±7.34	31.15±7.20	1.83±3.50	<0.001b,*
TAPSE (mm)	17.86±4.81	17.91±4.71	0.05±0.44	0.223b
6MWT (m)	395.74±61.54	447.77±76.54	52.03±63.62	<0.001b,*
Baseline heart rate (bpm)	78.20±13.63	79.29±13.69	1.09±11.82	0.318b
Post-6MWT heart rate (bpm)	99.42±16.86	103.72±19.67	4.30±17.76	0.014 b,*
Full tandem balance (seconds)	9.92±2.74	11.48±1.74	1.56±2.75	<0.001b,*
4-meter gait (seconds)	2.33±0.49	2.25±0.45	–0.08±0.41	0.047b,*
Gait speed (m/s)	0.58±0.12	0.56±0.11	–0.02±0.10	0.047b,*
5-times sit to stand (seconds)	12.24±3.82	8.72±3.22	3.52±3.66	<0.001 b,*
SPPB composite score (max 15)	11 (7-12)	12 (8-12)		<0.001c
Superior Chest Expansion (cm)	2.19±0.88	2.68±0.73	0.49±0.95	<0.001b,*
Inferior Chest Expansion (cm)	2.80±1.25	2.68±0.72	0.60±1.87	<0.001b,*
Dominant HGS (kg)	30.28±7.73	31.43±7.67	1.15±4.09	0.004b,*
Non-dominant HGS (kg)	28.15±7.94	29.25±8.59	1.10±4.34	0.010b,*
Tidal Inspiration Thickness	0.26±0.09	0.26±0.09	–0.00±0.08	0.972
Tidal Expiration Thickness	0.19±0.05	0.18±0.06	–0.00±0.65	0.549
Deep Inspiration Thickness	0.41±0.15	0.45±0.15	0.04±0.16	0.004
Deep Expiration Thickness	0.21±0.07	0.21±0.14	0.01±0.14	0.652
Dominant forearm thickness (cm)	2.20±0.57	2.16±0.52	–0.03±0.63	0.589b
Non-dominant forearm thickness left (cm)	2.11±0.54	2.30±0.170	0.18±1.80	0.291b
NT-proBNP (pg/ml)	816 (105-69230)	785 (105-50297)		0.172c

6MWT: 6-minute walk test; BMI: Body mass index; HGS, handgrip strength; SPPB, short physical performance battery; TAPSE, tricuspid annular plane systolic excursion.

All values are expressed as mean±SD, median (min-max), or number of cases (%).

an Analyzed using the Mann-Whitney U test

b Analyzed using independent Student's t-test

c Analyzed using Fisher's exact test

* Statistically significant at p=0.05.

rehabilitation completion, as shown in Table 2. Study demographics include a median age of 55 years, 9.35% are female, with a slightly obese BMI (26.44±4.90 kg/m2), and a reduced ejection fraction of 29.50±7.34%. It appeared that both responder levels combined significantly improved several parameters. Intracardiac changes include an increased post-6MWT heart rate by 4.30 beats, yielding a significantly higher 6MWT distance of 447.77±76.54 (improved 52.03±63.62, $p<0.001$). Functional testing with the SPPB also showed statistically significant improvement in all three components: postural balance, gait speed, 5-times sit-to-stand, and overall SPPB composite score. Among these improvements, 5 times sit-to-stand obtained the highest mean difference, with a reduction of 3.52±3.66 seconds compared to their baseline level. Extracardiac improvements could be seen in both respiratory and musculoskeletal components, as seen in chest expansion, which also improved in both superior and inferior measurements, as well as increased bilateral handgrip strength. Ultrasonographic measurements revealed a significant improvement only in diaphragmatic deep inspiration thickness. No statistically significant finding was observed in NT-proBNP improvement, although a trend toward lower values was noted after completion of rehabilitation.

The majority of the sample comprised good responders (63.56%), and approximately one-third

Table 3. The bivariate analysis of variables as predictors of mortality in patients with LtR-shunt CHD-associated PAH.

Variables	Poor Responder (n=39)			Good Responder (n=68)			After CR
	Baseline	After 3 months CR	Intragroup p-value	Baseline	After 3 months CR	Intragroup p-value	Intergroup p-value
Age (years)	53 (39-65)			56 (29-65)			0.038c
Female (n,%)	3 (7.69%)			7 (10.29%)			0.744e
BMI (kg/m2)	27.43±5.83	27.41±5.87	0.794b	25.88±4.22	25.91±4.25	0.556b	0.167a
Ejection fraction (%)	29.78±7.20	30.67±7.15	0.013b,*	29.34±7.46	31.43±7.27	<0.001b,*	0.602a
TAPSE (mm)	17.96±5.06	17.94±4.98	0.696b	17.80±4.69	17.89±4.58	0.137b	0.959a
6MWT (m)	410.26±61.44	407.33±72.50	0.595b	387.41±60.47	470.96±69.21	<0.001b,*	<0.001a,*
Baseline heart rate (bpm)	81.74±15.79	82.92±17.15	0.534b	76.16±11.89	77.21±10.85	0.441b	0.066a
Post-6MWT heart rate (bpm)	103.03±17.02	100.28±24.39	0.377b	97.35±16.43	105.69±16.24	<0.001b,*	0.086a
Full tandem balance (seconds)	9.86±3.02	10.81±2.63	0.039b,*	9.95±2.58	11.86±0.67	<0.001b,*	0.010a
4-meter gait (seconds)	2.28±0.50	2.32±0.51	0.557b	2.36±0.49	2.21±0.41	0.005b,*	0.118a
Gait speed (m/s)	0.57±0.12	0.58±0.13	0.557b	0.59±0.12	0.55±0.10	0.005b,*	0.095a
5-times sit to stand (seconds)	11.96±3.84	9.33±4.18	<0.001b,*	12.40±3.83	8.36±2.47	<0.001b,*	0.095a
SPPB composite score (max 15)	11 (7-12)	12 (8-12)	<0.001d,*	11 (8-12)	12 (10-12)	<0.001d,*	0.024c
Superior Chest Expansion (cm)	2.31±0.99	2.60±0.49	0.023b,*	2.12 ±0.80	2.72±0.83	<0.001b,*	0.180a
Inferior Chest Expansion (cm)	2.98±1.44	3.40±1.87	0.253b	2.70±1.12	3.39±1.16	<0.001b,*	0.486a
Dominant HGS (kg)	30.57±7.98	31.06±8.66	0.392b	30.12±7.65	31.65±7.11	0.005b,*	0.353a
Non-dominant HGS (kg)	28.48±9.10	28.27±10.54	0.796b	27.96±7.27	29.81±7.27	<0.001b,*	0.187a
Tidal Inspiration Thickness	0.25±0.08	0.25±0.10	0.679b	0.26±0.09	0.27±0.08	0.787b	0.148a
Tidal Expiration Thickness	0.19±0.06	0.19±0.08	0.890b	0.19±0.05	0.18±0.05	0.252b	0.355a
Deep Inspiration Thickness	0.43±0.16	0.43±0.18	0.938b	0.40±0.15	0.47±0.14	<0.001b,*	0.092a
Deep Expiration Thickness	0.21±0.08	0.23±0.20	0.571b	0.20±0.07	0.20±0.86	0.949b	0.172a
Dominant forearm thickness (cm)	2.26±0.61	2.12±0.53	0.130b	2.16±0.55	2.19±0.52	0.716b	0.258a

Non-dominant forearm thickness (cm)	2.17±0.55	2.61±2.73	0.339b	2.08±0.53	2.11±0.49	0.650b	0.071a
NT-proBNP (pg/ml)	1139 (105-7484)	895 (105-13790)	0.368d	701 (119-69230)	573 (119-50927)	0.288d	0.389c

performance battery; TAPSE, tricuspid annular plane systolic excursion.
All values are expressed as mean±SD, median (min-max), or number of cases (%).
a Analyzed using independent Student's t-test
b Analyzed using dependent Student's t-test
c Analyzed using Mann-Whitney U test
d Analyzed using Wilcoxon test
e Analyzed using Fisher's exact test

were classified as poor responders (36.44%); these comparisons are presented in detail in Table 3. The patient's age was younger in poor responders by 3 years, and the majority of subjects were male, with less than 15% of the sample being female. Similar baseline values were observed in EF, ranging below 30% and TAPSE < 18 mm in both groups. After completing rehabilitation, EF seemed to significantly improve in both groups ($p< 0.05$), although changes were mild and still classified as reduced (below 40%), good responders vividly show better improvement. Distance obtained in 6MWT was significantly different in between groups, after 3 months obtaining 407.33±72.50 in poor responder, as compared to 470.96±69.21 in good responder, where good responder had improved approximately 20% from baseline. Good responders had an overall significant improvement in all components of the SPPB, namely balance, gait speed, and sit-to-stand time ($p \leq 0.001$, 0.005, and <0.001, respectively), while poor responders did not achieve statistical significance in gait speed improvement. The SPPB composite scores were significantly different ($p=0.024$), with a minimum value of 10 in good responders and 8 in poor responders. The difference in the SPPB scores appeared to be influenced by the balance score, as it differed significantly between the groups ($p=0.010$), and the other two components did not reach statistical significance.

Chest expansions were seen to significantly improve in both superior and inferior measurements in good responders after rehabilitation completion, while poor responders also achieved overall improvement. Only superior measures were seen to be statistically significant. Similarly, musculoskeletal improvements were observed in both dominant and non-dominant HGS, obtaining an overall significant improvement in the good responder group, while only achieving an improvement trend in the other group. Regarding ultrasonographic parameters in both the diaphragm and anterior forearm measurements, only deep diaphragmatic inspiration thickness demonstrated a statistically significant improvement of approximately 17% in the good responder group, whereas the other parameters displayed trends of improvement. Despite these changes in both the respiratory and musculoskeletal systems, there was no significant difference in the final measurements between the groups. A graphical summary of improvement after 3-months between the responders is shown in Figure 2, where good responders showed an overall statistically significant improvement in most extracardiac components, except for NT-proBNP in the good and poor responder groups, as they were generally reduced after three months without reaching statistical significance ($p=0.288$ and 0.368, respectively). In contrast, poor responders also showed significant improvements in superior chest expansion, sit-to-stand time (depicted by lower extremity muscle strength), and postural balance.

Discussion

AThis study recruited 107 subjects with heart failure with reduced ejection fraction HFrEF to evaluate the effect of the BEST Exercise protocol on both cardiac and extracardiac outcomes. The cohort's median age was 55 years, with 9.35% female participants, and a mean BMI reflecting a mildly obese population (26.44±4.90 kg/m²). All these showed a highly contrasting population, as the present cohort is much younger, highly predominant

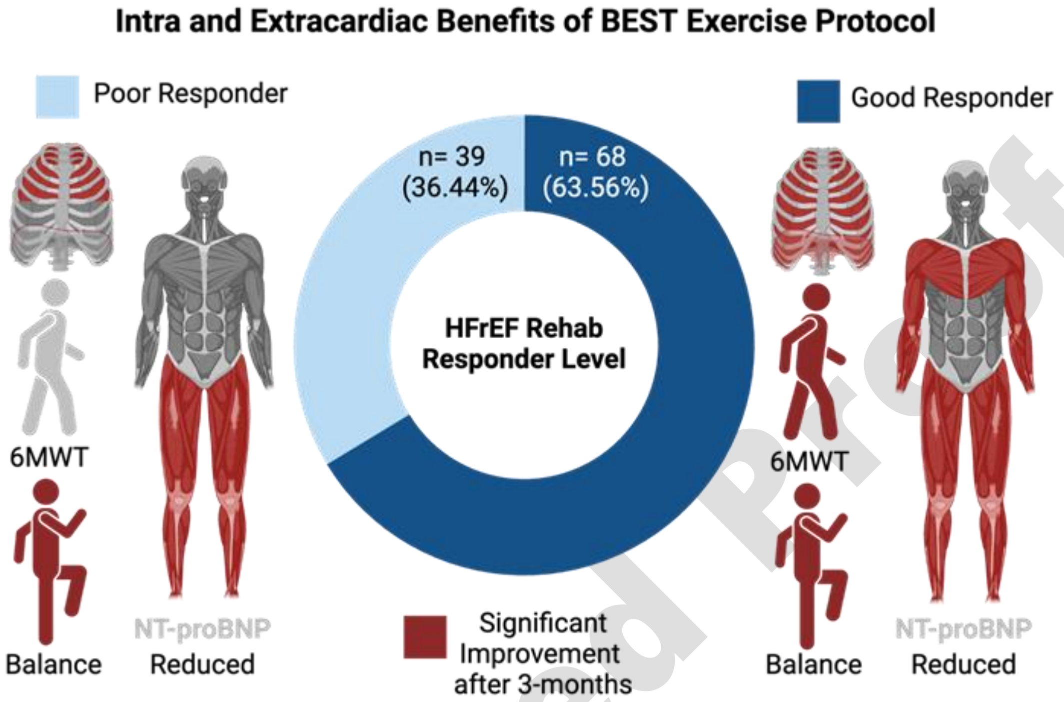

Figure 2. Graphical representation of significant improvements in all rehabilitation responder levels.

in males, and leaner compared to the previous similar study by Bakker with a median of 63 years, 69-81% males, and a BMI of 29±5.0 kg/m^2. Bakker et al. performed a similar study that defined both good and poor responders; their study also included HFpEF (approximately 30%), while the present study recruited only HFrEF subjects, thus presenting a higher severity of mean ejection fraction of 29.50±7.34%, indicating a younger yet notable cardiac impairment.[6] A similar interventional study by Laoutaris also reported an older age group with a mean of 63.9 years and the youngest being 59 years.[4] Within the highly classified population, the proportion of responders was the majority of good responders (63.56%), which was also in contrast to a previous study with only 45.16% of good responders.[6] Previous studies have also highlighted the differences between Asian HF and global epidemiology, and the current novel findings showed that the younger cohort exhibited a distinct characteristic, potentially possessing superior physical capacity, which may result in greater benefits from cardiac rehabilitation.[2]

Another study by Schutter et al., despite not being performed on an HF-specific cohort, touched upon younger age as a non-modifiable factor that leads to a better rehabilitation response, and conversely, a higher baseline VO2 would predispose to an inferior rehabilitation response.[7] These implications were seen vividly in the present cohort, as the good responder had initially lower baseline 6MWT when compared with the poor responder (387.41±60.47 m vs. 410.26±61.44 m respectively), with a substantially higher final 6MWT distance after rehabilitation completion (470.96±69.21 m vs. 407.33±72.50 m). Additionally, it could be seen that the younger cohort had a higher baseline 6MWT distance, which had not been reported previously in other published Asian HF studies that displayed varying results from 245.39±96.69 m in Indonesia,[13] 270 (180-367) m in Japan,[14,15] 312±92 m in Singapore,16 270.12±78.93 m in India,[17] and 150-450 m in China,[18] where almost all the published studies had a mean age of >60 years. In accordance with the most recent study on sarcopenia assessed using the Asian Working Group for Sarcopenia 2019 criteria, a 6MWT distance <300 m and HGS <28 kg were used as cutoff values to classify frailty.[14] When applied to the present study, it is apparent that the majority of the subjects can be categorized as robust, obtaining a baseline 6MWT of 387.41±60.47 m, and dominant HGS of 30.12±7.65 kg. Another cut-off study by Aida et al. emphasized the role of physical examination in older HF subjects with a median of 75 (71-80) years, which also supported the present results with 6MWT distance <400 m cut-off could be represented with HGS of 21.9 kg, both of which have been surpassed by the good and poor responder cohorts in the present study, being aligned with the robust physical capacity.[19] All of these studies showed how 6MWT distance is correlated with a better profile of extracardiac parameters, such as HGS.

Both good and poor responders exhibited significant improvements in extracardiac outcomes, although these improvements were more pronounced in good responders (Figure 2). Good responders showed statistically significant improvements in chest expansion, handgrip strength on both sides, short physical performance battery (SPPB), and 6MWT results after completion of rehabilitation using the BEST protocol. In contrast, poor responders demonstrated meaningful improvements in superior chest expansion, lower extremity muscle strength, and postural balance. It should be noted that ergo reflex is a key mechanism in heart failure that modulates cardiovascular and respiratory responses during physical activity.[5] It was previously shown that patients with HF may have diaphragmatic dysfunction due to systemic inflammation, increased peripheral resistance, and immobility in the HF pathology continuum.[20] Similarly, the majority of skeletal muscle dysfunction in patients is caused by increased peripheral resistance and low cardiac output, together often manifesting as myopathy, thus increasing ergoreflex sensitivity.[5] This heightened sensitivity, elicited by muscle contraction (mechanoreflex) through the musculoskeletal system and metabolite accumulation (metaboreflex) mediated by acid-base balance through the respiratory system, results in abnormal cardiovascular responses such as excessive vasoconstriction and increased heart rate.[3,5] Breathing exercises can help strengthen respiratory muscles and improve ventilatory efficiency, whereas strengthening exercises reduce muscle wasting and lower ergoreflex sensitivity by improving muscle function.[3–5,20] Essentially, endurance exercise improves peak oxygen uptake (VO2) and reduces sympathetic overactivity, helping to enhance cardiovascular efficiency; thus, it should always be prescribed for HF patients.[4,5,21] Together, these exercises restore a balanced autonomic response, enhance exercise tolerance, and alleviate HF symptoms, making the BEST protocol a key component of HF rehabilitation.[5,21]

Interestingly, the intracardiac biomarker NT-proBNP was reduced in both groups, in agreement with a previous meta-analysis.[22] Nevertheless, these reductions were not statistically significant, indicating that the effect of the exercise protocol on this cardiac biomarker may necessitate further investigation and potentially require the examination of additional biomarkers. A limitation of this study was the reliance on the 6MWT instead of cardiopulmonary exercise testing (CPET) with breath-by-breath analysis.[23] While the 6MWT is a more accessible and practical tool for clinical application, the CPET provides a more detailed and accurate assessment of cardiopulmonary function, which could offer deeper insights into the physiological changes induced by the BEST protocol. However, a previous study showed that utilization of the 6MWT distance with the Cahalin formula in HF subjects had sufficient correlation strength with CPET maximal oxygen uptake outputs.[24] Additionally, the use of 6MWT distance in HF aligns with real-world clinical settings, making the study's findings more applicable to general practice.[19] Another strength of this study lies in its focus on younger patients with HF, which is a novel category, demonstrating that the BEST protocol can lead to significant improvements in both intracardiac and extracardiac outcomes even in poor responders.

Conclusion

EIn conclusion, the Tailored BEST Exercise Protocol in heart failure rehabilitation demonstrated significant intracardiac and extracardiac benefits for both good and poor responders after three months of intervention. The majority of the study population was classified as good responders (63.56%), who exhibited statistically significant improvements in most extracardiac components, including chest expansion, handgrip strength, the 6-minute walk test (6MWT), and the short physical performance battery (SPPB), with the exception of NT-proBNP, which showed trends of reduction in both groups without statistical significance. Notably, poor responders, who comprised 36.44% of the sample, also achieved substantial improvements in superior chest expansion, sit-to-stand performance (indicating enhanced lower-extremity muscle strength), and postural balance. These findings highlight that even among poor responders, substantial extracardiac functional gains can be achieved, underscoring the broad applicability and efficacy of the protocol in heart failure rehabilitation. Further investigation is required to examine the long-term effects of tailored exercise interventions on NT-proBNP and other biomarkers to validate these findings.

Conflict of Interest

Hajime Katsukawa receives a salary from the Japanese Society for Early Mobilization (a nonprofit society) as a chair (full-time). All the other authors have declared that no competing interests exist.

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