Cardiopulmonary Exercise Testing in Adults with Congenital Heart Disease:

Can We Prognosticate and Improve Prognosis?

Running title: Rhodes; Exercise testing in congenital heart disease

Jonathan Rhodes, MD
Department of Cardiology, Children’s Hospital, Boston, MA

Address for Correspondence:
Jonathan Rhodes, MD
Department of Cardiology
Children’s Hospital
300 Longwood Avenue
Boston, MA 02115
Phone: 617-355-3491
Fax: 617-739-3784
E-mail: jonathan.rhodes@cardio.chboston.org

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The primary task of the cardiopulmonary system is to provide blood flow and oxygen in quantities sufficient to support the individual’s metabolic needs. The cardiopulmonary system is maximally stressed when an individual’s metabolic rate is increased, a condition that occurs most commonly during physical activity or exercise. Cardiopulmonary exercise testing (CPX) quantitatively assesses a patient’s capacity to adapt to the hemodynamic demands of exercise. Those who are found to have a cardiopulmonary system incapable of supporting normal amounts of exercise are likely to be less resilient, more vulnerable to the illnesses and more predisposed to health complications when confronting inevitable challenges of life. A weakened cardiopulmonary system is also likely to be more susceptible to further damage or injury. It is therefore not surprising that data from CPX has been found to carry powerful and important prognostic implications.

Indeed, past studies have found that the peak oxygen consumption (VO₂) is one of the best predictors of morbidity or mortality in a variety of cardiovascular conditions including congestive heart failure¹,², pulmonary hypertension³, tetralogy of Fallot⁴, transposition of the great arteries⁵, and Fontan circulations⁶. The paper by Inuzuka et al⁷ is the latest contribution to this literature. These investigators have collected a large and diverse cohort of patients with congenital heart disease and have used novel, sophisticated statistical analyses to further establish the clinical value of CPX in this patient population. Their study found that peak VO₂ and heart rate reserve (HRR) data can be used to generate estimates of 5 year survival across a wide spectrum of adults with congenital heart disease (CHD). This information will certainly inform and enhance clinical decision making in this unique group of patients. It is interesting to note that a previous study examining the relationship between CPX data and mortality in Fontan
patients also found peak VO₂ and chronotropic incompetence to be powerful independent
predictors of increased mortality⁶.

There are a number of anomalies in Inuzuka et al’s paper that must, however, be noted. Almost
regardless of diagnosis, the %predicted peak VO₂ of the patients included in their study was
surprisingly low, below levels typically found in reports from other tertiary care centers. For
instance, the median peak VO₂ for patients with simple lesions (who should have peak VO₂
approaching 100% of predicted) was only 70% of predicted, and one quarter of the patients had
peak VO₂ <54%predicted. The respiratory exchange ratio (RER) at peak exercise was also
inappropriately low. It averaged, only 1.07±0.13, suggesting that a large fraction (perhaps a
majority) of the patients did not approach their cardiovascular limit and/or expend an adequate
effort (an RER>1.09 has been suggested as a threshold indicative of a good effort⁸. A number of
factors may account for these anomalies. However, the most plausible and likely explanation is
that many of Inuzuka et al’s patients terminated exercise before reaching their cardiovascular
limit. This may constitute a serious shortcoming for a study that seeks to evaluate the prognostic
value of peak exercise data, for it permits factors unrelated to a subject’s cardiovascular health
(e.g. the patient’s level of motivation on the day of the CPX test) to contaminate the data and
analyses. As one might expect, the prognostic power of peak VO₂ and HRR were significantly
reduced in patients whose peak RER was <1.00. When these patients were excluded from the
analyses, the CPX variables identified as prognostic markers remained unchanged. Indeed, it is
likely that the prognostic power of the CPX data was even stronger when patients with low peak
RER were excluded. More importantly, as the authors suggest, these considerations imply that it
would be inappropriate and potentially misleading to use Inuzuka et al’s data to draw
conclusions concerning an individual patient’s prognosis if the patient did not achieve an adequate RER on his/her CPX test.

Another surprising finding from Inuzuka et al’s paper was the relatively weak prognostic power of the VE/VCO₂ slope. The VE/VCO₂ slope has been found to be one of the most powerful independent predictors of mortality in patients with CHF⁹, pulmonary hypertension³ and tetralogy of Fallot⁴. Its relationship to mortality in these conditions is probably due to the fact that the slope elevation is largely a consequence of, and proportional to pulmonary blood flow maldistribution (resulting in ventilation/perfusion mismatch and inefficient gas exchange) that develops as a consequence of pulmonary capillary wedge pressure elevation (in patients with CHF)⁹, progressive pulmonary vascular disease (in patients with pulmonary hypertension)³ and pulmonary artery stenoses (in patients with TOF)¹⁰. Similar considerations may account for the strong association between VE/VCO₂ slope elevation and mortality in patients who have undergone atrial repairs of transposition of the great arteries⁵. However, the VE/VCO₂ slope has not been related to prognosis among patients with Fontan physiology⁶. This observation is probably explained by the fact that the slope elevation commonly encountered among Fontan patients is likely to a large extent related to pulmonary blood distribution (and ventilation/perfusion mismatch) secondary to the absence of a pulmonary ventricle and the consequent lack of normal pulmonary artery pulsatility. This condition is common to all Fontan patients. Therefore, in contrast to the aforementioned conditions, among Fontan patients the VE/VCO₂ slope elevation is not proportional to disease progression/severity and does not carry strong prognostic significance. The inclusion of Fontan patients within their study population may therefore underlie Inuzuka et al’s anomalous findings regarding the prognostic value of the VE/VCO₂ slope.
The data from Inuzuka et al’s study raise two important questions. First, would interventions that improve patients’ peak VO₂ effectively improve their 5 year survival? Cardiologists and surgeons are adept at using medical and surgical techniques to optimize a CHD patient’s anatomy/physiology and reduce the impact of his/her residual hemodynamic lesions to the lowest level possible using current technology. In contrast, however, exercise/rehabilitation programs are underutilized in the CHD population. These programs have been found to improve peak VO₂ in patients with CHD\textsuperscript{11,12}. They also improve the peak VO₂ and prognosis of patients with acquired heart disease\textsuperscript{13}. Similar benefits may also accrue to the growing adult CHD population. Second, would interventions that improve the HRR of patients with CHD (e.g., a lower threshold for pacemaker implantation and/or more physiologic pacing algorithms for patients with pacemakers) improve their survival? Patients with pacemakers were excluded from Inuzuka et al’s HRR analyses, and their data therefore does not provide insights into this issue. Additional studies examining this question may be interesting and worthwhile.

**Conflict of Interest Disclosures:** None

**References:**


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