

Serial Exercise Testing in Patients with Congenital Heart Disease

Jonathan Rhodes, MD

Jonathan Rhodes, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115, the United States

Correspondence to: Jonathan Rhodes, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115, the United States

Email: jonathan.rhodes@cardio.chboston.org

Telephone: +1-617-355-7697 Fax: +1-617-739-3784

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ABSTRACT

Cardiovascular function is an important determinant of exercise function. Formal exercise testing can therefore provide clinically useful, quantitative and objective insights into a patient's cardiovascular status. Serial exercise studies evaluate the progress of an individual patient's exercise function over a period of time and provide clinicians with a unique perspective upon the natural history of congenital heart disease. They can also provide quantitative, objective data regarding the functional impact of various clinical interventions and often shed light on important physiologic processes that otherwise might not be appreciated.

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Key words: Heart disease; Congenital; Exercise test; Oxygen consumption

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WHY LONGITUDINAL AND SERIAL STUDIES?

Cross-sectional studies of exercise function, because they provide only a snapshot of a group of patients at a single point in time,

leave clinicians with many unanswered questions. For instance, cross-sectional studies cannot determine whether a patient with poor exercise function has experienced a progressive decline over time, or has always had a similar degree of exercise dysfunction^[1]. In the world of pediatric cardiology this issue is also complicated by the fact that the field has evolved rapidly over the past few decades. Innovations, both great and small, have dramatically affected the life expectancy and quality of life of patients with congenital heart disease. Researchers are therefore confronted by a clinical landscape that is always changing, in constant motion. Understanding the natural, or unnatural, history of individual congenital heart defects in this setting is therefore a complex affair and the inherent limitations of cross-sectional studies emerge as serious shortcomings. For example, if a study were to find that older subjects with a particular congenital heart defect performed less well than younger subjects, the study would be unable to unambiguously determine whether this observation was related to an era effect, i.e., less sophisticated cardiologic care available to the older subjects when they were young, or to a natural, time-related decline associated with the heart defect itself and unrelated to the medical advances achieved during the patients' lifetime. Indeed, the snapshots that cross-sectional studies provide are often blurred and hard to interpret.

Longitudinal studies (which, for the purpose of this paper, will be defined as studies that observe the natural evolution of exercise function in the absence of an intervention, in contrast to the term "serial exercise studies", which will refer to exercise tests performed before and after an intervention), on the other hand, evaluate the progress of individual patients over a period of time. They therefore can convey a more accurate and reliable picture of the natural history of congenital heart defects in the current era. The influence of era effects are also more readily appreciated and assessed.

The clinical importance of longitudinal exercise testing arises from the fact that the primary function of the cardiovascular system is to supply blood flow (and oxygen) in quantities sufficient to support the metabolic needs of the body. This function is maximally stressed

during physical activity (i.e., exercise)^[2]. Longitudinal assessments of an individual's exercise function can therefore provide unique and valuable insights into the capabilities and cardiovascular health of patients with congenital heart disease. These considerations also apply serial exercise studies, which can provided clinicians with objective, quantitative data regarding the effect of a cardiovascular intervention upon a patient's exercise function.

TECHNICAL ISSUES RELATED TO LONGITUDINAL STUDIES AND SERIAL EXERCISE TESTS

Body size and exercise capacity change rapidly during the pediatric years. These changes are especially dramatic during puberty. Furthermore, although gender-related differences in exercise capacity exist prior to puberty, these differences become more pronounced during and after the pubertal years. Exercise capacity also continues to change during adulthood. On average, peak \dot{V}_{O_2} declines by $\sim 0.7\%$ /year after age 21^[3]. Consequently, when comparing exercise test data from studies performed on an individual at different ages, the potential implications of these natural changes must be borne in mind. Because prediction equations (ideally) take these considerations into account, for peak \dot{V}_{O_2} and related variables [e.g., the oxygen pulse and the \dot{V}_{O_2} at the ventilatory anaerobic threshold (VAT)], it is usually best to express data as a percentage of predicted values, especially when the studies include patients in the pediatric and adolescent age groups^[2]. It must be noted, however, that the most commonly employed pediatric prediction equations were derived more than three decades ago in a group of 109 normal subjects^[4]. More recent studies have raised concerns about the applicability of these equations in the current era^[5]. Some have also suggested that account should be taken of seasonal changes in exercise function^[6].

Other exercise-test variables may also vary with age. For instance, Giardini *et al* recently reported that the \dot{V}_E/\dot{V}_{CO_2} slope declines during the pediatric years and then rises again during adulthood. When interpreting data from longitudinal studies, account must be taken of these natural changes as well^[7].

Patient effort can have a dramatic effect upon peak-exercise variables. Consequently, when comparing peak-exercise data from serial exercise tests, it is essential to ensure that an adequate effort was expended on both tests. Otherwise, the potential confounding effects of variable patient effort will make comparison of serial peak-exercise data uninterpretable or misleading. To achieve this goal, physiologic criteria for an adequate effort should be applied. Acceptable criteria include a respiratory exchange ratio (RER) ≥ 1.09 at peak exercise and/or a peak heart rate $>85\%$ of predicted at peak exercise (in the absence of a tachyarrhythmia)^[2]. Some investigators claim that the anaerobic metabolic pathways are less developed in children and therefore suggest that, for young subjects, a lower RER may be a more appropriate threshold^[8]. Of course, issues related to patient effort do not apply to data derived from submaximal exercise, e.g., the \dot{V}_{O_2} at the VAT and the \dot{V}_E/\dot{V}_{CO_2} slope.

CLINICAL UTILITY OF SERIAL EXERCISE TESTS

Serial exercise tests can provide quantitative, objective data regarding the benefits and/or effectiveness of therapeutic interventions that are undertaken for patients with congenital heart disease. The results of these studies are sometimes surprising and can reveal important physiologic phenomena that might otherwise be overlooked. A few studies selected from the pediatric cardiology literature, which

illustrate these points, will now be briefly reviewed.

Helber *et al* studied the exercise function of 31 adult patients before and after surgical ASD repair. Prior to surgery, the patients' exercise capacity was severely depressed (peak \dot{V}_{O_2} 13.1 mL/kg/min; $\sim 50\%$ of predicted). Four months post-operatively peak \dot{V}_{O_2} increased minimally (13.6 mL/kg/min). However, when tested 10 years post-op, peak \dot{V}_{O_2} had increased to normal levels (27.0 mL/kg/min; $\sim 95\%$ predicted). Similar patterns were observed for the peak work rate and the \dot{V}_{O_2} at the ventilator anaerobic threshold. The lack of improvement in exercise function at the 4 month post-operative visit was thought to be due to the debilitation associated with the trauma of surgery and inactivity during the convalescent period. The subsequent improvement in exercise function was attributed to a training effect that accompanied the resumption of normal physical activities. These observations underscored the important interaction between the cardiovascular and skeletal muscle systems^[9].

In 2008, Meadows *et al* reported the results of serial exercise tests in 20 Fontan patients before and after fenestration closure. Although transcatheter Fontan fenestration closure had previously been shown to engender an acute increase in arterial oxygen saturation, the procedure was also known to be associated with an acute decrease in systemic cardiac output and oxygen delivery. The sum result of these physiologic changes upon exercise capacity of Fontan patients had never been examined. The authors found that, although baseline and peak-exercise arterial oxygen saturations improved significantly after fenestration closure, there was no change in peak \dot{V}_{O_2} ($70.9 \pm 18.6\%$ to $74.0 \pm 18.6\%$, $p=NS$), heart rate, or O_2 pulse at peak exercise. They explained these findings by noting that, at peak exercise, oxygen uptake by the lungs is dependent upon the mixed venous oxygen saturation and the pulmonary blood flow, which in turn is determined the mean pulmonary artery pressure, the pulmonary vascular resistance and the mean left atrial pressure. Because oxygen extraction is maximized at peak exercise (and mixed venous oxygen saturation falls to the same low level, whether or not a fenestration is present), and because fenestration closure is unlikely to have a large impact upon the Fontan patient's pulmonary vascular resistance, pulmonary artery or left atrial pressure at peak exercise, fenestration closure is unlikely to have a dramatic effect upon peak \dot{V}_{O_2} . The authors also observed, however, that the \dot{V}_E/\dot{V}_{CO_2} slope fell in 20/20 patients after fenestration closure, and the end tidal pCO_2 at the VAT rose in 19/20 patients. This observation was attributed to the reduction in right to left shunting CO_2 -rich blood following fenestration closure^[10].

In contrast to the observations in Fontan patients, Rhodes *et al* reported that the peak \dot{V}_{O_2} of a patient with a large physiologic right to left shunt secondary to a pulmonary AV fistula improved following transcatheter occlusion of the fistula. In that case, the patent fistula impeded blood flow to the alveoli during exercise. Occlusion of the fistula allowed more blood to flow to the alveoli at peak exercise and thereby permitted greater oxygen uptake by the lungs at peak exercise. As with the Fontan patients, the elimination of the CO_2 -rich right to left shunt blood also engendered a decline in the \dot{V}_E/\dot{V}_{CO_2} slope and an increase in end tidal pCO_2 ^[11].

The results of serial exercise tests in tetralogy of Fallot patients undergoing pulmonary valve replacement surgery have been mixed. Some have found an improvement in exercise function^[12], others have not^[13-15]. The discrepancies are probably due, in part, to the time interval between the surgery and the post-operative exercise test; improvements in exercise function may not be observed until the deconditioning associated with the surgery and convalescence is reversed.

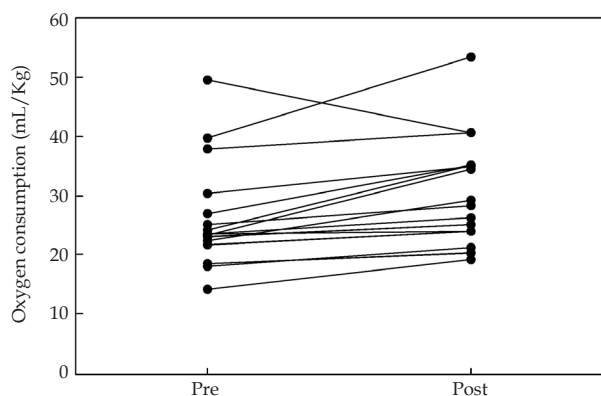


Figure 1 Effect of cardiac rehabilitation program on patients with congenital heart disease. Peak oxygen consumption rose in 15/16 subjects following cardiac rehabilitation; overall, oxygen consumption increased an average of 22% above baseline, pre-rehabilitation values. Pre: Pre-rehabilitation; Post: post-rehabilitation (From: Rhodes J *et al* Impact of cardiac rehabilitation on the exercise function of children with serious congenital heart disease. *Pediatrics*. 2005; 116:1339-1345 From: Rhodes J *et al* Impact of cardiac rehabilitation on the exercise function of children with serious congenital heart disease. *Pediatrics*. 2005; 116: 1339-1345.)

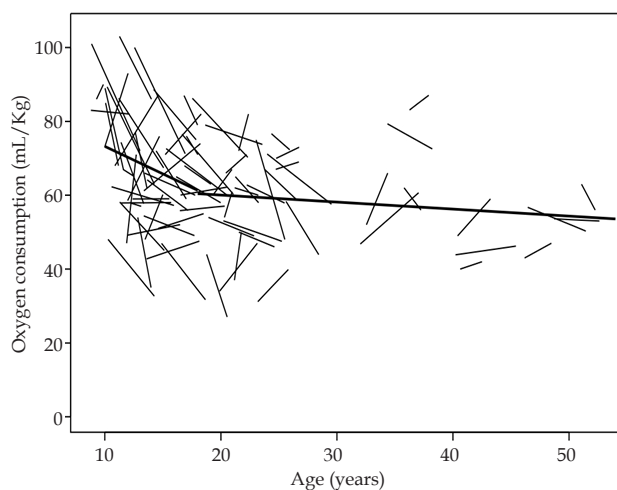


Figure 2 Longitudinal exercise function of patients following the Fontan procedure. Each thin line represents the regression line of exercise tests from an individual patient. The thick lines represent the average of all patients' regression lines before and after age 18 years. Percent predicted peak $\dot{V}O_2$ fell steeply prior to age 18; the decline was much more gradual thereafter. From: Fernandes SM *et al* Serial cardiopulmonary exercise testing in patients with previous fontan surgery. *Pediatr Cardiol*. 2010; 31: 175-180.

Several serial studies have documented acute improvements in the exercise function of patients with congenital heart disease have following participation in a formal exercise rehabilitation program (Figure 1)^[16-19]. Sustained benefits (more than 6 months after the termination of the rehabilitation program) have also been observed in rehabilitation subjects, but not in a group of control subjects with similar congenital heart defects observed during the same period^[20].

RESULTS OF LONGITUDINAL STUDIES OF EXERCISE FUNCTION IN CONGENITAL HEART DISEASE

There exists in the literature only a small number studies that have

focused upon the longitudinal exercise function of patients with congenital heart disease. In a study of 98 Fontan patients with serial exercise data, Fernandes *et al* found that the %predicted peak $\dot{V}O_2$ of patients with Fontan physiology tends to decline steeply during late childhood/adolescence and more slowly thereafter^[21]. The decline in peak $\dot{V}O_2$ appeared to be due primarily to a decline in the oxygen pulse at peak exercise. It was also associated with an increase in the $\dot{V}_E/\dot{V}CO_2$ slope during exercise. Multivariate analysis revealed that progressive impairment of the chronotropic response to exercise also accounted for some of the decline in peak $\dot{V}O_2$.

The observed steep decline in peak $\dot{V}O_2$ during late childhood/adolescence was attributed to the large increase in skeletal muscle mass that is associated with puberty. In normal individuals, this increase in muscle mass is accompanied by a commensurate increase in the ability to augment cardiac output (and oxygen delivery) during exercise. Consequently, peak $\dot{V}O_2$ (in mL/min) normally increases dramatically during the course of the adolescent years. However, unlike patients with normal, biventricular circulations, the Fontan patient's ability to increase cardiac output during exercise is limited. The increase in peak $\dot{V}O_2$ that is normally associated with puberty is therefore attenuated; consequently, % predicted values decline. The authors also observed that the decline in peak $\dot{V}O_2$ is more pronounced among male subjects compared to female subjects, and attributed this observation to the fact that the increase in muscle mass associated with male puberty typically exceeds that associated with female puberty^[21]. Giardini *et al* also analyzed serial exercise data from 53 patients with Fontan physiology. They too found a progressive decline in peak $\dot{V}O_2$ ^[22]. In contrast, Nir *et al* reported that the exercise function of 25 patients who had undergone a Fontan procedure between 1977 and 1989 remained stable^[23]. The initial peak $\dot{V}O_2$ of these patients from the early Fontan era was much lower than that reported in the more recent studies; this discrepancy probably accounted for the slower decline in Nir *et al*'s series.

Kipps *et al* analyzed serial exercise data from 70 patients who had undergone repair of Tetralogy of Fallot. They found a small annual decline in %predicted peak $\dot{V}O_2$. The decline was very variable, however. Once again, it was strongly associated with a concomitant decline in the oxygen pulse at peak exercise. An association between the decline in peak $\dot{V}O_2$ and a concomitant increase in the $\dot{V}_E/\dot{V}CO_2$ slope was also observed. Statistically significant associations were not observed between the rate of decline of %predicted peak $\dot{V}O_2$ and numerous clinical, echocardiographic and CMR variables^[24].

In another study, Kipps *et al* also analyzed longitudinal exercise data of 23 patients with Ebstein's anomaly. They observed a decline in %predicted peak $\dot{V}O_2$. The decline was steeper among patients <18 years of age. A decline in the oxygen pulse accounted for most of the decline in peak $\dot{V}O_2$. Multivariate modeling revealed that a decrease in the heart rate at peak exercise also contributed to the decline in peak $\dot{V}O_2$ ^[25].

In 2004, Roos-Hesslink *et al* reported the results of serial exercise tests in 50 patients with d-TGA palliated by a Mustard procedure. They found that the maximal exercise capacity of these patients averaged 84% of predicted in 1990 and declined to 72% of predicted in 2001. %Predicted peak heart rate did not decline during this time period. In contrast, Matthys *et al* detected no change in the exercise capacity during 6-17 years of follow-up in 16 patients who had undergone atrial switch procedures for d-TGA^[27].

Reybrouck *et al* reported the results of longitudinal exercise studies in 79 patients with a variety of congenital heart defects^[28]. These authors found that the $\dot{V}O_2$ at the VAT of patients with simple defects, who were not restricted from physical activity, remained

stable during the follow-up period. In contrast, patients with medically-imposed physical restrictions and/or significant residual hemodynamic lesions decreased significantly over time. In 2013, Muller *et al* reported the results of longitudinal exercise studies in 522 patients with a variety of congenital heart diseases. They observed a slow (1.01 ± 6.83 percentage point/yr) decline in peak VO₂ that appeared to be independent of diagnosis, heart disease severity, systemic ventricular morphology or age. The decline appeared to be steeper among patients who had a pacemaker^[1].

In summary, longitudinal studies have provided interesting and potentially important insights into the natural history of exercise function in patients with repaired congenital heart defects. They have revealed that a gradual deterioration in exercise function is common. In many patients and for many defects, deconditioning probably accounts for some of the decline. Undoubtedly other lesion-specific, reversible and irreversible phenomena also contribute to this process; the exact role of each factor remains to be elucidated.

Other studies have found that congenital heart disease patients with poor exercise function have a much higher mortality risk than those with well-preserved exercise function^[29-32]. The progressive decline in exercise function that has been observed in many longitudinal studies is therefore quite concerning. Are there any interventions that can effectively interrupt or reverse the decline in exercise function? Is a steep, sudden decline more concerning than a gradual decline? Serial exercise studies have demonstrated that various interventions can achieve acute, and sometimes sustained, improvements in exercise function. Will these improvements become associated with an improved long-term quality of life and a decreased mortality risk? Additional studies are needed to address these questions.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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Peer reviewer: Dr. Jan Muller, PhD, Clinical Exercise Physiologist, Department of Pediatric Cardiology and Congenital Heart Disease, Deutsches Herzzentrum München, Technische Universität München, Germany.