Exercise Physiology

Comprehensive Use of Cardiopulmonary Exercise Testing Identifies Adults With Congenital Heart Disease at Increased Mortality Risk in the Medium Term

Ryo Inuzuka, MD*; Gerhard-Paul Diller, MD, PhD*; Francesco Borgia, MD; Leah Benson, BSc, MSc; Edgar L.W. Tay, MBBS, MRCP; Rafael Alonso-Gonzalez, MD; Margarida Silva, MD; Menelaos Charalambides, MBBS, BSc; Lorna Swan, MD, FRCP; Konstantinos Dimopoulous, MD, MSc, PhD; Michael A. Gatzoulis, MD, PhD

Background—Parameters of cardiopulmonary exercise testing were recently identified as strong predictors of mortality in adults with congenital heart disease. We hypothesized that combinations of cardiopulmonary exercise testing parameters may provide optimal prognostic information on midterm survival in this population.

Methods and Results—A total of 1375 consecutive adult patients with congenital heart disease (age, 33±13 years) underwent cardiopulmonary exercise testing at a single center over a period of 10 years. Peak oxygen consumption (peak VO2), ventilation per unit of carbon dioxide production (VE/VO2 slope), and heart rate reserve were measured. During a median follow-up of 5.8 years, 117 patients died. Peak VO2, heart rate reserve, and VE/VO2 slope were related to midterm survival in adult patients with congenital heart disease. Risk of death increased with lower peak VO2 and heart rate reserve. A higher VE/VO2 slope was related to higher risk of death in noncyanotic patients, whereas the VE/VO2 slope was not predictive of mortality in cyanotic patients. The combination of peak VO2 and heart rate reserve provided the greatest predictive information after adjustment for clinical parameters such as negative chronotropic agents, age, and presence of cyanosis. However, the incremental value of these exercise parameters was reduced in patients with peak respiratory exchange ratio <1.0.

Conclusions—Cardiopulmonary exercise testing provides strong prognostic information in adult patients with congenital heart disease. Prognostication should be approached differently, depending on the presence of cyanosis, use of rate-lowering medications, and achieved level of exercise. We provide 5-year survival prospects based on cardiopulmonary exercise testing parameters in this growing population. (Circulation. 2012;125:250-259.)

Key Words: exercise test ■ heart defects, congenital ■ oxygen consumption ■ prognosis

Adults with congenital heart disease (CHD) are at increased risk of mortality and morbidity.1,2 Cardiopulmonary exercise testing (CPX) has emerged as an important tool for risk stratification and may guide clinicians in assessing prognosis and planning interventions.3 Although various studies have linked individual parameters of CPX such as peak oxygen consumption (peak VO2), heart rate increase during exercise, and ventilatory efficiency to prognosis in adult CHD patients,4-6 it remains uncertain how best to apply these parameters in clinical practice. In particular, it is unclear how these parameters should be best combined to obtain prognostic information. Furthermore, no previous study has attempted to relate these parameters or an algorithmic combination of them directly to midterm survival rates in adults with CHD. Such information would be a useful adjunct to the clinician when assessing, for example, the risk of an intervention compared with an estimation of risk under conservative management. Available data using conventional statistical analyses are not particularly useful in this regard because they provide relative risk estimates rather than actual projected risk.

Editorial see p 210
Clinical Perspective on p 259

We therefore assessed the relation between parameters of CPX and survival in a large number of adult CHD patients undergoing CPX at a tertiary center over a 10-year period.
Furthermore, we investigated how exercise parameters can best be combined to predict midterm survival.

Methods
We retrospectively analyzed all CPX performed in adult CHD patients (>14 years of age) between January 1999 and December 2008 at the Royal Brompton Hospital, London, UK. Patients were referred for exercise testing as part of our routine clinical follow-up protocols. The study population comprised 1375 adult CHD patients with various diagnoses (Table 1). This study was approved by the local ethics committee.

Clinical Data
Demographic information, medication, and medical and surgical history refer to the time of exercise testing. We addressed only the first exercise test for those who underwent multiple tests. A main diagnosis was determined for all patients from hospital records. If >1 cardiac lesion was present, the lesion considered hemodynamically most significant was recorded as the main diagnosis. Patients with simple lesions were defined as those with an atrial or ventricular septal defect, patent ductus arteriosus, or aortic coarctation. Patients with complex cyanotic heart disease were those with a functionally univentricular heart without Fontan-type repair and those with unrepaired pulmonary atresia and aortopulmonary collateral arteries. Cyanotic patients were defined as those with oxygen saturation of <90% at rest or patients who were known to desaturate with exercise. Negative chronotropic agents were defined as β-blockers, nondihydropyridine calcium channel blockers, sotalol, and amiodarone.

Cardiopulmonary Exercise Testing
CPX was performed on a treadmill according to a modified Bruce protocol.7 This includes a stage 0 in which patients walk at a velocity of 1 mph at a 5% gradient. All patients were encouraged to exercise to exhaustion. Ventilation, oxygen consumption, and carbon dioxide production were measured continuously with a respiratory mass spectrometer (Amis 2000; Innovision, Odense, Denmark), as described previously.4–6 Heart rate was measured by continuous ECG, and blood pressure was recorded manually by sphygmomanometry. Oxygen saturation was monitored con-
Cardiopulmonary Parameters

Peak VO\textsubscript{2} was defined as the mean of the highest 2 consecutive values of 15-second averages of VO\textsubscript{2}. Percentage predicted VO\textsubscript{2} was calculated from the regression equations of Wasserman et al.\textsuperscript{8} The ventilation per unit of carbon dioxide production (Ve/\textit{VCO}_2 slope) was obtained by linear regression analysis of the data acquired throughout the entire period of exercise.\textsuperscript{5,9} The ventilatory threshold (VT) was measured by the V-slope method supplemented by additional parameters such as change in respiratory exchange ratio, Pet\textsubscript{CO}_2 increase, and Ve/\textit{VCO}_2 increase as suggested in previous publications.\textsuperscript{8,10–12} Heart rate reserve (HRR) was calculated as the difference between peak and resting heart rates.\textsuperscript{3} Patients with a cardiac pacemaker or those who had sustained tachyarrhythmia or a higher degree of atrioventricular block during exercise testing were excluded from the HRR analyses. The maximal voluntary ventilation (MVV) was estimated by multiplying the forced expiratory volume in the first second (FEV\textsubscript{1}) by 40. The breathing reserve was calculated from the following equation: Breathing reserve (%) = 100 × (MVV – peak minute ventilation)/MVV.\textsuperscript{13} The respiratory exchange ratio (RER) was defined as the ratio of V\textit{CO}_2 to VO\textsubscript{2}.

Follow-Up

All patients were followed up at the Royal Brompton Hospital. Survival status and time to death were assessed through the health service computer system, which is linked to a national database maintained by the Office of National Statistics. We opted to use all-cause mortality as our end point to eliminate any possibility of bias arising from incorrect classification of the cause of death.

Statistical Analysis

Categorical variables are presented as percent, and comparisons between groups were performed with χ\textsuperscript{2} tests. Numeric variables are expressed as mean±SD or median (interquartile range), and comparisons between groups were performed with the Wilcoxon rank-sum tests. Univariate Cox proportional hazards analysis was used to assess the association between variables and all-cause mortality. Significant parameters were subsequently included in a multivariate Cox regression model in a stepwise forward procedure. Model selection was performed by minimization of the Akaike information criterion, and retention criteria were set at P<0.05. To account for the potential confounding effect of negative chronotropic agents in analyses of HRR, analyses were performed both with stratification by the use of negative chronotropic agents and with exclusion of patients who were on such medications.

Time-dependent receiver-operating characteristics (ROC) curves from censored survival data using the nearest neighbor estimator (the weighted Kaplan-Meier estimator) were used to compare the sensitivity and specificity of variables and to estimate midterm survival.\textsuperscript{15} Sensitivity and specificity of a variable x (at a value of c) were calculated as follows: sensitivity = (Pc−Sc)/(1−St) and specificity = (St−Sc)/St, where Sc is the estimated 5-year survival rate in patients with the variable x≥c, St is the estimated 5-year survival rate in the whole population, and Pc is the proportion of patients with the variable x≥c. Cutoff values for variables were determined from the ROC curves so that the sum of sensitivity and specificity was maximized.\textsuperscript{15}

A random survival forest method was used to account for potential nonlinear effects of variables and to estimate midterm survival.\textsuperscript{16,17} The random survival forest method involves obtaining bootstrap samples from the original cohort and using each sample to compute a prediction model based on a splitting rule. Predicted survival for each patient was calculated from each model and averaged over each model. The prediction model was applied to the out-of-bag (OOB) data (ie, 36.7% of the whole data not used for model construction) to calculate the OOB concordant index (c index), a measure of model discrimination, which is conceptually similar to the area under ROC curve. The predictive value of each variable was assessed with minimal depth.\textsuperscript{18} Variables with a large minimal depth split the decision tree near the terminal and thus are unlikely to greatly affect prediction, whereas those with a small minimal depth split the tree close to the root and are considered highly predictive. The variable importance represents another measure of the predictive value of a variable. It was calculated as the difference between the OOB c index obtained from the original OOB data and that obtained from the permuted OOB data, in which variables are randomly rearranged.\textsuperscript{16} It thus tests how robust a variable is to random noise. A value of P<0.05 was considered statistically significant. Analyses were performed with R version 2.10.1 and the survival, survivalROC, gamsls, and randomSurvivalForest packages.\textsuperscript{16,17,19,20} Examples of R codes used for the statistical analysis are included in the online-only Data Supplement.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Baseline characteristics of the 1375 consecutive adult CHD patients are presented in Table I. Seventy percent of patients had undergone previous sternotomy, and 28% of patients had a history of thoracotomy (not mutually exclusive). Overall, 51% of patients were in New York Heart Association class I, 39% were in class II, and only 10% were in class III. The vast majority of patients (89%) were in sinus rhythm at the time of exercise testing. Nine percent of patients had a cardiac pacemaker. Cyanosis was present in 16.4% of patients, the majority of whom were those with Eisenmenger syndrome, followed by patients with a functionally univentricular heart who had not undergone a Fontan type of repair (Table 1).

A gradual decline in percentage predicted peak VO\textsubscript{2} was observed across the spectrum of CHD (Figure 1). The lowest values were found in patients with Eisenmenger syndrome, followed by those with complex cyanotic heart disease, with 81% and 60% having severe exercise limitation (<50% predicted peak VO\textsubscript{2}), respectively. In comparison, only 19% of patients with simple lesions had severe limitation. VT was achieved by 81% of patients. Factors associated with failure to achieve VT included cyanosis (P<0.001) and New York Heart Association class III (P<0.001). The majority of patients terminated exercise because of fatigue (n=671) or dyspnea (n=484). Other reasons for test termination included dizziness (n=74), chest discomfort (n=48), relevant arrhythmias (n=35), ST-elevation on ECG (n=8), high or low blood pressure (n=7), or a substantial drop in oxygen saturation (n=3).

Exercise Parameters and Outcome

During a median follow-up period of 5.8 years (interquartile range, 3.3–8.2 years), 117 patients (8.5%) died. The causes of death included heart failure (n=41), sudden cardiac death (n=34), perioperative death (n=12), infection (n=5), pulmonary embolism (n=1), hemoptysis (n=1), brain hemorrhage (n=1), and malignancy (n=1). There were 21 unexpected out-of-hospital deaths for which we could not establish exact causes of death because no autopsy data were available. Table 2 illustrates mortality rates according to underlying diagnos-
tic subgroup. Peak $\dot{V}O_2$, VT, HRR, and $V\dot{E}/V\dot{CO}_2$ slope were identified as univariate predictors of death on Cox proportional hazards analysis, whereas breathing reserve was not related to survival (Table 3). Other univariate predictors included age, resting oxygen saturation, and use of negative chronotropic agents.

To assess the impact of underlying diagnosis on the predictive value of parameters of CPX, hazard ratios were compared between diagnostic groups. Although confidence intervals (CIs) varied as expected because of group size and different numbers of events, the hazard ratios were similar between different diagnoses (Figure 2).

Peak $\dot{V}O_2$ ($\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and percentage predicted peak $\dot{V}O_2$ correlated strongly with each other ($r=0.81$, $P<0.001$). Therefore, we chose percentage predicted $\dot{V}O_2$ for multivariate analysis because the area under the time-dependent ROC curve was higher for percentage predicted $\dot{V}O_2$ compared with the absolute value of peak $\dot{V}O_2$ in predicting prognosis (area under the time-dependent ROC curve, 0.71 versus 0.68).

On multivariate Cox analysis stratified by the use of negative chronotropic agents, peak $\dot{V}O_2$ (hazard ratio, 0.78 per 10% increase; 95% CI, 0.69–0.90; $P<0.001$), HRR (hazard ratio, 0.85 per 10-bpm increase; 95% CI, 0.77–0.94; $P<0.001$), and resting oxygen saturation per 1% (hazard ratio, 0.96; 95% CI, 0.93–0.99; $P=0.009$) emerged as independent predictors of mortality. The same independent pre-

---

**Table 2. Number of Deaths in Each Anatomic Subgroup**

<table>
<thead>
<tr>
<th>Anatomic Subgroup</th>
<th>Deaths, n</th>
<th>5-y Mortality Rate, a (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n=1375)</td>
<td>117</td>
<td>6.8 (5.3–8.2)</td>
</tr>
<tr>
<td>Simple lesion (n=215)</td>
<td>13</td>
<td>4.0 (0.96–7.0)</td>
</tr>
<tr>
<td>Valvular disease (n=166)</td>
<td>8</td>
<td>5.5 (1.3–9.6)</td>
</tr>
<tr>
<td>Repaired TOF (n=377)</td>
<td>12</td>
<td>2.9 (1.1–4.7)</td>
</tr>
<tr>
<td>Ebstein’s anomaly (n=66)</td>
<td>5</td>
<td>8.4 (0.96–15.3)</td>
</tr>
<tr>
<td>Systemic right ventricle (n=148)</td>
<td>13</td>
<td>6.8 (2.6–10.8)</td>
</tr>
<tr>
<td>Fontan (n=92)</td>
<td>16</td>
<td>16.3 (8.0–23.8)</td>
</tr>
<tr>
<td>Eisenmenger syndrome (n=81)</td>
<td>17</td>
<td>16.7 (7.9–24.7)</td>
</tr>
<tr>
<td>Complex cyanotic disease (n=65)</td>
<td>19</td>
<td>21.1 (9.4–31.3)</td>
</tr>
<tr>
<td>Others (n=165)</td>
<td>14</td>
<td>5.0 (1.3–8.6)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; TOF, tetralogy of Fallot.

*Mortality rates are based on the Kaplan-Meier estimator.

---

**Table 3. Univariate Predictors of All-Cause Mortality**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exercise parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak respiratory exchange ratio</td>
<td>0.80 (0.69–0.93)</td>
<td>0.004</td>
</tr>
<tr>
<td>Ventilatory threshold</td>
<td>0.86 (0.83–0.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak $\dot{V}O_2$</td>
<td>0.89 (0.87–0.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percentage predicted peak $\dot{V}O_2$ (10%)</td>
<td>0.67 (0.61–0.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate reserve (10 bpm) with exclusion of patients on NCAs</td>
<td>0.74 (0.67–0.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate reserve (10 bpm) with stratification by the use of NCAs</td>
<td>0.75 (0.69–0.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$V\dot{E}/V\dot{CO}_2$ slope</td>
<td>1.02 (1.02–1.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fall in oxygen saturation &gt;5% during exercise</td>
<td>2.9 (2.01–4.18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Other univariate predictors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.03 (1.02–1.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting oxygen saturation</td>
<td>0.91 (0.89–0.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NCAs</td>
<td>3.35 (2.33–4.81)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; $\dot{V}O_2$, oxygen consumption; NCA, negative chronotropic agent; and $V\dot{E}/V\dot{CO}_2$ slope, ventilation per unit increase in carbon dioxide production.
Percentage predicted VO2 (10% increase)

<table>
<thead>
<tr>
<th>Anatomical diagnosis</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple lesions</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Valvular lesions</td>
<td>0.01</td>
</tr>
<tr>
<td>Repaired tetralogy of Fallot</td>
<td>0.13</td>
</tr>
<tr>
<td>Systemic right ventricle</td>
<td>0.01</td>
</tr>
<tr>
<td>Ebstein's anomaly</td>
<td>0.05</td>
</tr>
<tr>
<td>Fontan</td>
<td>0.58</td>
</tr>
<tr>
<td>Complex cyanotic</td>
<td>0.15</td>
</tr>
<tr>
<td>Eisenmenger syndrome</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Hazard ratio

Heart rate reserve (10 beats/min increase)

<table>
<thead>
<tr>
<th>Anatomical diagnosis</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple lesions</td>
<td>0.08</td>
</tr>
<tr>
<td>Valvular lesions</td>
<td>0.08</td>
</tr>
<tr>
<td>Repaired tetralogy of Fallot</td>
<td>0.98</td>
</tr>
<tr>
<td>Systemic right ventricle</td>
<td>0.23</td>
</tr>
<tr>
<td>Ebstein's anomaly</td>
<td>0.44</td>
</tr>
<tr>
<td>Fontan</td>
<td>0.04</td>
</tr>
<tr>
<td>Complex cyanotic</td>
<td>0.14</td>
</tr>
<tr>
<td>Eisenmenger syndrome</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Hazard ratio

dictors were identified when patients on negative chronotropic agents were excluded from analysis (hazard ratio, 0.79 per 10%; 95% CI, 0.66–0.96; P = 0.02; hazard ratio, 0.85 per 10-bpm; 95% CI, 0.75–0.97; P = 0.01; and hazard ratio, 0.94 per 1%; 95% CI, 0.90–0.98; P = 0.002, for peak VO2, HRR, and resting oxygen saturation, respectively).

Subanalysis using the VE/VO2 slope up to the ventilatory compensation point instead of calculating the slope from entire exercise period was also performed. No major differences in the predictive value of these 2 methods of calculating VE/VO2 slope were found. Similar to the VE/VO2 slope calculated over the entire exercise period, the VE/VO2 slope calculated up to the ventilatory compensation point was a univariate predictor (hazard ratio, 1.03; 95% CI, 1.02–1.05; P < 0.001) but not a multivariate predictor of outcome. Because the area under the time-dependent ROC curve on ROC analysis was slightly higher for the VE/VO2 slope from the entire exercise period compared with the VE/VO2 slope up to the ventilatory compensation point (area under the time-dependent ROC curve, 0.68 and 0.61, respectively), we decided to use this parameter for all subsequent analyses.

Subgroup Analysis for Cyanotic Patients

Of the 225 cyanotic patients, 38 patients (16.9%) died during a follow-up period of 6.2 years (interquartile range, 3.4–7.9 years). HRR was a univariate predictor of death both with stratification by the use of negative chronotropic agents (hazard ratio, 0.81 per 10 bpm; 95% CI, 0.70–0.93; P = 0.004) and with exclusion of patients on negative chronotropic agents (hazard ratio, 0.78 per 10 bpm; 95% CI, 0.64–0.94; P = 0.01). Other univariate predictors were peak VO2 (hazard ratio, 0.77 per 10%; 95% CI, 0.63–0.95; P = 0.01) and resting oxygen saturation (hazard ratio, 0.93; 95% CI, 0.89–0.97; P < 0.001). VE/VO2 slope and VT were not related to outcome (P = 0.59 and P = 0.26, respectively).

On multivariate analysis, HRR (hazard ratio, 0.83 per 10 bpm; 95% CI, 0.72–0.97; P = 0.02) and resting oxygen saturation (hazard ratio, 0.95; 95% CI, 0.90–0.99; P < 0.04) were independent predictors of death with stratification by the use of negative chronotropic agents. When patients on negative chronotropic agents were excluded, HRR was the only independent predictor of outcome.

Estimation of Midterm Survival With a Nonparametric Model

To account for nonlinear effects of variables on survival and interaction between variables, models based on a random survival forest were created. Estimated 5-year survival as a function of peak VO2, HRR, and VE/VO2 slope are provided in Figure 3. The cutoff values of 64% for percentage predicted peak VO2 and 71 bpm for HRR were suggested by time-dependent ROC as being optimal. Although the VE/VO2 slope was not found to be predictive in cyanotic patients, a higher VE/VO2 slope was related to increased risk of death in the noncyanotic cohort, with a VE/VO2 slope of 39 suggested as an optimal cutoff value on the basis of the results of time-dependent ROC analysis.

Peak VO2 and HRR were found to be predictive in both cyanotic and noncyanotic patients. HRR was related to outcome even in patients treated with negative chronotropic agents.

Peak VO2, HRR, use of negative chronotropic agents, age, and oxygen saturation at rest were identified as the strongest predictive markers on random survival forest analysis. The OOB c index for nested random survival forest models with variables ordered according to their predictive value is shown in Figure 4. Although the top 5 variables improved the overall OOB c index and thus had complementary value in terms of prediction, others such as anatomic diagnosis did not add significantly to the accuracy of prediction. Based on a model using these 5 strongest variables, contour plots were constructed to provide estimated 5-year survival for different combinations of peak VO2 and HRR (Figure 5). OOB c indexes for random survival forest models using different combinations of variables were compared (Table 4). The model containing only peak VO2, HRR, use of negative chronotro-
tropic agents, and cyanosis achieved an OOB c index of 0.774, which was comparable to the best model using all of the top 5 variables (OOB c index, 0.784).

To further elucidate the effect of the exercise level on predictive value of CPX parameters, variable importance was compared between patients with low and high peak RER. As expected, the variable importance for peak $\dot{V}O_2$ and HRR was smaller in patients with peak RER compared with those with RER (0.012 versus 0.072), suggesting that peak $\dot{V}O_2$ and HRR in patients with low RER add little predictive information to pretest risk factors (ie, age, use of negative chronotropic agents, and low oxygen saturation). The same variables were identified as prognostic markers when patients with RER were excluded from analysis.

Discussion

This study shows that peak oxygen consumption, HRR, and $\dot{V}E/\dot{V}CO_2$ slope are related to midterm survival in adult CHD patients. Although the $\dot{V}E/\dot{V}CO_2$ slope is not predictive of outcome in cyanotic patients, a high $\dot{V}E/\dot{V}CO_2$ slope is related to increased risk of death in noncyanotic patients. The combination of peak $\dot{V}O_2$ and HRR provides the greatest predictive value in addition to readily available clinical parameters such as the use of negative chronotropic agents, age, and low oxygen saturation. Furthermore, our study suggests that the prognostic value of exercise parameters is compromised for patients unable to achieve a peak RER >1.0.

Consistent with the results of previous studies, exercise capacity was found to be reduced in adult CHD patients (mean peak $\dot{V}O_2$, 66% of predicted value; Table 1). The degree of exercise limitation varied across the spectrum of adult CHD, with cyanotic patients representing the most limited subgroup (Table 1 and Figure 1). The present study provides information on the distribution of percentage predicted peak $\dot{V}O_2$ in different diagnostic subgroups from a large number of contemporary patients (Figure 1). These data may be useful to clinicians for comparing the exercise capacity of a particular patient with that of patients in the same diagnostic group.

It has been argued that parameters that are largely effort independent such as VT or $\dot{V}E/\dot{V}CO_2$ slope may be better suited for estimating prognosis compared with peak $\dot{V}O_2$. The $\dot{V}E/\dot{V}CO_2$ slope reflects ventilation-perfusion mismatch and derangement of peripheral and central chemoreceptors. The main advantage of the $\dot{V}E/\dot{V}CO_2$ slope lies in its robustness and the fact that it can be obtained reliably with submaximal exercise because the relationship between ventilation and carbon dioxide production is linear.
up to the ventilatory compensation point, which occurs after the VT. In contrast, peak $V_\text{O}_2$ and HRR require maximal exercise tests and thus depend on patient effort. Perhaps surprisingly, in the present study, however, these effort-dependent parameters were much stronger compared with the submaximal parameters (VT and $V_\text{E}/V_\text{CO}_2$ slope) in predicting outcome.

According to current guidelines for CPX, peak RER is the most accurate and reliable marker of adequate effort, and a peak RER/1.10 should generally reflect submaximal cardiovascular effort. It has been suggested that the prognostic

<table>
<thead>
<tr>
<th>Variables for Random Survival Forest Model</th>
<th>OOB C Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate prediction</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.549</td>
</tr>
<tr>
<td>Oxygen saturation at rest</td>
<td>0.678</td>
</tr>
<tr>
<td>Ventilatory threshold</td>
<td>0.609</td>
</tr>
<tr>
<td>$V_\text{E}/V_\text{CO}_2$ slope (for noncyanotic patients)</td>
<td>0.617</td>
</tr>
<tr>
<td>Percentage predicted peak $V_\text{O}_2$</td>
<td>0.676</td>
</tr>
<tr>
<td>HRR</td>
<td>0.711</td>
</tr>
<tr>
<td>Multivariate prediction</td>
<td></td>
</tr>
<tr>
<td>Peak $V_\text{O}_2$ + NCAs</td>
<td>0.723</td>
</tr>
<tr>
<td>$V_\text{E}/V_\text{CO}_2$ slope + NCAs (for noncyanotic patients)</td>
<td>0.724</td>
</tr>
<tr>
<td>HRR + NCAs</td>
<td>0.739</td>
</tr>
<tr>
<td>NCAs + age + oxygen saturation at rest</td>
<td>0.739</td>
</tr>
<tr>
<td>Peak $V_\text{O}_2$ + HRR + NCAs + cyanosis</td>
<td>0.774</td>
</tr>
<tr>
<td>Peak $V_\text{O}_2$ + HRR + NCAs + age + oxygen saturation at rest</td>
<td>0.784</td>
</tr>
</tbody>
</table>

OOB indicates out-of-bag; $V_\text{E}/V_\text{CO}_2$ slope, ventilation per unit increase in carbon dioxide production; $V_\text{O}_2$, oxygen consumption; HRR, heart rate reserve; and NCA, negative chronotropic agent.

Figure 4. Predictive value of variables. Variables are ordered by predictive value assessed with the minimal depth method according to nested random survival forest (RSF) models. Improvement in out-of-bag concordant index (OOB c index) was observed when the top 5 variables (●) were added to the models, whereas other variables (○) did not further improve the accuracy of prediction. HRR indicates heart rate reserve; NCAs, negative chronotropic agents; Peak $V_\text{O}_2$, percentage predicted peak oxygen consumption; RER, respiratory exchange ratio; and VT, ventilatory threshold.

Figure 5. Estimated 5-year survival rate for different combinations of peak oxygen consumption and heart rate reserve. Five-year survival was estimated from the results of the random survival forest model with the use of peak oxygen consumption (peak $V_\text{O}_2$), heart rate reserve, use of negative chronotropic agents, age, and oxygen saturation at rest. Estimated 5-year survival is illustrated as contour plots for different combinations of peak $V_\text{O}_2$ and heart rate reserve. The contour plots are provided separately, depending on the presence of cyanosis and the use of negative chronotropic agents.
value of peak $\dot{V}O_2$ may be reduced in the presence of a low peak RER.33 Consistent with these results, we found that an RER $<1.0$ was related to substantial reduction of the predictive value of peak $\dot{V}O_2$ and HRR in the present study. Thus, although RER itself was not a strong predictor of survival, it affected the accuracy of the prediction based on parameters of CPX.

In the present study, 18% of patients failed to achieve VT. Factors affecting the ability to achieve VT were the presence of cyanosis and more pronounced heart failure symptoms. The precise mechanism by which cyanosis affects the achievement of VT is not well understood.34,35 Excessive ventilatory response and gas exchange abnormalities resulting from ventilatory-perfusion mismatch have been reported in cyanotic patients, which may result in ventilatory limitation during exercise.6 Another possible cause of failure to achieve VT in an adult CHD population may be skeletal muscle deconditioning. There is evidence that adults with CHD are deconditioned as a result of inappropriate restriction from participation in physical activities.36–38 In fact, Greutmann et al39 recently showed that the degree of respiratory and skeletal muscle weakness commonly present in adult CHD patients is comparable to that in patients with advanced heart failure in acquired heart disease. It is possible that patients with muscle weakness terminate CPX before the limits of the cardiovascular system are reached, which, in turn, would result in failure to achieve VT.

Chronotropic incompetence, a blunted increase in heart rate during exercise, is an established predictor of all-cause mortality in patients with ischemic heart disease40,41 and adults with CHD.5 It has been suggested that HRR is related to autonomic dysfunction, neurohormonal activation, and cardiac arrhythmias.5,42–44 In acquired heart failure, chronotropic response has been shown to relate to outcome even in patients treated with $\beta$-blockers.45 Our study demonstrates, for the first time in a congenital heart setting, that the prognostic value of HRR is maintained even in patients treated with medications affecting chronotropic response. The prognostic power of HRR may reflect the high predisposition to arrhythmic events and sudden cardiac death of the adult CHD population.46,47 Further studies are required to assess the relationship between HRR and sudden cardiac death, as well as other parameters of autonomic dysfunction (eg, heart rate variability and heart rate turbulence).

The present study reveals that the combination of peak $\dot{V}O_2$ and HRR is a strong predictor of midterm mortality in adult CHD patients. We speculate that this can be explained, at least in part, by a synergistic effect of the prognostic value of peak $\dot{V}O_2$ in predicting mainly heart failure–related death and that of HRR for arrhythmia-related mortality. Because arrhythmia and heart failure are the 2 most common causes of death in the adult CHD population,1 their combination is not only statistically significant but also theoretically appealing.

Cutoff values for CPX parameters in the present study were obtained from time-dependent ROC curve analysis. These cutoff values were related to a more pronounced decline in survival as estimated by the random survival forest model. Although using dichotomous cutoff values is clinically convenient, these cutoff values are, by necessity, artificial, and we contend that CPX parameters should be interpreted as continuous values. Furthermore, the prognostic value is greatest when parameters are interpreted in combination. To enable clinicians to estimate survival prospects for different combinations of peak $\dot{V}O_2$ and HRR, we provide contour plots for midterm survival in Figure 5.

Study Limitations
CPX was performed as part of our routine evaluation of patients in the adult CHD clinic. All patients were at a tertiary adult CHD center; therefore, it is possible that they may not represent the pattern of adult CHD that may exist in the community. Although this may affect the prevalence of exercise intolerance, it is unlikely to affect the relation between exercise parameters and outcome, which was the main aim of the study.

Assessing the prognostic value of CPX parameters in specific diagnostic subgroups of adult CHD was beyond the scope of this study. Other smaller studies have provided such information. We aimed to develop an algorithm applicable to all adult CHD patients independently of diagnosis. Although prognosis is undoubtedly influenced by the different pathophysiological mechanisms present in different diagnostic groups, the results of the present study support the notions that hazard ratios of CPX parameters are largely comparable across the spectrum of adults with CHD (Figure 2) and that anatomic diagnosis has limited impact on estimates of survival as long as oxygen saturations are taken into account (Figure 4).

Conclusions
The combination of peak $\dot{V}O_2$ and HRR as measured on CPX provides the greatest predictive information in addition to readily available clinical risk factors such as use of negative chronotropic agents, age, and low oxygen saturation in adults with CHD. Because CPX parameters are influenced by patient effort, prediction is more reliable when a peak RER $>1.0$ is achieved. Although the results of the present study require further external validation, this study provides estimates of 5-year survival based on CPX parameter for this growing population.

Acknowledgments
We wish to thank the exercise laboratory staff for their ongoing support.

Sources of Funding
Dr Diller and the Adult Congenital Heart Disease Program were supported by Actelion, UK. Dr Borgia received support by the Italian Society of Cardiology. Dr Alonso-Gonzalez received support by Fundacion Alfonso Martin Escudero, Madrid, Spain. Dr Dimopoulos has received support from the European Society of Cardiology. Dr Gatzoulis and the Royal Brompton Adult Congenital Heart Centre have received support from the Clinical Research Committee at the Royal Brompton Hospital and the British Heart Foundation. No funding was obtained from medical companies for this research and article.
Disclosures

None.

References


Cardiopulmonary exercise testing (CPX) has emerged as an important tool for risk stratification in adults with congenital heart disease. However, it remains uncertain how best to apply CPX parameters in clinical practice. Relating a CPX result to prognosis may be difficult for clinicians because previous studies based on conventional statistical analyses provide relative risk estimates rather than actual projected risk. Moreover, it is unclear how CPX parameters should be combined to best obtain prognostic information. We assessed the relation between CPX parameters and midterm survival in 1375 adult congenital heart disease patients at a tertiary center over a 10-year period (median follow-up, 5.8 years). Estimated 5-year survival rates as a function of peak oxygen consumption, heart rate reserve, and ventilation per unit of carbon dioxide production (V˙E/V˙CO₂ slope) were calculated. The combination of peak oxygen consumption and heart rate reserve provided the greatest predictive information after adjustment for clinical parameters such as negative chronotropic agents, age, and presence of cyanosis. However, the incremental value of these exercise parameters was reduced in patients with peak respiratory exchange ratio <1.0. CPX provides strong prognostic information in adult patients with congenital heart disease. Prognostication should be approached differently, depending on the presence of cyanosis, use of rate-lowering medications, and achieved level of exercise. We provide 5-year survival prospects based on CPX parameters in this growing population.
Comprehensive Use of Cardiopulmonary Exercise Testing Identifies Adults With Congenital Heart Disease at Increased Mortality Risk in the Medium Term

Ryo Inuzuka, Gerhard-Paul Diller, Francesco Borgia, Leah Benson, Edgar L.W. Tay, Rafael Alonso-Gonzalez, Margarida Silva, Menelaos Charalambides, Lorna Swan, Konstantinos Dimopoulos and Michael A. Gatzoulis

*Circulation*. 2012;125:250-259; originally published online December 6, 2011;
doi: 10.1161/CIRCULATIONAHA.111.058719

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/125/2/250

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2011/12/06/CIRCULATIONAHA.111.058719.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation* is online at:
http://circ.ahajournals.org//subscriptions/
SUPPLEMENTAL MATERIAL.

Examples of R Code used for statistical analysis
For correspondence relating to details of the statistical analysis and R codes, please contact Dr. Inuzuka (inuzukar-tky@umin.ac.jp) or Dr. Diller (gerhard.diller@googlemail.com) directly.
Analyses were performed using R version 2.10.1 and the packages survival, survivalROC, gamlss and randomSurvivalForest.
This is an example, the dataset is named 'data', and the following variables are used:

PVO2 = percentage predicted peak oxygen consumption
fu.time = follow up time (in months)
death = event of all-cause mortality (1 and 0)

R code starts here:

library(survival)
library(survivalROC)
library(gamlss)
library(randomSurvivalForest)
ntree <- 1000
month<-60 # follow up time set to 5 years

###########code example figure 3########

object<- rsf(Survrsf(fu.time, death)~ .,data = data, ntree=ntree, splitrule = "logrank", forest=T)
prob<-length(object$time[object$time<month])/length(object$time)
baseForest <- object$forest
predictors <- object$predictors
npts<-25
class(baseForest) <- c("rsf", "partial")
x <- predictors[, object$predictorNames == "PVO2"]
n.x <- length(unique(x))
x.uniq <- sort(unique(x))[unique(as.integer(seq(1, n.x, length = min(npts, n.x)))]
n.x <- length(x.uniq)
yhat <- yhat.se <- NULL
newdata.x <- predictors
n <- nrow(newdata.x)
for (l in 1:n.x) {
    newdata.x[, object$predictorNames == "PVO2"] <- rep(x.uniq[l], n)
    pred.temp <- 100 * exp(-predict.rsf(baseForest, newdata.x)$ensemble[, max(which(object$timeInterest <= quantile(object$time, probs = prob, na.rm = TRUE)))]
    yhat <- c(yhat, mean(pred.temp, na.rm = TRUE))
    yhat.se <- c(yhat.se, sd(pred.temp/sqrt(n), na.rm = TRUE))
}

# cut-off value

nobs <- NROW(data)
ROC <- survivalROC(Stime=data$fu.time, status=data$death, marker = data$PVO2, predict.time = 60, span = 0.25*nobs^(-0.20))
cutoff <- ROC$cut.values[ROC$TP - ROC$FP == min((ROC$TP - ROC$FP))]  

# plot figure
plot(x.uniq, yhat, pch = 19, cex = 1, col = 1, xlim = c(20, 100), ylim = c(85, 98), xlab = "Percent of predicted VO2, %", ylab = "Estimated 5-year survival, %", las = 1)

ast <- data.frame(cbind(x.uniq, yhat))
xmax = 150
mod4 <- gamlss(yhat ~ lo(x.uniq), data = ast, trace = FALSE)
aa <- centiles.pred(mod4, xname = "x.uniq", xvalues = 4: xmax, cent = c(2.5, 50, 97.5))
points(4: xmax, aa[4: xmax, 2], type = "l", lty = 2, lwd = 1.0)
points(4: xmax, aa[4: xmax, 3], type = "l", lwd = 2.0)
points(4: xmax, aa[4: xmax, 4], type = "l", lty = 2, lwd = 1.0)
abline(v = cutoff, lty = 2, col = "gray50")
text(cutoff, 85, round(cutoff))
object<-varSel(Survrsf(fu.time, death)~ .,data = data, method="md",do.trace=T)
pnames.order<-rownames(object$varselect)
n.pred <- length(pnames.order)
err <- rep(0, n.pred)
for (k in 1:n.pred){
rsf.f <- "Survrsf(fu.time, death)~"
rsf.f <- as.formula(paste(rsf.f,paste(pnames.order[1:k],collapse="+")))
err[k] <- rsf(rsf.f, data, ntree=ntree,splitrule="logrank")$err.rate[ntree]
}
imp.out <-
   as.data.frame(cbind(object$varselect$depth,round(object$varselect$vimp,5),round(err,5)
               ,round(-diff(c(0.5,err)),5)),row.names=as.character(pnames.order))
colnames(imp.out) <-c("Depth","vimp","Err","Drop Err")
print(imp.out)

plot(1:10,as.numeric(1-imp.out$Err[1:10]),pch=c(19,19,19,19,19,21,21,21,21,21),type="b",xlab="",ylab="OOB c-index for nested RSF models",xaxt="n",cex.lab=1.1)
text(1:10,as.numeric(1-imp.out$Err[1:10])+0.005,labels=rownames(imp.out)[1:10],srt=90,adj=0)
text(5.5,0.45,"Variables added according to predictive value",xpd=T,adj=0.5,cex=1.1)
 pv<-0.4
 text(5.5,pv,"Predictive value",xpd=T,adj=0.5,cex=1)
text(1,pv,"high",xpd=T,adj=0.5,cex=1)
text(10,pv,"low",xpd=T,adj=0.5,cex=1)
arrows(4,pv,2,pv,xpd=T,length=0.1,lwd=1.5)
arrows(7,pv,9,pv,xpd=T,length=0.1,lwd=1.5)