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European Journal of Cardiovascular Prevention & Rehabilitation published online 8 February 2011
DOI: 10.1177/1741826710389384

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Cardiopulmonary exercise testing in small abdominal aortic aneurysm: profile, safety, and mortality estimates

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(on behalf of the Stanford AAA SCCOR Investigators)

European Journal of Cardiovascular
Prevention & Rehabilitation
0(00) 1–8
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Cardiology 2011
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DOI: 10.1177/1741826710389384
ejcpr.sagepub.com



Abstract

Aim: Few data are available regarding exercise testing in patients with abdominal aortic aneurysm (AAA) disease. The purpose of this study was to evaluate safety and to characterize the hemodynamic and cardiopulmonary (CPX) response to exercise in a large group of patients with AAA.

Methods: Three hundred and six patients with AAA ≥ 3.0 to ≤ 5.0 cm (mean 72 ± 8 years) underwent CPX as part of a randomized trial of exercise training. CPX and hemodynamic responses, ischemic events, rhythm disturbances, and risk estimates based on treadmill scores were quantified and compared to an age-matched group of 2155 veterans referred for exercise testing for clinical reasons.

Results: Peak VO_2 was similar between patients with AAA and the referral group (20.0 ± 6 ml/kg/min; 77 percent of age-predicted and 20.3 ± 7 ml/kg/min; 80 percent of age-predicted, respectively). The incidence of exercise-induced hypotension and hypertension was higher in AAA patients versus the referral group (2.9 and 3.6 percent vs < 1.0 percent, $p < 0.001$), but there were no occurrences of ventricular tachycardia (≥ 3 beats) or other serious events in the AAA subjects. The Duke Treadmill Score and VA Treadmill Scores, which estimate annual cardiovascular events and all-cause mortality, respectively, were similar between groups.

Conclusions: Patients with AAA have a slightly higher incidence of hyper- and hypotensive responses to exercise than age-matched referrals, but no serious events related to CPX occurred. AAA patients can undergo maximal CPX safely and have risk scores based on treadmill test results that are similar to age-matched referral subjects. These findings extend recent studies using sub-maximal evaluations to stratify risk in patients considered for surgery, and support the routine use of exercise testing for risk evaluation and the functional assessment of patients with AAA.

Keywords

Abdominal aortic aneurysm, exercise testing, maximal oxygen uptake

Received 12 April 2010; accepted 25 July 2010

Introduction

Abdominal aortic aneurysm (AAA) is the 13th leading cause of death in the US, and is the third cause of sudden death in men >60 years of age.^{1,2} The prevalence of AAA is increasing in part due to the aging of the population. Awareness of AAA has increased significantly in recent years through educational campaigns from organizations such as the Vascular Disease Foundation, Aneurysm Outreach, the enactment of the 2007 Screening for Abdominal Aortic Aneurysm Effectively (SAAAVE) Act, and by the recent addition of ultrasound screening to the Medicare program.^{3–5}

Significant advances in the management of AAA have occurred over the last decade, including improvements in endovascular treatment techniques, refinements in

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screening, and trials designed to better define appropriate timing of interventions.^{3,6,7}

Cardiopulmonary exercise testing (CPX) has been shown to have numerous applications in a wide variety of cardiovascular conditions. These applications include assessment of functional capacity, differential diagnosis of cardiovascular and pulmonary limitations, evaluation of disability, and risk stratification.^{8–10} Although advances have occurred in related imaging technologies (e.g. exercise or pharmacologic radionuclide and echocardiographic techniques or computed tomography), the exercise test remains the recommended first-choice modality in the initial evaluation of cardiovascular disease.¹¹ Over the last two decades, a great deal of support has been generated for the use of CPX as a modality to assess the efficacy of therapy, stratify risk, and guide the appropriate use of interventions for a wide range of cardiovascular diseases.^{8–12}

While the CPX could potentially have similar applications in patients with AAA, limited data are available regarding exercise test responses in these patients. Presumably, this is because of limited awareness of AAA until recent years, and the tendency to refer these patients to pharmacologic stress testing because of concerns about safety. For example, while the American Heart Association (AHA) Guidelines on Exercise Testing review the applications of the test in a wide variety of cardiovascular and related conditions, AAA is not mentioned.¹¹ Likewise, exercise testing is not mentioned in the AHA/American College of Cardiology (ACC) Practice Guidelines on Vascular Disease.⁷ To our knowledge, only one study has reported on the safety of exercise testing in AAA.¹³ Since that study was a retrospective review of patient files, it was limited by selection bias because it is likely that most patients with AAA were not referred for the test. Although the CPX has been used to estimate pre- and post-operative risk among patients undergoing vascular surgery in recent years and few events associated with the test have been reported,^{14–16} its role in AAA patients has not been fully explored.

As part of a National Heart, Lung and Blood Institute (NHLBI) sponsored Specialized Center of Clinically Oriented Research Program (SCCOR) in AAA disease at Stanford University, we are conducting a randomized, prospective longitudinal trial to test the ability of supervised exercise training to modify AAA biology and early disease progression. Herein we report baseline data on the characteristics of maximal exercise testing in patients with AAA. By comparing responses of AAA patients to those of age-matched subjects referred for exercise testing for clinical reasons, our goals were to better define the use of CPX in patients

with AAA, determine its safety, and define risk estimates based on CPX data.

Methods

The current analysis is a sub-study of the Stanford AAA SCCOR program in which aortic diameter and AAA risk were quantified as a function of lifetime activity, exercise capacity, and exercise therapy to limit early disease progression. Data collected through July 2009 were included in this interim analysis.

Subjects and study design

The sample included a subset of participants with aortic diameter between 3.0 and 5.0 cm (63 percent had AAA size ≤ 3.9 cm and 37 percent had AAA size ≥ 4.0 cm) recruited for enrollment in a prospective, randomized trial of exercise therapy to suppress small AAA progression. The current analysis includes preliminary results of 306 exercise tests, derived largely from baseline visits among subjects considered for the larger 3-year exercise trial. Inclusion and exclusion criteria for the study are listed in Table 1. Subjects were recruited from Stanford University Medical Center, the Veterans Affairs Palo Alto Health Care System (VAPAHCS), and Kaiser Permanente of Northern California. Recruitment procedures and all study-related activities were reviewed and approved in advance by Institutional Review Boards (IRBs) at Stanford University (including VAPAHCS) as well as the Kaiser Permanente Division of Research and an independent Data Safety Monitoring Board (DSMB) organized by the NHLBI.

An age-matched group of subjects from the Veterans Exercise Testing Study (VETS) was used as a comparison group. The VETS study is an ongoing, prospective evaluation of subjects referred for exercise testing for clinical reasons at the VA Palo Alto Health Care System. The study addresses exercise test, clinical, and lifestyle factors and their association with health outcomes.^{17,18}

Exercise testing

Standardized medical examinations were performed prior to testing and medications were continued as prescribed. Medical history and drug information from medical records were obtained, questionnaires regarding lifetime physical activity and health history were completed and recorded on the day of the test, and aortic diameter measurement via transabdominal ultrasound was obtained. Symptom-limited exercise testing was performed using an individualized treadmill ramp

protocol as previously described.¹⁹ Protocols were individualized to fall within the recommended 8–12 minute range.^{10,19–21} Electrocardiograms were recorded digitally throughout rest, exercise, and for at least 8 minutes in recovery; blood pressure was determined manually at rest, every two minutes during exercise and at 1, 2, 5, and 8 minutes during recovery or until symptoms, ECG changes, and blood pressure stabilized. Testing was aborted for serious rhythm disturbances, ST segment depression (>2.0 mm horizontal or downsloping), moderately severe chest discomfort (3 on a 1–4 scale), or hyper- or hypotensive responses to exercise.^{11,21} In the absence of clinical indications for stopping, participants were encouraged to exercise until volitional fatigue, and the Borg 6 to 20 perceived exertion scale was used to quantify effort.²² Exercise capacity in metabolic equivalents (METs) was estimated from peak treadmill speed and grade.²¹

Ventilatory expired gas analysis was performed using a CosMed Quark b² metabolic system (Rome, Italy). Before each test, the equipment was calibrated in standard fashion using reference gases. Minute ventilation (VE, BTPS), oxygen uptake (VO₂, STPD) and carbon dioxide output (VCO₂, STPD) were acquired breath-by-breath, averaged over 30 seconds, and reported in rolling 10-second intervals.⁹ Peak VO₂ and peak respiratory exchange ratio (RER) were expressed as the highest averaged samples obtained during the exercise test. Determinations of the VE/VCO₂ slope ($y=mx+b$, m =slope) and the oxygen uptake efficiency slope

(OUES) ($VO_2 = a \log_{10} VE + b$)⁹ were available only among subjects with AAA. The percentage of age- and gender- predicted peak VO₂ was expressed using the equations of Wasserman et al.,¹² which consider height, weight, gender, and exercise mode.

Abnormal responses to exercise were classified using standard definitions.^{10,21} An exercise test exhibiting ≥ 1.0 mm horizontal or downsloping ST depression, exercise-induced chest pain, or both, was considered positive for ischemia. Exercise-induced hypotension was considered a decrease in systolic blood pressure >10 mmHg after an initial rise during exercise. Exercise-induced hypertension was defined as a systolic blood pressure >240 mmHg. Ventricular tachycardia was defined as ≥ 3 consecutive premature ventricular contractions. The Duke Treadmill Score (DTS) was calculated as: (exercise time) – 5 x (maximum ST segment deviation) – 4 x (treadmill angina index).²³ The treadmill angina index was scored from no angina to 2, in which no angina represents exercise-induced angina; 1 represents non-limiting angina; and 2 represents exercise-limiting angina. MET level achieved on the individualized ramp protocol was converted to time on the Bruce protocol when calculating the DTS.²⁴ The VA Treadmill Score was determined by: 5 x (CHF/digoxin + ST depression in mm) + (SBP change score) – (METs), where CHF = chronic heart failure; CHF/digoxin is coded as yes = 1; SBP = systolic blood pressure; and the SBP change score is scored as: 0 points: increase >40 mmHg; 1 point: increase 31–40 mmHg;

Table 1. Inclusion and exclusion criteria for exercise trial participation

Inclusion criteria:

1. Male or female patients with small AAA <5.0 cm in size
2. Ages 50–85 and ambulatory

Exclusion criteria:

1. Inability or unwillingness to complete exercise training for 3 years or a life expectancy of less than 5 years
2. Inability to participate in an exercise stress test or inability to exercise consistently because of orthopedic or musculoskeletal problems
3. Morbid obesity (BMI >39)
4. Weight gain or loss of 20 lb over the past three months
5. History of severe liver disease (INR >2, serum albumin <3.0 mg%, jaundice)
6. Unstable angina
7. Uncontrolled atrial fibrillation, defined as mean 24 h heart rate >85 beats/min, or 24 h maximal ventricular rate >150 beats/min; and uncontrolled ventricular arrhythmias, defined as recurrent ventricular tachycardia >3 beats in succession, or 24 h PVC count >20%
8. Critical aortic stenosis (peak systolic pressure gradient of >50 mmHg with an aortic valve orifice area of 0.75 cm² in an average size adult)
9. Class III/IV heart failure and/or ejection fraction <20%
10. Active pericarditis or myocarditis
11. Any embolism within the past 6 months
12. Thrombophebitis
13. Hospitalized due to an infectious disease within the past three months
14. Pulmonary disease with a drop in O₂ sat with exercise to 90% without oxygen

2 points: 21–30 mmHg; 3 points: increase 11–20 mmHg; 4 points: 0–11 mmHg; 5 points: reduction below standing SPB obtained before testing.²⁴ Both scores were expressed as estimated annual mortality.

Statistical analysis

Data are presented as mean \pm SD or as percentages. Comparisons between patients with AAA and VA referral subjects were made using unpaired *t*-tests for continuous data or chi-squared analyses for binary data.

Results

Clinical and demographic characteristics in AAA subjects and VA referral subjects are presented in Table 2. The groups were similar in terms of age and BMI, and both groups were 98 percent male. The AAA group was 82 percent Caucasian, 5 percent African-American, and 5 percent Hispanic, whereas the respective ethnicities were 78 percent, 7 percent, and 8 percent in the VA sample. Coronary artery disease, history of myocardial infarction, hypertension, and diabetes were higher in VA referral subjects compared to AAA patients. Use of medications, including statins, beta blockers, and ACE inhibitors was higher in AAA patients.

Exercise test responses for the two groups are presented in Table 3. Significant but minor differences were observed between groups in resting heart rate and

blood pressure. Respiratory exchange ratios of 1.10 and 1.09 were observed for AAA patients and VA referrals, respectively ($p=0.38$), suggesting that maximal efforts were achieved by both groups. Peak heart rate did not differ between groups; both groups achieved roughly 80 percent of their age-expected values using normative values developed by the VA.²⁵ Peak VO_2 was similar between VA referrals and AAA subjects (20.3 ± 7.3 and 20.0 ± 6.3 ml/kg/min, respectively; $p=0.54$), representing 77.4 ± 24 percent and 79.5 ± 29 percent when expressed as percentages of age- and gender-predicted values ($p=0.47$). While both groups achieved peak estimated MET values close to the age-expected normal standard, AAA subjects were slightly higher than VA referral subjects (96 vs 90 percent; $p=0.002$). Patients with AAA demonstrated a VE/VCO_2 slope of 0.30 ± 0.04 .

Hyper- and hypotensive responses occurred more frequently in AAA patients, but were rare in both groups. There were no occurrences of ventricular tachycardia in AAA patients, whereas the test was terminated for this reason in 1.5 percent of VA referrals. All occurrences of ventricular tachycardia were non-sustained and normalized spontaneously. Ischemic changes, including significant ST changes and exercise-induced angina, occurred more frequently in referral subjects compared to AAA subjects. Both the Duke and the VA Treadmill Scores were more abnormal in VA subjects, but annual risk estimates were similar between groups for both scores (≈ 3 percent for the Duke Score and ≈ 2.5 percent for the VA Score).

Table 2. Clinical and demographic characteristics in AAA subjects and VA referral subjects

Variables	AAA subjects (N = 306)	VA referrals (N = 2155)	p-value
Age	72 \pm 7.5	72 \pm 5.2	0.45
Height	69.6 \pm 3.2	68.8 \pm 3.3	0.007
Weight	194.2 \pm 27.8	186.6 \pm 33.6	0.01
BMI	28.2 \pm 4.1	27.7 \pm 4.6	0.45
Gender (% male)	98.4	97.6	0.93
Clinical history			
Coronary artery disease (%)	10.8	24.3	<0.001
Myocardial infarction (%)	5.9	13.2	<0.001
Hypertension (present) (%)	28.4	62.3	0.02
Currently smoking (%)	15.3	17.5	0.43
Pack years	32.9	23.9	<0.001
Diabetes (%)	7.8	17.5	<0.001
Maximal aortic diameter (cm)	4.3 \pm 1.3	–	–
Medications			
Statins (%)	80	15.5	<0.001
Beta-blockers (%)	42.1	23.4	<0.001
ACE/ARB (%)	44.8	27.8	<0.001

Table 3. Comparison of exercise test responses between patients with AAA and subjects referred for exercise testing for clinical reasons

Variables	AAA subjects (N = 306)	VA referrals (N = 2155)	p-value
Rest			
Heart rate (beats/min)	63 ± 11	70 ± 13	<0.001
Systolic blood pressure (mmHg)	132 ± 15	138 ± 20	<0.001
Diastolic blood pressure (mmHg)	75 ± 9	79 ± 20	<0.01
Maximal exercise			
Heart rate (beats/min)	127 ± 23	129 ± 22	0.13
Systolic blood pressure (mmHg)	184 ± 30	176 ± 27	<0.001
Diastolic blood pressure (mmHg)	80 ± 13	84 ± 26	<0.01
Perceived exertion	18.6 ± 1.4	16.7 ± 2.3	<0.001
Respiratory exchange ratio	1.10 ± 0.11	1.09 ± 0.15	0.38
Oxygen uptake (ml/kg/min)	20.0 ± 6.3	20.3 ± 7.3	<0.54
Estimated oxygen uptake (METs)	7.0 ± 2.6	6.4 ± 2.7	<0.001
Predicted VO ₂ ^a (%)	77.4 ± 24	79.5 ± 29	0.47
Predicted estimated METs ^b (%)	96 ± 36	90 ± 37	0.002
Reasons for stopping			
Hypotensive response (%)	2.9	0.19	<0.001
Hypertensive response (%)	3.6	0.65	<0.001
Ventricular tachycardia (≥3 beat run, %)	0	1.5	–
Claudication (%)	8.4	3.7	<0.001
Ischemic changes			
ST depression ≥1.0 mm (%)	11.1	36.6	<0.001
Angina (%)	1.6	10.7	<0.001
Prognostic scores			
Duke score (annual mortality)	4.7 ± 5 (3.1%)	1.6 ± 6 (3.5%)	<0.001
VA score (annual mortality)	–5.6 ± 3 (2.5%)	–4.1 ± 4 (2.5%)	<0.001

^aUsing equations from Wasserman et al.¹² ^bFrom normal standards derived from healthy VA referrals (Morris et al.²⁵)

Discussion

While the exercise test is recognized as having a great deal of value for assessing disability, stratifying risk, and evaluating therapy in a wide spectrum of cardiovascular conditions,^{8,9,11,21} specific applications for patients with AAA are lacking. Thus, there are several practical applications related to documenting the cardiopulmonary response to exercise in AAA. First, limited data exist on the use of exercise testing to risk stratify patients with AAA either during surveillance of small AAAs or in the pre- or post-operative functional evaluation of these patients. Second, regular exercise has been recommended in AAA because it has the potential to favorably affect AAA disease progression through direct influences on aortic hemodynamic conditions,^{26,27} in addition to the well-documented effects of exercise on inflammatory processes related to vascular health in general^{28,29} and AAA specifically.^{30,31} However, making appropriate activity

recommendations for AAA is difficult given the paucity of available data on the hemodynamic and cardiopulmonary response to exercise in these patients. Third, although functional evaluations have been used for the pre-operative evaluation of potential surgical AAA candidates,^{32–34} these evaluations lack context because few data exist on the expected exercise response of patients with AAA. Finally, the safety of maximal exercise testing in AAA is largely unknown.

One salient finding from the current study was the observation that symptom and/or sign-limited exercise testing is safe in AAA. We did not observe any responses serious enough to be considered an ‘event’ by conventional definitions.³⁵ While the occurrence of hyper- and hypotensive responses were slightly higher in AAA subjects than those among age-matched VA referrals (Table 2), the incidence of these responses was similar to other studies in subjects referred for exercise testing for clinical reasons.³⁶ Notably, there were no instances of sustained or non-sustained ventricular tachycardia in the AAA subjects. This contrasts

with: the incidence rate of 1.5 percent in age-matched subjects referred for exercise testing for clinical reasons (Table 2); an incidence rate of 1.0 percent previously reported by our lab³⁷ and rates ranging from 0.08 to 1.1 percent reported elsewhere.³⁸ The current study reflects baseline responses among AAA patients enrolled in a large 3-year randomized trial on the effects of exercise training on AAA progression. While the effects of training on physiological responses to exercise and AAA size will be the focus of future analyses, it is noteworthy that there have been no hemodynamic, arrhythmic, or other events related to in-house or home exercise training at this stage of the study.³⁹

Guidelines on exercise testing and training have generally not addressed patients with AAA, most likely due to the fact that AAA was not as widely recognized in the past as it is today, and the fact that little is known about exercise testing and physical activity in this population. One publication suggested that individuals with AAA should not undergo maximal exercise testing, that heart rate should not exceed 100 beats/min, and that excessive rises in double-product (systolic blood pressure x heart rate) be avoided due to concerns about the potential for rupture.⁴⁰ Pre-operative risk assessments in AAA have largely employed pharmacologic stress with dobutamine, ostensibly to avoid an excessive rise in systolic blood pressure.⁴¹ However, these limitations have been based on intuition rather than known risks associated with exercise in AAA. The ACC/AHA Practice Guidelines for the Management of Patients with Peripheral Vascular Disease⁷ suggest that it is unnecessary for AAA patients to be fearful of vigorous activity, and that efforts should be made to improve fitness in the event that surgery is required. In fact, moderate exercise has been shown to partially reverse the hemodynamic conditions associated with development of atherosclerosis in AAA,^{26,27} although the effects of more strenuous or sustained exercise on flow hemodynamics in AAA are largely unknown. To our knowledge, only one previous study has assessed the safety of maximal exercise testing in patients with AAA. Best et al.¹³ retrospectively evaluated 262 patients with AAA diameter >4.0 cm who had undergone exercise testing at the Mayo Clinic. One patient with a 6.1 cm diameter aneurysm was reported to have a rupture 12 hours after the exercise test. While this event may or may not have been related to the exercise test, this yielded a rupture rate of 0.4 percent. No other negative outcomes were associated with the maximal exercise tests in this sample. While there are a small number of recent reports using exercise or pharmacologic stress to risk stratify patients with AAA,^{16,34,42,43} none to our knowledge have reported on adverse events. It should be noted that by definition the patients in our trial had 'small' AAA (below the

threshold for surgical repair); thus, our results may not apply to patients with larger AAAs undergoing surgical repair for pre-operative risk assessment.

Subjects with AAA achieved an exercise capacity commensurate with 77 percent of the age-expected measured peak VO_2 ,¹² and 90 percent of the age-expected estimated MET level using normal standards derived from a healthy VA population.²⁵ These responses were similar to the larger sample of VA referral subjects (Table 2), and suggest that AAA is associated with a modest reduction in exercise tolerance. Given the similarity between AAA subjects and VA referrals, this reduction is unlikely to be related to AAA *per se*, but rather to the many co-morbidities common in these subjects that adversely impact exercise capacity (obesity, diabetes, lack of activity, etc). Documenting fitness levels in AAA subjects may be important given that pre-operative fitness levels have been associated with higher survival rates in individuals undergoing both cardiac^{9,14,16,34} and non-cardiac surgery.^{14,15} Both the VE/VCO_2 slope and ratio are CPX responses that have been increasingly recognized as powerful markers of risk, particularly in chronic heart failure, but also in the elderly, obese, and other conditions.⁹ Carlisle and Swart³⁴ recently evaluated 3-year mortality risk in a group of patients undergoing open AAA repair, and observed that the VE/VCO_2 ratio during exercise was the strongest predictor of 3-year mortality risk when compared to other clinical and exercise test variables, including AAA size. In the current study, this response was surprisingly normal, suggesting that the majority of these patients do not exhibit overt impairment in cardiac output, ventilation/perfusion mismatching, chemo- or muscle receptor sensitivity, or elevated pulmonary pressures in response to exercise.⁹ Again, our sample had early AAA disease (3–5 cm) and may not be directly comparable to other groups of AAA patients considered for surgery.

Treadmill scores, which incorporate clinical and exercise test responses, have been demonstrated to improve the diagnostic and prognostic characteristics of the test, and are widely recommended by guidelines as adjuncts to the exercise test to improve its clinical utility.¹¹ The Duke Treadmill Score (DTS) is the most widely used score and has been validated in patients referred for exercise testing for clinical reasons as well as many other populations (healthy subjects, women, the elderly, and others).²³ Estimates of cardiovascular events based on the DTS in the current study were significantly lower in AAA subjects compared to the age-matched referral subjects (3.5 vs 3.1 percent), although both event rates were within the age-expected range for 72-year-old individuals in the US.⁴⁴ The VA score has likewise been used in various populations undergoing exercise testing, and is a more population-specific score

that has been shown to outperform the DTS in Veterans.²⁴ We observed that annual mortality estimates from the DTS and VA scores were similar (2.5 percent). Compared to the DTS, the VA score puts less weight on ST-segment changes and, therefore, may be more appropriate to estimate risk in patients with AAA since fewer ischemic responses would be expected in these subjects. To our knowledge, however, there are no large studies that have followed AAA subjects for outcomes in the context of exercise testing, and therefore the extent to which these estimations can be applied to AAA is unknown. Nonetheless, these estimates based on clinical and exercise test data suggest that AAA subjects have cardiac event risks (for the DTS) and mortality risks (for the VA Score) that are similar to age-matched referrals without AAA disease. With extended funding, these scores could be validated in our cohort by following patients for longer-term health outcomes.

Conclusion

AAA patients undergo maximal CPX safely and have prognostic scores based on treadmill test results that are similar to age-matched referral subjects. Patients with AAA have a slightly higher incidence of hyper- and hypotensive responses to exercise than age-matched referrals, but no serious events related to CPX occurred. These findings have applications for the routine use of exercise testing for the functional evaluation of patients with AAA, for prescribing exercise, and they extend recent studies using maximal^{13,34} and sub-maximal^{42,43} evaluations to stratify risk in AAA patients considered for interventions.

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