High-intensity interval training vs. moderate-intensity continuous exercise training in heart failure with preserved ejection fraction: a pilot study

Siddhartha S. Angadi,1,2 Farouk Mookadam,2 Chong D. Lee,1 Wesley J. Tucker,1 Mark J. Haykowsky,3 and Glenn A. Gaesser1

1School of Nutrition and Health Promotion, Arizona State University, Phoenix, Arizona; 2Department of Cardiovascular Diseases, Mayo Clinic Arizona, Scottsdale, Arizona; and 3Faculty of Rehabilitation Medicine, University of Alberta, Edmonton, Alberta, Canada

Address for reprint requests and other correspondence: S. S. Angadi, Arizona State Univ., 550 N. Third St., Phoenix, AZ 85004 (e-mail: sangadi@asu.edu).

Heart failure with preserved ejection fraction (HFpEF) now accounts for most incident cases and, unlike heart failure with reduced ejection fraction (HFrEF), there are no guideline-recommended proven therapies that improve clinical outcomes for HFpEF (4).

Exercise training is established adjuvant therapy in heart failure (35). Although aerobic exercise training guidelines for treatment of HFrEF are well established, no consensus exercise training guidelines exist for management of HFpEF (29). This may be due to the modest number of published reports on the effects of exercise training in HFrEF (1, 9, 10, 15, 21, 22, 34). Existing guidelines for the use of exercise in heart failure recommend the use of moderate-intensity aerobic continuous training (MI-ACT) (2, 3, 17). However, there are several lines of evidence to suggest that high-intensity interval training (HIIT) may be preferred to MI-ACT for improving health outcomes in HFpEF. A recent meta-analysis found that HIIT was superior to MI-ACT for improving peak oxygen uptake (V\text{O}_2\text{peak}, weighted mean difference 2.14 ml O\text{2}·kg\text{-1}·min\text{-1}, 95% confidence interval 0.66–3.63) in patients with HFrEF (16). Studies ranged from 3 to 16 wk in length with improvements in V\text{O}_2\text{peak} and central hemodynamics occurring after just 3 wk of interval training (28). HIIT has also been reported to improve diastolic function in HFrEF (38), which may be relevant to patients with HFpEF because of the diastolic dysfunction inherent in HFpEF. The effect of MI-ACT on diastolic function in HFpEF is complex (36), with some studies reporting improvements in some measures of diastolic function (1, 9), and other studies reporting no improvements (10, 21, 22, 34). Finally, HIIT has also been shown to be more effective than MI-ACT for improving endothelial dysfunction in HFrEF (38). In the one published report that addressed this issue in HFpEF, MI-ACT did not improve endothelial dysfunction in this population (21). Endothelial dysfunction has been shown to be an independent prognostic marker in patients with HFrEF (18). To date there are no published efficacy studies of HIIT in HFpEF. Thus HIIT presents a unique, untested modality for exercise training in this population.

The purpose of this pilot study was to determine the efficacy of HIIT to improve endothelial dysfunction, V\text{O}_2\text{peak}, and diastolic dysfunction in patients with HFpEF. We hypothesized...
that 4 wk of HIIT would improve endothelial dysfunction, \( V_\text{O}_2\text{peak} \), and diastolic dysfunction to a greater extent than MI-ACT.

**MATERIALS AND METHODS**

The study was approved by the Mayo Clinic, Scottsdale and Arizona State University Institutional review boards, and study procedures were carried out after obtaining written informed consent in accordance to the Helsinki declaration (Clinical trials registration: NCT02147613). Nineteen adult patients that met the inclusion criteria, i.e., HFpEF diagnosis with New York Heart Association heart failure Class II-III symptoms, were enrolled between November 18, 2010 and April 3, 2012. Subjects were excluded if they had unstable angina, myocardial infarction in the past 4 wk, uncompensated heart failure, New York Heart Association class IV symptoms, complex ventricular arrhythmias (at rest or during the maximal exercise test), medical or orthopedic conditions that precluded treadmill walking, symptomatic severe aortic stenosis, acute pulmonary embolus, acute myocarditis, and medication noncompliance. Four subjects dropped out after enrollment: noncompliance with baseline test procedures \((n = 2)\), change in employment status \((n = 1)\), noncardiovascular illness \((n = 1)\). Drop-out was differential across groups. Subjects were on stable pharmacotherapy for >3 mo at study enrollment. Medication use was recorded and kept constant throughout the study (Table 1). All testing was performed following an overnight fast \((\geq 12 \text{ h})\). Testing time was kept constant to minimize the impact of diurnal variations in clinical variables measured. Postintervention testing was performed 72–96 h following the last training session to eliminate acute effects of exercise.

**Cardiopulmonary \( V_\text{O}_2\text{peak} \) exercise test.** Graded exercise testing was performed using the modified Bruce protocol by an exercise technologist who was blinded to group assignment. Treadmill grade and speed increased until volitional fatigue or test termination criteria were met. The decision to terminate the test was based on defined exercise testing guidelines established by the American College of Cardiology/American Heart Association (14). Twelve-lead EKG, ventilation \((V_e)\), and gas exchange were continuously monitored and recorded as 15-s averages using a Medigraphics Ultima Cardiopulmonary (St. Paul, MN) metabolic cart. Highest 15-s values were used for determination of \( V_\text{O}_2\text{peak} \). Ratio of peak \( V_e \) to peak carbon dioxide output \((\text{peak } V_e/V_\text{CO}_2)\) and the slope of \( V_e/V_\text{CO}_2 \) were used as indexes of ventilatory efficiency. The ventilation threshold was determined using ventilatory and gas exchange criteria as previously described (11). One subject from the HIIT group was unable to complete the post-training \( V_\text{O}_2\text{peak} \) test. For statistical analysis this subject’s pretraining treadmill test data were used for both pre- and posttraining time points.

**Assessment of left ventricular function.** Diagnosis of diastolic dysfunction and grade assignment was based on current guidelines for evaluation of left ventricular diastolic function (27). All research echocardiographic data were evaluated by two blinded board-certified cardiologists. Interobserver reliability was >0.9 for E, A waves, and for e’.

**Brachial artery flow-mediated dilation (FMD).** Endothelium-dependent dilation of the brachial artery (FMD) was measured by B-mode ultrasound (Terason t3000+, Burlington, MA) using Brachial Artery Reactivity Task Force guidelines (8). Images were analyzed by a blinded researcher using a previously validated, brachial artery edge-detection software (37). Intraclass correlation coefficients in our lab for baseline and peak diameter are 0.994 and 0.995, respectively (Chronbach \( \alpha = 0.976 \)).

**Exercise training.** All exercise training sessions were carried out at a single center. Subjects were randomized to either HIIT or MI-ACT. Because improvements in \( V_\text{O}_2\text{peak} \) have been observed within 3–4 wk of training (26, 28, 32), and FMD has been shown to improve within 2–4 wk of exercise training (37), a 4-wk training program was considered sufficient for this study. Subjects were scheduled to complete 12 treadmill training sessions over 4 wk (3 days/wk) at a phase II cardiac rehabilitation center with wireless EKG telemetry monitoring (leads II and V5). Compliance with the exercise program was very good with 13 subjects completing 100% of all assigned exercise sessions and 2 subjects completing 11 of 12 sessions. There were no reported incidents of musculoskeletal injury in either exercise group and no significant cardiac events.

Patients in MI-ACT began with 15 min of continuous exercise at 60% peak heart rate (PHR), increasing to 30 min of continuous exercise at 70% PHR by the start of the 2nd week. Patients in HIIT started with intervals of 2-min duration at 80–85% PHR, separated by

### Table 1. Baseline subject characteristics and changes after training

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>Sex</th>
<th>Pre</th>
<th>Post</th>
<th>( P )</th>
<th>Pre</th>
<th>Post</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>69.0 ± 6.1</td>
<td>8 m, 1 f</td>
<td>69.0 ± 6.1</td>
<td>8 m, 1 f</td>
<td>69.0 ± 6.1</td>
<td>8 m, 1 f</td>
<td>69.0 ± 6.1</td>
<td>8 m, 1 f</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.8 ± 5.1</td>
<td>29.8 ± 5.1</td>
<td>29.8 ± 5.1</td>
<td>29.8 ± 5.1</td>
<td>29.8 ± 5.1</td>
<td>29.8 ± 5.1</td>
<td>29.8 ± 5.1</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>134 ± 14</td>
<td>134 ± 14</td>
<td>134 ± 14</td>
<td>134 ± 14</td>
<td>134 ± 14</td>
<td>134 ± 14</td>
<td>134 ± 14</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>85 ± 8</td>
<td>85 ± 8</td>
<td>85 ± 8</td>
<td>85 ± 8</td>
<td>85 ± 8</td>
<td>85 ± 8</td>
<td>85 ± 8</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>101 ± 9</td>
<td>101 ± 9</td>
<td>101 ± 9</td>
<td>101 ± 9</td>
<td>101 ± 9</td>
<td>101 ± 9</td>
<td>101 ± 9</td>
</tr>
<tr>
<td>ACE-I</td>
<td>5/9</td>
<td>1/6</td>
<td>5/9</td>
<td>1/6</td>
<td>5/9</td>
<td>1/6</td>
<td>5/9</td>
</tr>
<tr>
<td>ARB</td>
<td>0/9</td>
<td>2/6</td>
<td>0/9</td>
<td>2/6</td>
<td>0/9</td>
<td>2/6</td>
<td>0/9</td>
</tr>
<tr>
<td>( \alpha)-( \beta )-Blockers</td>
<td>6/9</td>
<td>4/6</td>
<td>6/9</td>
<td>4/6</td>
<td>6/9</td>
<td>4/6</td>
<td>6/9</td>
</tr>
<tr>
<td>Coumadin</td>
<td>3/9</td>
<td>2/6</td>
<td>3/9</td>
<td>2/6</td>
<td>3/9</td>
<td>2/6</td>
<td>3/9</td>
</tr>
<tr>
<td>CCBs</td>
<td>2/9</td>
<td>1/6</td>
<td>2/9</td>
<td>1/6</td>
<td>2/9</td>
<td>1/6</td>
<td>2/9</td>
</tr>
<tr>
<td>CABG</td>
<td>0/9</td>
<td>1/6</td>
<td>0/9</td>
<td>1/6</td>
<td>0/9</td>
<td>1/6</td>
<td>0/9</td>
</tr>
<tr>
<td>PCI</td>
<td>1/9</td>
<td>0/6</td>
<td>1/9</td>
<td>0/6</td>
<td>1/9</td>
<td>0/6</td>
<td>1/9</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>4/9</td>
<td>0/6</td>
<td>4/9</td>
<td>0/6</td>
<td>4/9</td>
<td>0/6</td>
<td>4/9</td>
</tr>
<tr>
<td>DJD</td>
<td>3/9</td>
<td>1/6</td>
<td>3/9</td>
<td>1/6</td>
<td>3/9</td>
<td>1/6</td>
<td>3/9</td>
</tr>
</tbody>
</table>

Values are means ± SD. HIIT, high-intensity aerobic interval training; MI-ACT, moderate-intensity aerobic continuous training; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CCBs, calcium channel blockers; CABG, coronary artery bypass grafting; DBP, diastolic blood pressure; DJD, degenerative joint disease; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.
for a reduction in systolic blood pressure after MI-ACT ($P = 0.06$). Changes in systolic blood pressure, diastolic blood pressure, and mean arterial pressure were not related to markers of diastolic function ($E/e'$, $E/A$ ratio, left atrial volume index; all $r$ values $< 0.2$, $P > 0.4$).

$\text{V} \dot{O}_2\text{peak}$ increased by 9% after HIIT, from $19.2 \pm 5.2$ to $21.0 \pm 5.2$ ml·kg$^{-1}$·min$^{-1}$ ($P = 0.04$), but was unchanged after MI-ACT (Table 2). Ventilation threshold, $\text{Ve}/\text{VCO}_2$ slope, peak HR, respiratory exchange ratio, $\text{Ve}/\text{VCO}_2$, and rate-pressure product were not changed in either group.

Diastolic dysfunction grade was reduced after HIIT (Pre $2.1 \pm 0.3$ vs. Post $1.3 \pm 0.7$; $P = 0.02$; Table 3). This improvement in diastolic function after HIIT was accompanied by a reduction in $\text{E/e}'$ (Pre $0.92 \pm 0.26$ m/s vs. Post $0.78 \pm 0.29$ m/s, $P = 0.02$) and an increase in deceleration time (Pre $194 \pm 55$ ms vs. Post $225 \pm 40$ ms, $P = 0.02$). Additionally, a trend favoring HIIT was observed for a reduced left atrial volume index (HIIT = $-3.3 \pm 6.6$ ml/m$^2$ vs. MI-ACT = $+5.8 \pm 10.7$ ml/m$^2$; $P = 0.06$). No significant echocardiographic changes were observed after MI-ACT (Table 3). Brachial artery FMD did not change in either group (HIIT: Pre $6.9 \pm 3.7$%, Post $7.0 \pm 4.2$%; MI-ACT: Pre $8.1 \pm 4.1$%, Post $3.4 \pm 3.6$%).

The standardized effect sizes for $\text{V} \dot{O}_2\text{peak}$ and diastolic dysfunction grade in HIIT compared with MI-ACT were large ($d = 0.94$ and $-1.63$, respectively).

**RESULTS**

There were no significant differences in subject characteristics at baseline between groups (Table 1). Body weight did not significantly change in either group. Diastolic blood pressure was reduced after HIIT ($P = 0.05$) and a trend was observed for a reduction in systolic blood pressure after MI-ACT ($P = 0.06$). Changes in systolic blood pressure, diastolic blood pressure, and mean arterial pressure were not related to markers of diastolic function ($E/e'$, $E/A$ ratio, left atrial volume index; all $r$ values $< 0.2$, $P > 0.4$).

$\text{V} \dot{O}_2\text{peak}$ increased by 9% after HIIT, from $19.2 \pm 5.2$ to $21.0 \pm 5.2$ ml·kg$^{-1}$·min$^{-1}$ ($P = 0.04$), but was unchanged after MI-ACT (Table 2). Ventilation threshold, $\text{Ve}/\text{VCO}_2$ slope, peak HR, respiratory exchange ratio, $\text{Ve}/\text{VCO}_2$, and rate-pressure product were not changed in either group.

Diastolic dysfunction grade was reduced after HIIT (Pre $2.1 \pm 0.3$ vs. Post $1.3 \pm 0.7$; $P = 0.02$; Table 3). This improvement in diastolic function after HIIT was accompanied by a reduction in $\text{E/e}'$ (Pre $0.92 \pm 0.26$ m/s vs. Post $0.78 \pm 0.29$ m/s, $P = 0.02$) and an increase in deceleration time (Pre $194 \pm 55$ ms vs. Post $225 \pm 40$ ms, $P = 0.02$). Additionally, a trend favoring HIIT was observed for a reduced left atrial volume index (HIIT = $-3.3 \pm 6.6$ ml/m$^2$ vs. MI-ACT = $+5.8 \pm 10.7$ ml/m$^2$; $P = 0.06$). No significant echocardiographic changes were observed after MI-ACT (Table 3). Brachial artery FMD did not change in either group (HIIT: Pre $6.9 \pm 3.7$%, Post $7.0 \pm 4.2$%; MI-ACT: Pre $8.1 \pm 4.1$%, Post $3.4 \pm 3.6$%).

The standardized effect sizes for $\text{V} \dot{O}_2\text{peak}$ and diastolic dysfunction grade in HIIT compared with MI-ACT were large ($d = 0.94$ and $-1.63$, respectively).

**DISCUSSION**

To the best of our knowledge, this is the first randomized comparison trial to compare HIIT vs. MI-ACT for improving FMD, $\text{V} \dot{O}_2\text{peak}$, and diastolic dysfunction in HFpEF. The major new findings of this study were that HIIT improved $\text{V} \dot{O}_2\text{peak}$ by an average of 9% and diastolic dysfunction by $\sim 1$ grade. Specifically, 6 of 9 subjects in the HIIT group showed improvements in diastolic dysfunction grade (Table 3). This may have important health implications for patients with HFpEF because this disorder has no established or proven evidence-based pharmacotherapies that improve outcomes (5, 19). The lack of improvement in brachial artery FMD after MI-ACT is not surprising in view of a recent report showing that 16 wk of MI-ACT did not improve FMD in patients with HFpEF (21). The lack of improvement in endothelial function in our HIIT subjects could be due to the relatively short training program, or possibly due to the fact that baseline FMD in our subjects (7%) was not that impaired. It is also possible that exercise training does not affect vasodilatory function in patients with HFpEF (21) compared with patients with HFrEF (38).

Table 2. Effect of exercise training on cardiorespiratory parameters during the graded exercise test

<table>
<thead>
<tr>
<th></th>
<th>HIIT</th>
<th></th>
<th></th>
<th>MI-ACT</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>$P$</td>
<td>Pre</td>
<td>Post</td>
<td>$P$</td>
</tr>
<tr>
<td>$\text{V} \dot{O}_2\text{peak}$, ml·kg$^{-1}$·min$^{-1}$</td>
<td>19.2 ± 5.2</td>
<td>21.0 ± 5.2</td>
<td>0.04</td>
<td>16.9 ± 3.0</td>
<td>16.8 ± 4.0</td>
<td>0.93</td>
</tr>
<tr>
<td>$\text{V} \dot{O}_2$ at VT, ml·kg$^{-1}$·min$^{-1}$</td>
<td>12.2 ± 4.0</td>
<td>13.1 ± 3.5</td>
<td>0.23</td>
<td>11.1 ± 2.1</td>
<td>11.7 ± 2.4</td>
<td>0.60</td>
</tr>
<tr>
<td>Peak HR</td>
<td>130 ± 23</td>
<td>130 ± 18</td>
<td>0.96</td>
<td>121 ± 29</td>
<td>127 ± 21</td>
<td>0.86</td>
</tr>
<tr>
<td>Peak RER</td>
<td>1.13 ± 0.07</td>
<td>1.2 ± 0.12</td>
<td>0.70</td>
<td>1.11 ± 0.09</td>
<td>1.10 ± 0.08</td>
<td>0.64</td>
</tr>
<tr>
<td>Peak $\text{Ve}/\text{VCO}_2$</td>
<td>34.5 ± 9.7</td>
<td>33.5 ± 8.7</td>
<td>0.39</td>
<td>29.0 ± 1.8</td>
<td>29.5 ± 3.0</td>
<td>0.42</td>
</tr>
<tr>
<td>$\text{Ve}/\text{VCO}_2$ Slope</td>
<td>31.2 ± 11.5</td>
<td>31.6 ± 10.3</td>
<td>0.74</td>
<td>26.5 ± 2.4</td>
<td>26.7 ± 3.1</td>
<td>0.85</td>
</tr>
<tr>
<td>RPP at peak</td>
<td>20,567 ± 5,455</td>
<td>19,677 ± 4,853</td>
<td>0.46</td>
<td>20,681 ± 4,730</td>
<td>20,634 ± 3,573</td>
<td>0.98</td>
</tr>
<tr>
<td>TT, s</td>
<td>725 ± 185</td>
<td>777 ± 170</td>
<td>0.16</td>
<td>636 ± 204</td>
<td>696 ± 168</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Values are means ± SD. HR, heart Rate; RER, respiratory exchange ratio; RPP, rate-pressure product; TT, treadmill time; $\text{V} \dot{O}_2\text{peak}$, peak oxygen uptake; $\text{Ve}$, minute ventilation; $\text{VCO}_2$, carbon dioxide production; VT, ventilation threshold.
High-intensity interval training in HFrEF has been shown to improve markers of diastolic function (38). Similarly, moderate-intensity exercise training has been shown to improve diastolic stiffness in HFrEF (25). The effect of MI-ACT on diastolic function in HFP EF is complex (36), with some studies reporting improvements in some measures of diastolic function (1, 9), and other studies reporting no improvements (10, 21, 22, 34). The present results demonstrate a “proof of concept” that improvements in diastolic function in HFP EF may occur after as few as 4 wk of HIIT. The HIIT program used in the present study was comparable to that used in a study which showed improvements in diastolic function with HFrEF (38). In coronary bypass grafting patients undergoing HIIT, mitral inflow E velocity was reduced by 11% after just 4 wk of training, whereas MI-ACT had no effect on mitral inflow E velocity (26). Our HIIT subjects also demonstrated an 11% reduction in early mitral inflow E velocity (Table 3). The change in early mitral inflow velocity must be interpreted cautiously as it can be affected by a change in myocardial relaxation and/or alterations in preload. Deceleration time (Table 3) also increased, which is consistent with a shift from a grade II diastolic dysfunction (pseudonormalized pattern) to grade I (abnormal relaxation pattern) (27). Doppler deceleration time is a useful noninvasive index of diastolic function and is inversely related to left ventricular stiffness \((r = -0.81)\) (13).

In our HIIT patients favorable trends were observed for improvements in E/e', E/A ratio, and left atrial volume index. Even though these changes were very modest, due to the borderline nature of these diastolic abnormalities in our subjects, and in view of the diagnostic algorithm for evaluating left ventricular diastolic function by echocardiography (27), they likely contributed to significant grade reclassification. This may have important clinical implications as these diastolic dysfunction grades are important predictors of all-cause mortality (31).

The lack of improvement in diastolic dysfunction grade and other indexes of diastolic function in our MI-ACT group is consistent with other studies that showed no improvement in diastolic function after exercise training using predominantly (9) or exclusively (18, 19, 31) moderate-intensity exercise. Fujimoto et al. (10) used some high-intensity interval exercise during the last 5 mo of a 1-yr endurance training program in HFP EF, but the interval exercise comprised a very small percentage of the total exercise time and utilized very short interval durations that may not be optimal for improving exercise performance (33). Only two exercise training studies in HFP EF have reported improvements in diastolic function (1, 9). Alves et al. (1) trained subjects for 11 mo using an aerobic interval exercise program that was less intense than that used in the present study \((70\%–75\% \text{ of heart rate maximum})\), but included more intervals \((5–7)\) with shorter rest periods \((1 \text{ min})\). The 3-mo training program used by Edelman et al. (9) incorporated both aerobic and supplemental resistance exercise during half of the training program. Thus improvements in diastolic function in HFP EF may require either an interval-type exercise approach or a training program that includes a combination of aerobic and resistance exercise.

The fact that exercise training studies lasting 16 wk to 1 yr \((10, 21, 22, 34)\) have shown that moderate-intensity training does not improve indexes of diastolic dysfunction suggests that the lack of improvement in diastolic dysfunction grade in our MI-ACT subjects was not due to the short duration of the training program. However, indexes of diastolic function did not worsen in our MI-ACT group, or in the moderate-intensity training groups in previous studies \((10, 21, 22, 34)\). Therefore, MI-ACT may help prevent the decline in functional parameters typically seen in patients not assigned to an exercise intervention (9).

The mean improvement in \(\dot{V}_O_2\text{peak}\) of 1.8 ml·kg\(^{-1}\)·min\(^{-1}\) in our HIIT patients is comparable to increases of between 1.6 and 2.8 ml·kg\(^{-1}\)·min\(^{-1}\) reported in previous training studies of HFP EF patients using MI-ACT \((6, 8–11)\) and approximates the threshold \(1 \text{ ml·kg}^{-1}\)·min\(^{-1}\) or 10% for “clinically meaningful change” (20). Both HIIT (26) and MI-ACT \((23, 26, 32)\) have been shown to increase \(\dot{V}_O_2\text{peak}\) after just 4 wk. In post-coronary bypass grafting patients, Moholdt et al. (26) used a stronger overall HIIT stimulus than we employed in the present study \((90\% \text{ PHR vs. } 85–90\% \text{ PHR for high-intensity intervals and } 70\% \text{ PHR vs. } 50\% \text{ PHR for recovery intervals})\), and also had a higher training frequency \((5 \text{ vs. } 3 \text{ days/wk})\). The higher training frequency and greater exercise session duration \((46 \text{ vs. } 30 \text{ min for MI-ACT})\) may explain why the MI-ACT group in that study also improved \(\dot{V}_O_2\text{peak}\) after just 4 wk of training. Higher training intensity and/or frequency may also explain why others have found increases in \(\dot{V}_O_2\text{peak}\) after 4 wk of MI-ACT in HFrEF \((26, 32)\). Long-term efficacy of HIIT for improving both diastolic function and \(\dot{V}_O_2\text{peak}\) needs to be determined in HFP EF. However, exercise training programs...
lasting 12 wk in HFrEF (38) and 6 mo in coronary bypass grafting patients (26) have shown superiority of HIIT vs. MI-ACT for improving $VO_{2\text{peak}}$. Furthermore, a recent meta-analysis of exercise training in chronic heart failure concluded that the optimal intermittent exercise prescription for heart failure patients is a high-intensity program that uses relatively long work intervals (33).

Our pilot study has some limitations. Our subject population was predominantly male whereas HFPeF is more prevalent in women (30). This may limit the generalizability of our findings. Second, our sample size was small. However, other studies utilizing HIIT in HFrEF had similar sample sizes (16, 38). In a recent meta-analysis of the effects of aerobic interval training in HFrEF, 4 of 7 studies included in the analysis had interval training groups with sample sizes between 8 and 10 subjects (16), similar to that of our HIIT group. Another limitation of our study was that the exercise sessions were not strictly isocaloric, as has been reported in previous studies comparing HIIT and MI-ACT (26, 38). However, in our HIIT protocol the 4-min high-intensity intervals and the 3-min active recovery intervals were not as intense as those in HIIT protocols used previously (26, 38). Based on the relationship between %PHR and %$VO_{2\text{peak}}$ (12), the estimated total O2 consumed during both HIIT and MI-ACT exercise sessions (not including warm-up and cool-down, which were identical for both groups) differed by ~7% when adjusted for body weight (HIIT = 280 ml/kg vs. MI-ACT = 261 ml/kg). To be isocaloric the MI-ACT subjects would have had to extend each exercise session by ~2 min. In the DREW (Dose Response to Exercise in postmenopausal Women) trial, in which subjects exercised at an intensity similar to that of our MI-ACT group, an additional 2 min per exercise session could be expected to increase $VO_{2\text{peak}}$ by ~0.07% (~0.01 ml·kg$^{-1}$·min$^{-1}$) over 6 mo (6). Thus it is unlikely that the small inequality in O2 cost of the exercise sessions would have had any effect on the results of our 4-wk efficacy trial. Finally, length of follow-up was short and although we did not have any significant cardiovascular events during the study, this prevents us from definitively commenting on the safety of this exercise modality in patients with HFPeF.

In conclusion, our results show that significant improvements in $VO_{2\text{peak}}$ and diastolic function are possible after just 4 wk of HIIT in HFPeF. These improvements are consistent with previous findings on the effects of moderate-intensity exercise training programs of much longer duration in HFPeF. It is also important to note that HIIT was extremely well-tolerated in this cohort consisting predominantly of older (age range 49–80 yr), overweight/obese individuals with significant contributory co-morbidities (4 of 9 subjects had type 2 diabetes; Table 1). No significant cardiovascular events or musculoskeletal injuries were reported during training. The improvements in $VO_{2\text{peak}}$ and diastolic function may have important implications for health outcomes in this patient population. Rapid induction of cardiovascular benefits may be of particular importance in the management of heart failure because heart failure is not a reimbursable indication for cardiac rehabilitation in most states (20). Consequently, training protocols that are more efficient and less resource-intense may help make exercise training more widely available (20). We believe that the present study makes strides towards satisfying this need. The optimal dose of HIIT has not been established, although the intensity (~85–90% peak HR), interval length (4 min) and number (4), and between-interval recovery intensity (50% peak HR) and duration (3 min) are consistent with recent recommendations (2) and may be the optimal exercise prescription for heart failure patients (33). High-intensity interval training appears to be safe and well-tolerated in patients with HFrEF (2, 16, 38) and has been reported to be preferable to MI-ACT in HFrEF patients (38). Patient safety, adherence and hard clinical end-points remain to be examined in long-term clinical trials.

ACKNOWLEDGMENTS

We thank H. Bright, J. Walish, A. Royter, P. Thompson, B. Knight, and the rest of the staff at the cardiac rehabilitation facility at the Mayo Clinic, Scottsdale, AZ, for assistance.

This study has Clinical Trials Registration NCT02147613.

GRANTS

This study was supported by Mayo Clinic and Arizona State University Seed Grant 93016001.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES

Exercise in Heart Failure and Preserved Ejection Fraction • Angadi SS et al.


