Cardiopulmonary Fitness and Heart Rate Recovery as Predictors of Mortality in a Referral Population

Abhijeet Dhoble, MD, MPH; Brian D. Lahr, MS; Thomas G. Allison, PhD, MPH; Stephen L. Kopecky, MD

Background—Exercise testing provides valuable information in addition to ST-segment changes. The present study evaluated the associations among exercise test parameters and all-cause mortality in a referral population.

Methods and Results—We examined conventional cardiovascular risk factors and exercise test parameters in 6546 individuals (mean age 49 years, 58% men) with no known cardiovascular disease who were referred to our clinic for exercise stress testing between 1993 and 2003. The association of exercise parameters with mortality was assessed during a follow-up of 8.1±3.7 years. A total of 285 patients died during the follow-up period. Adjusting for age and sex, the variables associated with mortality were: smoking, diabetes, functional aerobic capacity (FAC), heart rate recovery (HRR), chronotropic incompetence, and angina during the exercise. Adjusting for cardiovascular risk factors (diabetes, smoking, body mass index, blood pressure, serum total, HDL, LDL cholesterol, and triglycerides) and other exercise variables in a multivariable model, the only exercise parameters independently associated with mortality were lower FAC (adjusted hazard ratio [HR] per 10% decrease in FAC, 1.21; 95% confidence interval [CI], 1.13 to 1.29; $P<0.001$), and abnormal HRR, defined as failure to decrease heart rate by 12 beats at 1 minute recovery (adjusted HR per 1-beat decrease, 1.05; 95% CI, 1.03 to 1.07; $P<0.001$). The additive effects of FAC and HRR on mortality were also highly significant when considered as categorical variables.

Conclusion—In this cohort of patients with no known cardiovascular disease who were referred for exercise electrocardiography, FAC and HRR were independently associated with all-cause mortality. (*J Am Heart Assoc*. 2014;3:e000559 doi: 10.1161/JAHA.113.000559)

Key Words: exercise test • fitness • mortality

A part from diagnosing obstructive coronary disease, exercise treadmill test (ETT) provides useful prognostic information such as an estimate of cardiopulmonary fitness,[1–3] chronotropic reserve,[4,5] blood pressure (BP) response,[6] heart rate recovery (HRR),[7,8] and ventricular ectopy.[9] Abnormalities in these variables have been shown to be associated with cardiovascular events and mortality in general population. Coronary heart disease (CHD) continues to be the leading cause of mortality in North America and Europe,[10] and accounts for more than half of the deaths. ETT provides a point estimate of cardiopulmonary fitness in the form of functional aerobic capacity (FAC), chronotrophic reserve, and heart rate recovery (HRR); all of which are affected by the level of physical activity in the last few months,[3,7,11] and are associated with adverse outcome. There is no large body of data that has evaluated the effect of a combination of exercise parameters on mortality in a referral population who are at increased risk of cardiovascular events, after accounting for conventional cardiovascular risk factors and other variables provided by an ETT such as ST-segment changes, blood pressure (BP) response, angina, and ventricular ectopy during exercise.

The purpose of this study was to examine the association of variables provided by an ETT in a referral population free of CHD and cancer, to determine the ability of these variables independently and in combination to predict all-cause mortality, after adjusting for conventional cardiovascular risk factors.

Methods

Study Population

The study consisted of retrospective observation of 9030 individuals residing in Olmsted County, Minnesota who under-

went ETT between 1993 and 2003 in our Exercise Testing Laboratory, Cardiovascular Health Clinic, Mayo Clinic, Rochester, MN. Study participants were referred by their employers, physicians, or were self-referred. The patients with age of either <25 or >85 years (n=292), previous cardiovascular disease including coronary and peripheral vascular disease, significant valvular heart disease, congenital heart disease, previous heart procedure or surgery (n=2082), and malignancy (n=39) were excluded. We also excluded patients who did not undergo ETT using Bruce, Naughton or modified Naughton protocols (n=71). Thus, after exclusion of 2484 patients, the final sample comprised of 6546 patients. The study was reviewed and approved by the Institutional Review Boards of Mayo Clinic and Olmsted Medical Center, and all the patients gave written informed consent to be included in a study.

Risk Factor Measurement

Baseline characteristics of the study population were recorded on the day of ETT. This included their age, sex, smoking status, family history of CHD, resting heart rate, BP, body mass index (BMI), history of comorbid conditions, medication use, and electrocardiogram (ECG). These patients also had fasting plasma tests within 6 months of ETT day. The plasma samples were measured in Mayo Clinic Laboratory facility for total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides (TG), glucose (FPG), and hemoglobin A1C if a patient had suspicion or diagnosis of diabetes mellitus. Diabetes was considered present if they either had physician-documented diagnosis of diabetes, were taking hypoglycemic medication/s, or hemoglobin A1C of ≥6.5%. Patients were considered current smokers if they have smoked in the last 30 days, and were considered past smokers if they were not a current smoker but have smoked ≥100 cigarettes in their lifetime.

Exercise Treadmill Test

Each patient underwent a symptom-limited maximal exercise testing using Bruce, Naughton, or modified Naughton protocol. Patients were discouraged from holding on to the handrails, and the test was only stopped if the patient requested to stop due to exhaustion, or the physician stopped the test due to medical reasons. The physicians stopped the test either due to symptoms or positive high-risk features, including a drop in systolic BP of >20 mm Hg with increasing workload, high-risk ST-changes, and sustained ventricular tachycardia. The parameters recorded during ETT were: symptoms, continuous heart rate and ECG, and every 3-minute BP recordings. A standardized recovery protocol was

followed. The patients were asked to be supine within 30 seconds of exercise. The patients were monitored during recovery for symptoms, vital signs, and ECG for the first 3 minutes if they were stable, or longer if any abnormalities were noted. Exercise duration was expressed in minutes and in percent of age- and gender-predicted value. Cardiopulmonary fitness was measured in the form of FAC, which was calculated as actual exercise duration/predicted exercise time × 100. Predicted exercise time was calculated depending on the treadmill protocol using previously published equations as following[12,13]: For Bruce protocol: for men: $16 - 0.11 \times$ age in years, for women: $13.3 - 0.1 \times$ age in years; for Naughton protocol: for men: $(60 - 0.5 \times$ age in years$)/1.75$, for women: $(55 - 0.5 \times$ age in years$)/1.75$; and for modified Naughton protocol: for men: $16.3 - 0.12 \times$ age in years, for women: $13 - 0.1 \times$ age in years. Heart rate recovery was calculated as peak heart rate − heart rate at 1 minute into recovery. It was considered abnormal if it was ≤12.[7,8] Maximal heart rate was calculated as $220 - $ age in years. Heart rate reserve was calculated as maximal heart rate − resting heart rate. Proportion of heart rate reserve used was then calculated as (peak heart rate − resting heart rate)/heart rate reserve × 100. Chronotrophic incompetence was considered present if proportion of heart rate reserve used was <80% or <62% if patient is taking a beta-blocker.[4] ECG was diagnosed positive for ischemia based on standard criteria recommended by latest guidelines.[14] In a patient with right-bundle branch block, only V_5 and V_6 leads were analyzed. Blood pressure response was considered hypotensive if there was a drop in systolic BP below baseline with increasing workload.[6,12]

Mortality Ascertainment

All patients were followed through May 2008 for all-cause mortality. Vital status for all patients were determined using Mayo Clinic registration database as previously described,[15] death certificate database from State of Minnesota, and Accurint (an institutionally approved web-based resource and location service). We excluded deaths within 60 days of follow-up to minimize potential bias due to serious underlying illness on mortality.

Statistical Analysis

Descriptive statistics on baseline variables are presented as median (range), mean (standard deviation [SD]), or count (percentage) as appropriate. The influence of conventional risk factors and ETT parameters on mortality was evaluated with Cox proportional hazards (PH) regression. Of these hypothesized risk factors, each was individually tested in models adjusted for age and sex, and those with complete data were all carried forward into the final multivariable

modeling. However, for the few lab parameters that had sizable amounts of missing data, only those showing evidence of an association with mortality (independent of age and sex) were selected for inclusion in multivariable analysis. To retain those subjects with these missing data, we used single imputation to fill in their values under the assumption this missing-ness occurred at random. Data was mostly complete for all the potential risk factors of interest, except for 7 variables (resting diastolic and systolic blood pressure, glucose, triglycerides, and total, HDL and LDL cholesterol), which were each 20% to 30% missing. Based on the age and sex-adjusted modeling results of these 7 parameters, 6 did not show any evidence of an association with mortality and thus were not carried forward into the multivariable modeling. For the one that did show some preliminary signal, serum glucose, we used a regression-based imputation method (using diabetes status as the primary predictor) to fill in missing glucose values. This allowed us to include serum glucose in the multivariable model, along with all other study variables that had complete data, and thus retain the entire cohort in the analysis set. In addition, the functional form (eg, the adequacy of assuming a linear effect) of each continuous variable was evaluated via graphical impressions from a p-spline plot, which uses a smoothing technique to estimate the mortality hazard function in relation to the range of values of the predictor. For the final multivariable model, the time-dependent c statistic is reported to summarize the model's discriminative performance, with bootstrap resampling used to correct for optimism in this measure. In order to evaluate the incremental prognostic values from FAC and HRR, measures of model performance were compared between 2 nested models with and without the effects of FAC and HRR using the likelihood ratio test, c-statistics, and integrative discrimination index (IDI). All analyses were carried out with the statistical software package SAS, version 9.1 (SAS Institute), except for the p-spline plots which were performed in R, version 2.13.0 (R Development Core Team).

Results

The cohort consisted of 6546 subjects. Their baseline demographic, laboratory, and exercise test characteristics are described in Table 1. Baseline characteristics according to FAC levels are given in the Table 2.

During a mean follow-up of 8.1±3.7 years, a total of 285 patients died, corresponding to a 10-year cumulative incidence of 5.1%. Out of 285 deaths, 106 were due to cardiovascular causes. Controlling for risk factors age and sex, variables that were significantly associated with increased rates of mortality were: current or past smoking, diabetes, typical angina during exercise, chronotropic incom-

petence, reduced HRR, and lower FAC. A full multivariable model identified the following as statistically significant, independent risk factors of mortality: increasing age, male gender, smoking, BMI (increasing BMI levels up to <40 corresponded to decreased risk of mortality, while increasing levels for BMI ≥40 were marginally associated with increased risk), and decreasing levels of FAC (per 10% decrease, for the range of values <100%: HR=1.21; 95% CI, 1.13 to 1.29; $P<0.001$) and HRR (per 1 beat decrease, for the range of values <25 beats: HR=1.05; 95% CI, 1.03 to 1.07; $P<0.001$) (Table 3). To estimate the optimism bias from the model selection process and then compute a bias-corrected c-statistic, we tested each bootstrap-selected model on the original data and measured its performance. Bias was estimated as the average difference in concordance [c]-statistic values between the bootstrap model and the test model, which was then subtracted from the "apparent" (ie, model c-statistic from original data) to obtain a bias-corrected c-statistic. We noted a high c-statistic of 0.835 reflecting high predictive accuracy of the original multivariable model, with a bias-corrected c-statistic of 0.824 indicating very little optimism bias in the original model fitting. A C-statistic of >0.8 is considered to represent excellent discriminative ability.[16]

To visually assess calibration, which is the model's ability to predict accurately the absolute level of risk that is subsequently observed, we plotted deciles of predicted 5-year survival from the Cox model by the empirical rates of surviving at least 5 years obtained from Kaplan-Meier. Note that in the Figure 1, predicted survival was captured both from the apparent model and the bootstrap (bias-corrected) model. For a reference of perfect calibration, the Y=X line is displayed.

From a sensitivity analysis of the final multivariable model re-fit with the continuous scales of FAC and HRR dichoto-mized at clinically useful cut-points (ie, FAC at <80% and HRR and ≤12 at 1 minute), both variables retained highly signif-icant associations with mortality independent of the other factors in the model (FAC <80%: HR=1.88; 95% CI, 1.42 to 2.47; $P<0.001$; and HRR ≤12: HR=2.13; 95% CI, 1.63 to 2.76, $P<0.001$). The Kaplan-Meier survival curves in Figure 2 help visualize this comparison of rates over time between subjects with below average FAC (<80%) versus above average FAC (≥80%), and subjects with abnormal HRR (≤12 beats at 1 minute) versus normal. Also, according to the combinations of these FAC and HRR groupings, patients who had above-average FAC and normal HRR had high rates of survival, whereas patients with low FAC and abnormal HRR demon-strated noticeably poorer survival (Figure 3), particularly after about 5 years of follow-up. In a separate analysis, no significant interaction was noted between FAC and HRR in relation to mortality.

Table 1. Baseline Demographic and Clinical Characteristics, Anthropometric Measurements, Medication Use, Laboratory Values, and Responses to Exercise During Stress Test

Characteristics	
Demographics/baseline characters	
Age	49.3 (41.4, 58.6)
Males	3807 (58%)
Ethnicity	
Caucasian	5272 (81%)
Others/not reported	1274 (19%)
Body mass index, kg/m^2	28.1 (25.0, 32.0)
Waist/Hip ratio	0.9 (0.8, 1.0)
Smoking	
Never	3440 (53%)
Past	2141 (33%)
Current	958 (15%)
Family history of coronary disease	3544 (54%)
Diabetes	609 (9%)
Medications	
Hypertension therapy	1565 (24%)
Lipid lowering therapy	388 (6%)
Resting BP, mm Hg	
Diastolic BP	80.0 (72.0, 88.0)
Systolic BP	126.0 (114.0, 140.0)
Fasting blood tests, mg/dL	
Total cholesterol	209.0 (183.0, 239.0)
HDL-cholesterol	46.0 (38.0, 56.0)
LDL-cholesterol	129.0 (106.0, 154.0)
Glucose	97.0 (90.0, 106.0)
Triglycerides	142.0 (101.0, 205.0)
Exercise test parameters	
Abnormal heart rate recovery at 1 minute	1618 (25%)
Functional aerobic capacity, %	84.2 (68.8, 98.7)
Premature ventricular beats	
None	4519 (69%)
≤5 /minute	1527 (23%)
>5 /minute	500 (8%)
Positive ST changes	432 (7%)
Chronotrophic incompetence	1578 (24%)
Blood pressure response	
Normal	5885 (90%)
Hypotensive	118 (2%)
Hypertensive	543 (8%)
Chest pain	
Absent	6059 (93%)

Table 1. Continued

Characteristics	
Atypical chest pain	325 (5%)
Typical angina	162 (2%)
Test protocol	
Bruce	5611 (86%)
Modified Bruce	780 (12%)
Naughton	103 (2%)
Modified Naughton	43 (1%)

BP indicates blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

In terms of whether those 2 parameters contribute prognostic importance beyond all the other predictor variables in the model, measures of performance were compared between 2 nested models with and without the effects of FAC and HRR. In particular, a likelihood ratio test demonstrated their combined effect (using a 2 degree of freedom test) was significant, as is the improvement in model c-statistic (from 0.806 to 0.835) with the addition of FAC and HRR to the multivariable model. Furthermore, IDI was assessed to demonstrate how far on average individuals were moving (in an appropriate direction) along the continuum of predicted risk between these 2 models. An aggregate measure of IDI, estimated as the equally weighted sum of improvement in predicted risk between subjects who were censored and those who died, showed an average improvement in prediction of 0.71% ($\pm$0.36%) in the models with FAC and HRR (P=0.046 from a one-sample t test).

Discussion

In this large referral cohort of consecutive patients from Olmsted County undergoing ETT, we examined conventional cardiovascular risk factors and ETT parameters, and their ability to predict all-cause mortality. Poor exercise tolerance in the form of FAC and abnormal HRR were independent predictors of death after adjusting for conventional cardiovascular risk factors during approximately 10 years follow-up period. The multivariable model used both these parameters as continuous variables and found a linear relationship with the mortality, ie, the risk of death increased for every 10% decrease in FAC below 100%, and for every one beat decrease in HRR below 25 at 1 minute. Expressed as groups using single cut-points, the categories of low exercise tolerance (indicated by FAC <80%) and severely abnormal heart rate recovery (of ≤12 beats at 1 minute) were also highly associated with increased risk of mortality. It should be noted that blood pressure, glucose, and lipids were appropriately controlled in most patients as indicated in Table 1.

Table 2. Baseline Characteristics According to the Level of FAC

Variable	FAC <80% (n=2763)	FAC >80% (n=3760)	*P* Value
Demographics/baseline characters			
Age	49.9 (40.6, 60.7)	49.0 (41.8, 57.3)	0.006
Males	1518 (55%)	2276 (61%)	<0.001
Ethnicity			0.002
Caucasian	2274 (82%)	2979 (79%)	
Others/not reported	489 (18%)	781 (21%)	
Body mass index (kg/m^2)	30.4 (26.7, 35.5)	26.7 (24.3, 29.9)	<0.001
Waist/Hip ratio	0.9 (0.8, 1.0)	0.9 (0.8, 0.9)	<0.001
Smoking			<0.001
Never	1256 (46%)	2175 (58%)	
Past	965 (35%)	1167 (31%)	
Current	539 (20%)	415 (11%)	
Family history of coronary disease	1448 (52%)	2091 (56%)	0.010
Diabetes	401 (15%)	205 (5%)	<0.001
Medications			
Lipid lowering therapy	178 (6%)	210 (6%)	0.148
Hypertension therapy	846 (31%)	711 (19%)	<0.001
Resting BP			
Resting diastolic BP	80.0 (72.0, 88.0)	80.0 (72.0, 88.0)	0.303
Resting systolic BP	126.0 (114.0, 140.0)	126.0 (114.0, 140.0)	0.910
Fasting blood tests, mg/dL			
Total cholesterol	210.0 (183.0, 239.0)	208.0 (183.0, 238.0)	0.266
HDL-cholesterol	44.0 (37.0, 53.0)	48.0 (40.0, 58.0)	<0.001
LDL-cholesterol	127.0 (104.0, 153.0)	130.0 (106.0, 154.0)	0.107
Glucose	99.0 (92.0, 112.0)	95.0 (89.0, 102.0)	<0.001
Triglycerides	159.5 (114.0, 227.0)	129.0 (92.0, 188.0)	<0.001
Exercise test parameters			
Abnormal heart rate recovery at 1 minute (<12/min)	999 (36%)	612 (16%)	<0.001
Chronotrophic incompetence	1136 (41%)	434 (12%)	<0.001
Premature ventricular beats			<0.001
None	1973 (71%)	2527 (67%)	
≤5 /minute	576 (21%)	948 (25%)	
>5 /minute	214 (8%)	285 (8%)	
Positive ST changes	184 (7%)	247 (7%)	0.885
Blood pressure response			<0.001
Normal	2404 (87%)	3460 (92%)	
Hypotensive	57 (2%)	61 (2%)	
Hypertensive	302 (11%)	239 (6%)	
Chest pain			<0.001
Absent	2508 (91%)	3529 (94%)	
Atypical chest pain	145 (5%)	180 (5%)	
Typical angina	110 (4%)	51 (1%)	

BP indicates blood pressure; FAC, functional aerobic capacity; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 3. Cox-Proportional-Hazard Analysis for Association of Variables With All-Cause Mortality in Univariate and Multivariable Models

Variable	Univariate (Unadjusted) Model Results	Age- and Sex-Adjusted Model Results	Full Multivariable Model Results*
Male gender	1.06 (0.83, 1.34) [0.639]	1.53 (1.20, 1.94) [<0.001]	1.39 (1.08, 1.80) [0.011]
Age (per 10 year increase)	2.42 (2.20, 2.67) [<0.001]	2.50 (2.27, 2.76) [<0.001]	1.97 (1.75, 2.21) [<0.001]
Ischemic ST changes	1.83 (1.28, 2.61) [<0.001]	1.12 (0.79, 1.61) [0.522]	1.04 (0.71, 1.53) [0.825]
Chronotrophic incompetence	2.50 (1.98, 3.16) [<0.001]	1.74 (1.37, 2.22) [<0.001]	1.09 (0.84, 1.42) [0.520]
FAC† (per 10% increase)	0.73 (0.70, 0.78) [<0.001]	0.79 (0.75, 0.84) [<0.001]	0.83 (0.78, 0.88) [<0.001]
BMI (per 1 kg/m² increase)			
Among those BMI<40	0.96 (0.93, 0.98) [0.002]	0.98 (0.95, 1.01) [0.115]	0.94 (0.92, 0.97) [<0.001]
Among those BMI ≥40	1.02 (0.92, 1.12) [0.732]	1.09 (0.98, 1.20) [0.114]	1.12 (0.99, 1.27) [0.082]
Smoking past/current	2.02 (1.59, 2.58) [<0.001]	1.79 (1.40, 2.30) [<0.001]	1.61 (1.25, 2.07) [<0.001]
Diabetes	2.10 (1.53, 2.88) [<0.001]	1.59 (1.16, 2.19) [0.004]	1.41 (0.89, 2.24) [0.147]
Total cholesterol (per 20 unit increase)	0.97 (0.91, 1.03) [0.317]	0.96 (0.90, 1.02) [0.223]	—
HDL (per 10 unit decrease)	1.06 (0.97, 1.17) [0.178]	1.00 (0.90, 1.10) [0.930]	—
LDL (per 20 unit increase)	0.98 (0.91, 1.06) [0.680]	0.98 (0.91, 1.06) [0.637]	—
Glucose (per 1 unit increase)	1.00 (1.00, 1.01) [0.006]	1.00 (1.00, 1.01) [0.081]	1.00 (0.99, 1.00) [0.540]
Triglycerides	1.00 (1.00, 1.00) [0.722]	1.00 (1.00, 1.00) [0.520]	—
Family history of coronary disease	0.70 (0.55, 0.88) [0.003]	0.91 (0.72, 1.15) [0.439]	0.95 (0.75, 1.20) [0.660]
Hypertension therapy	2.18 (1.71, 2.79) [<0.001]	1.17 (0.90, 1.51) [0.232]	1.06 (0.81, 1.38) [0.679]
Lipid lowering therapy	1.15 (0.70, 1.88) [0.574]	0.71 (0.43, 1.16) [0.176]	0.73 (0.44, 1.22) [0.229]
Hypotensive BP response	1.05 (0.44, 2.55) [0.908]	0.99 (0.41, 2.41) [0.990]	0.79 (0.32, 1.94) [0.605]
Typical angina during exercise	3.39 (2.15, 5.35) [<0.001]	1.77 (1.12, 2.80) [0.015]	1.52 (0.93, 2.48) [0.098]
Resting systolic BP	1.00 (1.00, 1.01) [0.543]	1.00 (0.99, 1.01) [0.821]	1.00 (0.99, 1.00) [0.512]
Resting diastolic BP	1.01 (1.00, 1.02) [0.204]	1.01 (1.00, 1.02) [0.143]	1.01 (1.00, 1.02) [0.130]
HR recovery‡ (per 1 beat increase)	0.89 (0.88, 0.91) [<0.001]	0.94 (0.92, 0.95) [<0.001]	0.95 (0.94, 0.97) [<0.001]
Premature atrial beats			
None	1.0 (ref) [F test P<0.001]	1.0 (ref) [F test P=0.461]	1.0 (ref) [F test P=0.469]
<5	1.77 (1.37, 2.29)	1.09 (0.84, 1.41)	1.18 (0.91, 1.53)
>5	3.59 (2.30, 5.61)	1.31 (0.83, 2.07)	1.08 (0.68, 1.72)
Premature ventricular beats			
None	1.0 (ref) [F test P<0.001]	1.0 (ref) [F test P=0.088]	1.0 (ref) [F test P=0.062]
<5	1.47 (1.13, 1.92)	1.06 (0.81, 1.39)	1.20 (0.91, 1.57)
>5	2.64 (1.86, 3.73)	1.48 (1.04, 2.11)	1.51 (1.00, 2.15)

BMI indicates body mass index; BP, blood pressure; FAC, functional aerobic capacity; HDL, high-density lipoprotein; HR, heart rate; HRR, heart rate recovery; LDL, low-density lipoprotein.
*Multivariable model had an apparent c-statistic of 0.835 and a bias-corrected c-statistic of 0.824.
†FAC: upper cap for FAC set at 100% to satisfy the assumption of linearity; reported risk only applies to those with FAC values <100%.
‡HRR: lower and upper caps for HRR set at 0 and 25 beats to satisfy the assumption of linearity; reported risk only applies to those with an HRR between 0 to 25 beats.
The values in parentheses indicate confidence interval, and the value in the bracket indicate P-value.

Almost all of these patients were evaluated by an internist or a cardiologist prior to their ETT, and were appropriately managed and counseled according to the current guidelines, which is reflected in their baseline clinical and laboratory characteristics.

We had almost complete data for all the potential risk factors of interest, except for laboratory variables which were each 20% to 30% missing. Among these, only serum glucose showed some preliminary signal and was therefore retained in the multivariable analysis. A regression-based method of single imputation was used to fill in missing glucose values, thereby allowing nearly the entire cohort to be included in the final multivariable model. We used death as an end-point, because it is a robust and clinically most relevant outcome. The methods
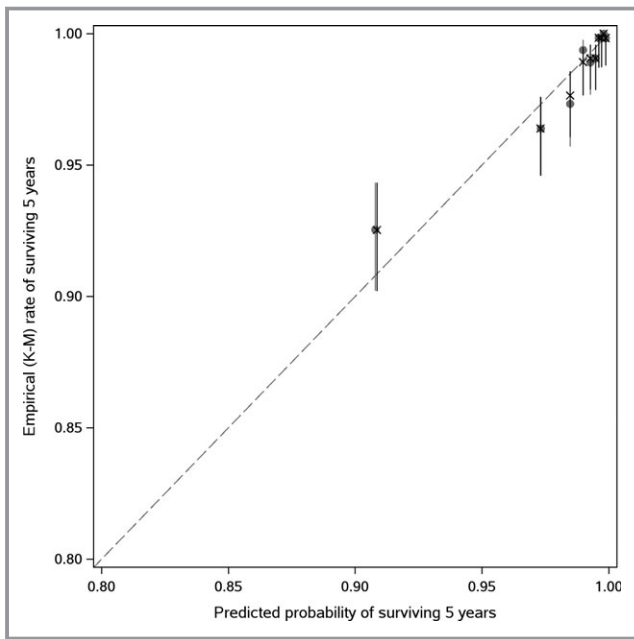
Figure 1. Model calibration plots (based on observed vs predicted survival at 5 years; X=resampling optimism added). K-M indicates Kaplan-Meier rates.
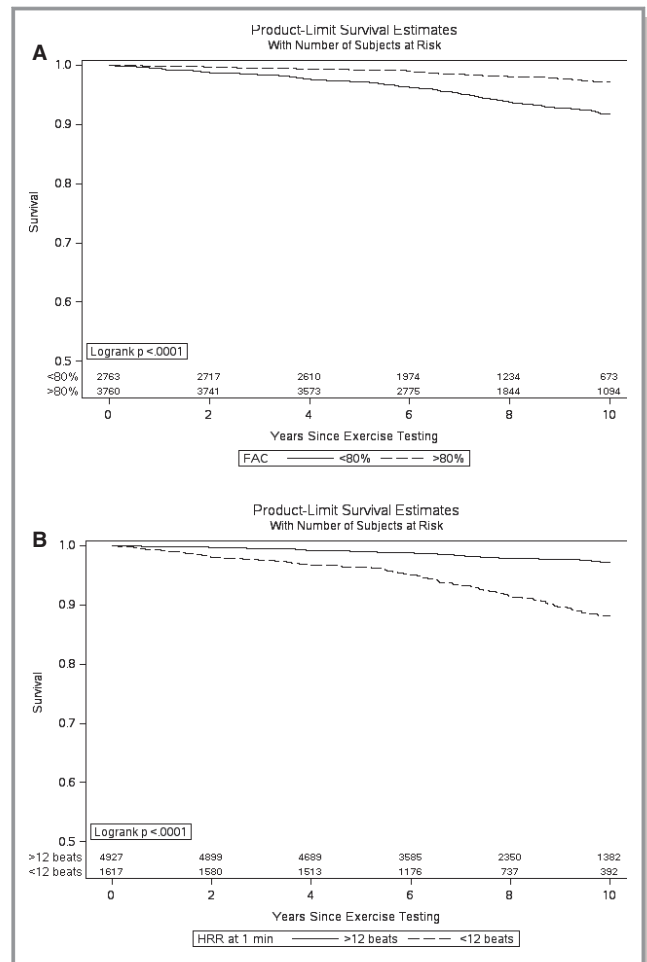

Figure 2. Kaplan-Meier survival curves after dichotomizing (A) functional aerobic capacity (FAC) at 80% (<80%: below average, ≥80%: average or above average) and (B) heart rate recovery (HRR) at 12 beats (≤12: abnormal, >12: normal).

used for ascertainment for deaths were vigorous, and provided follow-up for all the patients through 2008.

Although exercise capacity expressed in terms of metabolic equivalents is the common clinical measure of exercise tolerance, exercise capacity is strongly influenced by age and gender. Hence we used FAC as a measure of exercise capacity in our study. FAC is an excellent objective measure of total activity in recent months.[2,7] Low FAC reflects low cardiopulmonary fitness, and is a very strong known predictor of mortality and CV events,[3,17,18] even after accounting for Framingham[19] risk score. Sustaining or improving fitness level is associated with a lower risk of all-cause and CV mortality.[20] Our findings indicate that poor exercise tolerance provides important additional prognostic information, and confirms previous findings derived from community cohorts and health surveys,[17–19,21–23] and extends them by demonstrating an independent relationship between the level of cardiopulmonary fitness and death in referred patients at risk for CHD. Heart rate recovery refers to the inability of heart rate to appropriately decrease after exercise, and indicates autonomic imbalance and low fitness level, and has been shown to be associated with mortality and coronary disease, even after adjusting for conventional cardiovascular risk factors.[7,18,21] The precise mechanism is unknown, but an abnormal dynamic interaction between sympathetic and parasympathetic systems is thought to be one of the etiologies.

There are multiple long-term studies in the literature that are conducted on a relatively healthy population, such as community-derived cohorts[24,25] and health surveys.[26] Our study
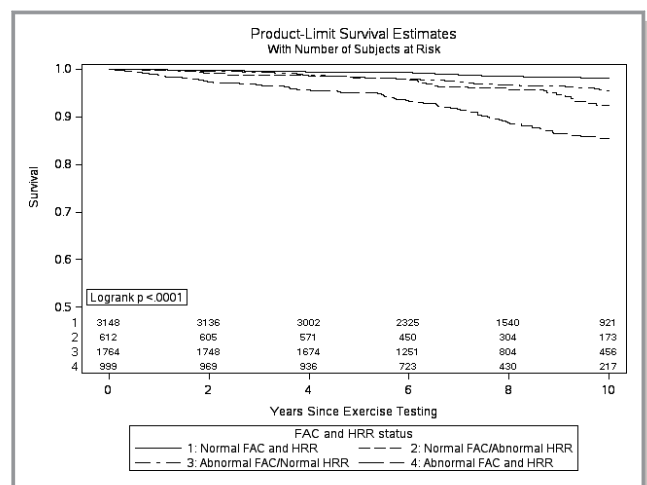
Figure 3. Survival as a function of fitness level and heart rate recovery (functional aerobic capacity [FAC] and HRR categorized at 80% and 12 beats, respectively).

focuses on a clinically more relevant population, ie, patients referred for exercise testing mostly by a physician for clinical indications. The reasons for referral in our cohort were several including, but not limited to dyslipidemia, family history of CHD, and nonspecific symptoms such as chest pain or dyspnea. There are very few studies in the literature that has looked at such a group.[23] In our cohort, less than half of the deaths were from cardiovascular causes. On further analysis, only exercise test variable associated with cardiovascular deaths was FAC.

There have been a few studies attempting to examine the relationship of combination of various exercise test parameters with the mortality.[18,27,28] The "Cooper Center Longitudinal Study" showed that the increasing number of abnormal exercise parameters was associated with increased all-cause and cardiovascular mortality, and that those having ≥3 abnormal exercise parameters had a 5-fold increased risk of all-cause mortality when compared with those without any exercise test abnormalities.[18] In a study of male veterans, a combination of chronotropic incompetence and an abnormal HR recovery strongly predicted cardiovascular mortality.[28] In a previous study from Olmsted County, a graded increase in mortality was reported as individuals exhibited multiple abnormal characteristics such as ST changes, chronotropic incompetence, and/or poor exercise capacity.[27] The current study concurs and adds to the limited number of studies that have examined the effects of multiple exercise parameters in combination on mortality. We found that the lower cardiopulmonary fitness, and abnormal heart rate recovery were each independently associated with adverse CV outcome, and that the combination of these 2 abnormalities were additive in nature.

Limitations

This study is limited by several factors, including the observational nature of our data. The cohort consisted of referral sample, and may be limited by potential selection bias. We also had some missing data, but it was accounted for by using a regression-based method of single imputation. The population of Olmsted County is primarily Caucasian,[29] and the findings may not apply to the other ethnic groups. The characteristics of our cohort are similar to those of non–Hispanic whites in the United States overall, except that a higher proportion of the residents are employed in the health-care sector.[29] It is beyond the scope of our study to determine whether altering physical fitness and heart rate recovery will improve survival.

Conclusion

In conclusion, exercise test provides useful prognostic information in a referred, relatively healthy population. Our findings add to the growing body of evidence that the lower cardiopulmonary fitness and abnormal heart rate recovery are associated with premature deaths. The effects of FAC and HRR are additive, meaning that risk of mortality is increased with impairment in either one and increased further with impairments in both. These results underscore the importance of exercise training in people at risk of coronary disease, in addition to addressing conventional cardiovascular risk factors.

Disclosure

None.

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