A Randomized Trial of Exercise Training in Abdominal Aortic Aneurysm Disease

JONATHAN MYERS[1], MARY MCELRATH[1], ALYSSA JAFFE[1], KIMBERLY SMITH[1], HOLLY FONDA[1], ANDREW VU[1], BRADLEY HILL[2], and RONALD DALMAN[3]

[1]Division of Cardiology, Veterans Affairs Palo Alto Health Care System, Palo Alto, CA; [2]Department of Vascular Surgery, Kaiser Permanente, Santa Clara, CA; and [3]Department of Surgery, Stanford University, Stanford, CA

ABSTRACT

MYERS, J., M. MCELRATH, A. JAFFE, K. SMITH, H. FONDA, A. VU, B. HILL, and R. DALMAN. A Randomized Trial of Exercise Training in Abdominal Aortic Aneurysm Disease. *Med. Sci. Sports Exerc.*, Vol. 46, No. 1, pp. 2–9, 2014. **Purpose**: Screening programs and greater public awareness have increased the recognition of early abdominal aortic aneurysm (AAA) disease. No medical therapy has proven effective in limiting AAA progression, and little is known regarding the safety and efficacy of exercise training in these patients. We evaluated the safety and efficacy of up to 3 yr of training in patients with early (≤5.5 cm) AAA disease. **Methods**: One hundred and forty patients with small AAAs (72 ± 8 yr) were randomized to exercise training (n = 72) or usual care (n = 68). Exercise subjects participated in a combination of in-house and home training for up to 3 yr. Cardiopulmonary exercise testing (CPX) was performed at baseline and 3, 12, 24, and 36 months. Comparisons were made for AAA expansion, safety, CPX responses, and weekly energy expenditure. **Results**: The average duration of participation was 23.4 ± 9.6 months; 81% of subjects completed ≥1 year. No adverse clinical events or excessive AAA growth rates related to training occurred. Exercise subjects expended a mean 1999 ± 1030 kcal·wk^{-1}. Increases in peak exercise time and estimated METs occurred at the 3-month and 1-, 2-, and 3-yr evaluations ($P < 0.01$ between groups). A significant between-group interaction occurred for $\dot{V}O_2$ at the ventilatory threshold (P = 0.02), and submaximal heart rate was significantly reduced among exercise subjects. Neither exercise status nor level of fitness significantly influenced rate of AAA enlargement. **Conclusions**: These results support the safety and efficacy of training in patients with small AAA, a population for which few previous data are available. Despite advanced age and comorbidities, training up to 3 yr was well tolerated and sustainable in AAA patients. Training did not influence rate of AAA enlargement. **Key Words:** EXERCISE TRAINING, EXERCISE TESTING, VASCULAR DISEASE, ANEURYSM, PHYSICAL ACTIVITY

Abdominal aortic aneurysm (AAA) disease is a degenerative condition of the infrarenal aorta. Progressive medial degeneration predisposes the aorta to weakening, enlargement and, ultimately, catastrophic rupture if left untreated. Smaller aneurysms enlarge at a generally predictable rate, with rupture risk increasing as a function of size, shape, and rate of enlargement (7,14). AAA rupture is the 13th leading cause of death in the United States, and it isthe third leading cause of sudden death in men older than 60 yr, accounting for roughly 4%–5% of sudden deaths (10,11). Once a relatively obscure condition, a great deal of knowledge has been gained in recent years regarding AAA prevalence, pathogenesis, outcomes, and treatment (8,12,16).

The combination of wider screening for AAA, including the recent addition of ultrasound screening to the Medicare program and greater public awareness, has led to increasing recognition of early AAA disease, defined as an aneurysm between 3.0 and 5.5 cm in diameter (5,12). Most (≈90%) AAAs detected through screening programs are small and fall below the 4.5- and 5.5-cm-diameter intervention thresholds currently recommended for surgical repair in women and men, respectively (8). Because therapeutic strategies to improve clinical outcomes in patients with presurgical AAA are lacking (5,8), many patients are left with an awareness that they have a potentially life-threatening illness that carries a small chance of sudden death in the months or years before eligibility for surgical repair. Although guidelines suggest that these patients should be advised to stop smoking and

Address for correspondence: Jonathan Myers, Ph.D., VA Palo Alto Health Care System, Cardiology 111C, 3801 Miranda Ave., Palo Alto, CA 94304; E-mail: drj993@aol.com.
Submitted for publication March 2013.
Accepted for publication June 2013.

0195-9131/14/4601-0002/0
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DOI: 10.1249/MSS.0b013e3182a088b8

make other lifestyle modifications known to reduce cardiovascular risk (8), nonsurgical therapies have proven minimally effective in preventing AAA progression (5,8,12,16).

One strategy with the potential to improve health and quality of life of AAA patients is exercise training. Patients with AAA are typically unfit and relatively sedentary, in part due to the many comorbid conditions associated with this condition (31). In patients with other manifestations of systemic cardiovascular disease, programs of exercise-based rehabilitation result in improved risk factor profiles, higher exercise capacity, and reduced morbidity and mortality (22,30). Moreover, regular exercise favorably influences numerous factors associated with AAA disease, including obesity, immobility, expression of proinflammatory cytokines, high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and low levels of fitness, among others (1,8,18,20,37). Patients with early AAA disease therefore represent a growing population that may potentially benefit from exercise therapy and secondary prevention. However, little is known regarding the effects of formal rehabilitation programs in patients with AAA.

As part of a National Heart, Lung and Blood–sponsored Specialized Center of Clinically Oriented Research Program in AAA disease at Stanford University, we performed a randomized, longitudinal trial on the effects of exercise therapy in patients with AAA. The primary aim of the study was to determine the effects of exercise training on AAA growth rates compared with usual care. The secondary aim was to determine the safety and efficacy of up to 3 yr participation in an exercise training program in patients with presurgical AAA disease.

METHODS

Study design, recruitment, and randomization. One hundred and forty subjects with small AAA, defined as an aortic diameter between 2.5 and 5.0 cm, were recruited from Stanford University Medical Center, the Veterans Affairs Palo Alto Health Care System (VAPAHCS), and the Kaiser Permanente of Northern California. Recruitment procedures and all study-related activities were reviewed and approved in advance 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. Written informed consent was obtained by all participants.

Of the 5-yr study, subjects participated in the exercise trial for up to 3 yr, depending on the point at which they were recruited. Recruitment continued through year 4 such that as many subjects as possible were exposed to exercise intervention or usual care for at least 1 year. Ambulatory male and female subjects between the ages of 50 and 85 yr with small AAA <5.0 cm were eligible for inclusion. Exclusion criteria included morbid obesity (BMI >39 $kg \cdot m^{-2}$), weight gain or loss ≥20 lb for the last 3 months, unstable angina, class II/IV heart failure or ejection fraction <20%, thrombophlebitis, and uncontrolled atrial fibrillation. The hypothesized treatment effect was a reduction in the population average AAA growth rate after exercise training compared with usual care. Initial aneurysm size was a covariate and check for interaction with the treatment effect because larger aneurysms grow more rapidly.

Cardiopulmonary exercise testing. Symptom-limited exercise testing was performed at baseline and after 3, 12, 24, and 36 months. An individualized ramp treadmill protocol was used such that test duration was targeted to fall within the recommended 8- to 12-min range as previously described (28). Standardized medical examinations were performed before testing, and medications were continued as prescribed. ECG was obtained at rest, each minute during exercise, and for at least 8 min during recovery; blood pressure was measured at rest, every other minute during exercise, and at 1, 2, 5, and 8 min during recovery or until symptoms, ECG changes, and blood pressure stabilized. In the absence of clinical indications for stopping, participants were encouraged to exercise until volitional fatigue, and the Borg 6–20 perceived exertion scale (RPE) was used to quantify effort (6). Exercise capacity in METs was estimated from peak treadmill speed and grade (4). Cardiopulmonary exercise test (CPX) responses were obtained using a CosMed Quark CPET metabolic system (Rome), calibrated in a standard fashion before each test. Minute ventilation ($\dot{V}_E$, BTPS), oxygen uptake ($\dot{V}O_2$, STPD), carbon dioxide production ($\dot{V}CO_2$, STPD), and other CPX variables were acquired breath by breath, reported as 10-s intervals, and averaged for 30 s. $\dot{V}_E$ 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. The ventilatory threshold (VT) was determined by two blinded reviewers using the V-slope method. Heart rate recovery was determined by the difference between peak HR and HR at 1 and 2 min postexercise.

Exercise training. Participants randomized to the exercise group underwent training at either the VAPAHCS rehabilitation facility, at home, or a combination of both, depending on travel requirements and related issues. Participants were initially provided with exercise prescriptions, educational materials regarding exercise training, and counseling regarding individualized program requirements. This was accomplished during a minimum of three supervised in-house sessions at baseline. The overall goal of training was to achieve a minimum mean energy expenditure of 1000 $kcal \cdot wk^{-1}$; however, for motivational purposes, subjects were encouraged to perform an hour of moderate activity/day (approximately 2000 $kcal \cdot wk^{-1}$). VAPAHCS sessions included treadmill, cycle ergometry, stair climbing, elliptical training, and rowing three times weekly for 45 min followed by 10 min of resistance exercise. The initial target intensity was 60% of HR reserve estimated from baseline testing, increasing to 80% as tolerated (3,4). HR was recorded every 5 min. Perceived exertion was targeted to fall within the range of 12–14 on the Borg 6–20 scale (6). ECG telemetry monitoring was provided for at least

2 wk and continued as indicated for selected participants (3). Total daily activity was estimated from a 7-day activity recall questionnaire previously validated for this purpose (34). Estimates of recreational energy expenditure were obtained from weekly telephone interviews with results recorded as both kcal and MET-hours per week (energy expenditure in METs times number of hours participation) (2). These weekly interviews served the purposes of recognizing study-related complications, quantifying energy expenditure, and encouraging subjects to comply with exercise prescriptions. Usual care subjects received no specific instructions regarding exercise, and physical activity patterns were not tracked.

Ultrasound measurements. Abdominal aortic ultrasound imaging was performed by one of two experienced registered vascular technologists (RVT). More than 95% of examinations were obtained by a single RVT; a second RVT performed the other 5%. Diameter measurements were obtained by a single, experienced investigator (RLD). Both the RVT and the individual making the diameter measurements were blinded to group randomization. Exams were performed on fasting patients, usually in the morning hours. Aneurysm size was determined by the maximal anterior–posterior diameter obtained in the sagittal imaging plane (25). Images were acquired with 3.5 MHz real-time sector scan heads on an ATL 5000 HDI system and archived on both WebPro (Accuson/Philips) and STENTOR electronic retrieval systems for later review. The technologist reviewed past imaging examinations before performing subsequent examinations to recognize specific acoustic features that identified areas of maximal enlargement.

Statistical analysis. Demographic and clinical variables at baseline between groups were compared using unpaired *t*-tests. A fixed-effects model was used to assess the primary outcome, AAA growth rates between exercise and usual care groups. Differences in exercise test responses were compared using multivariate ANOVA, with group (exercise vs usual care) and test (baseline, 3, 12, 24, and 36 months) as factors. *Post hoc* tests were performed using the Bonferroni method. Because the duration of exposure differed widely between subjects (ranging from 3 months to 3 yr) paired *t*-tests were also used to assess matched comparisons of exercise responses at each evaluation.

RESULTS

Study participants. A total of 3653 potential subjects with AAA underwent chart review for the three different phases of the larger AAA STOP trial. Of those, 2432 did not meet inclusion criteria, and of the remaining 1221 patients with early AAA disease, 140 subjects met eligibility criteria and agreed to participate in the exercise trial. Despite randomization, a difference was observed in prevalence of diabetes (30% vs 12% in the exercise and usual care groups, respectively, $P < 0.01$); subjects in the exercise group were also heavier than usual care subjects ($P = 0.002$) (Table 1). No other differences in clinical or demographic data were observed at baseline. No untoward events occurred during any exercise testing or training procedures. Three subjects in the exercise group and nine subjects in the usual care group underwent surgical repair of their aneurysms during the study, resulting in repair rates of 2.7 and 8.1 per 100 patients years, respectively ($P = 0.09$). The mean duration of participation was 23.4 ± 9.6 months; 81% of subjects completed at least 1 year in the trial.

TABLE 1. Demographic and clinical variables at baseline.

	Exercise ($n = 72$)	Usual Care ($n = 68$)	*P*
Demographics			
Age, mean ± SD (yr)	71.8 ± 7	71.3 ± 8	0.74
Gender (% male)	92	93	0.94
Race (% Caucasian)	85	74	0.09
BMI, mean ± SD ($kg \cdot m^{-2}$)	29.1 ± 4	27.0 ± 3	0.002
Clinical history (%)			
Coronary artery disease	22	34	0.14
Hypertension (present)	74	76	0.80
Peripheral vascular disease	14	18	0.56
Diabetes	30	12	0.01
Smoking (current)	11	21	0.22
Smoking history	82	79	0.39
Smoking, mean ± SD (pack-years)	32.9 ± 28	32.6 ± 30	0.96
Medications (%)			
ACE inhibitors/ARB	12	6	0.15
Beta blockers	42	51	0.28
Statins	83	78	0.32
Calcium channel blockers	18	79	0.92

Variables are presented as prevalence (%), unless otherwise noted.
BMI, body mass index; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.

Training intensity and energy expenditure. HR recordings in the exercise group documented an overall mean training intensity of 98.8% ± 10% expressed as a percentage of target HR, corresponding to a mean RPE of 12.9 ± 1.2. Training intensity did not differ appreciably between participants training at VAPAHCS (average HR = 96.8% ± 8% of target) versus those primarily training at home (average HR = 100.7% ± 11% of target). The mean overall energy expenditure for the exercise group was 1999 ± 1030 $kcal \cdot wk^{-1}$; this value represents the mean of each participant's energy expenditure during in which they were enrolled in the study. Although distributions were skewed, an energy expenditure of at least 1000 $kcal \cdot wk^{-1}$ was achieved by 85% of subjects, and 40% reported >2000 $kcal \cdot wk^{-1}$. This corresponded to a mean of 22.9±12.4 $MET \cdot h \cdot wk^{-1}$ of energy expenditure.

Cardiopulmonary exercise testing. CPX responses at the VT and maximal exercise are presented in Tables 2 and 3, respectively. The tables include subjects who completed matched visits at each evaluation and those whose tests were maximal and symptom limited (fatigue, shortness of breath, and claudication); differences in study numbers at each evaluation point are due to varying time during the study when a patient started their participation. Maximal efforts were expended during testing as evidenced by both exercise and usual care participants achieving mean RPE levels between 18 and 19 and mean respiratory exchange ratios ≈1.10 during each evaluation. Subjects in the exercise group demonstrated 28%, 37%, 37%, and 42% increases in

TABLE 2. Maximal exercise test responses in the exercise and usual care groups.

	Exercise Group											
	Baseline	3 Months	*P*	Baseline	12 Months	*P*	Baseline	24 Months	*P*	Baseline	36 Months	*P*
		n = 60			*n* = 53			*n* = 36			*n* = 21	
Exercise time (min)	488.3 ± 176	623.2 ± 207	<0.001	494.2 ± 181	679 ± 218	<0.001	497.2 ± 174	681.4 ± 193	<0.001	469 ± 153	665 ± 205	<0.001
Estimated METs	6.3 ± 2.3	7.6 ± 2.6	<0.001	6.4 ± 2.3	7.9 ± 2.6	<0.001	6.5 ± 2.3	8.2 ± 2.3	<0.001	6.5 ± 2.3	8.2 ± 2.5	<0.001
$\dot{V}O_2$ (mL $O_2 \cdot kg^{-1} \cdot min^{-1}$)	19.5 ± 5.8	20.4 ± 6.3	0.05	19.6 ± 6.0	20.9 ± 5.9	0.05	20.5 ± 6.0	20.6 ± 5.5	0.83	20.7 ± 6.0	20.9 ± 5.8	0.33
$\dot{V}O_2$ ($mL \cdot min^{-1}$)	1753 ± 500	1822 ± 562	0.13	1759 ± 536	1835 ± 528	0.19	1835 ± 545	1813 ± 538	0.75	1852 ± 610	1856 ± 564	0.95
Perceived exertion	18.3 ± 1.6	18.6 ± 1.3	0.18	18.3 ± 1.6	19.1 ± 1.0	0.002	18.4 ± 1.6	18.8 ± 1.2	0.26	18.2 ± 1.8	19.4 ± 0.67	0.01
RER	1.09 ± 0.14	1.13 ± 0.11	0.05	1.08 ± 0.13	1.12 ± 0.09	0.04	1.08 ± 0.12	1.13 ± 0.09	0.1	1.06± 0.12	1.11 ± 0.08	0.19
Submax HR (5 min)	111 ± 20	104 ± 20	<0.001	110 ± 22	102 ± 17	<0.001	111 ± 22	100 ± 20	<0.001	114 ± 22	100 ± 17	0.006
	Usual Care Group											
	Baseline	**3 Months**	***P***	**Baseline**	**12 Months**	***P***	**Baseline**	**24 Months**	***P***	**Baseline**	**36 Months**	***P***
		n = 61			*n* = 58			*n* = 46			*n* = 24	
Exercise time (min)	525.3 ± 182	529.4 ± 194	0.79	555 ± 183	537 ± 203	0.31	552.7 ± 195	489.4 ± 183	0.01	539.0 ± 203	499.5 ± 216	0.18
Estimated METs	7.2 ± 2.7	7.3 ± 2.8	0.70	7.4 ± 2.8	7.0 ± 2.6	0.04	7.4 ± 2.9	6.7 ± 2.6	<0.001	7.1 ± 2.7	6.5 ± 2.4	0.01
$\dot{V}O_2$ (mL $O_2 \cdot kg^{-1} \cdot min^{-1}$)	20.0 ± 6.4	19.8 ± 6.6	0.35	20.2 ± 6.5	19.6 ± 6.1	0.26	20.9 ± 6.5	19.3 ± 5.1	0.04	19.8 ± 6.9	17.5 ± 6.9	0.04
$\dot{V}O_2$ ($mL \cdot min^{-1}$)	1672 ± 666	1698 ± 602	0.67	1699 ± 689	1681 ± 599	0.78	1767 ± 678	1638 ± 432	0.12	1743 ± 758	1502 ± 561	0.03
Perceived exertion	18.7 ± 1.2	18.8 ± 1.7	0.49	18.6 ± 1.3	18.9 ± 1.1	0.05	18.7 ± 1.2	18.9 ± 1.1	0.34	18.5 ± 1.2	18.9 ± 1.4	0.27
RER	1.11 ± 0.11	1.11 ± 0.10	0.98	1.11 ± 0.11	1.0 ± 0.11	0.31	1.11 ± 0.13	1.08 ± 0.11	0.35	1.07 ± 0.08	1.07 ± 0.09	0.98
Submax HR (5 min)	110 ± 20	106 ± 21	0.06	107 ± 18	104 ± 19	0.09	105 ± 16	102 ± 16	0.04	104 ± 18	100 ± 19	0.07

TABLE 3. Exercise test responses at the ventilatory threshold in the exercise and usual care groups.

	Exercise Group											
	Baseline	3 Months	*P*	Baseline	12 Months	*P*	Baseline	24 Months	*P*	Baseline	36 Months	*P*
		n = 60			*n* = 53			*n* = 36			*n* = 21	
Exercise time (min)	177.1 ± 107	297 ± 172	<0.001	163.3 ± 106	294.4 ± 180	<0.001	160.3 ± 117	271 ± 144	<0.001	144.4 ± 104	239.4 ± 121	0.006
Estimated METs	3.6 ± 1.3	4.7 ± 1.7	<0.001	3.5 ± 1.4	4.7 ± 1.5	<0.001	3.5 ± 1.4	4.4 ± 1.3	<0.001	3.3 ± 1.2	4.2 ± 1.2	0.01
$\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	13.6 ± 4.5	15.0 ± 4.6	0.04	13.7 ± 4.7	15.0 ± 3.5	0.04	13.6 ± 4.9	14.2 ± 3.7	0.47	13.3 ± 4.9	13.0 ± 3.0	0.75
$\dot{V}O_2$ ($mL \cdot min^{-1}$)	1231 ± 376	1350 ± 387	0.04	1214 ± 400	1322 ± 299	0.05	1218 ± 404	1277 ± 369	0.37	1208 ± 457	1174 ± 327	0.73
RER	0.83 ± 0.08	0.89 ± 0.10	<0.01	0.82 ± 0.08	0.85 ± 0.11	0.12	0.80 ± 0.07	0.83 ± 0.09	0.06	0.81 ± 0.06	0.78 ± 0.008	0.31
Heart rate	100 ± 19	103 ± 19	0.22	99 ± 20	103 ± 18	0.25	99 ± 22	99 ± 18	0.96	98 ± 24	95 ± 15	0.61
	Usual Care Group											
	Baseline	**3 Months**	***P***	**Baseline**	**12 Months**	***P***	**Baseline**	**24 Months**	***P***	**Baseline**	**36 Months**	***P***
		n = 61			*n* = 58			*n* = 46			*n* = 24	
Exercise time (min)	262.7 ± 155	245.8 ± 193	0.54	293 ± 160	226 ± 127	0.007	267 ± 137	201 ± 123	0.03	319 ± 161	145 ± 51	<0.001
Estimated METs	5.1 ± 3.2	4.5 ± 1.9	0.12	5.4 ± 3.3	4.3 ± 1.4	0.02	5.5 ± 3.6	4.3 ± 1.6	0.05	6.1 ± 4.8	3.5 ± 0.63	0.03
$\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	15.7 ± 4.7	14.7 ± 5.5	0.13	16.0 ± 5.0	13.7 ± 4.3	0.004	16.5 ± 4.9	13.7 ± 3.4	<0.001	16.9 ± 5.0	11.4 ± 2.4	<0.001
$\dot{V}O_2$ ($mL \cdot min^{-1}$)	1344 ± 469	1232 ± 537	0.06	1370 ± 478	1172 ± 434	0.005	1428 ± 457	1177 ± 291	<0.001	1481 ± 509	1011 ± 320	<0.001
RER	0.88 ± 0.09	0.87 ± 0.10	0.63	0.89 ± 0.09	0.84 ± 0.11	0.004	0.90 ± 0.11	0.82 ± 0.10	0.001	0.91 ± 0.11	0.76 ± 0.05	<0.001
Heart rate	106 ± 20	102 ± 21	0.12	104 ± 18	94 ± 20	0.007	103 ± 16	94 ± 14	0.002	107 ± 18	88 ± 13	<0.001

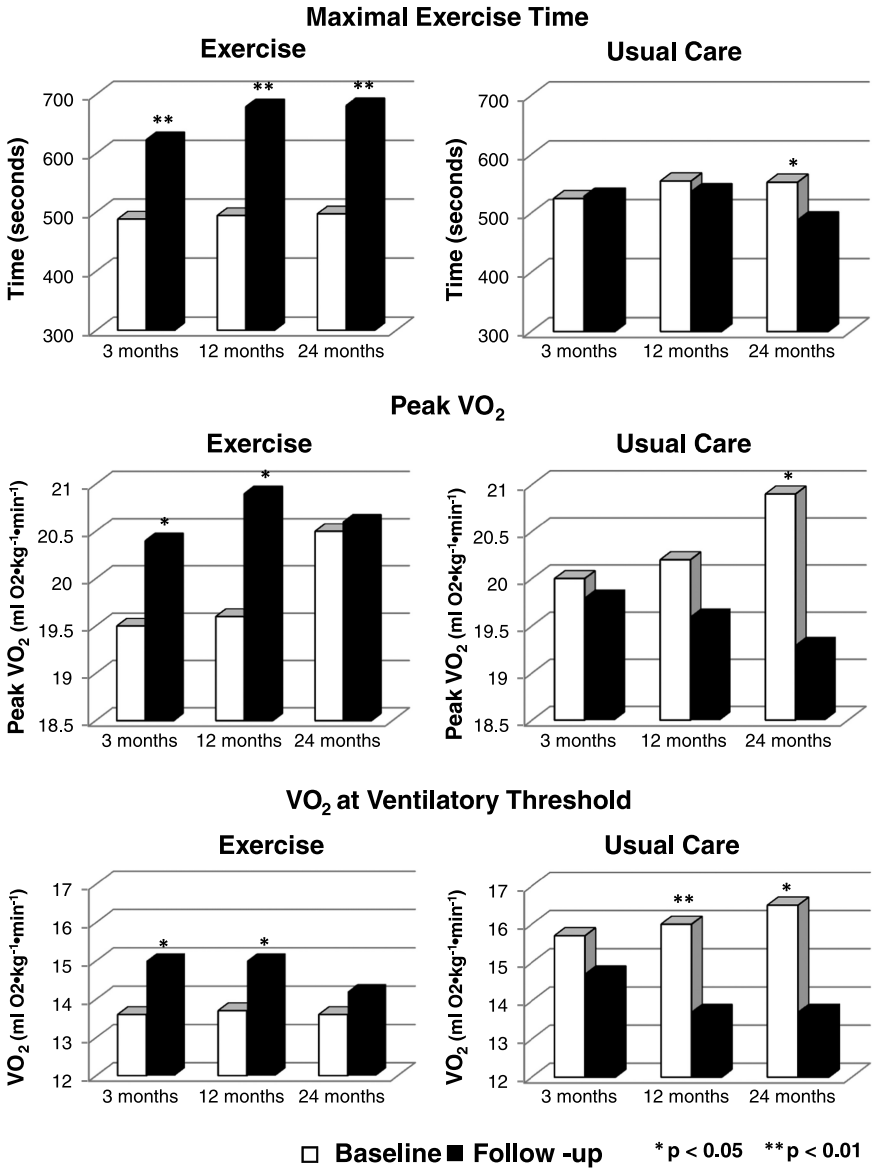

FIGURE 1—Comparisons of maximal exercise time, peak $\dot{V}O_2$, and $\dot{V}O_2$ at the VT in the exercise and usual care groups at 3 months, 1 yr, and 2 yr.

treadmill time at the 3-month, 1-yr, 2-yr, and 3-yr visits, respectively (all $P < 0.001$). Significant improvements were also observed for estimated METs at each evaluation, ranging from 21% to 26% (all $P < 0.001$). There was a significant interaction between groups for both exercise time and estimated METs ($P < 0.001$ and $P = 0.002$, respectively; Fig. 1). Peak $\dot{V}O_2$ was higher among exercise subjects at the 3-month and 1-yr evaluations, whereas peak $\dot{V}O_2$ was generally lower at each evaluation period among usual care subjects. There was also a significant interaction between groups for $\dot{V}O_2$ ($P = 0.02$), exercise time ($P < 0.001$), and estimated METs ($P < 0.001$) at the VT, with increases observed for exercise participants and decreases observed for usual care subjects. HR at a matched submaximal work rate was also significantly reduced in the exercise group, in the range of 7–14 bpm ($P < 0.01$). The $\dot{V}_E/\dot{V}CO_2$ slope was in the normal range at baseline for both groups (≈0.29) and did not change significantly in either group during the study period. Likewise, HR recovery at 1 and 2 min did not differ within or between groups.

Change in maximal AAA diameter. Mean changes in the primary outcome, maximal AAA diameter among matching subjects at 1, 2, and 3 yr, are presented in Table 4. Both groups exhibited overall growth rates of ≈5% per year, and these growth rates were not different between groups. The association between change in exercise capacity and change in AAA diameter at 1 yr is shown in Figure 2. There was a modest inverse association between change in exercise capacity and change in AAA diameter ($r = -0.17$, $P = 0.23$). Similarly, no significant association was observed between change in exercise capacity and change in AAA diameter at the 2-yr evaluation ($r = 0.03$, $P = 0.88$). Growth rates were also similar between groups in the subset of patients with AAA diameters >3.0 at baseline. Multivariate adjustment for baseline fitness, obesity, smoking,

TABLE 4. Mean AAA diameter (cm) in the exercise and usual care groups at 1, 2 and 3 years.

	Baseline	1 yr	95% CI for Change
Exercise	3.47 ± 0.51	3.62 ± 0.56	0.12–0.22
Usual care	3.37 ± 0.51	3.55 ± 0.56	0.15–0.28
Between group $P = 0.76$			
	Baseline	2 yr	95% CI for Change
Exercise	3.41 ± 0.40	3.73 ± 0.43*	0.23–0.39
Usual care	3.34 ± 0.50	3.72 ± 0.56**	0.29–0.47
Between group $P = 0.63$			
	Baseline	3 yr	95% CI for Change
Exercise	3.37 ± 0.46	3.92 ± 0.57**	0.35–0.61
Usual care	3.46 ± 0.60	3.94 ± 0.64**	0.42–0.66
Between group $P = 0.76$			

*$P < 0.05$ vs baseline. **$P < 0.01$ vs baseline.
CI, confidence interval.

statin use, and diabetes did not appreciably influence these associations.

DISCUSSION

The primary aim of the current study was to determine the effects of exercise training on AAA growth rates compared with usual care in subjects with small AAA. After a mean duration of approximately 2 yr of participation, no differences were observed in AAA growth rates between exercise and usual care groups (Table 4). The secondary aim was to determine the safety and efficacy of training in these patients. A salient finding from the current study was the observation that both maximal exercise testing and exercise training up to 3 yr were safe in patients with small AAA; we did not observe any responses serious enough to be considered an "event" by conventional definitions (26). In addition, marked improvements in exercise capacity were observed among exercise participants compared with usual care subjects (Tables 2 and 3). The latter finding is notable given recent efforts to broaden the referral base for cardiac rehabilitation to include nontraditional patients (3,22) and the paucity of such data in patients with AAA.

Change in maximal AAA growth rates. To our knowledge, no previous data are available regarding the effects of exercise training on aneurysm growth rates in patients with small AAA. Exercise training and higher levels of fitness are associated with lower systemic markers of inflammation relevant to AAA disease (15,33), and the possibility that regular exercise might limit AAA growth rate was an important impetus for our study. We observed that the intervention and usual care groups exhibited similar growth rates (Table 4 and Fig. 2). The change in AAA diameter tended to be slightly lower as exercise capacity improved at 1 year (Fig. 2) and the growth rate tended to be slightly lower overall in subjects in the exercise group at 1 and 2 yr (Table 4). The growth rates we observed (0.15–0.24 cm·yr^{-1}) were somewhat lower than those reported by surveillance studies of small AAA performed in the United States and United Kingdom (≈0.26–0.32 cm·yr^{-1}) (23,36). However, since growth rate is strongly dependent on baseline aneurysm size, it should be noted that the earlier trials enrolled patients with larger aneurysms at baseline (≥4.0 vs ≥2.5 cm in the current study) and that participants in the current trial were on average healthier, with a longer life expectancy than expected based on prior natural history studies of patients with early AAA disease (24).

Safety and adverse events. Monitoring by the Data Safety Monitoring Board throughout the trial indicated that no subjects in the intervention arm experienced excessive AAA growth rates. Although three subjects in the exercise group and nine subjects in the usual care group underwent surgical repair after beginning the study ($P = 0.09$), these rates were not unexpected, given the predictable growth rates in AAA and the duration of the study (7). In addition, both maximal symptom/sign-limited exercise testing and exercise training up to 3 yr were safe; during the 5-yr trial, there were no AAA-related symptoms or exercise-related clinical events during home or center-based training. Thus, while data remain limited in terms of the effects of training in patients with AAA, the current findings extend previous results from our group (31) and a pilot study from the UK (13), suggesting that patients with AAA can be safely referred to cardiac rehabilitation programs.

Energy expenditure and exercise capacity. We observed considerable increases in exercise capacity at each evaluation point among patients in the exercise group (Fig. 1), suggesting that the exercise stimulus from the combined rehabilitation center and home-based program was appropriate to achieve a training effect. A great deal of effort was devoted to activity surveillance, including case management, weekly phone calls, and logging of activities, HR, pedometer steps, and perceived exertion during daily activities. The overall mean energy expenditure among subjects in the exercise group was ≈2000 kcal·wk^{-1}, an

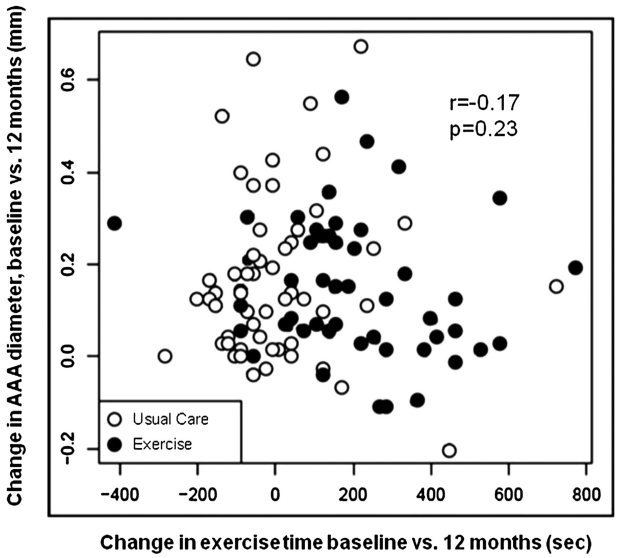

FIGURE 2—The relationship between change in exercise capacity and change in AAA diameter between baseline and 1-yr evaluations.

amount that corresponds to roughly 1 h of modest activity per day. This degree of energy expenditure is unique relative to other randomized trials of exercise training in post–myocardial infarction or heart failure subjects. For example, energy expenditure during typical outpatient rehabilitation programs has been reported to be 250–300 kcal per session (35), resulting in a weekly energy expenditure less than the 1000 kcal·wk^{-1} recommended for favorable changes in cardiovascular health (4). Although our estimates are no doubt higher because we included all recreational energy expenditure reported during a given week, our subjects also had the benefit of case management and continuous encouragement to remain active throughout each week in addition exercising at the rehabilitation center.

The marked improvements in exercise time (≈30%–40%) and estimated METs (20%–25%) after training were considerably higher than those in previous studies, including trials in patients with heart failure and elderly post–myocardial infarction subjects (9,17,32). These comparatively large changes in exercise capacity after training are likely a reflection of the rigorous surveillance and case-managed approach employed. Although significant increases in peak $\dot{V}O_2$ were observed at the 3-month and 1-yr evaluations, improvements in peak $\dot{V}O_2$ were relatively modest in comparison with exercise time and estimated METs. It is noteworthy that peak $\dot{V}O_2$ decreased significantly at the 2- and 3-yr evaluations among usual care subjects, suggesting that training may have prevented functional deterioration in these elderly patients with vascular disease. The greater response in treadmill time and estimated METs compared with measured $\dot{V}O_2$ is common after exercise training and is explained in part by the fact that these indices tend to increase due to habituation, greater efficiency of walking, and greater dependence on nonoxidative metabolism during exercise on follow-up testing (29). The comparatively modest increase in peak $\dot{V}O_2$ has been demonstrated in other elderly populations, particularly those with heart failure (9,17,32).

We also assessed other markers of the training response, including HR at a matched submaximal work rate, which decreased significantly in response to training at each evaluation point (Table 2). The reduction in submaximal HR is a well-recognized response to training in patients with cardiovascular disease and is indicative of an alteration in autonomic balance, resulting in the ability of the heart to achieve a similar cardiac output at a lower myocardial oxygen demand. We did not observe any changes in the $\dot{V}_E/\dot{V}CO_2$ slope, although a change in this index was not expected given the relatively normal ventricular function and normal baseline $\dot{V}_E/\dot{V}CO_2$ slope in our sample. A significant group/test interaction occurred for $\dot{V}O_2$ at the VT ($P < 0.02$), although this was in part due to the reduction observed among usual care subjects. This adaptation is beneficial in that lactate accumulation is widely known to be associated with metabolic acidosis, impaired energy production, hyperventilation, altered O_2 kinetics, and an impaired capacity to perform work (27). Similar to maximal exercise, the modest changes in $\dot{V}O_2$ at the VT were contrasted by marked improvements in exercise time and estimated METs at this point (Table 3), and these changes were most notable early in the training program.

Only one other group to our knowledge has assessed the effects of training in AAA. Kothmann et al. (21) recently studied 30 patients with small AAA randomized to either a 7-wk exercise intervention program or usual care. Baseline and posttraining exercise tests were only performed up to the VT due to safety concerns. After 7 wk of moderate intensity training, a 10% improvement in $\dot{V}O_2$ at the VT was observed in the exercise group, whereas control subjects remained unchanged. Although this represented a statistically significant increase, it did not reach the level of improvement the investigators defined *a priori* as clinically significant (≥2.0 mL O_2·kg^{-1}·min^{-1}). The effect of the program on maximal exercise capacity is unknown because the subjects were tested only to the VT. One adverse event was reported during exercise training, an incident of ventricular fibrillation that was successfully resuscitated. We similarly observed ≈10% improvements in $\dot{V}O_2$ at the VT at 3 months and 1 yr, which were slightly less than the 2.0-mL O_2·kg^{-1}·min^{-1} threshold designated as clinically significant by Kothmann et al. (21).

Limitations. The current study was part of a randomized trial, in which we had the luxury of monitoring patients more intensively than a typical rehabilitation program. Whether our results apply to more typical outpatient programs is unknown. The study was designed such that subjects participated in training for at least 1-yr and up to 3-yr, and differences in duration of participation may have influenced the study results. Although we demonstrated modest improvements in peak $\dot{V}O_2$, the major training response was observed using the less precise measure, exercise time. Our findings are largely applicable to males because 93% of the sample was male; this is a reflection of the four- to fivefold higher prevalence of AAA in males (19).

Summary. These results suggest that a program of exercise training did not influence AAA growth rates in patients with presurgical AAA. However, these data support the safety and efficacy of exercise training in patients with small AAA, a population for which few previous data are available. The center-based and home exercise program was effective in significantly improving conventional measures of exercise capacity, and no AAA-related or other adverse events occurred during testing or training. By improving functional status, exercise-based rehabilitation can play a role in the management of patients with early AAA disease.

This study was submitted on behalf of the Stanford AAA Specialized Center of Clinically Oriented Research Program Investigators and was funded by the National Heart, Lung, and Blood Institute.

Clinicaltrials.gov identifier: NCT00349947.

The authors have no conflicts of interest to report.

The results of this study do not constitute an endorsement by the American College of Sports Medicine.

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