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PRIME-HF: Novel Exercise for Older Patients with Heart Failure. A Pilot Randomized Controlled Study

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PRIME-HF: Novel Exercise for Older Patients with Heart Failure. A Pilot Randomized Controlled Study

Catherine Giuliano, MAppSci,*† 🐦 Itamar Levinger, PhD,*†‡ Sara Vogrin, MBiostat,‡§
Christopher James Neil, PhD,*†§a and Jason David Allen, PhD¶a

OBJECTIVES: To test the hypothesis that (1) older patients with heart failure (HF) can tolerate COMBined moderate-intensity aerobic and resistance training (COMBO), and (2) 4 weeks of Peripheral Remodeling through Intermittent Muscular Exercise (PRIME) before 4 weeks of COMBO will improve aerobic capacity and muscle strength to a greater extent than 8 weeks of COMBO.

DESIGN: Prospective randomized parallel open-label blinded end point.

SETTING: Single-site Australian metropolitan hospital.

PARTICIPANTS: Nineteen adults (72.8 ± 8.4 years of age) with heart failure with reduced ejection fraction (HFrEF).

INTERVENTION: Participants were randomized to 4 weeks of PRIME or COMBO (phase 1). All participants subsequently completed 4 weeks of COMBO (phase 2). Sessions were twice a week for 60 minutes. PRIME is a low-mass, high-repetition regime (40% one-repetition maximum [1RM], eight strength exercises, 5 minutes each). COMBO training involved combined aerobic (40%-60% of peak aerobic capacity [VO_{2peak}], up to 20 minutes) and resistance training (50-70% 1RM, eight exercises, two sets of 10 repetitions).

MEASUREMENTS: We measured VO_{2peak}, VO_2 at anaerobic threshold (AT), and muscle voluntary contraction (MVC).

RESULTS: The PRIME group significantly increased VO_{2peak} after 8 weeks (2.4 mL/kg/min; 95% confidence interval [CI] = .7-4.1; P = .004), whereas the COMBO group showed minimal change (.2; 95% CI −1.5 to 1.8). This produced a large between-group effect size of 1.0. VO_2 at AT increased in the PRIME group (1.6 mL/kg/min; 95% CI .0-3.2) but not in the COMBO group (−1.2; 95% CI −2.9 to .4), producing a large between-group effect size. Total MVC increased significantly in both groups in comparison with baseline; however, the change was larger in the COMBO group (effect size = .6).

CONCLUSION: Traditional exercise approaches (COMBO) and PRIME improved strength. Only PRIME training produced statistically and clinically significant improvements to aerobic capacity. Taken together, these findings support the hypothesis that PRIME may have potential advantages for older patients with HFrEF and could be a possible alternative exercise modality. **J Am Geriatr Soc 68:1954-1961, 2020.**

Keywords: heart failure; exercise; strength; aerobic; resistance

From the *Institute for Health and Sport (IHES), Victoria University, Melbourne, Australia; †Department of Cardiology, Western Health, Sunshine Hospital, Melbourne, Australia; ‡Australian Institute for Musculoskeletal Science (AIMSS), Melbourne, Australia; §Department of Medicine – Western Health, The University of Melbourne, Australia; and the ¶Department of Kinesiology, Curry School of Education & Division of Cardiovascular Medicine, University of Virginia, Charlottesville, Virginia.

Address correspondence to Catherine Giuliano, MAppSci, Institute for Health and Sport, Victoria University, Level 3, Western Centre for Health, Research and Education, Sunshine Hospital, 176 Furlong Road, St. Albans, Victoria, Australia. E-mail: catherine.giuliano@live.vu.edu.au.
Twitter: @CathGiuliano

aThese authors contributed equally to this study.

Chronic heart failure (CHF) is a complex syndrome affecting 1% to 2% of Western populations,[1] and approximately 80% of patients are older than 60 years.[2] Patients with CHF are characterized by shortness of breath, fatigue, and exercise intolerance.[3] Exercise rehabilitation is considered a cornerstone intervention for people with CHF, with guidelines recommending moderate-intensity aerobic modalities,[3,4] often in conjunction with resistance training.[4-6] However, a key limitation of these guidelines is that they arise largely from data involving a patient cohort sometimes 2 decades younger (range = 51-81 years)[7] than the median age at diagnosis of CHF (77 years).[7,8] Considering that older adults with CHF experience a high prevalence of comorbidities, impaired functional capacity, reduced muscle mass and strength, and a 5-year survival of

25%,[9-14] it is unclear whether they can actually tolerate current exercise guidelines or gain functional benefits.

It was recently demonstrated that older individuals with reduced peak aerobic capacity (VO_{2peak} 15-20 mL/kg/min) can benefit from a novel exercise regime known as Peripheral Remodeling through Intermittent Muscular Exercise (PRIME).[15,16] In brief, PRIME offers a hybrid aerobic-resistance program and was designed to address the peripheral tissue dysfunctions responsible for reduced VO_{2peak} in older adults, without imposing excess cardiovascular or musculoskeletal strain.[16] When PRIME is applied as a bridging therapy to combined aerobic and resistance training, participants experience greater increases in aerobic capacity, muscle strength, and physical function compared with combined training alone. This approach may offer potential advantages to older patients with central cardiovascular limitations; however, it is yet to be tested in clinical populations.

The aim of the current study was to test the hypothesis that (1) older patients with CHF can tolerate current exercise recommendations involving COMBbined moderate-intensity aerobic and resistance training (COMBO), and (2) 4 weeks of PRIME training followed by 4 weeks of COMBO will improve aerobic capacity and muscle strength to a greater extent than 8 weeks of the current recommended COMBO approach.

METHODS

Participants

Participants were recruited from the Western Health Heart Failure Clinic in Melbourne, Australia, following patient file review and an in-person interview. Inclusion criteria were (1) a diagnosis of HF with reduced ejection fraction (HFrEF) as defined by European Society of Cardiology Guidelines 2016,[3] (2) age 65 years and older, and (3) mild to moderate symptomatology (New York Heart Association [NYHA] class II-III). Exclusion criteria included any absolute contraindications to exercise for people with HFrEF, and relative contraindications were adjudicated by the study cardiologist. The algorithm for inclusion and exclusion criteria is supplied in Supplementary Figure S1. Patients meeting eligibility criteria were provided with information and invited to participate in the trial. Those who gave informed consent were scheduled for baseline testing and screening. The research protocol was approved by ethics committees from Melbourne Health and Victoria University.

Experimental Design

We used a prospective randomized open-label blinded endpoint parallel-group design. Participants were randomized to PRIME or COMBO training for an initial 4 weeks (phase 1). Following this, all participants completed 4 weeks of COMBO training (phase 2). Participants were randomized in a 1:1 ratio by an independent researcher (permuted block randomization with block size of 4, stratified by sex, with sequence saved in sequentially numbered opaque sealed envelopes), with treatment allocation revealed after baseline

exercise testing. Outcomes were assessed at baseline, 4 weeks, and 8 weeks by a blinded assessor.

Outcome Measures

Aerobic Capacity

Peak aerobic capacity (VO_{2peak}) was assessed using a symptom-limited graded exercise test on a Lode Corival cycle ergometer, with simultaneous 12-lead electrocardiogram. Heart rate (HR), blood pressure (BP), and rating of perceived exertion (RPE) were recorded throughout. The protocol began at 20 W and increased by 10 W in 2-minute stages, and it was terminated when the patient achieved more than 17 on the RPE scale and was unable to continue cycling within 10 rpm of target cadence or exhibited clinical signs and symptoms. The volume of oxygen uptake (VO_2) for each 10-second interval was calculated utilizing MedGraphics (Breezesuite CPX Ultim system) that was calibrated before each test.

Muscle Strength

Muscle strength was assessed using the three-repetition maximum (3RM) test, and then predicated 1RM was calculated using standardized equations.[17] Total muscle voluntary contraction (total MVC) was considered as the sum of the calculated 1RM for seven movements tested including chest press, leg press, seated row, triceps pushdown, latissimus pulldown, upright row, and hack squat.

Exercise Training Protocols

Training sessions were conducted twice per week for 8 weeks and lasted approximately 60 minutes including warmup and cooldown. Sessions were conducted at Victoria University and Sunshine Hospital and supervised by an accredited exercise physiologist. In the case of missed exercise sessions, catch-up sessions were offered.

Phase I (PRIME)

The PRIME regime followed the protocol previously described[15,16] and was adjusted minimally for this study group. The protocol included eight exercises of chest press, leg press, seated row, triceps pushdown, latissimus dorsi pulldown, upright row, hack squat, and calf raises, starting at 40% of predicted 1RM and at a 2:1:2 movement tempo (concentric: rest: eccentric). During each exercise, participants were allowed breaks as needed, with each for a minimum of 30 seconds. Progression was made first by decreasing the number of rest periods during each exercise. When the patient could complete the whole duration of the exercise (5 minutes) without rest, the load was increased by approximately 10%.

Phase I (COMBO)

The COMBO protocol was based on exercise recommendations for patients with HFrEF and included both aerobic and resistance exercises.[5] The aerobic component began at 10 to 15 minutes at a target exercise intensity of 40% to 50% of VO_{2peak}, corresponding to an RPE of 11 to 13, progressing gradually according to patient's tolerance to 20 minutes. Intensity was adjusted so the RPE remained in the target

zones. The resistance component involved eight exercises, two sets of 10 repetitions, initially prescribed at 50% to 60% 1RM. Thereafter, the load was increased by approximately 10% when the participant fell below an RPE target range of 11 to 13.

Phase II

In phase II, all participants completed 4 weeks of identical COMBO training as described earlier, with the starting intensity for the aerobic and resistance components recalculated from
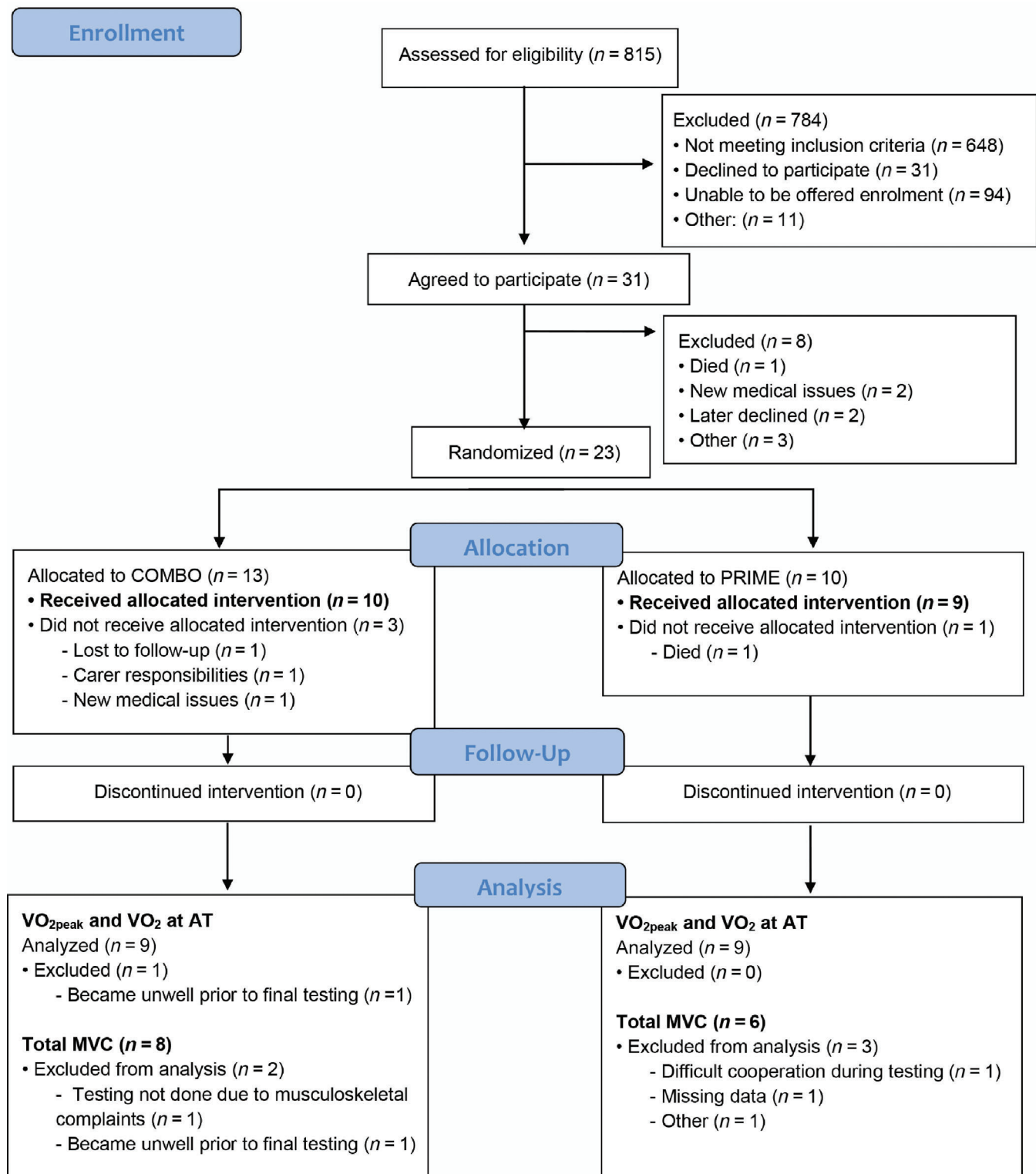
Figure 1. CONSORT flow diagram. AT, anaerobic threshold. COMBO, COMBined moderate-intensity aerobic and resistance training; MVC, muscle voluntary contraction; PRIME, Peripheral Remodeling through Intermittent Muscular Exercise. [Color figure can be viewed at wileyonlinelibrary.com]

Table 1. Baseline Participant Characteristics- Descriptive Statistics of Baseline Characteristics of Participants Who Completed the Entire Intervention[a]

Characteristics	All (19)	PRIME (9)	COMBO (10)
Age, y	72.8 (8.4)	68.1 (6.4)	77.0 (8.0)
Male, n (%)	15 (79)	7 (78)	8 (80)
BMI, kg/m^2	31.0 (4.8)	31.0 (5.5)	31.1 (4.3)
NYHA class II/III (number)	13/6	6/3	7/3
LVEF (%)	31.6 (7.0)	31.1 (6.3)	32 (2.5)
Comorbidities, n (%)			
CAD	17 (89)	8 (89)	9 (90)
HTN	14 (74)	6 (67)	8 (80)
DM Type 2	10 (53)	4 (44)	6 (60)
CKD	10 (53)	5 (56)	5 (50)
AF	9 (47)	4 (44)	5 (50)
PPM	5 (26)	2 (22)	3 (30)
AICD	3 (16)	1 (11)	2 (20)
COPD	2 (11)	0 (0)	2 (20)
Frailty criterion, n (%)			
Karnofsky performance ≥60, n (%)	17 (89)	8 (89)	9 (90)
Rockwood scale ≥5, n (%)	4 (21)	2 (22)	2 (20)
Resting hemodynamics			
Systolic BP, mm Hg	119.6 (15.2)	117.3 (13.4)	121.7 (17.0)
Diastolic BP, mm Hg	67.5 (11.5)	64.2 (9.0)	70.5 (13.1)
HR, bpm	74.7 (10.3)	80.9 (8.2)	69.1 (9.0)
Heart failure pharmacotherapy, n (%)			
β-Adrenergic receptor blocker	16 (84)	7 (78)	9 (90)
Diuretics	12 (63)	6 (67)	7 (70)
Aldosterone antagonist	9 (47)	8 (89)	1 (10)
ACE inhibitor/ARB	11 (58)	7 (78)	4 (40)
Digoxin	2 (11)	2 (11)	0 (0)
>10 medications	3 (16)	3 (33)	0 (0)
Performance indicators			
Peak VO$_2$, mL/kg/min	13.5 (3.2)	13.1 (3.3)	13.3 (3.2)
Total exercise time, sec	481 (211)	454.4 (197)	508 (233)
Total MVC	315 (25.3)	323.3 (50.8)	307.8 (31.4)
Functional performance			
TUG test	8.7 (2.9)	8.1 (2.7)	9.5 (3.0)
10MWT	7.0 (1.7)	6.8 (1.9)	7.3 (1.6)
FSST	10.0 (2.7)	9.1 (2.3)	11.1 (2.9)

Abbreviations: 10MWT, 10-Meter Walk Test; ACE, angiotensin converting enzyme; AF, atrial fibrillation; AICD, automated internal cardiac defibrillator; ARB, angiotensin II receptor blocker; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; COMBO, Combined Moderate-Intensity Aerobic and Resistance Training; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; FSST, Four Square Step Test; HR, heart rate; HTN, hypertension; LVEF, left ventricular ejection fraction; MVC, maximum voluntary contraction; NYHA, New York Heart Association; PPM, permanent pacemaker; PRIME, Peripheral Remodeling through Intermittent Muscular Exercise; TMVC, total maximum voluntary contraction; TUG, Time Up and Go; VO$_2$, volume of oxygen uptake during exercise.

[a]Data are expressed as mean (SD) unless otherwise stated.

repeat exercise testing, prescribed at 50% to 60% of VO_{2peak} for the aerobic component and 60% to 70% 1RM for the resistance component. Intensity was progressed according to RPE zones.

RPE, HR, and BP were monitored before, during, and after each training session. Individual HR and BP responses were monitored by the supervising exercise physiologist for signs of adverse responses or changing clinical status.

Volume load was calculated by repetitions [no.] × external load [kg], and aerobic exercise dose was estimated using published metabolic equations.[18]

Statistics

Given the novel nature of this study, a convenience sample size of 30 patients was used to estimate SD and effect sizes to inform power for a future definitive trial. Descriptive baseline characteristics data were presented as mean ± SD or frequency (percentage). Within-group comparisons between baseline and 8 weeks for all outcomes were analyzed with paired sample t tests and reported as mean with 95% confidence intervals (CIs). Between-group comparisons of improvement over 8 weeks were analyzed by Cohen's d effect sizes (due to the pilot nature of the trial). All statistical analyses were performed using GraphPad Prism v.7.04 for Windows (GraphPad Software, La Jolla, CA, USA; www.graphpad.com).

RESULTS

Participant Characteristics

Figure 1 presents the CONSORT flow diagram. Baseline characteristics are presented in Table 1. For the entire cohort, the mean age was 72.8 ± 8.4 years and approximately 80% of the participants were male. Baseline VO_{2peak} was 13.5 ± 3.2 mL/kg/min, body mass index was 31 ± 4.8 kg/m^2, and mean ejection fraction was 31.6 ± 7.0%. Common comorbidities were coronary artery disease (89%), hypertension (74%), and type 2 diabetes mellitus (53%). During the trial, all participants continued standard medical therapy as prescribed by their physician.

Training

Adherence and Side Effects

During phase I, all participants achieved more than 75% adherence (mean adherence = 97.3% ± 6.5). For phase II, 17 of 19 (89.5%) participants achieved more than 75% adherence (mean adherence = 96.1% ± 12.2). In total, 292 of the 304 target exercise sessions (96%) were completed by the 19 participants, with an average weekly session attendance of 1.6 sessions per week. None of the 19 participants who began the exercise interventions withdrew from the study. Mean total time to program completion (including testing visits) was 11.4 ± 1.4 weeks.

No major adverse events occurred during this study. Minor events included one unrelated exacerbation of HF and one unrelated chest infection. New musculoskeletal complaints occurred in four of the PRIME participants (on five occasions) and four of the COMBO participants

Table 2. Effects of PRIME and COMBO Interventions on Aerobic Capacity and Muscle Strength

	Baseline (0 wk)	Time point 1 (4 wk)	Time point 2 (8 wk)	Mean difference (0-8 wk)	Cohen's d between-group improvements (0-8 wk)
VO$_{2peak}$, mL/kg/min					
COMBO	13.4 (10.9 to 16.0)	13.2 (10.7 to 15.8)	13.6 (10.3 to 17.0)	.2 (−1.5 to 1.8)	1.0
PRIME	13.1 (10.6 to 15.5)	14.9 (12.3 to 17.5)	15.5 (12.6 to 18.3)	2.4 (.7 to 4.1)*	
VO$_2$ at AT, mL/kg/min					
COMBO	8.9 (6.9 to 10.9)	7.5 (6.4 to 8.6)	7.6 (5.7 to 9.6)	−1.2 (−2.9 to .4)	1.5
PRIME	7.7 (6.7 to 8.6)	8.6 (7.5 to 9.8)	9.2 (8.0 to 10.5)	1.6 (.0 to 3.2)	
Total MVC, kg					
COMBO	307.8 (257.3 to 358.3)	325.2 (266.4 to 384.0)	382.4 (326.8 to 438.0)	74.6 (39.4 to 110.0)*	.6
PRIME	323.3 (199 to 447.6)	359.6 (136.1 to 483.2)	374.9 (251.3 to 498.6)	48.6 (7.8 to 89.3)*	

Abbreviations: AT, anaerobic threshold; COMBO, COMBined moderate-intensity aerobic and resistance training; MVC, muscle voluntary contraction; PRIME, Peripheral Remodeling through Intermittent Muscular Exercise; VO$_2$, volume of oxygen uptake; VO$_{2peak}$, peak aerobic capacity.
*P < .05.

(on seven occasions). Complaints related to existing musculoskeletal injuries occurred in seven PRIME participants (27 occasions) and six from the COMBO group (11 occasions).

Training Loads

Details of the weekly training loads are presented in Table 2. By the final training week (week 8 of COMBO training), the participants initially allocated to PRIME and COMBO interventions were training at a weekly energy expenditure for the aerobic component of 169.7 ± 18.7 MET-min-wk^{-1} and 143.2 ± 9.2 MET-min-wk^{-1}, respectively (P = .2), and at a volume load for the resistive component of 9,075.7 ± 1,015.4 kg/wk and 8,067.0 ± 527 kg/wk, respectively (P = .4). RPEs were balanced between groups.

Effects of PRIME and COMBO

After 8 weeks of training, the PRIME group increased VO$_{2peak}$ significantly, by 2.4 mL/kg/min (95% CI = .7-4.1; P < .05), whereas the COMBO group showed a minimal change of .2 mL/kg/min (95% CI = −1.5 to 1.8) (Table 2). This produced a large between-group response effect size (Cohen's d) of 1.0. A clinically important improvement in VO$_{2peak}$ (defined as a >6% increase[19]) was observed in 60% of the PRIME group and 33% of the COMBO group after 8 weeks of training (Figure 2B).

The VO$_2$ at AT increased by 1.6 mL/kg/min (95% CI = .0-3.2) in the PRIME group, whereas a negative change (indicating a worsening of the clinical outcome) of −1.2 mL/kg/min (95% CI = −2.9 to .4) was observed in the COMBO group. This produced a large between-group effect size (Cohen's d = 1.5; Figure 2).

Total MVC increased significantly in both the PRIME (48.6 k; 95% CI = 7.8-89.3; P = .01) and COMBO groups (74.6 k; 95% CI = 39.3-110.0; P < .001) in comparison with baseline. The difference between groups produced a moderate between-group effect size of .6 (Figure 2).

DISCUSSION

We report that (1) older patients with HFrEF can safely perform current recommended exercise guidelines, despite these guidelines being formulated by data from younger cohorts, and (2) 4 weeks of PRIME before COMBO produced benefits for both aerobic power and strength, whereas 8 weeks of COMBO training provided no increase in aerobic power but superior strength gains. PRIME may provide a more beneficial exercise option for older patients with HFrEF, particularly those with both significant aerobic capacity and strength impairments.

The widely adopted exercise recommendations for patients with HFrEF involve moderate-intensity aerobic exercise in combination with resistance training.[3,4] These endorsements follow the consistent demonstration of improved functional capacity, reduced rates of hospitalization, and improved quality of life with exercise training.[3,4,7,20] As highlighted in the updated Cochrane review of 2019, the problem remains that older patients with HFrEF, who are often more functionally limited, are unrepresented in clinical trials. The current study successfully recruited a population reflective of the real-world patient, achieving a mean age of participants of 73 years and baseline VO$_{2peak}$ of 13.5 mL/kg/min.

As hypothesized, COMBO and PRIME training was safe and well tolerated by participants, with no major adverse events reported and an acceptable frequency of minor events related mainly to existing musculoskeletal injuries. The lack of improvement in VO$_{2peak}$ observed in the COMBO group is not unprecedented and was also reported in a meta-analysis of exercise training in older patients with HF.[21] Of note, the 2009 prospective trial by Brubaker et al involving 59 patients with HFrEF (mean age = 70.2 ± 5.1) demonstrated that after 16 weeks the exercise training group had 12% longer exercise time on the bike and 13% greater exercise workload than the control group, although there was no increase in VO$_{2peak}$.[22] Similarly, the HF-ACTION trial (mean age = 59 years) used a comparable exercise intervention and demonstrated a median increase in VO$_{2peak}$ of just 4% in the exercise group compared with the control after 3 months of training.[23] Combined, these findings may indicate a nonoxidative
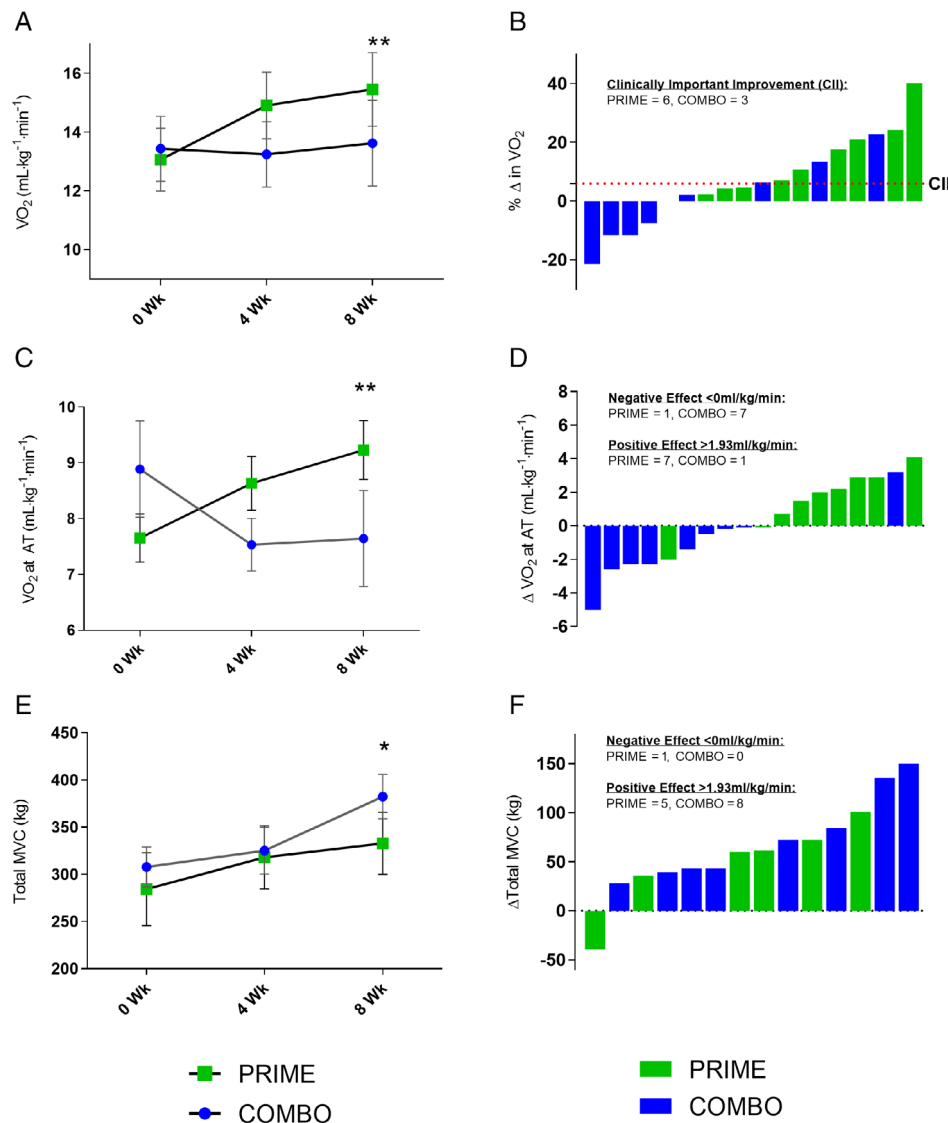
Figure 2. Group mean data at baseline, 4 weeks, and 8 weeks (left column) and waterfall graphs of individual training responses from baseline to 8 weeks to Peripheral Remodeling through Intermittent Muscular Exercise (PRIME) or COMBined moderate-intensity aerobic and resistance training (COMBO) treatment (right column), regarding peak aerobic capacity (VO_{2peak} mL/kg/min) (A and B); VO_2 at Anaerobic Threshold (AT) (VO_2 mL/kg/min) (C and D); and total weight lifted (total kg) (E and F). Dotted line f (tile b) indicates a clinically important improvement of 6%. Values are given as mean ± standard error of the mean. *Indicates moderate effect size (Cohen's d >.6 for between-group improvement 0-8 weeks). **Indicates large effect size (Cohen's d >1.0 between-group improvement 0-8 weeks).

muscle adaptation that may not be reflected in VO_{2peak} measurement.

In comparison, patients initially allocated to PRIME training exhibited a significant improvement in VO_{2peak} compared with baseline. The resultant difference between interventions (large effect size) suggests a potential superiority of PRIME for measures of aerobic capacity. According to the HF-ACTION trial, every 6% increase in VO_{2peak} is associated with a 5% lower risk of all-cause mortality and all-cause hospitalization[19] In this respect, initial allocation to PRIME training was also more frequently associated with improvements above this clinically important threshold, in comparison with participants in the COMBO group (Figure 2B; 66% vs 33% of participants). These increases

in aerobic fitness are noteworthy given that PRIME does not include a traditional aerobic training component such as walking or cycle training, whereas COMBO does.

For the outcome of maximal muscular strength, both PRIME and COMBO produced statistically significant increases from baseline; however, COMBO appeared superior to PRIME with a moderate effect size of .6. This finding is logical, given strength was trained with heavier weights and lower repetitions during COMBO. Upon reflection, a measure of muscular endurance may have been a useful additional outcome measure.

This pilot study was not powered to delineate mechanisms of change with PRIME training, but we speculate that the increases in aerobic capacity may be owing to a mitigation

of peripheral tissue maladaptations that are primarily responsible for exercise intolerance in HF according to the "muscle hypothesis" of HF.[24] By focusing initially on relatively small peripheral muscle masses, the PRIME regime aims to provide a *localized stimulus, not restricted by compromised or competing perfusion*. This approach is based on earlier work that showed increases in arm vasoreactivity and strength in both healthy young subjects and those with CHF following handgrip exercise.[25,26] Conceptually, this type of stimulus would allow a higher intensity exercise in the exercising tissue bed for longer periods than what could be achieved with whole-body or large muscle group exercise. This may allow for greater peripheral training adaptations that increase oxygen extraction and metabolic efficiency, therefore partially reversing exercise intolerance.

This study represents an important step in closing the age bias seen across clinical exercise studies and has provided the impetus for the development of a larger, definitively powered study. If indeed PRIME exercise is shown to benefit older patients with HF, cardiac rehabilitation providers and policy developers need to consider how exercise guidelines can be modified to include older patients with HF more effectively, so that the benefits of exercise can be offered, safely and effectively, to the full spectrum of HF patients including older persons. It may also be useful in other disease states where central impairments limit exercise capacity, such as pulmonary disease.

The study has some potential limitations. First, women represented only 20% of our study population. The misrepresentation of older women is encountered in clinical trials and in cardiac rehabilitation programs, and it represents both a failure of clinicians to refer such patients, as well as logistic difficulties encountered by older women in attending these programs.[20,27] Furthermore, we did not include patients with HF with preserved ejection fraction (HFpEF), who represent approximately 50% of the HF population.[28] Patients with HFpEF are usually older than those with HFrEF and may have more peripheral limitations to exercise tolerance.[29] Future studies should include patients with both HF subtypes and consider strategies to improve the representation of women. In addition, although Cohen's d strongly suggested positive effects to aerobic capacity outcomes in favor of the PRIME group, the pilot sample size is relatively small, and a larger powered study is required to assess accurately the effects of PRIME vs COMBO exercise training.

In conclusion, among a sample of older patients with HFrEF, we found that although traditional exercise and PRIME exercise approaches were well tolerated, only PRIME training produced positive changes to aerobic capacity in conjunction with increases in muscular strength. Taken together, these findings support the hypothesis that PRIME may have potential advantages for older patients with HFrEF and could be a possible alternative exercise modality.

ACKNOWLEDGMENTS

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Supplementary Figure S1: Algorithm of inclusion and exclusion criteria. Adapted from the Exercise and Sports Science Australia Position Statement on exercise training and chronic heart failure.[5]