Heart Failure

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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Objectives	The purpose of this study was to evaluate the mechanisms 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_2), is the primary chronic symptom in HFPEF and is improved by ET. However, the mechanisms are unknown.
Methods	Forty stable, compensated HFPEF outpatients (mean age 69 ± 6 years) were examined at baseline and after 4 months of ET (n = 22) or attention control (n = 18). The VO_2 and its determinants were assessed during rest and peak upright cycle exercise.
Results	After ET, peak VO_2 in those patients was higher than in control patients (16.3 ± 2.6 ml/kg/min vs. 13.1 ± 3.4 ml/kg/min; p = 0.002). That was associated with higher peak heart rate (139 ± 16 beats/min vs. 131 ± 20 beats/min; p = 0.03), but no difference in peak end-diastolic volume (77 ± 18 ml vs. 77 ± 17 ml; p = 0.51), stroke volume (48 ± 9 ml vs. 46 ± 9 ml; p = 0.83), or cardiac output (6.6 ± 1.3 l/min vs. 5.9 ± 1.5 l/min; p = 0.32). However, estimated peak arterial-venous oxygen difference was significantly higher in ET patients (19.8 ± 4.0 ml/dl vs. 17.3 ± 3.7 ml/dl; p = 0.03). The effect of ET on cardiac output was responsible for only 16% of the improvement in peak VO_2.
Conclusions	In elderly stable compensated HFPEF patients, peak arterial-venous oxygen difference was higher after ET and was the primary contributor to improved peak VO_2. This finding suggests that peripheral mechanisms (improved microvascular and/or skeletal muscle function) contribute to the improved exercise capacity after ET in HFPEF. (Prospective Aerobic Reconditioning Intervention Study [PARIS]; NCT01113840) (J Am Coll Cardiol 2012;60: 120–8) © 2012 by the American College of Cardiology Foundation

Approximately 50% or more of heart failure (HF) patients living in the community have HF with preserved left

ventricular ejection fraction (HFPEF), and the proportion is higher among women and the very elderly (1,2). 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 (3–8)—dyspnea on exertion and exertional fatigue—and reduced quality of life (4). 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 (9).

Exercise intolerance can be objectively measured as reduced peak exercise oxygen consumption (VO_2) by expired gas analysis, a technique that is valid and reproducible,

including in elderly patients with HFPEF (10,11). In accordance with the Fick equation, reduced peak VO_2 results from either reduced cardiac output (CO), peripheral arterial-venous oxygen difference (A-VO_2 Diff), or both. Results from several cross-sectional studies have suggested that decreased peak VO_2 in elderly HFPEF patients is due to reduced peak CO secondary to blunted chronotropic, inotropic, and vasodilator reserve (6,7), whereas others have suggested that it is due to reductions in both peak CO and A-VO_2 Diff (3,12,13) or primarily due to reduced peak A-VO_2 Diff secondary to impaired skeletal muscle oxidative metabolism (14).

Many studies have reported that endurance exercise training improves peak VO_2 in patients with HFREF (15–18), and that this improvement results from favorable changes in cardiac (15,19–21), peripheral vascular (19), and skeletal muscle function (20,22–24), that increase oxygen delivery to and utilization by the active muscles (i.e., increased A-VO_2 Diff). In contrast, there have been only 4 studies of exercise training in patients with HFPEF (25–28). In our recent report of the first randomized, controlled, single-blind trial of exercise training in elderly patients with HFPEF (26), we found that 4 months of endurance exercise training significantly increased peak VO_2, and this was recently confirmed in a multicenter trial (28). However, the mechanisms responsible for the improvement in peak VO_2 with exercise training in HFPEF have not been examined. That can be challenging as it requires simultaneous measurement of VO_2 and its determinants during peak exercise (29). 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 mechanisms of the improvement in peak VO_2 after exercise training, and particularly the relative contributions of the components of the Fick equation, CO, and A-VO_2 Diff.

Methods

Study design and subjects. The study design, subjects, and inclusion criteria have previously been described (4,26). 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 (26) who had adequate acoustic windows for the evaluation of left ventricular (LV) volumes during upright rest and cycle exercise by 2-dimensional echocardiographic imaging. At baseline, subjects performed a cardiopulmonary exercise test with 2-dimensional echo-cardiography and were then randomly assigned 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, Med-Graphics, Minneapolis, Minnesota) (4,26). The initial power output was set at 12.5 W for 2 min, increased to 25 W for 3 min, followed thereafter by 25 W increments every 3 min until volitional exhaustion. Peak VO_2 was calculated as the highest oxygen consumed over the last 30 s of peak exercise (4,26).

Rest and exercise echocardiography. Resting and exercise echocardiograms were performed as previously described (4,13,26) by an experienced, registered echo-sonographer using a Philips Sonos 5500 (Andover, Massachusetts) ultrasound imaging system fitted with multifrequency transducer. Standard 2-dimensional images were obtained in the parasternal long-axis and short-axis views and apical 4- and 2-chamber views. During exercise, the sonographer focused on capture of optimal apical 4-chamber views for LV volume assessment (13). Left ventricular end-diastolic and end-systolic volumes were calculated using the single plane ellipsoid apical 4-chamber area-length method (30,31) by a second experienced echo-sonographer who did not participate in image acquisition and who was blinded to the subject's randomization group allocation (31). 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 (30,32). All results were averaged from 3 single-beat digital cineloops (4,13). We have previously validated 2-dimensional echocardiographic volume measurements of end-diastolic volume against end-diastolic volume derived from radionuclide angiography (Fick stroke volume divided by radionuclide angiography ejection fraction) in elderly persons and reported excellent day-to-day reproducibility and intraobserver and interobserver variability (13).

Continuous heart rate and noninvasive blood pressure (cuff sphygmomanometer) were acquired at rest and exercise. Stroke volume, CO, and systemic vascular resistance were derived from standard equations (13). The A-VO_2 Diff was calculated by using the Fick equation (VO_2 divided by CO) (13). Circulatory power was calculated as VO_2 times systolic blood pressure (33).

Endurance exercise training. As previously described, medically supervised endurance exercise training was performed 3 days a week for 4 months, during which time the exercise intensity progressively increased from 40% to 70% heart rate reserve (26). Exercise training sessions consisted of walking on a track and cycling on a Schwinn Airdyne (Louisville, Colorado) for up to as much as 60 min per session including warm up and cool down. Any missed sessions were made up

Abbreviations and Acronyms

ANCOVA = analysis of covariance

A-VO_2 Diff = arterial-venous oxygen difference

CO = cardiac output

HF = heart failure

HFPEF = heart failure and preserved ejection fraction

HFREF = heart failure and reduced ejection fraction

LV = left ventricular

VO_2 = exercise oxygen consumption

so all subjects completed a minimum of 40 of 48 training sessions (26).

Attention control group. The attention control subjects were contacted every 2 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 (26). 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 ± SD, and were tested using the 2-sample t test for continuous data and percentages and tested using Fisher's exact test for dichotomous data or the 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 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 VO_2 after exercise training (34). The mediation analysis consisted of fitting 3 ANCOVA models as follows:

Model 1. $VO_2 = a_1 + b_1 BVO_2 + c_1 EX$, where BVO_2 is baseline peak 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 on peak VO_2 of randomization to the exercise group.

Model 2. Mediator $= a_2 + b_2 BVO_2 + c_2 EX + d_2 VO_2$. If EX does not have an independent effect on the mediator, then the variable cannot be a significant mediator for VO_2. Assuming it is, then:

Model 3. $VO_2 = a_3 + b_3 BVO_2 + c_3 EX + d_4$Mediator. The coefficient c_3 is an estimate of the independent effect of EX on peak VO_2 not accounted for by the effect of EX on the mediator and its association with peak VO_2. The mediation effect is estimated by c_1 minus c_3. The percent of the effect EX had on peak 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 (34).

All statistical tests were performed at the 5% 2-sided level of significance.

Results

Baseline characteristics. As previously reported (26), 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

Table 1	Patient Characteristics			
Characteristic	**Exercise (n = 22)**	**Control (n = 18)**	**p Value**
Age, yrs	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, m²	1.85 ± 0.21	1.80 ± 0.18	0.44
BMI, kg/m²	29.6 ± 5.7	31.3 ± 7.1	0.40
NYHA functional 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
History of pulmonary edema	2 (9)	5 (28)	0.21
Diabetes mellitus	2 (9)	4 (22)	0.38
History of 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

Values are mean ± SD or count (%).

ACE = angiotensin-converting enzyme; BMI = body mass index; BSA = body surface area; NYHA = New York Heart Association.

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 years vs. 71 years, p = 0.24); body mass index (30.4 vs. 30.4, p = 0.93), weight (79.4 kg vs. 79.2 kg, p = 0.97), and percent female (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 estimate A-VO₂ Diff (Tables 2 and 3).

Effects of endurance training on peak exercise variables. Peak VO₂ was significantly higher after 4 months of endurance exercise training compared to attention control (16.3 ± 2.6 ml/kg/min vs. 13.1 ± 3.4 ml/kg/min) (Table 2). The change in peak VO₂ 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 (26). The respiratory exchange ratio was similar between groups (1.15 ± 0.09 vs. 1.13 ± 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 con-

| Table 2 | Rest and Peak Exercise Oxygen Consumption and its Determinant at Baseline and Follow-Up After Exercise Training |

Variable	Group	Rest			Peak Exercise			Reserve (Peak–Rest)		
		Baseline	Follow-Up	p Value	Baseline	Follow-Up	p Value	Baseline	Follow-Up	p Value
VO$_2$, 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	1,285 ± 313		806 ± 226	1,014 ± 286	
VO$_2$, 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, beats/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·mm Hg	CON	492 ± 133	478 ± 180	0.65	2,337 ± 525	2,295 ± 687	0.002	1,846 ± 523	1,817 ± 608	<0.001
	EX	546 ± 172	484 ± 102		2,609 ± 643	3,080 ± 712		2,084 ± 592	2,596 ± 670	
A-VO$_2$ Diff, 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	

Values are mean ± SD. The p value represents comparison between the groups of the follow-up least-square means after adjustment for baseline.

A-VO$_2$ Diff = arterial-venous oxygen difference; CON = attention control; EX= endurance exercise training; Grp = group assignment; VO$_2$ = exercise oxygen consumption.

trols (139 ± 16 beats/min vs. 131 ± 20 beats/min, p = 0.03; and 69 ± 17 beats/min vs. 57 ± 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 ± 18 ml vs. 77 ± 17 ml, p = 0.51), end-systolic volume (30 ± 11 ml vs. 31 ± 13 ml, p = 0.58), stroke volume (48 ± 9 ml vs. 46 ± 9 ml, p = 0.83), CO (6.6 ± 1.3 l/min vs. 5.9 ± 1.5 l/min, p = 0.32), systolic (187 ± 22 mm Hg vs. 178 ± 28 mm Hg, p = 0.19), diastolic (89 ± 10 mm Hg vs. 84 ± 8 mm Hg, p = 0.43) or mean arterial pressures (122 ± 12 mm Hg vs. 116 ± 14 mm Hg, p = 0.22), or systemic vascular resistance (1,499 ± 303 dyns/s/cm^5 vs. 1631 ± 440 dyns/s/cm^5, p = 0.32

(Tables 2 and 3, Fig. 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 ± 13% vs. 45 ± 14%, p = 0.46). However, estimated peak and reserve A-VO$_2$ Diff were significantly greater after endurance exercise training compared to attention controls (19.8 ± 4.0 ml/dl vs. 17.3 ± 3.7 ml/dl, p = 0.03; and 10.5 ± 4.2 ml/dl vs. 7.2 ± 3.3 ml/dl, p = 0.01) (Table 2, Fig. 1). Finally, peak and reserve circulatory power were significantly greater after endurance training (Table 2). **Relative contributions of CO and A-VO$_2$Diff to the improvement in peak exercise VO$_2$ after endurance training.** We performed a mediation analysis to: 1) estimate the effect of endurance exercise training on peak exercise VO$_2$;

| Table 3 | Rest and Peak Exercise Hemodynamics at Baseline and After Exercise Training |

Hemodynamics		Rest			Peak Exercise		
Variable	Group	Baseline	Follow-Up	p Value	Baseline	Follow-Up	p Value
Systolic blood pressure, mm Hg	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, mm Hg	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, mm Hg	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·s/cm^5	CON	2,824 ± 941	2,929 ± 654	0.24	1,632 ± 374	1,631 ± 440	0.32
	EX	2,973 ± 1,009	2,784 ± 753		1,569 ± 417	1,499 ± 303	
Pulse pressure, mm Hg	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, mm Hg/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	

Values are mean ± SD. The p value represents comparison of least-square means at final visit after adjustment for baseline values.
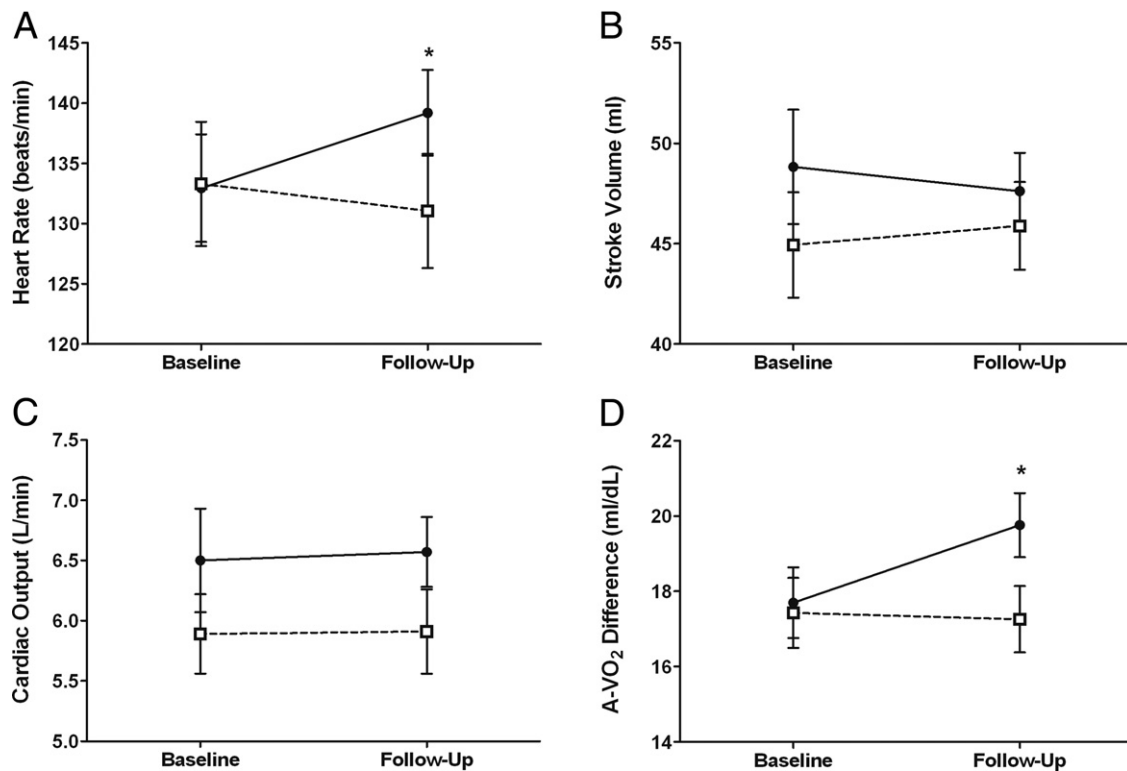
Abbreviations as in Table 1.

Figure 1   **Peak Exercise Data at Baseline and 4-Month Follow-Up**

Peak exercise data at baseline and 4-month follow-up for **(A)** heart rate, **(B)** stroke volume, **(C)** cardiac output, and **(D)** arterial-venous oxygen (A-VO$_2$) difference. **Solid circles** and **solid lines** represent the group randomly assigned to exercise training; **open squares** and **dashed line** represent patients randomly allocated to the attention control group. Values displayed at each time point are raw mean ± SE. *p = 0.03. All p values are from the analysis of covariance model based on comparison of least-square means at follow-up after adjustment for baseline values.

2) estimate the contribution of CO to the increase in peak exercise VO$_2$ resulting from endurance training; and 3) estimate the contribution of factors other than CO to the increase in peak VO$_2$ from endurance training. Based on ANCOVA, endurance training increased peak VO$_2$ by 19.8% compared to attention control. Considering CO as a mediator of the effect of training on peak VO$_2$, a model estimating the effect on peak VO$_2$ while controlling for CO indicated that the magnitude of the effect of training on peak VO$_2$ 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$_2$). Thus, 84% (16.6/19.8 = 84%) of the training-related improvement in peak VO$_2$ was due to factors other than cardiac output (i.e., improved A-VO$_2$ Diff).

Discussion

In the growing population of elderly persons, HFPEF is the most common form of HF (1,2). 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 (9). 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$_2$ Diff estimated from the Fick equation was the primary contributor to the increase in peak VO$_2$ that resulted from endurance exercise training, whereas peak exercise stroke volume and CO were not significantly changed (Table 2, Fig. 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 (18,35–38), nearly all of which have shown substantial improvements in exercise capacity, to date there have been only 4 reported studies of exercise training in patients with HFPEF (25–28). A critical question in such studies is the mechanisms underlying the training-related improvement in exercise capacity. However, this requires measurement of VO$_2$ and its determinants during peak exercise, which can be challenging in humans (9,29). As a result, a relatively small number of the training studies in HFREF patients have been able to examine this question (15–17,19,21,22,39,40), and ours 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. (19,22) reported that 6 months of endurance exercise training increased peak exercise heart rate and CO. In contrast, Sullivan et al. (16) and others (17,39,40) reported no significant change in peak stroke volume and CO after endurance exercise training in HFREF patients, and that increased peak A-VO$_2$ Diff measured invasively by direct oximetry was the major contributor to improved exercise capacity. Dubach et al. (21) found that 2 months of high-intensity endurance training improved both peak exercise CO and A-VO$_2$ Diff in HFREF patients. Taken together, studies performed in HFREF patients suggest that the increased peak VO$_2$ after 2 to 6 months of endurance exercise training is due to increased peak CO and/or A-VO$_2$ 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 (16,17,19–21,40,41).

These prior investigations in patients with HFREF already discussed (16,17,39) and others involving healthy subjects (42–44), including several that measured peak A-VO$_2$ Diff by direct oximetry, support the plausibility of our results indicating that the improvement in peak exercise VO$_2$ in elderly HFPEF patients after 4 months of endurance training was due primarily to an increased peak A-VO$_2$ Diff. Of note, this is contrary to our a priori hypothesis during the design of the trial. We had hypothesized, on the basis of our earlier report in a small number of patients (3), that increased peak LV stroke volume and cardiac output would be the primary contributors to an endurance training related increase in peak VO$_2$. 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$_2$ Diff (13). It is noteworthy that even in our early cross-sectional comparison study, an unheralded finding was that A-VO$_2$ Diff, measured invasively by direct oximetry, was impaired during exercise in HFPEF patients (3), an observation recently confirmed by Bhella et al. (14). Thus, 3 published studies from 3 separate laboratories, using 3 different techniques, have shown that at baseline before exercise training, HFPEF patients have reduced peak exercise A-VO$_2$ Diff and this contributes to their reduced peak VO$_2$. To measure peak A-VO$_2$ Diff, 1 used direct oximetry, 1 used the Fick technique with acetylene rebreathing measurements of cardiac output, and 1 used the Fick technique with cardiac output measured by 2-dimensional echocardiography volumes (3,13,14).

The finding of increased peak A-VO$_2$ Diff indicates that after exercise training there was an improvement in either diffusive oxygen transport by 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 after exercise training (45). 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 (5). 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 (6,46,47). 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 finding suggests that the increase in peak A-VO$_2$ 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$_2$ 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 (48–51). Bhella et al. (14) also recently reported that elderly HFPEF patients have impaired skeletal muscle oxidative metabolism. Studies involving 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 of HFREF patients and of healthy elderly subjects that have demonstrated that exercise training produces a variety of favorable skeletal muscle adaptations, including increased percent oxidative fibers (22), oxidative enzyme activity (20,22–24,50), and capillary density (23). Further studies will be required to determine the specific vascular and/or skeletal muscle mechanisms underlying the finding in the present study of a training-mediated increase in peak A-VO$_2$ Diff in HFPEF patients.

The results of prior mechanistic studies of endurance training in patients with HFREF (16,17) and in healthy elderly subjects (42,44) 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 (22,41), we found that training did increase peak heart rate, representing a possible mitigation of the chronotropic incompetence that was described by our group (3,29,52) and subsequently confirmed by others (6,7) 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. (42,43) reported that the increase in peak VO_2 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_2 Diff. In contrast, the increased peak VO_2 in healthy elderly women was due entirely to an increase in peak A-VO_2 Diff as peak exercise stroke volume, heart rate, and CO were unchanged after training (42,43). Of note, nearly all of the HFREF patients in prior mechanistic exercise trials were men (18), whereas the majority of patients in the present study of HFPEF were women, reflecting the sex distribution of HFPEF in the general population (2).

The intensity of the prescribed training program can also impact rest and exercise cardiovascular function. Wisloff et al. (53) 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 HRFEF. Nechwatal et al. (40) 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. 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 (54,55). 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. (33) 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 mm Hg had significantly greater event-free survival compared to HFREF patients whose circulatory power was 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, so our rest and peak exercise CO values may have been underestimated (30,31,56). However, our baseline peak CO values are similar to that reported by Ennezat et al. (8) in older HFPEF patients during cycle exercise at a similar peak power output to our subjects, although they are slightly lower than the peak exercise values reported by Borlaug et al. (6) in HFPEF patients.

The A-VO_2 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 of elderly outpatients and would have involved significant participant burden and risk. Instead, A-VO_2 Diff was estimated using the Fick equation where VO_2 measured by expired gas analysis is divided by measured CO. The Fick technique has been used to calculate A-VO_2 Diff in a number of recent physiologic studies investigating mechanisms of exercise intolerance that have included HFPEF patients (13,14,56–58). Our peak A-VO_2 Diff values were somewhat higher than those reported by others (14,59,60), possibly due to under-estimation of CO. However, the absolute change in peak A-VO_2 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 (16,21). 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 individual subjects, comparisons of CO and estimated A-VO_2 Diff between groups are valid.

Although the Doppler indexes at supine rest in the overall group indicated the presence of abnormal LV diastolic filling (13), due to technical limitations including merging of the E-wave 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 that are challenging in studies such as ours that require serial assessments in elderly outpatients and involve significant human research subject risk (57).

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, body mass index, and diuretic use. Because our study involved serial, exhaustive exercise tests and 4 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 (61,62), the diagnosis of HFPEF can be difficult and that remains a limitation to this and most HFPEF investigations.

In the mediation analysis, measurement error of cardiac output could potentially introduce positive bias. That would be inversely proportional to the coefficient of variation. The reliability of cardiac output measurement in our laboratory 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 patents was due primarily to increased peak A-VO$_2$ Diff. This finding suggests that peripheral vascular, microvascular, 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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