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Exercise Testing and Training in Children With Congenital Heart Disease

Jonathan Rhodes, MD; Ana Ubeda Tikkanen, MD; and Kathy J. Jenkins, MD, MPH

The primary function of the cardiopulmonary system is to provide blood flow (and oxygen) in quantities sufficient to support the metabolic needs of the body. The capacity of the cardiopulmonary system to fulfill this function is maximally stressed when an individual's metabolic rate is increased, a condition that occurs most commonly during physical activity/exercise. A number of physiological changes accompany and facilitate the accommodation of the circulatory system to the hemodynamic demands of exercise (Figure 1). In normal individuals, these changes (which during upright exercise include a tripling of the resting heart rate, a >60% reduction in systemic and pulmonary vascular resistance, and a >50% increase in stroke volume) can ultimately produce a >5-fold increase in cardiac output. The increase in cardiac output is accompanied by enhanced ventricular preload (as the ventricles move up their Starling curves to accommodate the increased workload), a doubling of systolic and mean pulmonary artery pressures (most of the increase in pulmonary artery pressures is due to the concomitant rise in left-sided filling pressures; the increase in transpulmonary pressure gradient is relatively small), and a more modest increase in systemic arterial pressures.¹⁻⁴

Congenital heart disease (CHD) may, in a variety of ways and to a variable extent, adversely affect these hemodynamic adaptations. For instance, patients with a Fontan procedure lack a pulmonary ventricle. They therefore cannot increase their pulmonary blood flow and pressures normally (and consequently cannot maintain their ventricular preload and systemic blood flow) during exercise.⁵ Patients with tetralogy of Fallot and other CHDs often have congenital and/or acquired abnormalities of their pulmonary vasculature and therefore may be unable to reduce their pulmonary vascular resistance normally. Patients with complex CHD often have sinus node dysfunction and may be incapable of developing a normal heart rate (HR) response to exercise.⁶ Ventricular dysfunction, residual shunts, valvular disorders, and associated pulmonary and skeletal muscle disorders may also impair the cardiopulmonary response to exercise.

An evaluation of a CHD patient's ability to exercise can therefore impart important information on the health of a child's cardiopulmonary system and provide valuable insights into the factors that might be limiting a child's ability to perform physical activities. The assessment of a child's or

adolescent's exercise function, however, poses unique challenges related to the patient's size and maturity. In addition, the dramatic changes that occur in the cardiopulmonary and musculoskeletal systems during the pediatric years complicate the interpretation of data acquired during these assessments. These considerations must be taken into account when children with CHD are evaluated.

Most of the clinical tests employed by the pediatric cardiologist assess the cardiopulmonary system when the patient is at rest. Although valuable, these tests do not necessarily predict the manner in which the cardiopulmonary system will respond to the demands of exercise, nor do they reliably inform the clinician about a patient's true capacity to perform physical activities. To acquire this information, assessments of exercise function must be undertaken. A number of tools are available to the clinician seeking to address this issue. The strengths and limitations of these tools will now be reviewed.

History

Assessments of a CHD patient's cardiopulmonary status should certainly include questions about the patient's exercise tolerance. It is important to recognize, however, that data derived from the responses to these questions must be interpreted cautiously.⁷ In a study of adolescents and young adults with CHD, Diller et al⁸ found that that self-reporting of exercise capacity is unreliable and that New York Heart Association class (a classification system based on the patients' self-reported symptoms) underestimated the true degree of exercise limitation. Indeed, "asymptomatic" CHD patients (New York Heart Association class I) had exercise capacities comparable to those of older adult subjects with congestive heart failure secondary to acquired heart disease. This discrepancy is probably to a large extent due to the fact that patients with CHD have never known what it feels like to have a normal cardiopulmonary system and therefore have an unrealistic concept of the normal "asymptomatic" state.

More complex instruments (such as the Child Health Questionnaire-Parental Form 50 and the Short Form-36 and other quality of life questionnaires) have encountered similar difficulties. For instance, in a study of 564 patients aged >14 years, with a variety of CHDs, Gratz et al⁹ found that self-reported physical functioning was a poor predictor of

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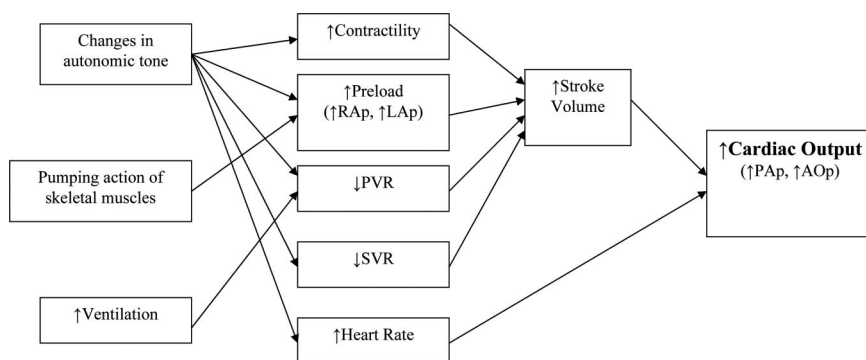


Figure 1. Some of the physiological changes that accompany and facilitate the accommodation of the circulatory system to the hemodynamic demands of exercise. RAp indicates right atrial pressure; LAp, left atrial pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; PAP, pulmonary artery pressure; and AOP, aortic pressure.

exercise capacity and that most patients with CHD severely overestimated their level of physical functioning.

The difficulties associated with deriving reliable data from patient self-reports are further compounded when the patient is a child or when the reports must be obtained from the parents of the patient.⁷ For instance, in the multicenter Pediatric Heart Network Fontan Study, the Child Health Questionnaire Physical Functioning Summary Score correlated poorly with results from formal exercise testing.¹⁰ In addition, there was a significant discrepancy between the patient's perception of his/her level of physical functioning compared with the parents' perception (parents perceived that their children were more impaired).

The 6-Minute Walk Test

The 6-Minute Walk Test (6MWT) requires a patient to walk as far as he/she can in 6 minutes. The course is a straight path 30 m (or 100 ft) in length; the patient must turn each time he/she reaches the end of the course. The patient is encouraged to cover as much ground as possible during the 6 minutes, but his/her pace should not be directly influenced by the examiner.¹¹ Portable pulse oximetry may be incorporated into the test, but the patient's heart rhythm and ECG are not monitored.

The advantages of the 6MWT are that it is easy to perform, does not require sophisticated equipment, and mimics activities of daily living.¹¹ It has therefore commonly been used in drug trials for adults with congestive heart failure or pulmonary hypertension. However, in all but the most limited patients, it is a submaximal test. Consequently, although it correlates fairly well with peak oxygen consumption in highly symptomatic patients, its utility and validity in patients with "only" mild or moderate impairments is dubious.¹² Indeed, the reliability and meaning of the 6MWT for patients who can walk >400 m has been questioned.¹³ In addition, the test is strongly influenced by patient motivation and other factors (such as leg length, body weight, orthopedic issues, and the ability to turn quickly at the ends of the course) unrelated to the cardiopulmonary system. It is difficult to control for or to quantify the influence of these variables on the outcome (distance walked) of the 6MWT. Hence, for any individual patient the test has a rather small "signal to noise ratio." Although these issues are mitigated somewhat in drug trials that include large numbers of patients, they make the interpretation of an individual's test (or serial studies in 1 individual) ambiguous and difficult. On account of these

considerations, the utility of the 6MWT in children with CHD is limited.

Finally, although the incidence of serious adverse events during a 6MWT is extremely low, having highly symptomatic patients exercise to (near) the limit of their capabilities, with limited monitoring, in a public corridor, appears imprudent.

Exercise Testing With ECG Monitoring

Exercise testing may be undertaken in conjunction with 12-lead ECG monitoring. The Bruce treadmill protocol is commonly employed for this purpose^{14,15}; endurance time is used as an index of exercise capacity. Nomograms are available for calculating the predicted, normal endurance time.¹⁴ For pediatric subjects, the normal range may be quite broad, however, and the clinical utility of this index is therefore somewhat limited. Endurance time is also heavily influenced by factors unrelated to the cardiopulmonary system (eg, obesity, orthopedic issues) and therefore often does not provide reliable information on a patient's cardiopulmonary status. This issue is further complicated by factors particularly relevant to pediatric exercise testing. Specifically, with this testing modality, it is often difficult to confidently ascertain whether a child has expended an optimal effort. A child's self-reported symptoms are subjective and potentially unreliable indicators of effort expenditure. Depending on the peak HR as an index of patient effort is also unreliable because many patients with postoperative CHD have sinus node dysfunction and/or are on medications that may impair the chronotropic response to exercise. Hence, the ability of exercise testing with ECG monitoring to provide objective quantitative information on a patient's exercise capacity is suboptimal. This testing modality also provides little information on the factors that may be responsible for a CHD patient's exercise intolerance.

Exercise testing with ECG monitoring is useful for detecting abnormal blood pressure responses, exercise-induced rhythm disturbances, ST changes, and arterial oxygen desaturation (when pulse oximetry is employed). In conjunction with myocardial perfusion imaging or stress echocardiography, it can also detect evidence of myocardial ischemia during exercise.¹⁵ For pediatric subjects with CHD, the presence or absence of exercise-induced ST-T abnormalities is not helpful with regard to the question of myocardial ischemia because of the presence of intraventricular conduction delays, baseline abnormalities, and ventricular

hypertrophy (especially in single ventricles) and the absence of normative data.

The treadmill speeds used for the higher levels of the Bruce protocol may be too fast for small children. Under these circumstances, alternative protocols or modifications of the Bruce protocol may be employed (although interpretation of endurance time then becomes even more problematic). Bicycle protocols may also be used.¹⁵ For these protocols, the peak work rate, rather than the endurance time, is used as an index of exercise capacity. Equations are available for calculating the predicted, normal peak work rate on the basis of a patient's age, gender, and size. The limitations associated with peak work rate as an index of cardiopulmonary function are similar to those described for the endurance time.

Cardiopulmonary Exercise Testing

In cardiopulmonary exercise testing, ECG monitoring is supplemented with expiratory gas analysis. For this analysis, a patient breathes room air through a mouthpiece (or face mask). The air passing through the mouthpiece is continually sampled, and the instantaneous concentrations of O₂ and CO₂ are ascertained. The volume of air passing through the mouthpiece is also measured. From these measurements, breath-by-breath estimates of oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), minute ventilation ($\dot{V}_E$), end-tidal PO₂, and end-tidal PCO₂ can be generated. These estimates can then be used to calculate clinically useful parameters that are particularly relevant to the assessment of patients with CHD. A number of these parameters will now be enumerated and discussed.

Peak $\dot{V}O_2$

For most normal individuals (and especially for individuals with cardiovascular disease), peak $\dot{V}O_2$ is limited by the amount of O₂ that the cardiopulmonary system can deliver to the exercising muscles. This in turn is limited by the ability of the circulatory system to increase cardiac output during exercise. Hence, peak $\dot{V}O_2$ (ie, the highest rate of $\dot{V}O_2$ detected during a progressive exercise test) is an excellent indicator of the capabilities of a patient's cardiovascular system.

Unfortunately, determining normal values for peak $\dot{V}O_2$ (in mL O₂ per minute) is not straightforward. Peak $\dot{V}O_2$ varies with age; it tends to increase and reach a maximum during adolescence/early adulthood and to decline progressively thereafter. It also differs significantly between males and females, especially after puberty. Normal values for peak $\dot{V}O_2$ are also dependent on body size; larger individuals can consume more oxygen than smaller individuals. The relationship between body mass and peak $\dot{V}O_2$ is, however, quite complicated. During exercise, adipose tissue consumes virtually no O₂ compared with skeletal muscle. Hence, merely normalizing peak $\dot{V}O_2$ for body mass ignores this important biological fact and can be misleading. The relationship between peak $\dot{V}O_2$ and body surface area or other anthropomorphic measurements is also complex. Normalizing peak $\dot{V}O_2$ for lean body mass or skeletal muscle mass is theoretically appealing, but accurate estimation of these parameters is difficult and impractical outside of the research setting.

Hence, normal values for peak $\dot{V}O_2$ are usually calculated from prediction equations, based on age, gender, height, and/or weight, that have been generated from a group of normal subjects. Ideally, the equation selected for an individual patient should have been generated with the use of a similar exercise protocol and from a population whose age and demographic background are similar to the patient's. For pediatric subjects, few studies have generated these kinds of data. The most widely used prediction equations are drawn from the study of Cooper and Weiler-Ravell.¹⁶ These investigators studied a group of 107 healthy children and adolescents aged 6 to 17 years and generated prediction equations based on gender and height (by relying on height rather than weight, the potential confounding effects of adiposity/obesity on the predictions are theoretically mitigated). The limitations of these prediction equations must, however, be recognized. They tend to generate unrealistically low values for small children. Hence, for subjects <130 cm tall, we calculate the predicted peak $\dot{V}O_2$, using the patient's ideal weight for height, on the basis of data from the study of Cooper and Weiler-Ravell that found that the peak $\dot{V}O_2$ of an average prepubescent boy was 42 mL/kg per minute and for an average prepubescent girl was 38 mL/kg per minute. For subjects aged ≥18 years, the equation of Jones et al,¹⁷ which generates predictions on the basis of age, height, body mass, and gender (height is weighted much more heavily than body mass), is theoretically appealing and has gained wide acceptance.¹⁸ The Wasserman equation, based on ideal body weight, is also widely used¹⁸ (albeit somewhat more cumbersome) and may have superior predictive power.¹⁹ Whichever equations are chosen by a laboratory, the validity of the predictions for the population served by the laboratory should be established by testing a number of normal subjects and confirming that the predicted values agree well with the results of these tests.¹⁸

Measurements of peak $\dot{V}O_2$ have been found to possess important clinical implications for patients with CHD. Peak $\dot{V}O_2$ has been found to be an independent predictor of death and/or hospitalization for patients with repaired tetralogy of Fallot,²⁰ patients who have undergone atrial switch procedures for transposition of the great arteries,²¹ patients with pulmonary hypertension,^{22,23} and patients with Fontan surgery.²⁴

HR During Exercise

During a progressive exercise test, HR increases linearly in proportion with $\dot{V}O_2$, from baseline levels to peak HR. The normal peak HR, for treadmill exercise, may be estimated from the following equation: peak HR = 220 – age (years).²⁵ Peak HR during bicycle exercise tends to be 5% to 10% lower,²⁶ and therefore it is reasonable to multiply the predicted peak HR derived from this equation by 0.925 if a bicycle exercise protocol is used.

Patients with sinus node dysfunction cannot increase their HRs to normal levels at peak exercise. In addition, the HR versus $\dot{V}O_2$ relationship tends to be depressed below the expected normal curve. In contrast, patients who cannot increase forward stroke volume normally during exercise tend to compensate by increasing their HRs more rapidly than normal during exercise, and the HR versus $\dot{V}O_2$ relationship is

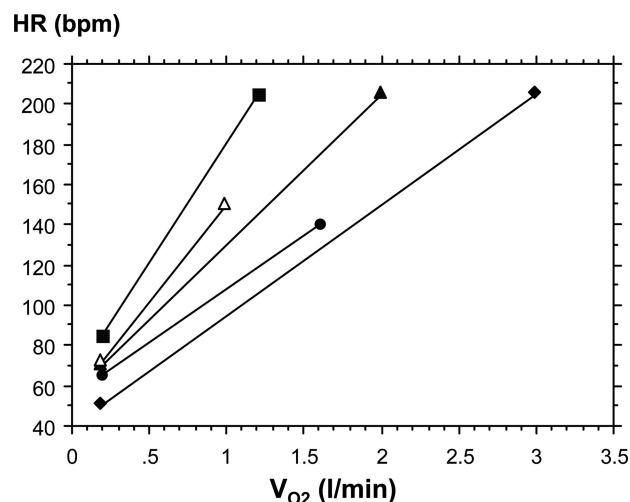


Figure 2. Influence of various clinical conditions on the relationship between HR and $\dot{V}O_2$ during exercise. Variation of HR with respect to $\dot{V}O_2$ during a progressive exercise test for a hypothetical 50-kg, 15-year-old normal subject (solid triangle), athlete (diamond), patient with a depressed chronotropic response (circle), patient with a depressed stroke volume response (square), and patient with both a depressed chronotropic and stroke volume response (open triangles) is shown. Note that the athlete's peak O_2P (peak oxygen consumption divided by peak HR) is above normal. The patient with a depressed stroke volume response has a below-normal peak O_2P and partially compensates for this condition by increasing HR more rapidly than normal, causing the slope of the HR- $\dot{V}O_2$ curve to be abnormally steep. In contrast, the patient with a depressed chronotropic response has an abnormally flattened curve and cannot achieve a normal peak HR, although a partial compensation for the chronotropic deficiency is achieved by increasing the peak $\dot{V}O_2$ (ie, stroke volume) to above-normal levels. (This pattern is also encountered in patients with structurally normal hearts who are receiving β -blocker therapy.) The patient with the depressed chronotropic and stroke volume response still has a steeper-than-normal slope but cannot achieve a normal peak HR and cannot compensate for this chronotropic deficiency by increasing stroke volume. This individual's peak $\dot{V}O_2$ is therefore more depressed than that of any of the other subjects. Reprinted with permission of the publisher from Rhodes.²⁷ Copyright © 2006, Elsevier.

elevated. Patients with impairment of both the chronotropic and stroke volume response to exercise may have “pseudo-normalization” of the HR versus $\dot{V}O_2$ relationship but would be unable to achieve a normal peak HR. Athletes, on the other hand, tend to have a larger-than-normal increase in stroke volume during exercise. Their HR versus $\dot{V}O_2$ relationship therefore appears depressed below the expected curve, but their peak HR is normal (Figure 2).²⁷

Recent adult studies have focused on the HR reserve (peak HR–resting HR) and the chronotropic index [$100 \times (\text{HR reserve}) / (\text{predicted peak HR} - \text{resting HR})$]. These new indices have not been studied widely in pediatric patients, and their relevance to this population remains uncertain.^{28,29}

Chronotropic incompetence (ie, an inability to increase HR to >80% of predicted at peak exercise) is common after surgery for CHD^{6,28,30,31} and has been associated with a poor prognosis.³⁰

Oxygen Pulse

The oxygen pulse (O_2P) at peak exercise is related to the forward stroke volume at peak exercise and is therefore, for

the clinician, one of the most useful indices available from the exercise physiology laboratory. The relationship between the O_2P and stroke volume is best understood by dividing both sides of the Fick equation by HR, as follows:

$$\dot{V}O_2 / \text{HR} = O_2P = (\text{cardiac output}) / (\text{HR}) \times (O_2 \text{ extraction})$$

O_2 extraction is equal to arterial O_2 content minus mixed venous O_2 content. These variables are in turn determined by the hemoglobin concentration and the corresponding O_2 saturations. Most patients with repaired CHDs have normal arterial O_2 saturations and normal hemoglobin concentrations. Furthermore, at peak exercise, O_2 extraction is maximized, and it has been found that the mixed venous O_2 saturation at peak exercise varies little across a wide spectrum of cardiovascular function. Hence, under most circumstances, O_2 extraction at peak exercise will vary little from patient to patient, and the O_2P will be proportional to forward stroke volume.³² Normal values for O_2P at peak exercise will, of course, be dependent on patient size, age, and gender. Normal values may be calculated by dividing the predicted peak $\dot{V}O_2$ by the predicted peak HR.¹⁸

The limitations associated with the O_2P concept must be borne in mind when these data are interpreted. In patients with depressed arterial O_2 content at peak exercise (eg, patients with anemia or patients with significant arterial desaturation), O_2 extraction at peak exercise would be less than normal and the O_2P would therefore underestimate stroke volume. In contrast, polycythemia increases arterial O_2 content and would therefore cause the O_2P to overestimate the stroke volume. Solely on the basis of Starling factors, relative bradycardia at peak exercise should engender a compensatory increase in the stroke volume and hence the O_2P at peak exercise. Consequently, in patients with low peak-exercise HRs, the absence of a compensatory increase in O_2P , above normal predicted values, is in fact abnormal.

The O_2P tends to be depressed in patients with conditions that impair their ability to increase forward stroke volume to appropriate levels at peak exercise. Patients with depressed ventricular function,³³ severe obstructive lesions, severe valvular regurgitation,^{34,35} and pulmonary or systemic vascular disease^{22,23,36} often have a low peak-exercise O_2P .

The O_2P is often depressed in patients who have undergone a Fontan procedure, even in the absence of ventricular or valvular dysfunction.²⁸ In these patients, the low O_2P probably reflects the absence of a pulmonary ventricle and the limited ability of the passively perfused pulmonary vascular bed to accommodate the high rate of blood flow normally present at peak exercise (a physiological function that greatly influences the exercise capacity of Fontan patients). Indeed, the O_2P is one of the strongest correlates of peak work rate in patients with Fontan circulations.²⁸

Skeletal muscle abnormalities that impair oxygen extraction, such as glycogen storage diseases, mitochondrial and other metabolic defects, or severe deconditioning, will also cause the O_2P to be depressed.

Young patients with chronic aortic regurgitation usually have well-preserved exercise function and peak-exercise O_2P .^{34,37} In these patients, the fall in systemic vascular resistance that normally accompanies exercise tends to lessen the severity of the regurgitation during exercise. In addition, the left ventricular

dilation typically present in chronic aortic regurgitation helps to maintain forward stroke volume and usually compensates effectively for the hemodynamic burden imposed by the leaky valve. (In the subset of patients with poor exercise function, however, a low O_2P is almost always present.) Similar factors may also help to preserve the exercise function of patients with other valvular insufficiency lesions.³⁸

Respiratory Exchange Ratio

If a patient does not expend a maximal or near maximal effort on an exercise test, the peak exercise data may not accurately reflect the true status of his/her cardiopulmonary system. Optimal interpretation of peak exercise data therefore requires information on the effort expended by the patient. Measurements of the respiratory exchange ratio (RER) during exercise often help to provide this important information.

The RER is the ratio of $\dot{V}CO_2$ over $\dot{V}O_2$. At rest, the RER is usually determined primarily by the stoichiometry of the chemical equations describing the aerobic metabolism of the fuels that the body uses to support its metabolic activities. For the aerobic metabolism of carbohydrates, 1 mol of CO_2 is produced for every mole of O_2 that is consumed; for fats, 1 mol of CO_2 is produced for every 1.5 mol of O_2 consumed. Hence, at rest, the RER is usually ≈ 0.85 (ie, somewhere between 0.67 and 1.00). During a progressive exercise test, as the anaerobic threshold is passed and an increasing fraction of the energy required by the exercising muscles is derived from anaerobic metabolism, $\dot{V}CO_2$ rises out of proportion to $\dot{V}O_2$, and the RER rises progressively. An RER ≥ 1.09 is considered to be compatible with a good effort. (Some investigators believe that the anaerobic metabolic pathways are less developed in children and therefore believe that, for young subjects, an RER ≥ 1.05 is a more appropriate threshold.) If a patient's RER at peak exercise is < 1.09 , it is likely that exercise was not terminated on account of insufficient O_2 delivery to the exercising muscles.^{39,40}

Ventilatory Anaerobic Threshold

During a progressive exercise test, the anaerobic threshold occurs when aerobic metabolism, limited as it is by the amount of O_2 delivered by the cardiovascular system, is insufficient to meet the energy requirements of the exercising muscles. The anaerobic threshold is a physiological phenomenon that is not affected by patient effort or motivation and may be determined on a submaximal exercise test. Consequently, it is an excellent index of the capacity of the cardiovascular system to support the hemodynamic demands of exercise. Because anaerobic metabolism produces CO_2 (through the buffering of lactic acid by bicarbonate) but does not consume O_2 , during a progressive exercise test the ventilatory anaerobic threshold (VAT) is marked by an increase in $\dot{V}CO_2$ out of proportion to the associated increase in $\dot{V}O_2$.

Prediction equations exist for the calculation of normal values for the VAT on the basis of age, size, and gender.¹⁶ VAT is also commonly expressed as a percentage of predicted peak $\dot{V}O_2$. In the absence of cardiovascular disease, VAT rarely falls below 40% of predicted peak $\dot{V}O_2$. However, VAT is often depressed below this value in patients with conditions that significantly impair the ability to increase

cardiac output or oxygen delivery appropriately during exercise.^{41,42} In children with CHD, the VAT is often depressed in a manner similar to, although milder than, the peak $\dot{V}O_2$.²⁸ Therefore, when peak $\dot{V}O_2$ data are available, VAT data do not often provide significant additional information. The HR at the VAT has been recommended as the target HR for rehabilitation training.

$\dot{V}E/\dot{V}CO_2$ Slope

Empirically, it has been observed that $\dot{V}E$ rises linearly in proportion with $\dot{V}CO_2$ during a progressive exercise test until a point above the VAT, when the accumulating lactic acidosis engenders a compensatory increase in $\dot{V}E$ out of proportion to the increase in $\dot{V}CO_2$. The $\dot{V}E/\dot{V}CO_2$ slope is the slope of the linear portion of this curve. It may be thought of as an index of gas exchange efficiency during exercise, equivalent to the number of liters of air that must be breathed out to eliminate 1 L of CO_2 .⁴³ In pediatric patients, the $\dot{V}E/\dot{V}CO_2$ slope should be < 28 .

The $\dot{V}E/\dot{V}CO_2$ slope is often elevated in patients with tetralogy of Fallot,²⁰ congestive heart failure,^{44–46} atrial switch procedures,²¹ and pulmonary hypertension.^{22,23} In these patients, $\dot{V}E/\dot{V}CO_2$ slope elevation has been associated with an increased risk of mortality. Although multiple factors may influence the $\dot{V}E/\dot{V}CO_2$ slope, pulmonary blood flow maldistribution and consequent ventilation/perfusion (V/Q) mismatch are probably the most important pathophysiological processes that underlie these observations and associations.^{47,48}

Efficient gas exchange across the alveolar/capillary membrane requires optimal V/Q matching. Patients who have undergone repair of tetralogy of Fallot often have residual pulmonary artery stenoses that cause pulmonary blood flow maldistribution, which in turn has been linked to $\dot{V}E/\dot{V}CO_2$ slope elevation and depressed peak $\dot{V}O_2$.^{48–50} These stenoses can have a particularly deleterious effect on the physiology of the postoperative tetralogy of Fallot patient and a strong, negative impact on a patient's prognosis. Effective relief of these stenoses has been associated with improvements in peak $\dot{V}O_2$ and the $\dot{V}E/\dot{V}CO_2$ slope (Figure 3).⁴⁸

Patients with CHF have pulmonary blood flow maldistribution as a consequence of the elevated pulmonary capillary wedge pressure that accompanies CHF.^{47,51} As ventricular function deteriorates and the wedge pressure rises, the pulmonary blood flow maldistribution (and consequent V/Q mismatch) worsens, and the $\dot{V}E/\dot{V}CO_2$ slope progressively rises. This strong link between pulmonary capillary wedge pressure and the $\dot{V}E/\dot{V}CO_2$ slope probably accounts for the prognostic power of the $\dot{V}E/\dot{V}CO_2$ slope in this patient population. In a similar manner, for patients who have had an atrial switch procedure for transposition of the great arteries, elevation of the $\dot{V}E/\dot{V}CO_2$ slope probably reflects the progressive systemic ventricular dysfunction that often develops in these patients as they age.

In patients with pulmonary hypertension, pulmonary blood flow maldistribution results from pulmonary vascular obstructive disease. As the vascular obstruction progresses, the pulmonary blood flow maldistribution worsens, gas exchange within the lungs becomes more and more inefficient, and the $\dot{V}E/\dot{V}CO_2$ slope rises. Hence, for patients with this condition, the $\dot{V}E/\dot{V}CO_2$ slope reflects the extent of disease within the

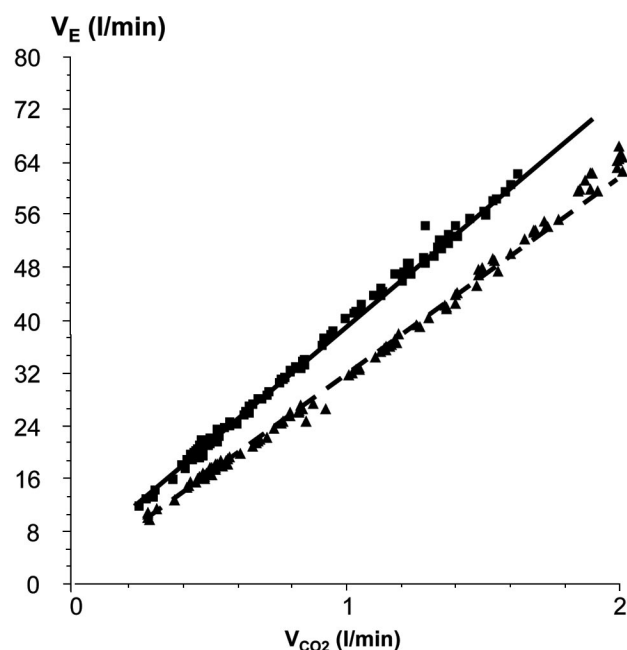


Figure 3. Relationship between $\dot{V}_E$ and $\dot{V}_{CO_2}$ in a patient with tetralogy of Fallot before and after successful pulmonary artery balloon angioplasty that increased left pulmonary artery blood flow from 13% to 35% of the total pulmonary blood flow. Square symbols are data points before angioplasty; triangular symbols are data points after angioplasty. The solid line represents the linear portion of the $\dot{V}_E/\dot{V}_{CO_2}$ relationship before angioplasty (the slope of the line is the $\dot{V}_E/\dot{V}_{CO_2}$ slope). The dashed line is the relationship after angioplasty. Note that, after the angioplasty, the patient's $\dot{V}_E$ was lower for any given $\dot{V}_{CO_2}$. The $\dot{V}_E/\dot{V}_{CO_2}$ slope fell from 35 to 29 and was associated with an increase in the peak $\dot{V}_{O_2}$ from 18.8 to 23.7 mL/kg per minute and a rise in the end-tidal P_{CO_2} at the anaerobic threshold from 32 to 36 mm Hg.

pulmonary vasculature.^{22,23} (This physiology may also be relevant to patients with transposition of the great arteries who develop pulmonary vascular obstructive disease after an atrial switch procedure.)

The $\dot{V}_E/\dot{V}_{CO_2}$ slope is also almost always elevated in patients with Fontan procedures.^{52,53} Once again, this observation is probably due, to a large extent, to pulmonary blood flow maldistribution (and associated V/Q mismatch) secondary to the absence of a pulmonary ventricle.⁵⁴ In Fontan patients, however, the degree of $\dot{V}_E/\dot{V}_{CO_2}$ slope elevation is not strongly associated with increased mortality because, in contrast to the aforementioned conditions, the elevated slope is intrinsic to the patients' single ventricle physiology and not closely related to the progression/severity of the underlying cardiovascular disease process.²⁴

Right to left intracardiac or intrapulmonary shunting will also cause the $\dot{V}_E/\dot{V}_{CO_2}$ slope to be elevated. The shunting allows CO_2 -rich systemic venous blood to enter the systemic arterial circulation. The consequent increase in arterial PCO_2 is sensed by chemoreceptors, inducing central nervous system respiratory centers to increase the patient's respiratory drive (and $\dot{V}_E$) and causing the $\dot{V}_E/\dot{V}_{CO_2}$ slope to rise. The resulting alveolar hyperventilation reduces the PCO_2 of the blood returning from the lungs and helps to normalize the patient's arterial PCO_2 . Eliminating right to left shunting (eg, by closing

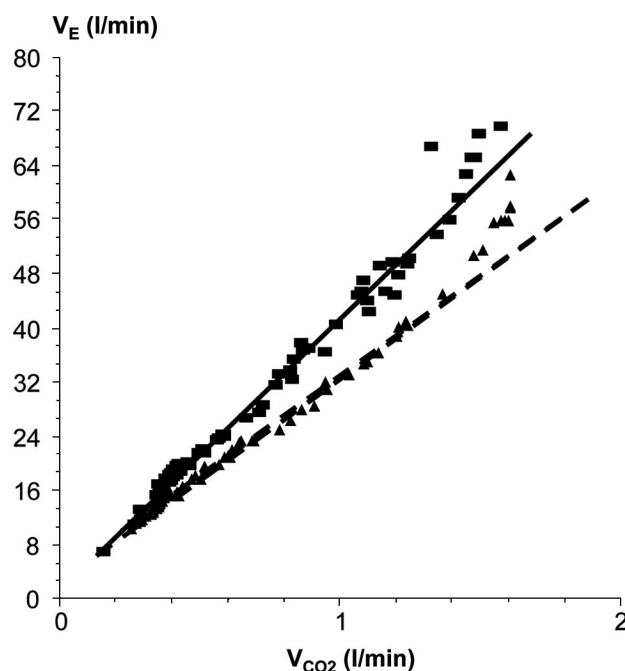


Figure 4. Relationship between $\dot{V}_E$ and $\dot{V}_{CO_2}$ in a patient with fenestrated Fontan before and after successful fenestration closure. Square symbols are data points before fenestration closure; triangular symbols are data points after closure. The solid line represents the linear portion of the $\dot{V}_E/\dot{V}_{CO_2}$ relationship before closure (the slope of the line is the $\dot{V}_E/\dot{V}_{CO_2}$ slope). The dashed line is the relationship after closure. Note that, after the fenestration closure, the patient's $\dot{V}_E$ was lower for any given $\dot{V}_{CO_2}$. The $\dot{V}_E/\dot{V}_{CO_2}$ slope fell from 41 to 30 and was associated with an increase in the end-tidal P_{CO_2} at the anaerobic threshold from 26 to 34 mm Hg. Peak $\dot{V}_{O_2}$ fell from 34.5 to 34.4 mL/kg per minute.

a Fontan patient's fenestration; Figure 4) almost always produces a reduction in the $\dot{V}_E/\dot{V}_{CO_2}$ slope.⁵⁵

Assessments of Pulmonary Function

The exercise capacity of normal individuals is usually limited by cardiovascular, rather than respiratory, factors. By this, we mean that the $\dot{V}_E$ at peak exercise is usually less than the maximum voluntary ventilation (the maximum amount of air that a subject can breathe in and out in 1 minute). The maximum voluntary ventilation is usually estimated by measuring the maximum amount of air a subject can breathe during 12 seconds of maximal hyperventilation and multiplying this quantity by 5. This maneuver requires a degree of patient cooperation that is often beyond the capacity of young subjects. Alternatively, the maximum voluntary ventilation may be estimated by multiplying the FEV_1 (from baseline spirometry) by 40.⁵⁶ (Some recommend multiplying the FEV_1 by 35.) The breathing reserve is the percentage of a subject's maximum voluntary ventilation that is not used at peak exercise and normally measures $\approx 30\%$.¹⁸ Patients with isolated cardiovascular disease typically have high breathing reserves because they have a greater cardiovascular limitation. Many patients with CHD, however, also have coexistent pulmonary problems. Measurement of the breathing reserve (as well as baseline spirometry) often helps to elucidate the factors contributing to a patient's exercise intolerance.

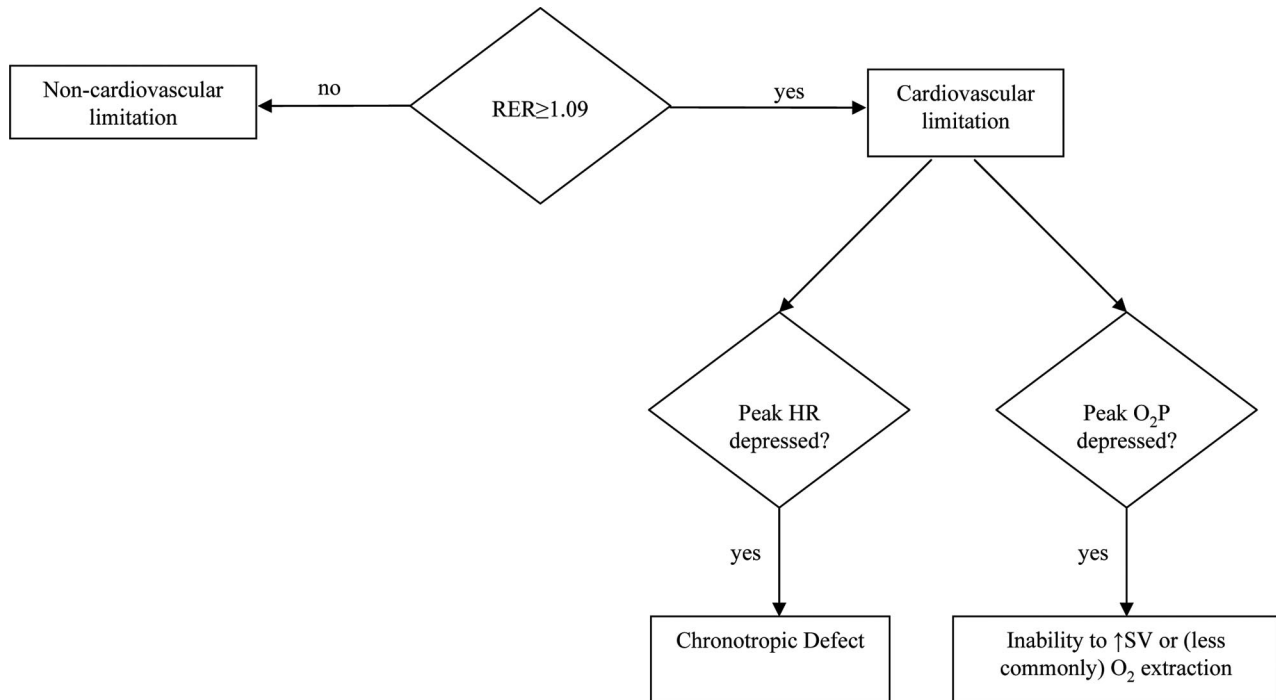


Figure 5. Algorithm for initial categorization of patients with low peak $\dot{V}O_2$. SV indicates stroke volume.

Interpretation of data from exercise tests in patients with CHD is also often enhanced by measurements of end-tidal PCO_2 . In healthy individuals, end-tidal PCO_2 approximates arterial PCO_2 . Consequently, at rest and at low exercise intensities, end-tidal PCO_2 measures ≈ 40 mm Hg. However, when exercise continues at intensities above the anaerobic threshold, arterial PCO_2 should fall as a compensatory respiratory alkalosis develops in response to the accumulating lactic acidosis. This fall should be accompanied by an almost parallel decline in the end-tidal PCO_2 .⁵⁷ Certain conditions sometimes encountered in patients with CHD, such as airway obstruction or hypoventilation secondary to obesity, will impede (and may even reverse) this normal decline. End-tidal PCO_2 measurements can help to identify this pathophysiology. In contrast, patients with CHD associated with V/Q mismatch often have low end-tidal PCO_2 .^{49,50,55} In these subjects, air from alveoli with high V/Q ratios (and hence low PCO_2) dilutes air from other alveoli and causes end-tidal PCO_2 to fall to levels below the arterial PCO_2 . Right to left shunting is also associated with low end-tidal PCO_2 measurements because the patient must reduce the PCO_2 of the blood returning from the alveoli to compensate for the hypercapnic blood that shunts from right to left (during exercise, the PCO_2 of systemic venous blood may approach 60 mm Hg).⁵⁵

Other Measurements

For some patients with CHD, data from other technologies can fruitfully complement and supplement data from standard cardiopulmonary exercise testing. Stress echocardiography can be used to assess the effect of exercise on right ventricular and pulmonary artery pressures, gradients across obstructions, valvular regurgitation, and ventricular function.^{58,59} Exercise flow-volume loops can provide additional insights into the pulmonary function during exercise.⁶⁰ Near-infrared spectroscopy technology may provide interesting data on tissue oxygenation during

exercise.^{61,62} Blood sampling and/or invasive hemodynamic measurements can provide important physiological data.^{1,5,63} Although these technologies may be invaluable in research settings, as well as in some special clinical circumstances, their role in routine clinical testing is yet to be established.

Patients with low peak $\dot{V}O_2$ may be categorized, on the basis of the RER, HR, and O_2P at peak exercise, according to the algorithm illustrated in Figure 5. Additional data from cardiopulmonary exercise testing and other modalities can then be used to more specifically pinpoint the factor(s) most likely to be responsible for the patient's poor exercise performance and to help to identify potential therapeutic strategies most likely to effectively alleviate the exercise intolerance. In addition, comparing a CHD patient's cardiopulmonary exercise testing data with data from normal subjects or with data from patients with similar types of CHD could help to guide decisions about the timing of interventions. Serial studies in the same patient can also be extremely valuable in this regard and can also be used to objectively assess the effectiveness of any interventions that are undertaken. The cardiopulmonary exercise testing abnormalities typically encountered among patients with various forms of CHD are presented in Table 1.

Safety of Exercise and Exercise Testing

Cardiopulmonary exercise testing for children with CHD is an extremely low-risk testing modality. Since 2002, almost 15 000 exercise tests have been undertaken at our institution without encountering a serious testing-related complication. Nevertheless, the value of any information that might be derived from cardiopulmonary exercise testing should always be weighed carefully against the theoretical risks associated with the test. Patients with certain conditions (such as acute myocardial or pericardial inflammatory disease, severe out-

Table 1. Cardiopulmonary Exercise Testing Abnormalities Encountered in Pediatric Patients With Various CHDs

Defect	↓ Peak $\dot{V}O_2$	↓ Peak HR	↓ O_2 Pulse	↑ $\dot{V}_E/\dot{V}CO_2$	↓ VAT
Repaired TOF/truncus arteriosus	+++	++	+++	+++	++
Fontan	++++	+++	++++	++++	+++
PVOD	++++	+	++++	++++	++++
Ebstein anomaly	+++	++	+++	++	++
Status post atrial switch	+++	++	+++	++	++
Aortic valve disease	++	+	++	+	++
Coarctation	++	+	++	+	+++
Dilated cardiomyopathy	++++	+	++++	++	++++
Hypertrophic cardiomyopathy	++	+	++	+	++
Isolated PR	+	+	+	+	+

TOF indicates tetralogy of Fallot; PVOD, pulmonary vascular obstructive disease; PR, pulmonary regurgitation, post valvuloplasty; peak $\dot{V}O_2$, oxygen consumption at peak exercise; peak HR, heart rate at peak exercise; O_2 pulse, oxygen pulse at peak exercise; $\dot{V}_E/\dot{V}CO_2$, slope of the linear portion of minute ventilation vs carbon dioxide production curve; VAT, ventilatory anaerobic threshold; +, rarely present; ++, sometimes present; +++, often present; and +++++, usually present. This table assumes that the patient is not receiving β -blocker or other antiarrhythmic therapy that might impair the chronotropic response to exercise.

flow tract obstruction for which surgical intervention is clearly indicated, severe aortic dilation) should, in general, not be tested.¹⁵

Regular exercise is associated with many physical, psychological, and social benefits and is a key factor in prevention of acquired cardiovascular diseases. These benefits should not be denied to most children with CHD. Historically, “guidance” documents have tended toward conservative restrictions on exercise participation despite an absence of clear-cut data. Fortunately, these conservative recommendations are changing. Indeed, the 36th Bethesda Conference⁶⁴ recommended that, with rare exceptions, patients with mild CHD such as mild semilunar valve stenoses (congenital or residual), small shunt lesions, or mild aortic coarctations be permitted to participate competitively in all sports. Even patients with successful arterial switch procedures or excellent tetralogy of Fallot repairs may participate in competitive sports without restriction provided that they have normal exercise tests, no evidence of ventricular dysfunction, normal or near-normal right heart pressures and chamber sizes, no significant residual shunts, and no tachyarrhythmias on ambulatory ECG or exercise testing. Although patients with more serious congenital or residual heart anomalies are advised to avoid high-intensity competitive sports, these recommendations do not necessarily preclude participation in these activities in a less competitive, recreational environment. For these patients, the numerous benefits of regular exercise should be weighed carefully against the potential risks of these activities. Exercise testing, as well as other testing modalities, can help to inform this assessment. We believe that, in most cases, the risk/benefit ratio for regular exercise will be judged to be favorable, and we strongly encourage clinical research in this important area.

Cardiac Rehabilitation for Children With CHD

When subjected to formal cardiopulmonary exercise testing, it has been found that children with “repaired” CHD often

have reduced exercise capacity.^{28,37,65–70} Residual hemodynamic lesions certainly account for some of this phenomenon. However, it has been observed that children with CHD often lead relatively sedentary lifestyles, perhaps on account of restrictions imposed on them by physicians, parents, teachers, coaches, or the children themselves.^{71,72} Any disability related to their CHD may therefore be compounded by deconditioning. This component of their disability should respond to exercise training.

Although theoretically appealing, proof of this concept has, until recently, been hard to come by. Goldberg et al⁷³ studied 26 patients with repaired tetralogy of Fallot or ventricular septal defects and found that a 6-week home exercise program with the use of stationary bicycles improved peak work capacity but had no effect on peak $\dot{V}O_2$. Ruttenberg et al⁷⁴ studied 12 patients with a variety of CHDs and reported that a 9-week program based on a jogging and walking regimen improved treadmill endurance time but did not improve peak $\dot{V}O_2$. Fredriksen et al⁷⁵ found that 55 patients with a variety of CHDs, who participated in a training program that introduced them to several sports and other physical activities, achieved a small (<5%) improvement in endurance time and no improvement in peak $\dot{V}O_2$ normalized for body weight. Minamisawa et al⁷⁶ studied 11 children and young adults with Fontan procedures and reported that a 2- to 3-month home exercise program produced only small ($\approx 7\%$) improvements in peak $\dot{V}O_2$ and peak work rate.

In contrast, Bradley et al⁷⁷ found, in a study of 9 patients with tetralogy of Fallot or transposition of the great arteries, that a 12-week rehabilitation program improved endurance time and achieved a 21% increase in peak $\dot{V}O_2$. However, their data suggested that their findings may have been due to increased effort rather than an objective improvement in exercise function. Balfour et al⁷⁸ reported data from 6 patients with CHD who completed a 3-month rehabilitation program. They found a 20% increase in peak $\dot{V}O_2$ after rehabilitation. However, their study was quite small, was plagued by a high

Table 2. Cardiac Rehabilitation Studies in Patients With CHD

Study	n	Diagnosis	Program Duration, wk	Sessions per Week	Time per Session, min	Type	Control	Impact on Peak $\dot{V}O_2$ (mL/kg per Minute), %	Comment
Goldberg ⁷³	26	16 TOF, 10 VSD	6	3	<45	Home-based	No	Unchanged	Other parameters improved
Ruttenberg ⁷⁴	12	3 TOF, 3 TGA, 1 AVC, 5 AS	9	3	45	Facility-based	No	Unchanged	Large (50%) dropout rate; other parameters improved
Bradley ⁷⁷	9	5 TGA, 9 TOF	12	2	60	Facility-based	No	↑ 20	Internally inconsistent data; RER not measured; improvements may be effort related
Balfour ⁷⁸	6	1 Fontan, 5 other	12	3	60	Facility-based	No	↑ 20	Large (>50%) dropout rate
Fredriksen ⁷⁵	55	12 TGA, 8 ASD/VSD, 11 LVOTO, 3 RVOTO, 10 TOF, 4 Fontan, 7 other	20	2	NA	Facility-based and home-based	Yes	Unchanged	Large program variability; other parameters improved
Minamisawa ⁷⁶	11	Fontan	8–12	2–3	30	Home-based	No	↑ 7	
Opocher ⁷⁹	10	Fontan	32	2	30–45	Facility-based and home-based	No	↑ 11	
Rhodes ^{80,81}	16	12 Fontan, 4 other	12	2	60	Facility-based	Yes	↑ 16	Rehabilitation patients' improvement was sustained 7 mo after the program and was significantly superior to that of control subjects

TOF indicates tetralogy of Fallot; VSD, ventricular septal defect; TGA, transposition of the great arteries; AVC, atrioventricular canal; AS, aortic stenosis; LVOTO, left ventricular outflow tract obstruction; and RVOTO, right ventricular outflow tract obstruction.

dropout rate, and could not exclude the possibility that the improvement was due solely to increased effort. In a study of 10 children with Fontan procedures, Opocher et al⁷⁹ detected an 11% improvement in peak $\dot{V}O_2$ after an 8-month, primarily home-based exercise program. None of these studies was well controlled, however, nor did they provide insights into the mechanisms responsible for the observed improvements.

More recently, Rhodes et al⁸⁰ reported that, in a study of 16 children with serious CHD, a 12-week rehabilitation program was associated with a 17% increase in peak $\dot{V}O_2$. Improvements in the $\dot{V}O_2$ at the VAT were even more substantial. Most of the improvement appeared to be due to an increase in the O_2P at peak exercise. Peak HR and peak RER were similar in the prerehabilitation and postrehabilitation studies, indicating that the observed improvements could not be ascribed to a better effort in the postrehabilitation study. The improvements were sustained 6 to 9 months after the termination of the rehabilitation program (1 year after the prerehabilitation study) and were associated with improvements in lifestyle, perceived exercise function, self-esteem, and emotional state. Improvements in exercise function and other areas were not observed in a control group comprised of 18 children with similar diagnoses observed over the same time period.⁸¹

The mechanisms responsible for the rehabilitation patients' improved peak $\dot{V}O_2$ and O_2P were not elucidated. The magnitude of the improvements appears to be too great to be explained solely by increased O_2 extraction. A rehabilitation-related increase in forward stroke volume at peak exercise therefore seems likely, although whether the increase is related to vascular, muscular, or cardiological factors remains uncertain.

The favorable results achieved in the study of Rhodes et al were ascribed to the low patient/staff ratio and the age-appropriate environment/activities that were incorporated into the rehabilitation program.⁸⁰ However, data on the optimal design of pediatric cardiac rehabilitation programs do not exist, and further investigations are needed to elucidate the most effective rehabilitation strategies for children with CHD. Furthermore, reliance on a facility-based rehabilitation program is, for many patients, impractical, and the costs of these programs are not covered reliably by most third-party payers. Home-based programs, possibly supported by Internet and/or social networking technologies, may represent a practical and attractive alternative to facility-based programs. It is, in any event, unfortunate that restrictive medical insurance policies and/or unfavorable institutional priorities cause the benefits of cardiac rehabilitation to be unavailable to most children with CHD.

Conclusion

The acquisition and interpretation of exercise test data from children and adolescents with CHD present clinicians with some unique challenges. The information gained from these studies can, however, be quite valuable and often provides unique insights into a patient's clinical status and prognosis. Cardiac rehabilitation programs also have the potential to benefit many patients with CHD. Unfortunately, the limited experience with (Table 2) and availability of these programs has caused the benefits of cardiac rehabilitation to be unavailable to most children with CHD.

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Disclosures

None.

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