Conclusions—We sought to determine whether treadmill exercise time may be of value as an initial prognostic screening tool in ambulatory patients with impaired systolic function who are referred for cardiopulmonary exercise testing.

Methods and Results—We studied 2231 adult systolic heart failure patients (27% of whom were women) who underwent cardiopulmonary stress testing using a modified Naughton protocol. We assessed the value of treadmill exercise time for prediction of all-cause death and a composite of death or United Network for Organ Sharing status 1 heart transplantation. During a mean follow-up of 5 years, 742 patients (33%) died. There were 249 United Network for Organ Sharing status 1 heart transplants (11%). Treadmill exercise time was predictive of death and the composite outcome in both women and men, even after accounting for peak oxygen consumption and other clinical covariates (adjusted hazard ratio of lowest versus high sex-specific quartile for prediction of death 1.70, 95% confidence interval 1.05 to 2.75, \( P=0.03 \); for prediction of the composite outcome, 1.75, 95% confidence interval 1.15 to 2.66, \( P=0.009 \)). For a 1-minute change in exercise time, there was a 7% increased hazard of death (eg, comparing 480 to 540 seconds, hazard ratio =1.07, 95% confidence interval 1.02 to 1.12, \( P=0.004 \)).

Key Words: heart failure ■ exercise ■ sex ■ prognosis

Peak oxygen consumption (\( \text{VO}_2 \)) remains one of the most powerful single predictors of mortality for heart failure patients with severe systolic left ventricular dysfunction.\(^1,3\) Current guidelines suggest ambulatory patients be considered for transplantation when the peak \( \text{VO}_2 \) is \(<14 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \), or \(<12 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) in the setting of \( \beta \)-blockade.\(^3\) Although cardiopulmonary exercise testing routinely is used to determine candidacy for heart transplantation, it is not known whether a simple measurement of treadmill exercise time may be of comparable value as an initial prognostic screening tool. We sought to evaluate whether (1) treadmill exercise time predicts survival in heart failure patients with systolic dysfunction, (2) treadmill exercise time adds incremental prognostic value beyond established risk factors, including peak \( \text{VO}_2 \), and (3) a model with treadmill exercise time in addition to established risk factors better classifies risk than a model with established risk factors alone.

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From the Departments of Cardiovascular Medicine (E.H., E.Z.G., R.C.S.), Quantitative Health Sciences (H.I.), and Cardiothoracic Surgery (E.H.B.) at the Cleveland Clinic and Case Western Reserve University School of Medicine (E.H., R.C.S.), Cleveland, Ohio; and the Division of Prevention and Population Sciences (M.S.L.), National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.109.848382/DC1. The content of this article is the responsibility of the authors alone and does not necessarily reflect the views or policies of the US Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the US government. Reprint requests to Michael S. Lauer, MD, FACC, FAHA, Director, Division of Prevention and Population Science, National Heart, Lung, and Blood Institute, National Institutes of Health, Rockledge Center II, 6701 Rockledge Dr, Room 10122, Bethesda, MD 20892. E-mail lauerm@nhlbi.nih.gov

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3189

Exercise Physiology

Importance of Treadmill Exercise Time as an Initial Prognostic Screening Tool in Patients With Systolic Left Ventricular Dysfunction

Eileen Hsich, MD; Eiran Z. Gorodeski, MD, MPH; Randall C. Starling, MD, MPH; Eugene H. Blackstone, MD; Hemant Ishwaran, PhD; Michael S. Lauer, MD

Background—We sought to determine whether treadmill exercise time may be of value as an initial prognostic screening tool in ambulatory patients with impaired systolic function who are referred for cardiopulmonary exercise testing.

Methods and Results—We studied 2231 adult systolic heart failure patients (27% of whom were women) who underwent cardiopulmonary stress testing using a modified Naughton protocol. We assessed the value of treadmill exercise time for prediction of all-cause death and a composite of death or United Network for Organ Sharing status 1 heart transplantation. During a mean follow-up of 5 years, 742 patients (33%) died. There were 249 United Network for Organ Sharing status 1 heart transplants (11%). Treadmill exercise time was predictive of death and the composite outcome in both women and men, even after accounting for peak oxygen consumption and other clinical covariates (adjusted hazard ratio of lowest versus high sex-specific quartile for prediction of death 1.70, 95% confidence interval 1.05 to 2.75, \( P=0.03 \); for prediction of the composite outcome, 1.75, 95% confidence interval 1.15 to 2.66, \( P=0.009 \)). For a 1-minute change in exercise time, there was a 7% increased hazard of death (eg, comparing 480 to 540 seconds, hazard ratio =1.07, 95% confidence interval 1.02 to 1.12, \( P=0.004 \)).

Conclusions—Because cardiopulmonary stress testing is not available in every hospital, treadmill exercise time with a modified Naughton protocol may be of value as an initial prognostic screening tool. (Circulation. 2009;119:3189-3197.)

Key Words: heart failure ■ exercise ■ sex ■ prognosis

Peak oxygen consumption (\( \text{VO}_2 \)) remains one of the most powerful single predictors of mortality for heart failure patients with severe systolic left ventricular dysfunction.\(^1,3\) Current guidelines suggest ambulatory patients be considered for transplantation when the peak \( \text{VO}_2 \) is \(<14 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \), or \(<12 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) in the setting of \( \beta \)-blockade.\(^3\) Although cardiopulmonary exercise testing routinely is used to determine candidacy for heart transplantation, it is not known whether a simple measurement of treadmill exercise time may be of comparable value as an initial prognostic screening tool. We sought to evaluate whether (1) treadmill exercise time predicts survival in heart failure patients with systolic dysfunction, (2) treadmill exercise time adds incremental prognostic value beyond established risk factors, including peak \( \text{VO}_2 \), and (3) a model with treadmill exercise time in addition to established risk factors better classifies risk than a model with established risk factors alone.

Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.
weight, and stress results were obtained at the time of stress testing and prospectively recorded in our electronic database. Biventricular pacemakers were not reported separately from other pacemakers during database entry. Glomerular filtration rate was estimated with the Cockcroft-Gault equation. Left ventricular ejection fraction was determined either by echocardiography, left ventriculography, or ECG-gated myocardial perfusion imaging. If a patient underwent >1 metabolic stress test with a modified Naughton protocol, only the first test was considered. Serum laboratory tests within 3 months of the cardiopulmonary study were included, and only the laboratory tests closest to the stress test date were used.

Cardiopulmonary Stress Testing
Cardiopulmonary stress testing was symptom limited, and patients were strongly advised to not use the handrails for support. Details on our laboratory’s protocols have been published previously. Briefly, the test was performed with a modified Naughton protocol that increases workload \(\approx 1\) metabolic equivalent every 2 minutes. Results were recorded on a MediGraphics cardiopulmonary system (Medical Graphics Corp, St Paul, Minnesota). Oxygen consumption, carbon dioxide production, minute ventilation, tidal volume, heart rate, blood pressure, and respiratory rate were obtained at rest, every 30 seconds during exercise, and during recovery. Total duration of exercise, henceforth referred to as treadmill exercise time, was recorded to the nearest second.

End Points
The primary end points were all-cause mortality and a composite of all-cause mortality or United Network for Organ Sharing (UNOS) status 1 heart transplantation during a mean follow-up of 5 years (maximum for survivors, 11 years). Mortality data were obtained by linking our database with the US Social Security Administration Death Index. We validated this approach previously, yielding a sensitivity of 97%, which is equivalent to a 97% follow-up rate. All-cause mortality or United Network for Organ Sharing (UNOS) status 1 heart transplantation was based on Organ Procurement and Transplantation Network data as of June 18, 2008. All events (death or heart transplantation) were censored as of April 1, 2008.

Statistical Analysis
Baseline characteristics were reported as sex-specific quartiles of treadmill exercise time. Continuous variables were expressed as means with SDs, and categorical variables were expressed as frequencies. Serum laboratory tests before October 1999 were systematically unavailable on our electronic database. We used informed imputation to fill in these missing values by constructing regression models for each laboratory measure on all other characteristics of our existing database except for outcome (10% of creatinine clearance, blood urea nitrogen, glucose, and sodium values were imputed, and 15% of serum hemoglobin values were imputed).

We generated Kaplan–Meier plots relating treadmill exercise time to all-cause mortality. The composite of death and UNOS status 1 heart transplantation yielded similar sex-specific results (online-only Data Supplement Figure 1). In both women and men, treadmill exercise time predicted survival (death or death/UNOS status 1 transplantation), with the worst survival in the quartile with the lowest
treadmill exercise time. After adjustment for all the variables listed in Table 1, including peak VO₂, in a Cox proportional hazards model, a shorter exercise time remained associated with an increase hazard of death (Table 2) and of death and UNOS status 1 heart transplantation (online-only Data Supplement Table I). For a 1-minute change in exercise time, there was a 7% increased hazard of death (eg, for a comparison of 480 to 540 seconds, hazard ratio 1.07, 95% confidence interval [CI] 1.02 to 1.12, P = 0.004). To determine whether the imputed laboratory values affected our data, we performed a sensitivity analysis leaving out all laboratory variables and found similar results (hazard ratio 1.08, 95% CI 1.03 to 1.13, P = 0.002).

We further evaluated the association of treadmill exercise time and survival for the subgroup of patients with peak VO₂ ≥14 mL · kg⁻¹ · min⁻¹. Even among these lower-risk patients, lower treadmill exercise time predicted worse outcomes in both women and men (Figure 2; online-only Data Supple-
ment Figure II). In this subset of patients with high peak \( V\dot{O}_2 \), a 1-minute change in exercise time also yielded a 7% increased hazard of death in a fully adjusted model (ie, for a comparison of 480 to 540 seconds, hazard ratio 1.07, 95% CI 1.00 to 1.14, \( P = 0.04 \)).

The c-indices of the models that contained all variables including exercise time were 0.723 for all-cause death and 0.744 for the composite of death and UNOS status 1 heart transplantation. The OOB c-indices, a more conservative measure, of the models that contained all variables including treadmill exercise time were 0.698 (95% CI 0.670 to 0.726) for all-cause death (Table 3) and 0.727 (95% CI 0.703 to 0.751) for the composite outcome of death and UNOS status 1 heart transplantation (online-only Data Supplement Table II), which indicates moderate discriminatory ability. There were no notable differences between the models that contained clinical variables and either peak \( V\dot{O}_2 \), treadmill exercise time, or both. Treadmill exercise time was among the top 3 most important contributors to discriminative prediction in both sets of models (Figure 3; online-only Data Supplement Figure III).

To better compare model performance within clinical categories, we classified patients into low-risk (\( <15\% \)) and high-risk (\( \geq 15\% \)) categories of 1-year risk, with these cut points based on the observed national 1-year survival after heart transplantation. We compared models with and without treadmill exercise time by cross-classifying predicted risks, stratified by whether or not the patients died (Figure 4) or developed the composite end point of death or transplantation (online-only Data Supplement Figure IV). If an additional variable were to add no predictive value, all points would fall on the line of identity. A spread around the line indicates modulation of predicted risk; if the variable correctly modulates predicted risk, there should be a greater preponderance of events above the line of identity. Clinical variables and

Table 2. Treadmill Exercise Time and Outcome: Cox Proportional Hazards Analyses

<table>
<thead>
<tr>
<th>Model: Death</th>
<th>Hazard Ratio (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treadmill exercise time as a continuous variable*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>2.23 (2.00–2.49)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adjusted for age and sex</td>
<td>2.23 (1.98–2.50)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adjusted for age, sex, history of CAD, and peak ( V\dot{O}_2 )</td>
<td>1.54 (1.23–1.92)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Multivariable adjusted</td>
<td>1.40 (1.12–1.76)</td>
<td>0.004</td>
</tr>
<tr>
<td>Treadmill exercise time as a dichotomous variable†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>4.91 (3.86–6.24)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multivariable adjusted</td>
<td>1.70 (1.05–2.75)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease.

*Comparisons are between the 25th percentile (317 seconds in women, 360 seconds in men) and 75th percentile (600 seconds in women, 657 seconds in men).

†Comparisons between quartile 1 (\(<316\) seconds in women, \(<358\) seconds in men) and quartile 4 (\(>602\) seconds in women, \(>659\) seconds in men).
usage of peak VO₂ (Figure 4A) or treadmill exercise time (Figure 4B) improved net reclassification for the outcome of death and the composite outcome (online-only Data Supplement Figures IV-A and IV-B). However, there were no significant differences in net reclassification between a model with clinical variables and treadmill exercise time versus clinical variables and peak VO₂ (Figure 4C; online-only Data Supplement Figure IV-C).

The integrated discrimination improvement (a reclassification measure that is not limited to predetermined categories of risk) for a model with treadmill exercise time was 1.9% \( (P<0.0001; \text{Figure 4B}) \) for the outcome of death and 3.4% \( (P<0.001; \text{online-only Data Supplement Figure IV-B}) \) for the composite outcome. There were no significant differences in integrated discrimination improvement between a model with clinical variables and treadmill exercise time versus clinical variables and peak VO₂ (Figure 4C; online-only Data Supplement Figure IV-C).

### Discussion

In a large cohort of patients with impaired left ventricular systolic function who underwent the same cardiopulmonary stress testing protocol, we found that treadmill exercise time predicted survival and yielded similar prognostic value to peak oxygen consumption (peak VO₂). Even among low-risk patients with a peak VO₂ \( >14 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \), those who had a lower treadmill exercise time had markedly worse outcomes. The present findings are consistent with the hypothesis that exercise capacity is a valuable initial prognostic screening tool in patients with systolic left ventricular dysfunction.

The present study expands on previous work demonstrating the prognostic power of exercise capacity.\(^{12,13}\) Exercise capacity (ie, treadmill time or “estimated” metabolic equivalents) is predictive of survival in both healthy adults and those with known coronary artery disease.\(^{14–16}\) Exercise tolerance reflects a number of prognostically important factors, including cardiac function, endothelial function, pulmonary function, oxygen-carrying capacity, and autonomic nervous system balance; however, its usefulness as a prognostic

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**Table 3. OOB Concordance Index Values for Cox Regression Models**

<table>
<thead>
<tr>
<th></th>
<th>All-Cause Death: OOB Concordance Index (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical variables only</td>
<td>0.672 (0.646–0.698)</td>
</tr>
<tr>
<td>Peak VO₂ only</td>
<td>0.675 (0.662–0.688)</td>
</tr>
<tr>
<td>Time only</td>
<td>0.666 (0.651–0.681)</td>
</tr>
<tr>
<td>Peak VO₂+time only</td>
<td>0.679 (0.666–0.692)</td>
</tr>
<tr>
<td>Clinical variables+peak VO₂</td>
<td>0.699 (0.673–0.725)</td>
</tr>
<tr>
<td>Clinical variables+time</td>
<td>0.697 (0.671–0.723)</td>
</tr>
<tr>
<td>Clinical variables+peak VO₂+time</td>
<td>0.698 (0.670–0.726)</td>
</tr>
</tbody>
</table>
screening tool in patients with systolic left ventricular dysfunction is less established.

Treadmill exercise time has not been used in most heart failure survival models, but it has been explored previously in at least 3 heart failure studies. In the Captopril-Digoxin Research Group report, exercise time on a modified Naughton protocol was deemed to have no significant prognostic value; however, the cohort was relatively healthy, because patients who exercised less than 240 seconds were excluded, and the average exercise time was quite high at 558 seconds. In a small study of 60 heart failure patients, there was a high degree of correlation between treadmill exercise time and peak $\dot{V}O_2$; however, owing to the small sample size, that study did not have the power to determine prognostic significance. More recently, a cohort of 31 children with idiopathic cardiomyopathy who underwent cardiopulmonary stress testing with a modified Naughton protocol were followed up prospectively for a median of 1282 days, and 20 of them died or underwent heart transplantation. Both univariable and multivariable analyses showed treadmill exercise time to be predictive of outcome.

Can a simple exercise stress test replace cardiopulmonary stress testing for patients being evaluated for heart transplantation? Possibly, but we do not advocate this approach. By both OOB change in c-index and integrated discrimination improvement, we found that peak $\dot{V}O_2$ is a more powerful predictor of mortality than treadmill exercise time. Other researchers have also found measured peak $\dot{V}O_2$ to be a better predictor than either estimated peak $\dot{V}O_2$ or work rate. Another advantage of cardiopulmonary stress testing is the ability to measure patient effort (ie, respiratory exchange ratio). When patients achieve an adequate level of effort, peak $\dot{V}O_2$ is a reliable and reproducible measurement and does not depend on the use of only 1 exercise protocol. Exercise time may not be as reproducible, based on the results of HF-ACTION (Heart Failure and A Controlled Trial Investigation Outcomes of exercise trainIng), which repeated within 7 days a baseline exercise study in 401 patients with systolic heart failure (87% of whom used a modified Naughton protocol); the study noted that the peak $\dot{V}O_2$ was unchanged, but exercise time increased by 26 seconds on average. Cardiopulmonary stress testing can also help identify noncardiac causes for shortness of breath.

However, cardiopulmonary stress testing is not available in every hospital, and therefore, treadmill exercise time may be a reasonable screening tool for physicians to determine prognosis and need for referral to advanced heart failure treatment centers. On the basis of the present data, treadmill exercise times of less than 5 minutes 17 seconds for women and less than 6 minutes for men may be useful cutoff values when a modified Naughton protocol is used, because in the present study cohort, this corresponded to approximately a 15% 1-year mortality rate. Future research in other cohorts will be needed to verify our findings.

The strengths of the present study include a large sample size with a large number of hard events, prospective data collection, adequate power to present sex-specific results, and the recording of treadmill exercise time to the nearest second. All end points were determined by query of databases outside our center. Deaths were determined by Social Security files, whereas UNOS 1 transplantation was determined by direct query of UNOS files. Of note, 20% of patients who experienced UNOS 1 transplantation underwent transplantation outside our center; thus, an ascertainment bias based on consideration of only events known to Cleveland Clinic information systems was avoided. Body mass index was calculated on the basis of direct measures of height and weight. We adjusted for >35 clinical/demographic variables, which included sex, peak $\dot{V}O_2$, and coronary artery disease, and still found a longer exercise time interval to be associated with a lower hazard of death. We also used both traditional (c-index) and contemporary statistical discrimination and reclassification methods to assess model performance.

The c-index values reported here are lower than those we reported previously for a similar cohort. We now have adopted a more sophisticated and conservative method (OOB
c-index) than what we used previously. This approach effectively simulates numerous internal validations, and as expected, model performance would be worse if applied to the entire original data set.

Limitations include that this was a single-center study with only patients who could ambulate on a treadmill. Because the cohort included patients from 1997, there were only a few patients who used aldosterone antagonists, there was modest β-blocker usage, and 25% of patients had an ICD. However, these proportions all compare favorably to what is seen in registries that have been published recently.28–31 Biventricular pacemakers were not reported separately during database entry, but most are identified in the ICD category, because at our institution, biventricular pacemakers are almost always implanted with an ICD. Therefore, when adjusting for all possible confounding variables, we included those with an ICD alone and with an ICD combined with a biventricular pacemaker. Laboratory tests such as measurement of B-type natriuretic peptides were not included in the baseline characteristics because they were not routinely obtained at our center between 1997 and 2007. Although B-type natriuretic peptide has prognostic value, it has not been used in other heart failure survival models.17,32–35 Like all epidemiological studies, we also cannot account for variables that change with time that may have an impact on death, such as patients receiving an ICD after the cardiopulmonary stress test or changes in medication with time. However, this limitation is inherent in all studies that have confirmed the value of cardiopulmonary stress testing as a prognostic tool. We also did not compare treadmill exercise time to indices of ventilatory inefficiency such as the Ve/VCO₂ slope, PETCO₂, oscillatory ventilation, and oxygen uptake efficiency slope, which are more powerful risk predictors than peak VO₂. These indices require minute-by-minute measurements that were not available in the present database.

Despite these limitations, we found that treadmill exercise time is a powerful and independent predictor of outcomes in both women and men with impaired left ventricular systolic function.

Figure 4. Reclassification: One-year low-risk (<15%) and high-risk (≥15%) survival categories are cutoffs based on the observed national 1-year survival rate after heart transplantation. The end point is death, and improvement of classification is expressed as net reclassification improvement (NRI), which is dependent on the predefined cutoffs, and integrated discrimination improvement (IDI), which is not limited to predetermined risk categories. If a variable adds no predictive value to the model, all points fall on the dark line of identity within each figure. A spread around the line indicates modulation of predicted risk; if the variable correctly modulates predicted risk, there should be a greater preponderance of events (red open circles) above the line of identify. A, Model with clinical variables and peak VO₂ compared with model with only clinical variables. Peak VO₂ with cardiac risk factors improved classification in 74 patients (23 who died, 51 who survived) but worsened it in 71 patients (4 who died, 67 who survived), with an IDI of 2.4%. B, Model with clinical variables and treadmill exercise time compared with model with only clinical variables. Treadmill exercise time with cardiac risk factors improved classification in 70 patients (21 who died, 49 who survived) but worsened it in 68 patients (4 who died, 64 who survived), with an IDI of 1.9%. C, Model with clinical variables and treadmill exercise time compared with model with clinical variables and peak VO₂ improved classification in 43 patients (6 who died, 37 who survived) but worsened it in 46 patients (8 who died, 38 who survived), with an IDI of −0.4%, which was not statistically significant.
function, even after accounting for peak oxygen consumption. These findings have potentially important implications for our understanding of the clinical pathophysiology of systolic cardiac dysfunction, as well as for finding optimal pathways to screen heart failure patients for possible transplantation. Because cardiopulmonary stress testing is not available in every hospital, treadmill exercise time with a modified Naughton protocol may be of value as an initial prognostic screening tool.

Sources of Funding

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Disclosures

None.

References


Physicians often refer patients with advanced heart failure for exercise testing with metabolic gas exchange measurements to assess suitability for cardiac transplantation. Peak oxygen consumption and other metabolic measures are known to be powerful predictors of mortality. We asked whether treadmill exercise time according to a standardized protocol might be comparable to peak oxygen consumption for assessment of prognosis. We analyzed the outcomes of 2231 patients with systolic heart failure who all underwent metabolic exercise stress testing on a modified Naughton protocol. During a mean follow-up of 5 years, 742 patients (33%) died, and 249 patients (11%) underwent heart transplantation urgently. We found that after accounting for baseline clinical characteristics, treadmill exercise time performed similarly to peak oxygen consumption for predicting poor outcome. For a 1-minute change in exercise time, there was a 7% increased hazard of death (eg, comparing 480 to 540 seconds, hazard ratio = 1.07, 95% confidence interval 1.02 to 1.12, \( P = 0.004 \)). Mortality rates were particularly high for women who exercised less than 5 minutes and 17 seconds and for men who exercised less than 6 minutes. Our findings suggest that treadmill exercise time may be valuable as an initial prognostic screening tool in patients with advanced heart failure.

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Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2009/06/15/CIRCULATIONAHA.109.848382.DC1
Appendix Figure Legends

Appendix Figure 1. Kaplan-meier plots for (A) women and (B) men, stratified by quartiles of treadmill exercise time. (A) Women (N=602) Quartile 1: 21-315 seconds, Quartile 2: 317-478 seconds, Quartile 3: 480-600 seconds, Quartile 4: 603-1320 seconds. (B) Men (N=1629) Quartile 1: 35-357 seconds, Quartile 2: 360-480 seconds, Quartile 3: 484-657 seconds, Quartile 4: 660-1415 seconds.

Appendix Figure 2. Kaplan-meier plots for (A) women and (B) men with peak VO$_2$≥14, stratified by tertiles of increasing treadmill exercise time. (A) Women: Tertile 1: < 518 seconds, Tertile 2: 518-639 seconds, Tertile 3: ≥ 640 seconds. (B) Men: Tertile 1: < 511 seconds, Tertile 2: 511-682 seconds, Tertile 3: ≥ 683 seconds. Peak VO$_2$= peak oxygen consumption

Appendix Figure 3. Change in out-of-bagging determined prediction error. Only the 10 most important variables are shown. Results are based on 100 bootstrapped samples

Appendix Figure 4. Reclassification: One year low-risk (<15%) and high-risk (≥15%) survival categories are cut-offs based on the observed national 1-year survival after heart transplantation. The improvement of classification to predict death or need for UNOS status 1 heart transplantation is expressed as net reclassification improvement (NRI) which is dependent on the pre-defined cut-offs and integrated discrimination improvement (IDI) which is not limited to pre-determined risk categories. If a variable adds no predictive value to the model, all points fall on the dark line of identity within each figure. Spread around the line indicates
modulation of predicted risk; if the variable correctly modulates predicted risk, there should be
a greater preponderance of events (red open circles) above the line of identity.  A. Model with
clinical variables and peak VO₂ compared to model with only clinical variables.  Peak VO₂
with cardiac risk factors improved classification in 150 patients (14 who died, 136 who
survived) but worsened it in 120 patients (10 who died, 110 who survived) with an IDI of 4.7%
B. Model with clinical variables and treadmill exercise time compared to model with only
clinical variables.  Treadmill exercise time with cardiac risk factors improved classification in
143 patients (15 who died, 128 who survived) but worsened it in 120 patients (8 who died, 112
who survived) with an IDI of 3.8%  C. Model with clinical variables and treadmill exercise
time compared to model with clinical variables and peak VO₂ improved classification in
85 patients (11 who died, 74 who survived) but worsened it in 72 patients (9 who died, 63 who
survived) with an IDI of -0.8% which was not statistically significant.
Appendix Table 1. Treadmill Exercise Time and Outcome: Cox Proportional Hazards Analyses

<table>
<thead>
<tr>
<th>Model: <em>Death or UNOS 1 Transplant</em></th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treadmill exercise time as a continuous variable*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>2.26 (2.05 to 2.49)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Adjusted for age and sex</td>
<td>2.33 (2.11 to 2.58)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Adjusted for age, sex, history of CAD, and peak VO$_2$</td>
<td>1.37 (1.13 to 1.67)</td>
<td>.002</td>
</tr>
<tr>
<td>Multivariable adjusted</td>
<td>1.34 (1.10 to 1.63)</td>
<td>.004</td>
</tr>
</tbody>
</table>

| Treadmill exercise time as a dichotomous variable^ |     |
| Unadjusted                                      | 5.20 (4.20 to 6.43) | <.0001 |
| Multivariable adjusted                         | 1.75 (1.15 to 2.66) | .009  |

* Comparisons are between the 25$^{th}$ percentile (317 seconds in women, 360 seconds in men) and 75$^{th}$ percentile (600 seconds in women, 657 seconds in men)

^ Comparisons between quartile 1 (<316 seconds in women, <358 seconds in men) and quartile 4 (>602 seconds in women, >659 seconds in men)
**Appendix Table 2.** Out of Bag (OOB) Concordance Index Values For Cox Regression Models

<table>
<thead>
<tr>
<th></th>
<th>Death or UNOS 1 transplantation</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Concordance Index (95% Confidence Intervals)</td>
</tr>
<tr>
<td>Clinical variables only</td>
<td>0.699 (0.679 to 0.719)</td>
</tr>
<tr>
<td>Clinical variables + Peak VO₂</td>
<td>0.726 (0.702 to 0.750)</td>
</tr>
<tr>
<td>Clinical variables + Time</td>
<td>0.722 (0.698 to 0.746)</td>
</tr>
<tr>
<td>Clinical variables + Peak VO₂ + Time</td>
<td>0.727 (0.703 to 0.751)</td>
</tr>
</tbody>
</table>
Appendix Figure 1.

A. Women

Death or UNOS 1 Transplantation

Log-rank $\chi^2=91$, df=3, $P<.001$

B. Men

Death or UNOS 1 Transplantation

Log-rank $\chi^2=244$, df=3, $P<.001$
Appendix Figure 2.

A. Women, Peak VO$_2$$\geq$14

Death or UNOS 1 Transplantation

Log-rank $\chi^2=12$, df=2, P=.002

B. Men, Peak VO$_2$$\geq$14

Death or UNOS 1 Transplantation

Log-rank $\chi^2=78$, df=2, P<.001
Change in Prediction Error for Outcome of Death or UNOS 1 Transplantation

- Peak Oxygen Consumption
- Male Gender
- Treadmill Exercise Time
- Blood Urea Nitrogen
- Digoxin
- Serum Sodium
- Beta-Blocker
- Body Mass Index
- Age
- Defibrillator

For Outcome Of Death or UNOS 1 Transplantation

Change in Prediction Error
1-Year Risk Predicted by Model Containing Clinical Variables and Peak VO₂

A. Dead or Tx at 1-year

Alive at 1-year

NRI 4.4% (P=.04)
IDI 4.2% (P<.001)

1-Year Risk Predicted by Model Containing Clinical Variables

B. Dead or Tx at 1-year

Alive at 1-year

NRI 4.5% (P=.03)
IDI 3.4% (P<.001)

1-Year Risk Predicted by Model Containing Clinical Variables and Treadmill Exercise Time

C. Dead or Tx at 1-year

Alive at 1-year

NRI 0.04% (P=0.98)
IDI -0.8% (P=0.99)

1-Year Risk Predicted by Model Containing Clinical Variables and Peak VO₂