Exercise Training Improves Ventilatory Efficiency in Patients With a Small Abdominal Aortic Aneurysm

A RANDOMIZED CONTROLLED STUDY

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Purpose: To investigate the effects of exercise training on ventilatory efficiency and physiological responses to submaximal exercise in subjects with small abdominal aortic aneurysm (AAA).

Methods: Sixty-five male patients (72.3 ± 7.0 years) were randomized to exercise training (n = 33) or usual care group (n = 32). Exercise subjects participated in a training groups for 3 mo. Cardiopulmonary exercise testing was performed before and after the study period and peak $\dot{V}O_2$, the ventilatory threshold (VT), the oxygen uptake efficiency slope (OUES), and the $\dot{V}E_2/\dot{V}CO_2$ slope were identified. Baseline work rates at VT were matched to examine cardiopulmonary responses after training.

Results: Significant interactions indicating improvements before and after training in the exercise group were noted for time ($P < .01$), $\dot{V}O_2$ ($P < .01$), and work rate ($P < .01$) at the VT. At peak effort, significant interactions were noted for time ($P < .01$) and work rate ($P < .01$), while borderline significance was noted for absolute ($P = .07$) and relative ($P = .04$) $\dot{V}O_2$. Significant interactions were observed for the OUES both when using all exercise data ($P = .04$) and when calculated up to the VT ($P < .01$). For the $\dot{V}E_2/\dot{V}CO_2$ slope, significance was noted only when calculated up to the VT ($P = .04$). After training, heart rate, $\dot{V}E$, $\dot{V}O_2$ and respiratory exchange ratio were significantly attenuated for the same baseline work rate only in the exercise group (all $P < .01$).

Conclusions: Exercise training improves ventilatory efficiency in patients with small AAA. In addition, patients who exercised exhibited less demanding cardiorespiratory responses to submaximal effort.

Key Words: abdominal aortic aneurysm • cardiorespiratory fitness • exercise training • oxygen uptake efficiency slope • ventilatory efficiency

Abdominal aortic aneurysm (AAA) disease is a degenerative condition of the infrarenal aorta that can be lethal.[1,2] Abdominal aortic aneurysm rupture is responsible for up to 30 000 deaths per year in the United States, a mortality rate that is close to that reported for prostate cancer.[2,3] Male gender, advanced age, family history, and smoking are well-documented risk factors for AAA.[1-3] Greater public awareness and wider screening programs have led to increased detection of small AAA, defined as an aneurysm diameter between 3.0 and 5.5 cm.[1,3,4] Surgical repair is currently the only effective treatment to prevent rupture and is commonly reserved for aneurysms 5.5 cm or greater.[2,5] Patients diagnosed with presurgical "small" AAA are left with the awareness that they carry a life-threatening condition before eligibility for surgery, a period termed "watchful waiting." Strategies to improve physiological status and quality of life in these patients are needed.

Exercise training has been consistently demonstrated to be beneficial in a variety of cardiovascular conditions, although limited data exists in terms of AAA.[6-11] Abdominal aortic aneurysm patients with preserved exercise capacity have been shown to exhibit better postsurgical outcomes,[12] and exercise therapy has been recommended to limit functional decline and improve overall risk status in persons with AAA disease during the presurgical period.[13] However, the effects of exercise in patients with AAA have been explored in only a handful of studies,[14-18] most of which had small sample sizes.[16-18] Interestingly, although these few studies have consistently reported increased time to exhaustion and work rate achieved (ie, metabolic equivalents [METs] calculated from treadmill speed and grade) after training, peak oxygen uptake ($\dot{V}O_2$), the standard metric of cardiorespiratory fitness, was not significantly improved[15,17] or only tended to improve.[14,18] While a higher work rate achieved is an important outcome of exercise training, lack of consistent improvements in peak $\dot{V}O_2$ might underestimate the benefits of training. On the other hand, improvements in $\dot{V}O_2$ at the ventilatory threshold (VT) have been shown to be more responsive to training than peak $\dot{V}O_2$.[14,17,18] Notably, an improved VT may translate into attenuated physiological responses to a submaximal workload, but this has yet to be investigated in patients with AAA.

In 1996, Baba et al[19] introduced the concept of the oxygen uptake efficiency slope (OUES) as an objective measure of ventilatory efficiency. The OUES has been shown to be reproducible,[20] and its prognostic value has been demonstrated in patients with heart failure (HF)[21] and in other populations.[22,23] Improvements in the OUES have been reported following exercise training in patients with coronary artery disease[10,22] and patients with HF.[24,25] In addition, the slope of the relationship between ventilation ($\dot{V}E$) and carbon dioxide (CO_2) output ($\dot{V}E/\dot{V}CO_2$ slope) is a compelling predictor of mortality in patients with HF,[26-28] and there is evidence that this marker of ventilatory inefficiency is improved by exercise training.[29] However, indices of ventilatory inefficiency have not been examined in patients with AAA. The purpose of this study was to investigate the effects of exercise training on the OUES, $\dot{V}E/\dot{V}CO_2$ slope, and physiological responses to submaximal effort in patients with early AAA. We hypothesized that 3 mo of training

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would improve these indices and thus provide further evidence to support exercise therapy in patients with AAA.

METHODS

PARTICIPANTS

Subjects were recruited from Stanford University Medical Center, the Veterans Affairs Palo Alto Health Care System (VAPAHCS), and Kaiser Permanente of Northern California. Patients with small AAA (diameter between 2.5 and 5 cm), ambulatory, and between 50 and 85 years of age were eligible for inclusion. Detailed information regarding recruitment and randomization procedures have been previously described.[14,15] Exclusion criteria included the inability to complete the exercise training or testing for other health reasons, a life expectancy of <5 years; morbid obesity (BMI >39 kg/m^2); weight change of ≥20 lb over the past 3 mo; severe liver disease (international normalization ratio >2, serum albumin <3.0 g/dL); unstable angina or atrial fibrillation; critical aortic stenosis; class III/IV HF and/or ejection fraction <20%; thrombophlebitis; and active pericarditis or myocarditis. Participants had medical history information extracted from medical records, and all subjects completed questionnaires regarding physical activity and health history. Abdominal aortic ultrasound imaging was performed (maximal anterior-posterior diameter obtained in the sagittal imaging plane) by an experienced registered vascular technologist and diameter measurements were determined by a vascular surgeon.

Written informed consent was obtained from each participant and the study procedures were approved by the institutional review boards at Stanford University (including VAPAHCS), the Kaiser Permanente Division of Research in Oakland, California, and an independent Data Safety Monitoring Board organized by the National Heart, Lung and Blood Institute.

CARDIOPULMONARY EXERCISE TESTING

Participants underwent a symptom-limited cardiopulmonary exercise test (CPET) on a treadmill at baseline and after 3 mo. An individualized ramp protocol was used, targeting test duration to be within the recommended 8- to 12-min range, as previously described.[30] Speed and grade were recorded such that each participant repeated exactly the same work rate pattern on the baseline and 3-mo tests. Before testing, standardized medical examinations were performed, and medications were continued as prescribed. A 12-lead electrocardiogram was obtained at rest, each minute during exercise, and for at least 8 min during recovery; blood pressure was measured manually at rest, every 2 min during exercise, and at 2, 5, and 8 min during recovery. In the absence of clinical indications for stopping, participants were encouraged to exercise until volitional fatigue, and the Borg 6-20 perceived exertion scale was used to quantify effort.[31] Exercise capacity in METs was estimated from treadmill speed and grade[32] to provide a quantitative measure of each participant's achieved work rate. Throughout the test, cardiopulmonary responses were continuously measured using a Quark CPET metabolic system (CosMed, Rome, Italy). Volume and gas calibrations were performed according to the manufacturer's specifications before each test. Minute ventilation ($\dot{V}E$, body temperature and pressure, saturated), oxygen uptake ($\dot{V}O_2$, standard temperature and pressure, dry [STPD]), carbon dioxide production ($\dot{V}CO_2$, STPD), and other CPET variables were acquired breath by breath, reported as 10-sec intervals, and averaged over 30 sec. The VT was considered the breakpoint in the relationship between $\dot{V}CO_2$ as a function of $\dot{V}O_2$ throughout the exercise test and was determined by 2 blinded, experienced reviewers using the V-slope method and the ventilatory equivalents for oxygen (O_2) and CO_2.[14,33] Importantly, time from baseline and external work rate (speed and grade) at the VT were carefully recorded to examine cardiopulmonary responses at the same time point after the intervention period.

VENTILATORY EFFICIENCY CALCULATIONS

$\dot{V}E$ and $\dot{V}CO_2$ responses throughout exercise were used to calculate the $\dot{V}E/\dot{V}CO_2$ slope via least squares linear regression, using the equation: $\dot{V}E$ (L/min) $= m(\dot{V}CO_2$ (L/min)) $+ b$, where $m = \dot{V}E/\dot{V}CO_2$ slope. The $\dot{V}E/\dot{V}CO_2$ slope, which reflects the rate of increase in minute ventilation per unit increase in CO_2 production, is a noninvasive measurement of ventilatory efficiency that has been shown to be useful in assessing disease severity and prognosis in a variety of cardiopulmonary conditions.[28,34,35] A heightened slope is associated with reduced ventilatory efficiency and represents augmented ventilation for a given $\dot{V}O_2$. The relationship between $\dot{V}E$ and $\dot{V}CO_2$ was evaluated up to the VT,[36-38] as well throughout the entire exercise test. The OUES was computed as described by Baba et al,[19] using the equation: $\dot{V}O_2 = a \log 10\ \dot{V}E + b$, in which a is the OUES, the constant that represents the rate of increase in $\dot{V}O_2$ relative to $\dot{V}E$. A steeper slope indicates better ventilatory efficiency during exercise.[19] Values for OUES were determined using exercise data up to the VT (OUESvt), as well as throughout the entire exercise test (OUESmax).[25]

EXERCISE TRAINING PROGRAM

Participants assigned to the exercise group underwent a 3-mo training program, with sessions lasting approximately 1 hr, and were performed at either the VAPAHCS rehabilitation facility, at home, or a combination of both. Subjects were provided with exercise prescriptions, educational materials regarding exercise training, and counseling regarding individualized program requirements. This was accomplished during a minimum of 3 supervised in-house sessions at baseline. The overall goal of training was to achieve a minimum mean energy expenditure of 1000 kcal/wk, although participants were encouraged to perform 1 hr of predominantly moderate activity per day (approximately 2000 kcal/wk). Training sessions at the VAPAHCS included treadmill, cycle ergometry, stair climbing, elliptical and rowing 3 times weekly for 45 min followed by 10 min of resistance exercises. Both heart rate (HR) and ratings of perceived exertion were utilized to monitor exercise intensity. The initial target intensity was 60% of HR reserve calculated from baseline testing, increasing gradually as tolerated. Heart rate was recorded every 5 min and perceived exertion was targeted to fall within the range of 12 to 14 on the Borg 6-20 scale.[31] Electrocardiographic telemetry monitoring was provided initially and continued as indicated for selected participants.[39] Total daily activity was estimated from a previously validated 7-d activity recall questionnaire.[40] Estimates of recreational energy expenditure were obtained from daily activity logs and weekly telephone interviews with results recorded as both kcal and MET-hours per week.[41] These weekly interviews served the purposes of recognizing exercise-related complications, quantifying energy expenditure, and encouraging subjects to comply with their exercise prescriptions. Usual care subjects received no specific instructions regarding exercise.

STATISTICAL ANALYSES

The Kolmogorov-Smirnov test was used to verify normality of data distribution. Linear regression and Pearson coefficients were used to examine relationships between indices of ventilatory efficiency and clinical and other CPX variables. Independent-sample *t* tests were performed for between-group comparisons for continuous variables at baseline, while chi-square tests were employed for categorical variables. The effects of exercise training were analyzed using mixed ANOVA models (time by group) with Bonferroni post hoc tests. The within-subjects factor was time (baseline and 3 mo) and the between-subjects factor was group (exercise and usual care). Data were considered significant at $P < .05$ and statistical analyses were performed using the 20.0 version of SPSS (IBM). Data are expressed as mean ± standard deviation.

RESULTS

BASELINE CHARACTERISTICS

A total of 65 patients (mean age of 72.3 ± 7.0 years) who were randomly assigned into an exercise training group (n = 33) or usual care (n = 32) participated in the study. Baseline characteristics for the entire study sample as well as by group allocation are shown in Table 1. No significant between-group differences were observed for age, height, weight, body mass index, race, smoking status, smoking history, or AAA diameter. The most commonly used medications were angiotensin-converting enzyme inhibitors (39.2%), β-blockers (41.2%), diuretics (37.2%), statins (72.5%), and calcium channel-blockers (16.3%), with no differences between groups. The most prevalent coexisting conditions were hypertension (73%), coronary artery disease (31.5%), peripheral arterial disease (15%), and diabetes (22.6), with no differences between groups except for presence of diabetes; despite randomization, this condition was higher in the exercise group (34 vs 11.3%, $P = .01$).

CARDIOPULMONARY EXERCISE TESTING

A mean maximal respiratory exchange ratio (RER) of 1.10 ± 0.08 and rate of perceived exertion of 18.5 ± 1.3 suggest that participants achieved maximal effort. The OUES and $\dot{V}E/\dot{V}CO_2$ slope were calculated for all participants (mean values 2.07 and 30.5, respectively). The OUES was negatively associated with age ($r = -0.40$; $P < .01$), and was positively related to $\dot{V}O_2$ peak ($r = 0.72$; $P < .01$) and estimated METs ($r = 0.39$; $P = .01$). The association between the $\dot{V}E/\dot{V}CO_2$ slope and age was not statistically significant ($r = 0.22$; $P = .09$), whereas it was negatively related to $\dot{V}O_2$ ($r = -0.32$; $P = .02$) and estimated METs ($r = -0.39$; $P < .01$).

EFFECTS OF EXERCISE TRAINING

No AAA-related events occurred during exercise testing or training procedures. Cardiorespiratory responses to exercise testing at baseline and after 3 mo are presented in Table 2. Significant interactions were noted for exercise time, $\dot{V}O_2$, and estimated METs (all $P < .01$) at the VT. Post hoc analyses revealed that these results were driven by significant increases in the exercise group, while a significant decrease was noted for $\dot{V}O_2$ in the usual care group. At maximum effort, significant interactions were noted for time ($P < .01$), relative $\dot{V}O_2$ peak (mL/kg/min) ($P = .04$), and estimated METs ($P < .01$), with significant increases in the exercise group. For absolute $\dot{V}O_2$ peak (mL/min), a trend was noted ($P = .07$).

The effects of exercise training on the OUES and $\dot{V}E/\dot{V}CO_2$ slope are presented in Figures 1 and 2, respectively. A significant interaction was observed for the OUES both when using all exercise test data (panel A) ($P = .04$) and when calculated up to the VT (panel B) ($P < .01$). For the $\dot{V}E/\dot{V}CO_2$ slope, significance was noted only when calculated up to the VT (panel B) ($P = .04$). Heart rate, $\dot{V}E$, $\dot{V}O_2$ and RER at baseline VT and at a matched work rate after training are presented in Figure 3. Significant interactions for each of these variables were observed, with attenuated responses in the exercise group (all $P < .01$).

DISCUSSION

Studies on the effects of exercise training in AAA disease are limited and additional data in this area would be informative to better understand the role of exercise therapy in the management of this condition. This study aimed to examine the effects of exercise training on indices of ventilatory inefficiency, including the OUES, $\dot{V}E/\dot{V}CO_2$ slope, and physiological responses to submaximal work rates in patients with early, presurgical AAA. The salient findings suggest that exercise training improves ventilatory efficiency in these patients, with the improvements more apparent at the VT than maximum effort. Notably, similar to patients with reduced ventricular function, we observed that these indices were significantly related to age, estimated METs (a measure of achieved work rate), and peak $\dot{V}O_2$ at baseline, suggesting that they may have clinical value in gauging the severity of disease. Moreover, in contrast to usual care subjects, patients who underwent exercise training showed attenuated cardiorespiratory responses to a matched submaximal work rate after the training period. Taken together, these findings provide novel support for the benefits of training in a condition for which few previous data are available, and help to elucidate the role of exercise training in patients awaiting AAA repair.

The OUES was initially proposed by Baba et al[19] as an objective and effort-independent measure of ventilatory efficiency, and subsequent studies demonstrated this index to

Table 1

Baseline Descriptive Characteristics by Total Sample and Groups

		Groups		
	All Patients (N = 65)	Exercise (n = 33)	Usual Care (n = 32)	*P* Value
Age, y	72.3 ± 7.0	72.8 ± 6.4	71.8 ± 7.6	.57
Body weight, kg	86.6 ± 11.1	87.2 ± 11.9	85.6 ± 12.2	.46
Height, cm	175.8 ± 8.6	174.3 ± 9.7	177.2 ± 7.2	.20
Body mass index, kg/m^2	28.0 ± 3.3	28.8 ± 3.4	27.6 ± 3.2	.08
Race, % Caucasian	80	84.8	75	.43
Smoking, % current	10.4	8.7	12	.69
Smoking, % with history	81.2	85.9	78	.47
Aneurysm diameter, cm	3.7 ± 0.5	3.7 ± 0.6	3.7 ± 0.5	.90

Table 2

Effects of Exercise Training on Exercise Test Responses at the Ventilatory Threshold and at Maximal Exercise[a]

	Exercise (n = 33)		Usual Care (n = 32)		
	Baseline	**Post-training**	**Baseline**	**Post-training**	***P* Values for Interaction**
Ventilatory threshold					
HR, beats/min	104.5 ± 18.7	105.0 ± 21.8	106.3 ± 21.6	104.6 ± 20.7	.68
RER	0.85 ± 0.09	0.85 ± 0.10	0.87 ± 0.11	0.85 ± 0.10	.79
Time to VT, sec	216.1 ± 119.0	301.3 ± 159.2[b]	271.3 ± 188.6	255.9 ± 184.0	<.01
$\dot{V}O_2$ mL/kg/min	13.3 ± 3.3	15.0 ± 3.4[b]	15.6 ± 4.7	14.3 ± 3.8[b]	<.01
$\dot{V}O_2$ mL/min	1154.1 ± 313.5	1298.0 ± 300.9[b]	1359.2. ± 435.6	1241.9 ± 420.8[b]	<.01
Estimated METs	3.7 ± 1.4	4.8 ± 2.0[b]	4.8 ± 2.5	4.6 ± 2.4	<.01
Peak exercise					
HR, beats/min	127.7 ± 22.5	128.6 ± 23.8	128.0 ± 20.7	130.4 ± 13.0	.81
RER	1.09 ± 0.09	1.11 ± 0.09	1.11 ± 0.10	1.10 ± 0.09	.30
Time to peak, sec	487.5 ± 175.8	637.6 ± 204.5[b]	564.8 ± 168.6	529.9 ± 181.6	<.01
$\dot{V}O_2$, mL/kg/min	18.8 ± 4.8	19.9 ± 4.5[b]	19.7 ± 5.5	19.6 ± 6.0	.04
$\dot{V}O_2$, mL/min	1653.3 ± 430.6	1740.6 ± 490.1	1715.2 ± 514.9	1710.8 ± 550.9	.07
Estimated METs	5.8 ± 1.9	6.9 ± 1.9[b]	7.5 ± 2.5	7.4 ± 2.4	<.01
RPE	18.4 ± 1.6	18.4 ± 1.4	18.6 ± 1.5	18.8 ± 1.7	.83

Abbreviations: HR, heart rate; MET, metabolic equivalent; $\dot{V}O_2$, oxygen uptake; VT, ventilatory threshold; RPE, rating of perceived exertion; RER, respiratory exchange ratio.
[a]Data are reported as mean ± standard deviation.
[b]Significantly different compared to baseline in the same group ($P \leq .05$).

be reproducible[20] and to have strong prognostic value in patients with cardiovascular disease.[21,22] In addition, the OUES has been shown to respond favorably to exercise training.[10] To our knowledge, the present study is the first to address the OUES response to training in patients with AAA; we observed that 3 mo of exercise training improved the OUES, suggesting that this parameter may be a useful supplement to other functional indices in the evaluation of these patients. Physiological mechanisms underlying an impaired OUES include early metabolic acidosis,[10,19,20] which was

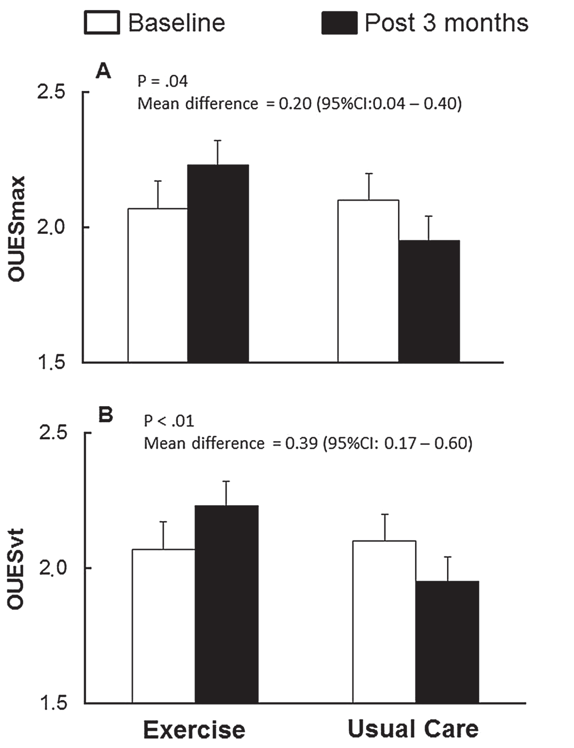

Figure 1. Oxygen uptake efficiency slope (OUES) calculated using the entire exercise test (OUESmax) (panel A) and using exercise data up to the ventilatory threshold (OUESvt) at baseline and after 3 mo in the exercise and usual care groups.

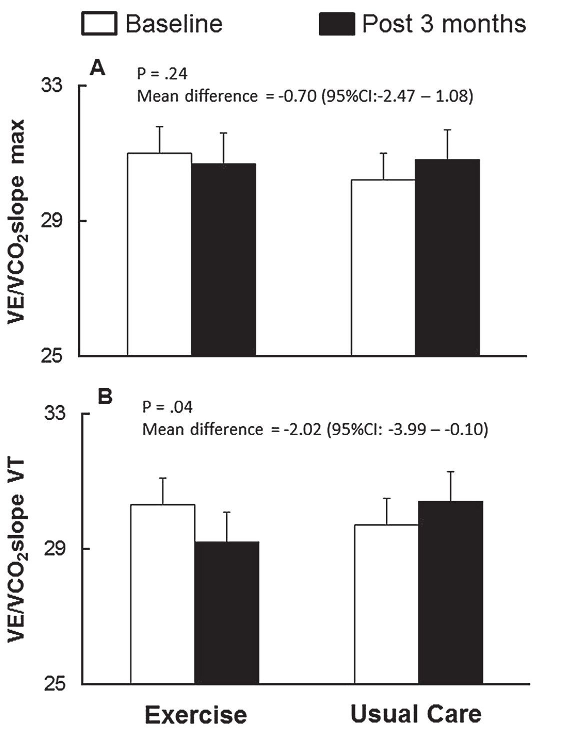

Figure 2. $\dot{V}E/\dot{V}CO_2$ slope calculated using the entire exercise test ($\dot{V}E/\dot{V}CO_2$ slope max) (panel A) and using exercise data up to the ventilatory threshold ($\dot{V}E/\dot{V}CO_2$ slope VT) at baseline and after 3 mo in the exercise and usual care groups. Abbreviations: $\dot{V}E$, minute ventilation; $\dot{V}CO_2$, carbon dioxide output.

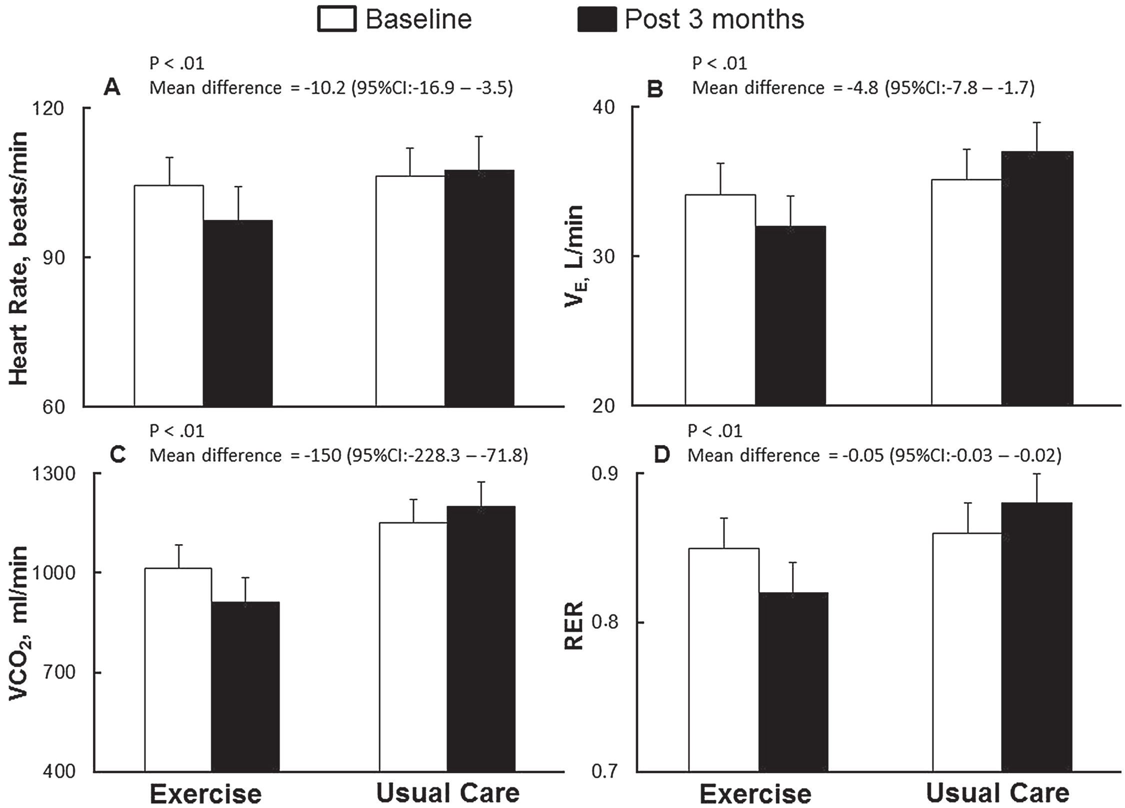

Figure 3. Heart rate (panel A), minute ventilation ($\dot{V}_E$) (panel B), carbon dioxide output ($\dot{V}CO_2$) (panel C), and respiratory exchange ratio (RER) (panel D) at baseline ventilatory threshold and at the same time and workload after the intervention period in the exercise and usual care groups.

presumably delayed after training in the present study, given the significant increases in work rate and $\dot{V}O_2$ at the VT. In accordance with this mechanism, a recent systematic review demonstrated that change in the VT was the strongest contributor to a change in OUES following exercise training.[42] An increase in the OUES indicates that a given oxygen uptake is achieved with lower ventilatory demand (ie, more efficient ventilation) at submaximal workloads. Although a recent report[22] showed that a training-induced improvement in the OUES was associated with decreased risk of mortality in patients with coronary artery disease, its implications for outcome assessment in AAA require further exploration.

Measures of ventilatory inefficiency have been shown to be related to the severity of cardiovascular and pulmonary disease[35] and to predict mortality.[28,34,43] Although research has been conducted to examine the $\dot{V}_E/\dot{V}CO_2$ slope response to exercise training in patients with chronic HF[24] and other high-risk populations,[29] little is known regarding the effects of training on these parameters in AAA disease. Notably, the baseline $\dot{V}_E/\dot{V}CO_2$ slope in the current study was negatively associated with peak $\dot{V}O_2$ and maximal work rate, suggesting its role in gauging the severity of AAA disease. We observed that when using data up to the VT, exercise training significantly reduced the V_E/VCO_2 slope, indicating that the ventilatory response to exercise is improved following training.

An additional finding was that subjects who underwent exercise training exhibited an attenuated cardiorespiratory demand at a matched submaximal work rate compared with usual care subjects. Specifically, heart rate, $\dot{V}_E$,$\dot{V}CO_2$, and RER at a work rate matched to the baseline VT were significantly reduced in the exercise group. Reduced cardiopulmonary demand for a given submaximal effort suggests an increase in cardiopulmonary reserve and potentially enables activities of daily living to be performed with less dependence on oxygen-independent metabolism.[44] In fact, individuals who have higher physiological demand to submaximal tasks experience greater degrees of difficulty performing free-living activities and tend to be less physically active.[45] Reduced heart rate at a submaximal work rate is a classic physiologic response to aerobic training[46]; we observed a 10 beats/min reduction in this measure ($P < .001$; Figure 3). This reflects a reduction in myocardial demand to a given work rate and suggests lessened cardiovascular stress associated with daily activities.

This study has several strengths and limitations. The randomized controlled design, sample size, and novelty of the results are strengths. The fact that we monitored patients more intensively than a typical rehabilitation program might raise the question as to whether our results apply to more typical outpatient programs. The study was conducted in men, reflecting the 4- to 5-fold higher prevalence of AAA disease in men,[1,2] and the results may not be applicable to women. Finally, while it was not within the scope of this study to evaluate the safety of exercise training in this population, the fact that no subjects in the intervention arm experienced complications, in conjunction with previous data from our group[14,15] and a pilot study in the United Kingdom,[17] suggests that patients with early AAA can be safely referred to cardiac rehabilitation programs.

The current findings suggest that physical training improves exercise efficiency in subjects with small AAA, a population for which scarce previous data are available. Exercise training improved the OUES and $\dot{V}_E/\dot{V}CO_2$ slope, parameters that have strong prognostic value. In addition, patients who exercised exhibited less demanding cardiorespiratory responses to a matched submaximal workload, a finding with implications for the ability to perform activities of daily living. These findings provide support for the concept that exercise training promotes positive physiological adaptations in subjects with early AAA and thus may play a role in the management of this condition.

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