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## Effect of Endurance Training on the Determinants of Peak Exercise Oxygen Consumption in Elderly Patients with Stable Compensated Heart Failure and Preserved Ejection Fraction

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### Abstract

**Objective**—Evaluate the mechanism(s) for improved exercise capacity after endurance exercise training (ET) in elderly patients with heart failure and preserved ejection fraction (HFPEF).

**Background:** Exercise intolerance, measured objectively by reduced peak oxygen consumption (VO<sub>2</sub>), is the primary chronic symptom in HFPEF and is improved by ET. However, the mechanism(s) are unknown.

**Methods**—Forty stable, compensated HFPEF outpatients (mean age 69 ± 6 yrs) were examined at baseline and after 4 months of ET (n=22) or attention control (n=18). VO<sub>2</sub> and its determinants were assessed during rest and peak upright cycle exercise.

**Results**—Following ET, peak VO<sub>2</sub> was higher than controls (16.3 ± 2.6 vs. 13.1 ± 3.4 ml/kg/min; p=0.002). This was associated with higher peak heart rate (139 ± 16 vs. 131 ± 20 beats/min; p=0.03), but no difference in peak end-diastolic volume (77 ± 18 vs. 77 ± 17 ml; p=0.51), stroke volume (48 ± 9 vs. 46 ± 9 ml; p=0.83), or cardiac output (6.6 ± 1.3 vs. 5.9 ± 1.5 L/min; p=0.32). However, estimated peak arterial-venous oxygen difference (A-VO<sub>2</sub> Diff) was significantly higher in ET (19.8 ± 4.0 vs. 17.3 ± 3.7 ml/dl; p=0.03). The effect of ET on cardiac output was responsible for < 15% of the improvement in peak VO<sub>2</sub>.

**Conclusions**—In elderly stable compensated HFPEF patients, peak A-VO<sub>2</sub> Diff was higher following ET and was the primary contributor to improved peak VO<sub>2</sub>. This suggests that

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peripheral mechanisms (improved microvascular and/or skeletal muscle function) contribute to the improved exercise capacity after ET in HFPEF.

## Keywords

Heart failure; preserved ejection fraction; exercise; elderly; peripheral

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## Introduction

Approximately 50% or more of heart failure (HF) patients living in the community have preserved left ventricular ejection fraction (HFPEF), and the proportion is higher among women and the very elderly<sup>1, 2</sup>. As in patients with HF and reduced EF (HFREF), the primary chronic symptoms in HFPEF, even when well compensated, are those of severe exercise intolerance<sup>3-8</sup> - dyspnea on exertion and exertional fatigue -and reduced quality of life<sup>4</sup>. However, the pathophysiology of exercise intolerance in this large and growing group of patients is not well understood and there are relatively few data regarding its treatment<sup>9</sup>.

Exercise intolerance can be objectively measured as reduced peak exercise oxygen consumption (peak  $\text{VO}_2$ ) by expired gas analysis, a technique that is valid and reproducible, including in elderly patients with HFPEF<sup>10, 11</sup>. In accordance with the Fick equation, reduced peak exercise  $\text{VO}_2$  results from either reduced cardiac output (CO), peripheral arterial-venous oxygen difference (A- $\text{VO}_2$  Diff), or both. Results from several cross-sectional studies have suggested that decreased peak  $\text{VO}_2$  in elderly HFPEF patients is due to reduced peak CO secondary to blunted chronotropic, inotropic and vasodilator reserve<sup>6, 7</sup>, while others have suggested that it is due to reductions in both peak CO and A- $\text{VO}_2$  Diff<sup>3, 12, 13</sup> or primarily due to reduced peak A- $\text{VO}_2$  Diff secondary to impaired skeletal muscle oxidative metabolism.<sup>14</sup>

Many studies have reported that endurance exercise training improves peak  $\text{VO}_2$  in patients with HFREF,<sup>15-18</sup> and that this improvement results from favorable changes in cardiac<sup>15, 19-21</sup>, peripheral vascular<sup>19</sup>, and skeletal muscle function<sup>20, 22-24</sup>, that increase oxygen delivery to and utilization by the active muscles (i.e. increased A- $\text{VO}_2$  Diff). In contrast, there have been only 4 studies of exercise training in patients with HFPEF<sup>25-28</sup>. In our recent report of the first randomized controlled, single-blind trial of exercise training in elderly patients with HFPEF<sup>26</sup>, we found that 4-months of endurance exercise training significantly increased peak  $\text{VO}_2$ , and this was recently confirmed in a multicenter trial<sup>28</sup>. However, the mechanism(s) responsible for the improvement in peak  $\text{VO}_2$  with exercise training in HFPEF have not been examined. This can be challenging since it requires simultaneous measurement of  $\text{VO}_2$  and its determinants during peak exercise<sup>29</sup>. Thus, the aim of this study was to evaluate the acute cardiovascular and metabolic responses during upright cycle exercise before and after 4-months of endurance exercise training in elderly patients with chronic HFPEF. Our goal was to determine the mechanism(s) of the improvement in peak  $\text{VO}_2$  after exercise training, and particularly the relative contributions of the components of the Fick equation, CO and A- $\text{VO}_2$  Diff.

## Methods

### Study design and subjects

The study design, subjects, and inclusion criteria have previously been described<sup>4, 26</sup>. Briefly, HFPEF patients were recruited by review of clinic visits and hospital discharge records from Wake Forest Medical Center. The subjects in this report are a subset of those from our recently reported randomized, single-blind trial of exercise training<sup>26</sup> who had adequate acoustic windows for the evaluation of left ventricular (LV) volumes during

upright rest and cycle exercise by two-dimensional echocardiographic imaging. At baseline, subjects performed a cardiopulmonary exercise test with two-dimensional echocardiography and were then randomized to either 4-months of endurance exercise training or attention control.

### **Cardiopulmonary Exercise Testing Protocol**

Exercise testing was performed as previously described in the upright position on an electrically braked cycle ergometer with expired gas analysis (CPX-2000, MedGraphics, Minneapolis, Mn)<sup>4, 26</sup>. The initial power output was set at 12.5 watts for 2 min, increased to 25 watts for 3 min, followed thereafter by 25 watt increments every 3 min until volitional exhaustion. Peak  $\text{VO}_2$  was calculated as the highest oxygen consumed over the last 30 seconds of peak exercise.<sup>4, 26</sup>

### **Rest and Exercise Echocardiography**

Resting and exercise echocardiograms were performed as previously described<sup>4, 13, 26</sup> by an experienced, registered echocardiographer using a Philips Sonos 5500 (Andover, MA) ultrasound imaging system fitted with multi-frequency transducer. Standard two-dimensional images were obtained in the parasternal long and short axes, and apical four and two chamber views. During exercise, the sonographer focused on capture of optimal apical 4-chamber views for LV volume assessment<sup>13</sup>. Left ventricular end-diastolic and end-systolic volumes were calculated using the single plane ellipsoid apical four-chamber area-length method<sup>30, 31</sup> by a second experienced echocardiographer who did not participate in image acquisition and who was blinded to the subject's randomization group allocation<sup>31</sup>. Adequate images for evaluation of LV volumes were defined as a well-aligned LV without apical foreshortening and with the ventricular endocardial contours well visualized for tracing<sup>30, 32</sup>. All results were averaged from 3 single-beat digital cineloops<sup>4, 13</sup>. We have previously validated 2-D echocardiographic volume measurements of end-diastolic volume against end-diastolic volume derived from radionuclide angiography (Fick stroke volume  $\div$  radionuclide angiography ejection fraction) in elderly persons and reported excellent day-to-day reproducibility and intra- and inter-observer variability<sup>13</sup>.

Continuous heart rate and non-invasive blood pressure (cuff sphygmomanometer) were acquired at rest and exercise. Stroke volume, CO, and systemic vascular resistance were derived from standard equations<sup>13</sup>. The A- $\text{VO}_2$  Diff was calculated by using the Fick equation ( $\text{VO}_2 \div \text{CO}$ )<sup>13</sup>. Circulatory power was calculated as  $\text{VO}_2 \times$  systolic blood pressure<sup>33</sup>.

### **Endurance exercise training**

As previously described, medically supervised endurance exercise training was performed 3 days/week for 4 months during which time the exercise intensity progressively increased from 40% to 70% heart rate reserve<sup>26</sup>. Exercise training sessions consisted of walking on a track and cycling on a Schwinn Airdyne (Louisville, Colo) for up to as much as 60 min/session including warm-up and cool-down. Any missed sessions were made up so all subjects completed a minimum of 40 out of 48 training sessions<sup>26</sup>.

### **Attention control group**

The attention control subjects were contacted every two weeks during which time the conversations focused on study retention, reminders and encouragement regarding attendance of upcoming study visits, and collection information on any new medical events they experienced since prior contact<sup>26</sup>. The subjects were not provided with information regarding exercise.

## Statistical Analysis

Comparison of the baseline characteristics of the attention control and endurance exercise trained randomized groups were made by showing the mean and standard deviation and tested using the two-sample t-test for continuous data and percentages and tested using the Fisher's exact test for dichotomous data or chi-square test for categorical data. Testing for the statistical significance of the effect of the exercise training was performed by analysis of covariance (ANCOVA) using the 4 month follow-up value of each outcome with the baseline measure of that outcome as a covariate. The assumption of normality of the residuals and equal variances for the ANCOVA model were checked. Because peak  $\text{VO}_2$  was positively skewed, analyses of this variable were based on logarithmic transformation. A mediation analysis was performed to estimate the effect of exercise training on peak CO and its relative contribution to the change in peak  $\text{VO}_2$  following exercise training.<sup>36</sup> The mediation analysis consisted of fitting three ANCOVA models: Model 1:  $\text{VO}_2 = a_1 + b_1 \text{BVO}_2 + c_1 \text{EX}$ , where  $\text{BVO}_2$  is baseline peak  $\text{VO}_2$  and EX is an indicator indicating being assigned to the exercise training group. The coefficient  $c_1$  estimates the overall (or total) effect being randomized to the exercise group had on peak  $\text{VO}_2$ . Model 2:  $\text{Mediator} = a_2 + b_2 \text{BVO}_2 + c_2 \text{EX} + d_2 \text{VO}_2$ . If EX does not have an independent effect on the Mediator, then the variable cannot be a significant mediator for  $\text{VO}_2$ . Assuming it is then Model 3:  $\text{VO}_2 = a_3 + b_3 \text{BVO}_2 + c_3 \text{EX} + d_3 \text{Mediator}$ . The coefficient  $c_3$  is an estimate of the independent effect of EX on peak  $\text{VO}_2$  not accounted for by EX's effect on the mediator and its association with peak  $\text{VO}_2$ . The mediation effect is estimated by  $c_1 - c_3$ . The percent of the effect EX had on peak  $\text{VO}_2$  that was explained by the mediator is expressed as  $(1 - c_3/c_1) \times 100\%$ . Goodman's unbiased estimated of the standard error was used<sup>34</sup>. All statistical tests were performed at the 5% two-sided level of significance.

## Results

### Baseline characteristics

As previously reported<sup>26</sup>, a total of 46 participants completed the 4 month study (24 randomized to endurance exercise training and 22 randomized to attention control). Among these, there were 40 subjects (22 endurance exercise trained and 18 attention control) who had adequate rest and exercise echocardiographic images for the determination of LV volumes during rest and exercise and these subjects are the focus of the present report. There were no significant baseline differences in key demographic or clinical characteristics between the 2 treatment groups (Table 1). Further, there were no significant differences in any key variables in the subset of subjects in this report compared to the larger trial including age (69 vs. 71 yrs,  $p = 0.24$ ); BMI (30.4 vs. 30.4,  $p = 0.93$ ); weight (79.4 kg. vs. 79.2 kg,  $p = 0.97$ ); and percent females (88% vs. 85%,  $p = 1.0$ ).

### Effects of Endurance Training on Variables Obtained at Rest

There were no significant differences between groups after the 4-month intervention in resting heart rate, end-diastolic volume, end-systolic volume, stroke volume, CO, systolic, diastolic or mean arterial blood pressures, systemic vascular resistance, or estimated A- $\text{VO}_2$  Diff (Tables 2 and 3).

### Effects of Endurance Training on Peak Exercise Variables

Peak  $\text{VO}_2$  was significantly higher following 4 months of endurance exercise training compared to attention control ( $16.3 \pm 2.6$  vs.  $13.1 \pm 3.4$  ml/kg/min; Table 2). The change in peak  $\text{VO}_2$  and heart rate for the subjects in this study ( $+2.3$  ml/kg/min and  $+6$  beats/min, respectively) was similar to that previously reported for the entire cohort of endurance exercise trained subjects.<sup>26</sup> The respiratory exchange ratio was similar between groups (1.15

$\pm 0.09$  vs.  $1.13 \pm 0.11$ ;  $p=0.18$ ) and in both was  $> 1.10$  indicating an exhaustive level of effort. Peak and reserve (peak exercise minus rest) heart rate were significantly higher after 4 months of endurance training compared to attention controls ( $139 \pm 16$  vs.  $131 \pm 20$  beats/min,  $p=0.03$ ; and,  $69 \pm 17$  vs.  $57 \pm 17$  beats/min,  $p=0.01$ , respectively).

After 4-months of endurance training, there were no significant differences between groups for peak exercise LV end-diastolic volume ( $77 \pm 18$  vs.  $77 \pm 17$  ml,  $p=0.51$ ), end-systolic volume ( $30 \pm 11$  vs.  $31 \pm 13$  ml,  $p=0.58$ ), stroke volume ( $48 \pm 9$  vs.  $46 \pm 9$  ml,  $p=0.83$ ), CO ( $6.6 \pm 1.3$  vs.  $5.9 \pm 1.5$  L/min,  $p=0.32$ ), systolic ( $187 \pm 22$  vs.  $178 \pm 28$  mmHg,  $p=0.19$ ), diastolic ( $89 \pm 10$  vs.  $84 \pm 8$  mmHg,  $p=0.43$ ) or mean arterial pressures ( $122 \pm 12$  vs.  $116 \pm 14$  mmHg,  $p=0.22$ ), or systemic vascular resistance ( $1499 \pm 303$  vs.  $1631 \pm 440$  dyns/sec/cm<sup>5</sup>,  $p=0.32$ ) (Tables 2 and 3, Figure 1). The percent reduction in systemic vascular resistance from rest to peak exercise in exercise group compared to controls was also unchanged after training ( $44 \pm 13\%$  vs  $45 \pm 14\%$ ;  $p=0.46$ ). However, estimated peak and reserve A-VO<sub>2</sub> Diff were significantly greater after endurance exercise training compared to attention controls ( $19.8 \pm 4.0$  vs.  $17.3 \pm 3.7$  ml/dl,  $p=0.03$ , and  $10.5 \pm 4.2$  vs.  $7.2 \pm 3.3$  ml/dl,  $p=0.01$ , Table 2 and Figure 1). Finally, peak and reserve circulatory power were significantly greater after endurance training (Table 2).

### Relative Contributions of CO and A-VO<sub>2</sub> Diff to the Improvement in Peak Exercise VO<sub>2</sub> following Endurance Training

We performed a mediation analysis in order to 1) estimate the effect of endurance exercise training on peak exercise VO<sub>2</sub>; 2) estimate the contribution of CO to the increase in peak exercise VO<sub>2</sub> resulting from endurance training; and 3) estimate the contribution of factors other than CO to the increase in peak VO<sub>2</sub> from endurance training. Based on ANCOVA, endurance training increased peak VO<sub>2</sub> by 19.8% compared to attention control. Considering CO as a mediator of the effect of training on peak VO<sub>2</sub>, a model estimating the effect on peak VO<sub>2</sub> while controlling for CO indicated that the magnitude of the effect of training on peak VO<sub>2</sub> that was explained by its effect on CO was 3.2% (or in relative terms  $3.2/19.8 = 16\%$  of the total improvement in peak VO<sub>2</sub>). Thus, 84% ( $16.6 \div 19.8 = 84\%$ ) of the training-related improvement in peak VO<sub>2</sub> was due to factors other than cardiac output (i.e. improved A-VO<sub>2</sub> Diff).

## Discussion

HFPEF is the most common form of HF in the growing population of elderly persons<sup>1, 2</sup>. Exercise intolerance is the primary manifestation in outpatients with chronic HFPEF even when patients are stable and compensated, however its pathophysiology and treatment are not well understood<sup>9</sup>. This study evaluated the effect of 4- months of endurance exercise training on cardiovascular and metabolic responses to acute cycle exercise in older HFPEF patients. The main new finding of this study was that increased peak exercise A-VO<sub>2</sub> Diff estimated from the Fick equation was the primary contributor to the increase in peak VO<sub>2</sub> that resulted from endurance exercise training, whereas peak exercise stroke volume and CO were not significantly changed (Table 2 and Figure 1). These findings provide potential insight into the pathophysiology of exercise intolerance in HFPEF and the design of future treatments specifically focused on addressing it.

Although there have been many reports of the effect of exercise training in patients with HFREF<sup>18, 35-38</sup>, nearly all of which have shown substantial improvements in exercise capacity, to date there have been only four reported studies of exercise training in patients with HFPEF<sup>25-28</sup>. A critical question in such studies is the mechanism(s) underlying the training-related improvement in exercise capacity. However, this requires measurement of VO<sub>2</sub> and its determinants during peak exercise which can be challenging in humans<sup>9, 29</sup>. As

a result, a relatively small number of the training studies in HFREF patients have been able to examine this question<sup>15-17, 19, 21, 22, 39, 40</sup>, and to our knowledge this is the first to do so in elderly patients with stable compensated HFPEF.

Given that there are no comparable data on the determinants of the training-related improvement in exercise capacity in HFPEF, a review of data in HFREF patients is instructive. In HFREF patients, Hambrecht et al.<sup>19, 22</sup> reported that 6 months of endurance exercise training increased peak exercise heart rate and CO. In contrast, Sullivan et al.<sup>16</sup> and others<sup>17, 39, 40</sup> reported no significant change in peak stroke volume and CO after endurance exercise training in HFREF patients, and that increased peak A-VO<sub>2</sub> Diff measured invasively by direct oximetry was the major contributor to improved exercise capacity. Dubach et al.<sup>21</sup> found that 2 months of high-intensity endurance training improved both peak exercise CO and A-VO<sub>2</sub> Diff in HFREF patients. Taken together, studies performed in HFREF patients suggest that the increased peak VO<sub>2</sub> after 2 to 6 months of endurance exercise training is due to increased peak CO and/or A-VO<sub>2</sub> Diff. When present, increased peak CO was due primarily to increased peak heart rate as peak stroke volume was not significantly increased after training in any of these studies in HFREF patients<sup>16, 17, 19-21, 40, 41</sup>.

These prior investigations in patients with HFREF discussed above<sup>16, 17, 39</sup> and others in healthy subjects<sup>42-44</sup>, including several that measured peak A-VO<sub>2</sub> by direct oximetry, support the plausibility of our results indicating that the improvement in peak exercise VO<sub>2</sub> in elderly HFPEF patients following 4 months of endurance training was due primarily to an increased peak A-VO<sub>2</sub> Diff. Of note this is contrary to our *a priori* hypothesis during the design of the trial. We had hypothesized, based upon our earlier report in a small number of patients<sup>3</sup>, that increased peak LV stroke volume and cardiac output would be the primary contributors to an endurance training related increase in peak VO<sub>2</sub>. However, our recently published cross-sectional analysis of the baseline exercise test results indicated that the strongest determinant of the severely reduced exercise capacity in HFPEF patients compared to age-matched, healthy control subjects was reduced peak A-VO<sub>2</sub> Diff<sup>13</sup>. It is noteworthy that even in our early cross-sectional comparison study, an unheralded finding was that A-VO<sub>2</sub> Diff, measured invasively by direct oximetry, was impaired during exercise in HFPEF patients.<sup>3</sup> an observation recently confirmed by Bhella and associates<sup>14</sup>. Thus, three published studies from three separate laboratories, using three different techniques, have shown that at baseline before exercise training, HFPEF patients have reduced peak exercise A-VO<sub>2</sub> difference and this contributes to their reduced peak VO<sub>2</sub>. To measure peak A-VO<sub>2</sub> diff, one used direct oximetry, one used the Fick technique with acetylene rebreathing measurements of cardiac output, and one used the Fick technique with cardiac output measured by two-dimensional echo volumes.<sup>3, 13, 14</sup>

The finding of increased peak A-VO<sub>2</sub> Diff indicates that after exercise training there was an improvement in either diffusive oxygen transport via improved peripheral vascular, microvascular function and/or increased oxygen utilization by the active muscles. The available data do not allow us to discern which of these was operational in the present study. In HFREF patients, peripheral arterial dilation is impaired and improves following exercise training<sup>45</sup>. However, we have previously reported that resting and flow-mediated increases in leg blood flow in elderly HFPEF patients are not significantly impaired and are similar to those of age-matched healthy subjects<sup>5</sup>. We and others have shown in cross-sectional analyses that arterial stiffness is markedly increased in HFPEF patients and is related to their reduced exercise capacity<sup>6, 46, 47</sup>. In the present study, we did not perform formal measurements of arterial stiffness at rest or during exercise. However, after exercise training peak and the percent change in systemic vascular resistance were unchanged and the ratio of pulse pressure to stroke volume, a crude measure of arterial stiffness, although borderline

reduced at rest ( $p = 0.053$ ; Table 3), was not different at peak exercise. This suggests that the increase in peak A-VO<sub>2</sub> Diff may be due to improved microvascular function and/or skeletal muscle adaptations that results in increased oxygen utilization by the active muscles.

The suggestion that improved skeletal muscle adaptations may have contributed to the training-related improvement in peak VO<sub>2</sub> is supported by a variety of other data. Several cross-sectional studies have shown that HFREF patients and healthy elderly subjects have alterations in skeletal muscle bulk, composition, and function that correlate with their reduced exercise capacity<sup>48-51</sup>. Bhella et al. also recently reported that elderly HFPEF patients have impaired skeletal muscle oxidative metabolism<sup>14</sup>. Studies in a wide variety of animal models and human subjects indicate that skeletal muscle has a large capacity for favorable remodeling induced by exercise. Most relevant to elderly HFPEF patients are several studies in HFREF patients and in healthy elderly subjects which have demonstrated that exercise training produces a variety of favorable skeletal muscle adaptations, including increased percent oxidative fibers<sup>22</sup>, oxidative enzyme activity<sup>20, 22-24, 50</sup> and capillary density<sup>23</sup>. Further studies will be required to determine the specific vascular and/or skeletal muscle mechanism(s) underlying the finding in the present study of a training-mediated increase in peak A-VO<sub>2</sub> Diff in HFPEF patients.

The results of prior mechanistic studies of endurance training in patients with HFREF<sup>16, 17</sup> and in healthy elderly subjects<sup>42, 44</sup> also support the plausibility of our results indicating that endurance exercise training did not significantly enhance peak exercise left ventricular end-diastolic volume, end-systolic volume, or stroke volume in elderly HFPEF patients. As seen in patients with HFREF<sup>22, 41</sup>, we found that training did increase peak heart rate, representing a possible mitigation of the chronotropic incompetence that was described by our group<sup>3, 29, 52</sup> and subsequently confirmed by others<sup>6, 7</sup> in patients with HFPEF. However, the increased peak exercise heart rate did not translate into a significant training-related increase in peak exercise CO.

The lack of an increase in peak exercise stroke volume with endurance exercise training may be related to sex-related differences in the effect of endurance exercise training on cardiac function. Specifically, Spina et al. reported that the increase in peak VO<sub>2</sub> after endurance training in healthy elderly men was primarily due to an augmented peak stroke volume and CO and to a lesser extent to increased A-VO<sub>2</sub> Diff<sup>42, 43</sup>. In contrast, the increased peak VO<sub>2</sub> in healthy elderly women was due entirely to an increase in peak A-VO<sub>2</sub> Diff as peak exercise stroke volume, heart rate and CO were unchanged after training<sup>42, 43</sup>. Of note, nearly all of the HFREF patients in prior mechanistic exercise trials were men<sup>18</sup> whereas the majority of patients in the present study of HFPEF were women, reflecting the sex-distribution of HFPEF in the general population<sup>2</sup>.

The intensity of the prescribed training program can also impact rest and exercise cardiovascular function. Wisloff et al. reported that high-intensity interval aerobic training was superior to continuous moderate intensity endurance exercise training for improving resting ejection fraction, peripheral vascular function and skeletal muscle mitochondrial biogenesis in elderly men with HFREF<sup>53</sup>. Nechwatal et al. found that short-term high-intensity aerobic interval training significantly increased peak exercise stroke volume and CO and reduced systemic vascular resistance but there was no change in these outcomes after moderate intensity continuous endurance training in patients with HFREF<sup>40</sup>. Thus, we cannot exclude the possibility that high-intensity aerobic interval training could result in significant improvements in peak exercise cardiac function in HFPEF.

The type of exercise training can also impact results. Our study utilized endurance training only. However, resistance training has been shown to significantly increase skeletal muscle

mass and strength as well as improve aerobic capacity specifically in elderly men and elderly women<sup>54, 55</sup>. Our observations regarding the contribution of peripheral mechanisms to the training-related improvements in exercise capacity suggest that this modality should be specifically examined in future training studies of elderly HFPEF patients.

Cohen-Solal et al.<sup>33</sup> previously reported that peak exercise circulatory power was the single best predictor of survival in HFREF patients. Specifically, over a 25-month follow-up period, HFREF patients with a peak circulatory power >3,047 mmHg had significantly greater event-free survival compared to HFREF patients whose circulatory power below this value. Our finding that 16-weeks of endurance training increased peak circulatory power above this threshold value may have important prognostic implications for elderly HFPEF patients.

## Study Limitations

Two-dimensional echocardiography can systematically underestimate LV volumes such that our rest and peak exercise CO values may have been underestimated<sup>30, 31, 56</sup>. However, our baseline peak CO values are similar to that reported by Ennezat et al. in older HFPEF patients during cycle exercise at a similar peak power output to our subjects<sup>8</sup>, although they are slightly lower than the peak exercise values reported by Borlaug et al. in HFPEF patients<sup>6</sup>.

A-VO<sub>2</sub> Diff was not measured by direct oximetry. Although desirable, this would have involved invasive catheterization of pulmonary and systemic arteries during exhaustive upright exercise at baseline and again at follow-up in elderly outpatients which would have involved significant participant burden and risk. Instead, A-VO<sub>2</sub> Diff was estimated using the Fick equation where VO<sub>2</sub> measured by expired gas analysis is divided by measured CO. The Fick technique has been used to calculate A-VO<sub>2</sub>Diff in number of recent physiologic studies investigating mechanisms of exercise intolerance including HFPEF patients<sup>13, 14, 56-58</sup>. Our peak A-VO<sub>2</sub> Diff values were somewhat higher than reported by others<sup>14, 59, 60</sup>, possibly due to under-estimation of CO. However, the absolute change in peak A-VO<sub>2</sub> Diff with exercise training in our HFPEF patients is similar to that found after exercise training in HFREF patients in studies in which it was measured by direct oximetry using invasively obtained systemic and pulmonary arterial blood samples<sup>16, 21</sup>. Most importantly, because key variables were measured at all testing times using identical methods in both groups, and because we assessed changes in reserve capacity (rest minus peak values) within individuals, comparisons of CO and estimated A-VO<sub>2</sub> Diff between groups are valid.

Although the Doppler indexes at supine rest in the overall group indicated the presence of abnormal LV diastolic filling<sup>13</sup>, due to technical limitations including merging of the E and A wave, these were not measured during upright exercise. Tissue Doppler was not performed; therefore, changes in LV systolic and diastolic function may have occurred that we were unable to detect. However, any physiologically significant changes in this regard may have been expected to impact rest and peak exercise stroke volume which was not changed after the 4 month training program. Although all patients had normal mitral valve morphology and function at rest, we cannot exclude the possibility that exercise-induced mitral regurgitation could have impacted peak stroke volume. Intracardiac hemodynamics were not measured, as these require invasive techniques which are challenging in studies such as ours that require serial assessments in elderly outpatients and involve significant human research subject risk<sup>57</sup>.

Our patients met objective, standardized criteria for heart failure, and had features that closely match patients with HFPEF in other published studies, including in the



characteristics of diastolic filling, BMI, and diuretic use. Because our study involved serial, exhaustive exercise tests and four months of exercise training, patients were required to be stable and compensated with no recent hospitalizations or medication changes. Thus, they would be expected to have less severe symptoms and biomarker abnormalities than patients with high rates of recent hospitalization and decompensation. Nevertheless, as recently reviewed by others the diagnosis of HFPEF can be difficult<sup>61, 62</sup>, and this remains a limitation to this and most HFPEF investigations.

In the mediation analysis, measurement error of cardiac output could potentially introduce positive bias. This would be inversely proportional to the coefficient of variation. The reliability of cardiac output measurement in our lab is > 90%. Thus, we believe that the potential for positive bias is relatively modest.

## Conclusions

The improvement in peak exercise capacity after 4 months of endurance exercise training in elderly stable compensated HFPEF patients was due primarily to increased peak A-VO<sub>2</sub> Diff. This suggests that peripheral vascular, micro-vascular, and/or skeletal muscle function were improved and resulted in increased diffusive oxygen transport or greater oxygen utilization by the active skeletal muscle.

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## Abbreviations

|                              |  |
|------------------------------|--|
| <b>A-VO<sub>2</sub> Diff</b> | arterial-venous oxygen difference.             |
| <b>CO</b>                    | cardiac output.                                |
| <b>HF</b>                    | Heart failure.                                 |
| <b>HFPEF</b>                 | Heart failure and preserved ejection fraction. |
| <b>Peak VO<sub>2</sub></b>   | Peak exercise oxygen consumption.              |

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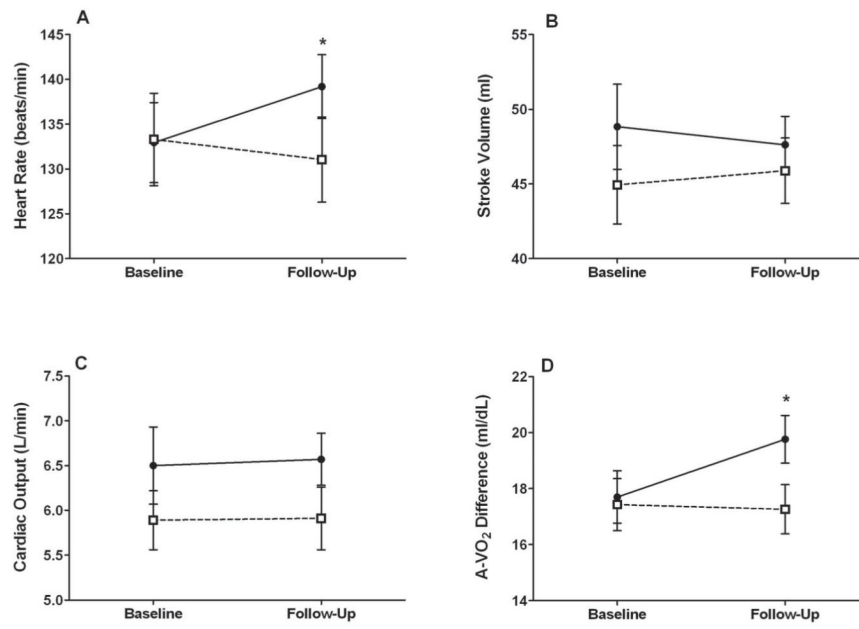
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**Figure 1.**

Peak exercise data at baseline and 4 month follow-up. Solid circles with solid line represent the group randomized to exercise training; open squares with dashed line represent those randomized to the attention control group. Values displayed at each time point are raw mean  $\pm$  SE. \* = p-value of 0.03. P-values are from the analysis of covariance model based on comparison of least square means at follow-up following adjustment for baseline values.

**Table 1**  
**Participant Characteristics**

| Characteristic           | Exercise (N=22) | Control (N=18) | P-Value |
|--------------------------|-----------------|----------------|---------|
| Age (years)              | 70 ± 6          | 68 ± 5         | 0.43    |
| Women                    | 18 (82)         | 17 (94)        | 0.36    |
| Caucasian                | 20 (91)         | 14 (78)        | 0.38    |
| Body Weight (kg)         | 79 ± 17         | 79 ± 17        | 0.94    |
| BSA (m <sup>2</sup> )    | 1.85 ± 0.21     | 1.80 ± 0.18    | 0.44    |
| BMI (kg/m <sup>2</sup> ) | 29.6 ± 5.7      | 31.3 ± 7.1     | 0.40    |
| NYHA class               |                 |                |         |
| II                       | 14 (64)         | 12 (67)        | 1.0     |
| III                      | 8 (36)          | 6 (33)         | 1.0     |
| Diastolic Function       |                 |                |         |
| Normal                   | 5 (25)          | 3 (17)         | 0.70    |
| Abnormal relaxation      | 13 (65)         | 11 (61)        | 1.0     |
| Pseudonormal             | 2 (10)          | 4 (22)         | 0.39    |
| Hx pulmonary edema       | 2 (9)           | 5 (28)         | 0.21    |
| Diabetes mellitus        | 2 (9)           | 4 (22)         | 0.38    |
| Hx hypertension          | 18(82)          | 13 (72)        | 0.71    |
| Current medication       |                 |                |         |
| ACE-inhibitors           | 7 (32)          | 3 (17)         | 0.46    |
| Digoxin                  | 4 (18)          | 3 (17)         | 1.0     |
| Diuretics                | 12 (55)         | 11 (61)        | 1.0     |
| Beta-blockers            | 7 (32)          | 3 (17)         | 0.46    |
| Calcium Antagonists      | 10 (45)         | 8 (44)         | 1.0     |
| Nitrates                 | 2 (9)           | 0 (0)          | 0.49    |

Data are presented as mean (SD), or count (%); BSA- body surface area; BMI- body mass index; NYHA- New York Heart Association; ACE- angiotensin converting enzyme.

**Table 2**  
**Rest and Peak Exercise Oxygen Consumption and Its Determinant at Baseline and Follow-up after Exercise Training**

| Variable                            | Grp | Rest      |           | P value | Peak Exercise |            | P value | Reserve (Peak - Rest) |            | P value |
|-------------------------------------|-----|-----------|-----------|---------|---------------|------------|---------|-----------------------|------------|---------|
|                                     |     | Baseline  | Follow-up |         | Baseline      | Follow-up  |         | Baseline              | Follow-up  |         |
| VO <sub>2</sub> , ml/min            | CON | 261 (51)  | 256(59)   | 0.68    | 998 (211)     | 997 (255)  | 0.003   | 735 (207)             | 734 (230)  | 0.001   |
|                                     | EX  | 289 (100) | 271(55)   |         | 1095 (250)    | 1285 (313) |         | 806 (226)             | 1014 (286) |         |
| VO <sub>2</sub> , ml/kg/min         | CON | 3.4 (0.7) | 3.4 (0.9) | 0.96    | 12.9 (2.7)    | 13.1 (3.4) | 0.002   | 9.4 (2.6)             | 9.5 (3.0)  | <0.001  |
|                                     | EX  | 3.8 (1.4) | 3.5 (0.8) |         | 14.0 (2.5)    | 16.3 (2.6) |         | 10.3 (2.3)            | 12.8 (2.4) |         |
| Heart Rate, b/min                   | CON | 77 (13)   | 74 (13)   | 0.62    | 133 (22)      | 131 (20)   | 0.03    | 56 (17)               | 57 (17)    | 0.01    |
|                                     | EX  | 75 (17)   | 71 (16)   |         | 133 (21)      | 139 (16)   |         | 59 (19)               | 69 (17)    |         |
| End Diastolic Volume, ml            | CON | 70(22)    | 70 (22)   | 0.41    | 76 (22)       | 77 (17)    | 0.51    | 6 (7)                 | 8 (9)      | 0.20    |
|                                     | EX  | 71 (22)   | 72 (20)   |         | 79 (25)       | 77 (18)    |         | 9 (9)                 | 5 (9)      |         |
| End Systolic Volume, ml             | CON | 31 (14)   | 31 (15)   | 0.61    | 31 (16)       | 31(13)     | 0.58    | 0 (5)                 | 0 (4)      | 0.98    |
|                                     | EX  | 30 (12)   | 30 (11)   |         | 30 (13)       | 30 (11)    |         | 0 (5)                 | 0 (6)      |         |
| Stroke Volume, ml                   | CON | 39 (11)   | 39 (10)   | 0.059   | 45 (10)       | 46 (9)     | 0.83    | 6 (5)                 | 8 (7)      | 0.09    |
|                                     | EX  | 41 (12)   | 43 (10)   |         | 49 (13)       | 48 (9)     |         | 8 (8)                 | 5 (5)      |         |
| Cardiac Output, L/min               | CON | 3.1 (0.7) | 2.8 (0.7) | 0.24    | 5.9 (1.4)     | 5.9 (1.5)  | 0.32    | 3.1 (0.9)             | 3.4 (1.1)  | 0.56    |
|                                     | EX  | 3.1 (1.0) | 3.0 (0.8) |         | 6.5 (2.0)     | 6.6 (1.3)  |         | 3.4 (1.6)             | 3.8 (1.0)  |         |
| Circulatory Power, ml/kg/min*mmHg   | CON | 492 (133) | 478 (180) | 0.65    | 2337 (525)    | 2295 (687) | 0.002   | 1846 (523)            | 1817 (608) | <0.001  |
|                                     | EX  | 546 (172) | 484(102)  |         | 2609 (643)    | 3080 (712) |         | 2084 (592)            | 2596 (670) |         |
| A-VO <sub>2</sub> Difference, ml/dL | CON | 8.6(2.0)  | 9.2 (2.3) | 0.99    | 17.4 (3.9)    | 17.3 (3.7) | 0.03    | 8.2 (3.0)             | 7.2 (3.3)  | 0.01    |
|                                     | EX  | 9.7 (2.7) | 9.8 (2.7) |         | 17.7 (4.4)    | 19.8 (4.0) |         | 8.3 (4.2)             | 10.5 (4.2) |         |

Data in the 4 blocks to the left of each p-value are raw means  $\pm$  SD for each group at baseline and follow-up. The p-value represents comparison between the groups of the follow-up least square means after adjustment for baseline. Grp = group assignment; CON = attention control; EX= endurance exercise training.



**Table 3**  
**Rest and Peak Exercise Hemodynamics at Baseline and Following Exercise Training**

| Variable  | Grp | Rest        |             |         | Peak Exercise |             |         | P value |
|---|-----|-------------|-------------|---------|---------------|-------------|---------|---------|
|   |     | Baseline    | Follow-up   | P value | Baseline      | Follow-up   | P value |         |
| Systolic blood pressure, mmHg                         | CON | 146 (22)    | 140 (21)    | 0.49    | 184 (25)      | 178 (28)    | 0.19    |         |
|   | EX  | 147 (20)    | 138 (16)    |         | 186 (29)      | 187 (22)    |         |         |
| Diastolic blood pressure, mmHg                        | CON | 80 (9)      | 78 (9)      | 0.89    | 84 (9)        | 84 (8)      | 0.43    |         |
|   | EX  | 82 (7)      | 80 (10)     |         | 88 (9)        | 89 (10)     |         |         |
| Mean arterial pressure, mmHg                          | CON | 102 (12)    | 99 (13)     | 0.77    | 117 (14)      | 116 (14)    | 0.22    |         |
|   | EX  | 104 (9)     | 99 (10)     |         | 121 (13)      | 122 (12)    |         |         |
| Systemic vascular resistance, dyn-sec/cm <sup>5</sup> | CON | 2824 (941)  | 2929 (654)  | 0.24    | 1632 (374)    | 1631 (440)  | 0.32    |         |
|   | EX  | 2973 (1009) | 2784 (753)  |         | 1569 (417)    | 1499 (303)  |         |         |
| Pulse pressure, mmHg                                  | CON | 66 ± 17     | 62 ± 15     | 0.28    | 99 ± 19       | 94 ± 24     | 0.26    |         |
|   | EX  | 65 ± 18     | 58 ± 12     |         | 97 ± 25       | 99 ± 19     |         |         |
| Pulse pressure/Stroke Volume, mmHg/ml                 | CON | 1.83 ± 0.77 | 1.72 ± 0.56 | 0.053   | 2.32 ± 0.78   | 2.11 ± 0.56 | 0.41    |         |
|   | EX  | 1.68 ± 0.57 | 1.42 ± 0.42 |         | 2.08 ± 0.68   | 2.07 ± 0.55 |         |         |

Data are presented as mean (SD). P-value represents comparison of least square means at final visit following adjustment for baseline values. Grp = group assignment; CON = attention control; EX = endurance exercise training.