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.

Jonathan Rhodes, MD

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

Email: jonathan.rhodes@cardio.chboston.org

Received: November 11, 2014

Revised: December 3, 2014

Accepted: December 8, 2014

Published online: February 10, 2015

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)\(^{[1]}\). 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 VO\(_2\) declines by \(-0.7\%/\text{year}\) after age 21\(^{[1]}\). 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 VO\(_2\) and related variables [e.g., the oxygen pulse and the V\(_{\text{CO2}}\) 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\(^{[3]}\). More recent studies have raised concerns about the applicability of these equations in the current era\(^{[4]}\). Some have also suggested that account should be taken of seasonal changes in exercise function\(^{[5]}\).

Other exercise-test variables may also vary with age. For instance, Giardini et al recently reported that the \(V_{\text{E}}/V_{\text{CO2}}\) 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\(^{[6]}\).

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 exercise tests, which can provide clinicians with objective, quantitative data regarding the effect of a cardiovascular intervention upon a patient’s exercise function.

**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 VO\(_2\) 13.1 mL/kg/min; \(~50\%\) of predicted). Four months post-operatively peak VO\(_2\) increased minimally (13.6 mL/kg/min). However, when tested 10 years post-op, peak VO\(_2\) had increased to normal levels (27.0 mL/kg/min; \(~95\%\) predicted). Similar patterns were observed for the peak work rate and the VO\(_2\) 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 VO\(_2\) (70.9±18.6% to 74.0±18.6%, \(p=\text{NS}\)), 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 VO\(_2\). The authors also observed, however, that the \(V_{\text{E}}/V_{\text{CO2}}\) 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 VO\(_2\) 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 \(V_{\text{E}}/V_{\text{CO2}}\) 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.
Rhodes J. Serial cardiopulmonary exercise testing

There exists in the literature only a small number of 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 VO₂ of patients with Fontan physiology tends to decline steeply during late childhood/adolescence and more slowly thereafter[21]. The decline in peak VO₂ appeared to be due primarily to a decline in the oxygen pulse at peak exercise. It was also associated with an increase in the VO₂/VO₂CO₂ slope during exercise. Multivariate analysis revealed that progressive impairment of the chronotrophic response to exercise also accounted for some of the decline in peak VO₂.

The observed steep decline in peak VO₂ 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 VO₂ (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 VO₂ that is normally associated with puberty is therefore attenuated; consequently, % predicted values decline. The authors also observed that the decline in peak VO₂ 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].

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

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Oxygen consumption (mL/Kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>40</td>
<td>80</td>
</tr>
<tr>
<td>50</td>
<td>100</td>
</tr>
</tbody>
</table>

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].

There exists in the literature only a small number of 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 VO₂ of patients with Fontan physiology tends to decline steeply during late childhood/adolescence and more slowly thereafter[21]. The decline in peak VO₂ appeared to be due primarily to a decline in the oxygen pulse at peak exercise. It was also associated with an increase in the VO₂/VO₂CO₂ slope during exercise. Multivariate analysis revealed that progressive impairment of the chronotrophic response to exercise also accounted for some of the decline in peak VO₂.

The observed steep decline in peak VO₂ 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 VO₂ (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 VO₂ that is normally associated with puberty is therefore attenuated; consequently, % predicted values decline. The authors also observed that the decline in peak VO₂ 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].

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].

In another study, Kipps et al also analyzed serial exercise data from 23 patients with Ebstein’s anomaly. They observed a decline in %predicted peak VO₂. The decline was more gradual, 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 VO₂ and a concomitant increase in the VO₂/VO₂CO₂ slope was also observed. Statistically significant associations were not observed between the rate of decline of %predicted peak VO₂ and numerous clinical, echocardiographic and CMR variables[26].

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 VO₂ 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[20,21]. 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.

REFERENCES

1 Muller J, Ewert P, Hager A. Only slow decline in exercise capacity in the natural history of patients with congenital heart disease: A longitudinal study in 522 patients. European journal of preventive cardiology 2013
3 Jones NL. Clinical exercise testing. Philadelphia: W.B. Saunders; 1997: 131-134
10 Meadows J, Lang P, Marc G, Rhodes J. Fontan fenestration closure has no acute effect on exercise capacity but improves ventilatory response to exercise. J Am Coll Cardiol 2008; 52: 108-113

253 © 2015 ACT. All rights reserved.


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