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Exercise capacity is the strongest predictor of mortality in patients with peripheral arterial disease

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Abstract

Objective—The objective of this study was to assess the predictive value of clinical and exercise test variables in patients with peripheral arterial disease (PAD).

Methods—725 PAD patients referred for exercise testing at the Palo Alto Veterans Hospital between 1997 and 2011 were subjected to a customized symptom-limited ramp treadmill protocol. Detailed clinical and exercise test data were collected at baseline and patients were followed for a mean of 11.3±6.3 years.

Results—During follow up, there were 364 deaths. Baseline exercise capacity was 7.0±2.6 Metabolic equivalents (METs) among survivors and 5.5±2.4 METs in those who died (P<.001). Although several physiologic parameters differed between survivors and non-survivors, age-adjusted Cox regression revealed that exercise capacity was the strongest independent predictor of mortality. Each additional MET achieved was associated with age-adjusted 18% and 20% reductions in all-cause and cardiovascular mortality, respectively (P<.001 for both). This variable surpassed all classical risk factors (including smoking and history of congestive heart failure) as well as all measured exercise test responses (including symptoms and ECG abnormalities).

Conclusions—Amongst PAD patients, reduced exercise capacity is the most powerful harbinger of long term mortality. This factor has predictive power beyond traditional risk factors and confirms the critical importance of fitness in this cohort.

Keywords

Peripheral artery disease; PAD; exercise; stress test; MET; survival

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Introduction

Recent efforts have focused on identifying improved prognostic indicators for patients with atherosclerotic disease. The aim of this approach is to identify those who stand to benefit the most from aggressive risk factor reduction and directed therapies. Exercise testing has been an area of intense focus, given its relatively low cost, non-invasive nature, and ability to provide prognostic information beyond traditional risk factor assessment [1]. In a number of recent studies, exercise capacity has been a particularly powerful predictor of mortality and other adverse events. In elderly subjects, those with hypertension, and those that are obese, exercise capacity has in fact been shown to be the strongest predictor of both all-cause and cardiovascular mortality[2–4]. Remarkably, this single variable provided more prognostic information than each of the classical risk factors or even the Framingham risk score [4]

To our knowledge, the association between survival and exercise capacity during standardized treadmill exercise testing has not been evaluated in patients with PAD. Accordingly, we aimed to study the association between simple physiological parameters and long term survival in a large cohort of PAD patients from the Veterans Exercise Testing Study (VETS). Ultimately, our goal was to define exercise test parameters which could identify patients at risk, compare these to traditional risk factors and provide important prognostic information to subjects with vascular disease.

Methods

The VETS cohort is an ongoing, prospective evaluation of veteran subjects referred for exercise testing for clinical reasons, designed to address exercise test, clinical, and lifestyle factors and their association with health outcomes [2,5,6]. From the VETS cohort, a list of approximately 10,000 male veterans who had undergone a maximal treadmill test for clinical reasons at the VA Palo Alto Health Care System between 1997 and 2011 for clinical indications was formed. This list was used to query the VA computerized database to identify patients with a history of PAD entered at the time the exercise test was performed. A total of 725 subjects were identified as having PAD by history, by claudication during their exercise test, or both. Historical information that was recorded at the time of the exercise test included previous MI by history or Q wave, cardiac procedures, heart failure, hypertension, hypercholesterolemia (>220 mg/dl), intermittent claudication, chronic obstructive pulmonary disease, cancer, end stage renal disease, diabetes, stroke, smoking status (current, past), and use of cardiac medications (categorical only, anticoagulants were not differentiated).

The current study evaluated only data available at the baseline visit as part of a clinically-referred exercise test and the association of these data with cardiovascular and all-cause mortality. Clinical and historical variables were defined in a standard fashion through a history and physical performed at the time of the test by a cardiology fellow, and this historical information was confirmed by computerized records. The exercise test interpretation was over-read by an attending physician.

Exercise testing

Patients underwent symptom-limited treadmill testing using an individualized ramp treadmill protocol such that test duration was targeted to fall within the recommended 8–12 minute range, as previously described [1,7]. Electrocardiograms (ECGs) were obtained at rest, each minute during exercise, and for at least 8 minutes during recovery; blood pressure was measured at rest, every minute during exercise and at 1, 2, 5, and 8 minutes during recovery or until symptoms, ECG changes, and blood pressure stabilized. Standard criteria for termination were employed, including moderately severe angina, >2.0 mm abnormal ST depression, a sustained drop in systolic blood pressure or serious rhythm disturbances. 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 degree of effort[8,9]. Blood pressure was taken manually and exercise capacity (in metabolic equivalents [METs]) was estimated from peak treadmill speed and grade[10]. No test was classified as incomplete or indeterminate, medications were not withheld, and age-predicted maximal target heart rates were not used as end points. The exercise tests were performed, analyzed and reported using a standard protocol incorporating a computerized database with all definitions and measurements prospectively defined [11].

Outcomes

The main outcome variable was all-cause mortality; cardiovascular death was also recorded. The California Health Department Service and Social Security Death Indices were used to ascertain the vital status of each patient as of December 31, 2011. Accuracy of deaths was reviewed by two clinicians blinded to exercise test results and confirmed using the Veterans Affairs computerized medical records.

Statistical Analysis

NCSS software (Kayesville, Utah) was used for all statistical analyses. Unpaired t-tests were used for comparisons of continuous variables, and chi-square tests were used to compare dichotomous variables between patients who survived and those who died. Cox proportional hazards analysis was performed to determine which clinical and exercise test variables were independently associated with all-cause and cardiovascular death. Survival analyses were adjusted for age. Hazard ratios were calculated along with their 95% confidence intervals. Receiver-operating-characteristic (ROC) curves were constructed to determine the discriminatory accuracy of exercise capacity and other key variables to predict survival. An exploratory univariate survival analysis was initially performed, and the strongest univariate predictors of risk were entered into a step-wise multivariate analysis. Kaplan-Meier curves were constructed to assess overall survival with time, and to compare survival among subjects with high and low exercise capacity. The log-rank test was used to compare Kaplan Meier curves.

Results

The sample included all 708 males and 17 females PAD patients. Their mean age was 62.0±9.1 years. The mean follow up period was 11.3 years (SD±6.3) and there were 364 deaths (50.2% of the total sample) for an average annual mortality of 4.4%; 36.3% of the deaths were due to cardiovascular causes. Baseline demographic variables, clinical history, and medications in the entire cohort and between those who survived and those who died are presented in Table 1.

A comparison of exercise test responses between those who died and those who survived is presented in Table 2. Maximal heart rate (130± 21 vs. 122± 23, $p<0.001$) and exercise capacity (7.0±2.6 versus 5.5±2.4 METs, $p<0.001$) were higher among those who survived, while the proportion of subjects with an abnormal resting ECG was higher among those who died (34.3 vs. 56.9%, $p<0.001$). A higher proportion of non-survivors was limited by claudication, experienced rhythm abnormalities, and had a hypotensive response to exercise. However, ischemic responses were similar between groups.

Univariate predictors of all-cause mortality were age, exercise capacity, pack-years of smoking, history of heart failure, maximal heart rate, and maximal systolic blood pressure. Age-adjusted multivariate proportional hazards analysis for both all-cause and cardiovascular mortality as the outcome is presented in Table 3. Exercise capacity was the strongest predictor of all-cause mortality (hazard ratio [HR] 0.83, 95% CI 0.79–0.88, $p<0.001$; area under the ROC curve 0.64). Exercise capacity remained the strongest predictor when adjusted for age (HR 0.85, 95% CI 0.81–0.90, $p<0.001$). The only other predictors of all-cause mortality were pack-years smoking (HR 1.01, 95% CI 1.0–1.01, $p=0.001$) and history of heart failure (HR 1.92, 95% CI 1.34–2.76, $p<0.001$; area under the ROC curve 0.54). Similarly, the strongest predictor of cardiovascular mortality was exercise capacity; an age-adjusted 20% reduction cardiovascular mortality was observed for each MET achieved. The only other predictors of cardiovascular mortality were age and history of heart failure.

Figure 1 illustrates overall survival across the follow-up, and compares subjects who achieved <5 METs and ≥5 METs for exercise capacity. Survival among those achieving ≥5 METs was significantly better than those with lower exercise capacity $p<0.001$). Age-adjusted relative risks for cardiovascular and all-cause mortality based on quartiles of exercise capacity are presented in Figure 2. For both outcomes, relative risks decreased as exercise capacity increased (p for trend <0.001); the greatest outcome benefits were observed between the least fit group (<4 METs) and quartiles two and three (4–6 and 6–8 METs, respectively), while the two highest-fit quartiles had similar mortality rates.

Discussion

In this report, we show for the first time that total exercise capacity, defined as METs achieved during a treadmill exercise test, is the strongest predictor of survival among clinical and exercise test variables in a large cohort of patients with PAD. We observed that this factor predicts both cardiovascular as well as all-cause mortality, and is independent of other traditional risk factors and measured exercise parameters. Similar to patients with other forms of cardiovascular disease [3], we observed an age-adjusted 17% reduction in total mortality, and an age-adjusted 20% reduction in cardiovascular mortality with each additional MET achieved on a treadmill test. To our knowledge, the prognostic value of this exercise test parameter has not previously been reported in patients with PAD, and these findings support the routine use of exercise capacity when evaluating these patients.

Several prior studies have documented a therapeutic role for exercise in PAD [12–14], but few have assessed the role of exercise capacity as a prognosticator in this patient population. de Liefde and colleagues previously reported that a hypertensive response to exercise was associated with adverse outcomes in PAD patients [15]. However, this study employed a single stage submaximal test, and did not assess maximal exercise capacity. In the current study, a hypertensive response to exercise was not found to be a predictive factor. McDermott and colleagues recently showed that several office-based measures of walking could predict survival [16,17], but they did not directly assess overall fitness or exercise capacity, parameters that have been shown to be highly predictive in other cohorts, including patients suspected of having coronary disease, patients with heart failure, and normal subjects [1–6,18]. Herein we observed that simply moving from the lowest quartile of cardiovascular fitness into the next lowest category was associated with 20–30% reductions in cardiovascular and all-cause mortality. From an epidemiological perspective, this association between a modest difference in fitness level and higher rates of survival is quantitatively greater than the benefits derived from the best known interventions for PAD. In fact, exercise capacity was superior to all other factors measured in the current study. Based on the significant prognostic power of this single variable, we believe that exercise capacity should be given as much consideration as traditional risk factors, especially when considering the likelihood of long term survival in the PAD patient.

Our results are consistent with recent evidence that has linked PAD to a lifetime of physical inactivity. It is well known that the sedentary state is a risk factor for major adverse cardiovascular events [2,19]. Individuals with PAD are known to be relatively sedentary, and it has been assumed that the limitations of impaired limb perfusion were responsible for their reduced physical activity. However, most patients with PAD do not complain of intermittent claudication[20], which has been attributed in part to their lack of activity. Most recently, we have found in a cohort of 1381 individuals referred for cardiac catheterization that lifetime physical activity (as assessed by a standardized and validated questionnaire) was positively correlated to the ankle-brachial index [21]. Individuals in the quintile with the least lifetime recreational activity had twice the risk of PAD by comparison to those with the most activity [Notably, the reduction in the prevalence of PAD with increasing activity was not linear; the largest reduction occurred between the group with essentially no recreational activity and the next least active group]. Thus, PAD may in part be a manifestation of the sedentary state[19]. Taken together, it is becoming increasingly clear that identifying those with the lowest exercise capacity is important not only to help predict the presence and severity of PAD, but also to prognosticate the future risk of death.

We did not directly test the hypothesis that raising one’s achievable MET level through exercise training could reclassify a subject into a lower risk category. In addition, fitness is an attribute (not a behavior) that has a strong genetic component [22]. However, physical activity is the only known method for developing overall fitness, and prior studies have shown that supervised exercise training has the added benefit of reducing claudication symptoms and extending walking distance amongst PAD patients [12,13,23]. Future prospective randomized studies are indicated to measure whether exercise programs can not only improve quality of life[14], but also reduce morbidity and mortality in this high risk cohort.

This report has several limitations that warrant consideration. Our cohort was comprised largely of men, and therefore the prognostic utility of exercise capacity in women is not defined. It is worth noting, however, that a recent meta-analysis of exercise testing studies in both men and women showed that achieved METs was equally powerful in healthy subjects of each gender [3]. Also, ankle brachial indices (ABIs) were not recorded at the time of exercise testing, and we therefore could not ascertain an interaction between severity of PAD and the prognostic capacity of the exercise test, although ABI has previously been shown to correlate weakly with pain free walking [24]. Finally, enrollment for this study began nearly 15 years ago and many subjects were prescribed a regimen that would not be considered maximal medical therapy by today’s standards. Thus, it is not clear if a ‘modern’ medical regimen would attenuate the observed association, or if it would continue to have predictive capacity, as reported in other cohorts.

In conclusion, this study shows the prognostic utility of exercise capacity for the patient with PAD. Exercise capacity on a standardized exercise test is more predictive of long term survival than any traditional risk factor or other measured physiologic parameter. These results raise the hope that event-free survival might be increased in these patients by increasing their exercise capacity, and suggest this as an area of future study.

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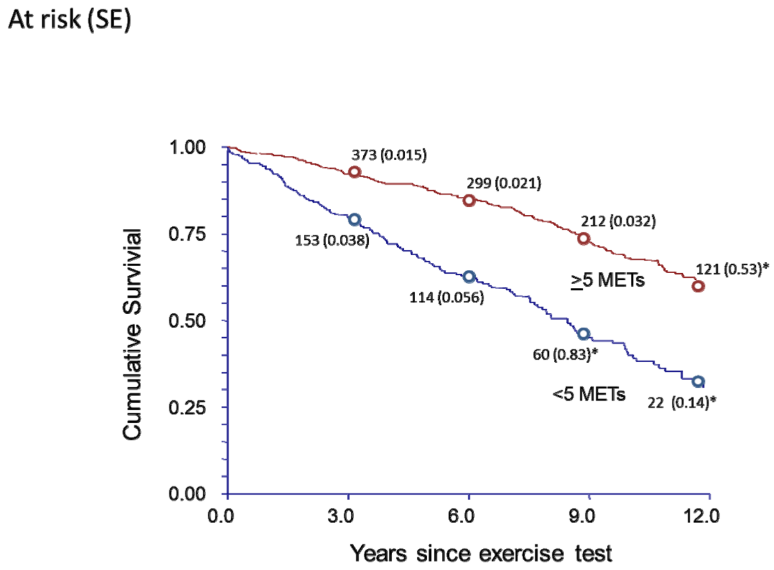

Figure 1.

Kaplan-Meier curve showing cumulative survival among subjects achieving >5 METs and those achieving <5 METs. Numbers given along the curves are patients at risk at each time interval; numbers in parentheses are standard errors (p<0.001 between groups).
*indicates standard error >10%.

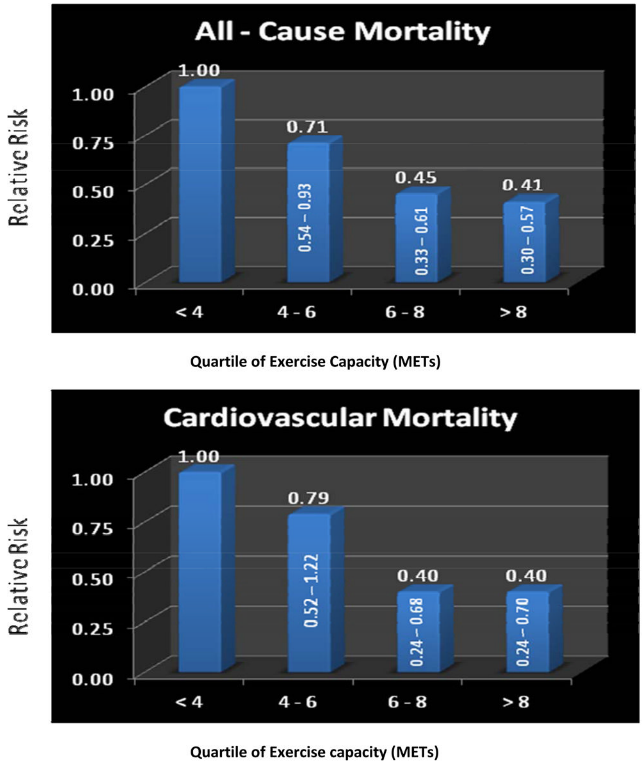

Figure 2.

Relative risks for all-cause (top) and cardiovascular mortality (bottom) based on quartiles of exercise capacity (p for trend < 0.001).

Table 1

Clinical and Demographic Characteristics of the Sample (N±SD of %)

Demographics	**All**	**Survivors**	**Non-survivors**	**p Value**
	n = 725	**n = 361**	**n = 364**	
Age (years)	62.0 ± 9.1	59.5 ± 8.4	64.6 ± 8.4	< 0.001
Follow-up Years	11.3 ± 6.25	15.2 ± 4.8	7.5 ± 5	< 0.001
Height (in)	68.9 ± 3.2	68.8 ± 3.3	69 ± 3.2	0.42
Weight (lbs)	186.8 ± 36.7	191.4 ± 38.5	182.2 ± 34.2	< 0.001
Male	708 (97.7)	350 (97)	358 (98.4)	NS
Female	18 (2.3)	11 (3)	6 (1.6)	NS
Clinical History				
Diabetes	113 (15.6)	59 (16.3)	54 (14.8)	0.58
Hypertension	468 (64.6)	238 (65.9)	230 (63.1)	0.44
Claudication	496 (68.4)	250 (69.3)	246 (67.6)	0.63
Heart Failure	61 (8.4)	16 (4.4)	45 (12.4)	< 0.001
Stroke	49 (6.8)	20 (5.5)	29 (8.0)	0.19
Pulmonary Disease	102 (14.1)	50 (13.9)	52 (14.3)	0.87
Smoking History	486 (67)	259 (71.7)	227 (62.4)	0.007
Pack Years Smoking	32.8 ± 32.3	32.3 ± 30.3	33.3 ± 34.2	0.68
Hyperlipidemia	283 (39)	161 (44.6)	122 (33.5)	< 0.001
Cholesterol (mg/dL)	205.3 ± 54.5	209 ± 57	196.4 ± 47.5	0.16
HDL (mg/dL)	43.4 ± 17.3	42.8 ± 18.8	45.0 ± 13.6	0.47
Medications				
Digoxin	56 (7.7)	21 (5.8)	35 (9.6)	0.05
Beta Blockers	183 (25.2)	103 (28.5)	80 (22)	0.04
Calcium Antagonist	286 (39.4)	130 (36)	156 (42.9)	0.05
Nitrates	239 (33)	93 (25.8)	146 (40.1)	< 0.001
Antihypertensives	233 (32.1)	97 (26.9)	136 (37.4)	0.002
Antiarrhythmics	18 (2.5)	2 (0.6)	16 (4.4)	<0.001
ACE Inhibitors	116 (16)	83 (23)	33 (9.1)	< 0.001
Anticoagulants	172 (23.7)	120 (33.2)	52 (14.3)	< 0.001

Table 2

Exercise Test Responses

Variables	All	Survivors	Non-survivors	p-value
Resting Heart Rate (bpm)	77 ± 15	77 ± 15	77 ± 15	0.99
Resting SBP (mm/Hg)	137 ± 22	135 ± 21	138 ± 23	0.14
Resting DBP (mm/Hg)	80 ± 12	80 ± 12	80 ± 11	0.88
Maximal Heart Rate (bpm)	126 ± 22	130 ± 21	122 ± 23	< 0.001
Maximal SBP (mm/Hg)	175 ± 29	178 ± 28	173 ± 30	0.009
Maximal DBP (mm/Hg)	87 ± 33	86 ± 15	87 ± 44	0.8
Heart Rate Recovery (2 min)	95 ± 21	96 ± 20	89 ± 22	0.25
Exercise Capacity (METs)	6.23 ± 2.6	7.0 ± 2.6	5.5 ± 2.4	< 0.001
Peak Perceived Exertion	17 ± 2	17 ± 2	17 ± 3	0.07
Normal Rest ECG	273 (37.7)	164 (45.4)	109 (29.9)	< 0.001
Abnormal Rest ECG	331 (45.7)	124 (34.3)	207 (56.9)	< 0.001
Reasons for Stopping Exercise[*]				
Angina	149 (20.6)	77 (21.3)	72 (19.8)	0.74
Fatigue	103 (14.2)	66 (18.3)	37 (10.2)	0.001
Shortness of Breath	82 (11.3)	54 (15)	28 (7.7)	0.002
Leg Fatigue	76 (10.5)	48 (13.3)	28 (7.7)	0.01
Claudication	483 (66.6)	227 (62.9)	256 (70.3)	0.03
Other Leg Pain	77 (10.6)	45 (12.5)	32 (8.8)	0.11
Submaximal Target	21 (2.9)	7 (1.9)	14 (3.8)	0.13
Dysrhythmias	61 (8.4)	17 (4.7)	44 (12.1)	<0.001
ST Changes	35 (4.8)	13 (3.6)	22 (6)	0.12
Other Chest Pain	12 (1.7)	8 (2.2)	4 (1.1)	0.24
Hypotension	14 (1.9)	2 (0.6)	12 (3.3)	0.007

[*] Note that more than one reason for stopping may be recorded.

SBP-systolic blood pressure

DBP–diastolic blood pressure

Table 3

Multivariate proportional hazards analysis for each predictor alone and then combined.

All-Cause Mortality				
	Hazard Ratio	**95% Confidence Interval**	**p value**	**Regression Coefficient**
Model 1				
Exercise Capacity	0.83	0.79 – 0.88	< 0.001	−0.18
Model 2				
Age	1.03	1.01 – 1.04	< 0.001	0.03
Exercise capacity	0.85	0.81 – 0.90	< 0.001	−0.15
Model 3				
Age	1.03	1.01 – 1.04	< 0.001	0.03
Exercise capacity	0.85	0.81 – 0.90	< 0.001	−0.16
Pack-years	1.01	1.00 – 1.01	0.001	0.006
Model 4				
Age	1.03	1.01 – 1.05	<0.001	0.03
Exercise capacity	0.87	0.82 – 0.91	<0.001	−0.14
Pack-years	1.01	1.0 – 1.01	0.001	0.005
Heart failure history	1.92	1.34 – 2.76	<0.001	0.65

Cardiovascular Mortality				
	Hazard Ratio	**95% Confidence Interval**	**p value**	**Regression Coefficient**
Model 1				
Exercise capacity	0.80	0.73 – 0.87	< 0.001	−0.22
Model 2				
Age	1.03	1.01 – 1.06	0.02	0.03
Exercise capacity	0.82	0.75 – 0.90	< 0.001	−0.19
Model 3				
Age	1.03	1.01 – 1.06	0.007	0.03
Exercise capacity	0.84	0.76 – 0.92	< 0.001	−0.18
Heart failure history	2.24	1.3 – 3.9	0.004	0.81